Elective Stenting in Small Coronary Arteries: Lessons Learnt from Recent Trials

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Intracoronary stenting is an established treatment modality for patients with symptomatic coronary artery disease. It has been shown to be superior to conventional balloon angioplasty in reducing the incidence of abrupt vessel closure and late restenosis. However, most studies that have documented the benefit of elective stent implantation following angioplasty, including the BENESTENT\(^1\) and STRESS\(^2\) trials, had excluded lesions in vessels with a diameter of less than 3.0 mm. Currently, more than a third of coronary lesions treated with angioplasty are estimated to be in vessels smaller than 3.0 mm (in a few studies, the proportion is even about 50\%).\(^3,4\) As the population is aging and with the increasing incidence of diabetes mellitus, this proportion is likely to increase further. The issue of small vessel stenting has special importance for us, as Indians are believed to have smaller coronary arteries. In addition, stent use continues to have several limitations, such as high cost and in-stent restenosis. In small vessels, the stents remain useful if the result of conventional balloon angioplasty are suboptimal or in bail-out situations (provisional stenting). However, the role of elective stenting (stenting all cases, even if the result of balloon angioplasty is optimal) is not well defined. In the last few years, new data have emerged addressing this question.

Definition of “Small” Coronary Artery

Evaluation of data on stenting in this subgroup of patients is complicated by the fact that different criteria have been used by studies to define “small” coronary artery. The upper cut-off for reference vessel diameter has varied from 2.5 to 3.0 mm. Earlier studies had mostly defined vessels <3.0 mm in diameter as small coronary vessels while more recent trials have tended to use cut-off values of 2.75 or 2.5 mm. The lack of a uniform definition makes it difficult to compare results of different trials.

Important Issues Involved in Small Vessel Stenting

There are a number of procedural concerns and long-term issues while performing angioplasty in small coronary arteries. Since smaller vessels have little margin for error, the risks of procedural complications and restenosis rates may be higher in these vessels.

Procedural issues: These are: (i) difficulty in reaching the lesion site as small vessels tend to be peripheral and the stent may have to pass through a number of bends and curves before reaching the site. Therefore, the primary success rate of stenting such arteries may not be as high as that of larger vessels, especially if the stents used are not trackable and flexible. (ii) The chances of stent dislodgement are higher as stents may need to be placed in distal lesions after passing through a small and tortuous vessel. With the availability of balloon-mounted stents, this is usually not a major problem. (iii) The choice of stent itself may be an issue since routine stents deployed in small coronary vessels have a higher metal-to-artery ratio. This may increase the risk of subsequent problems such as subacute thrombosis and restenosis.

In spite of these procedural difficulties, most of the recent studies have shown that stents can be safely placed in small coronary arteries and with good immediate results. This has been possible due to the availability of better stents, which are more trackable and less rigid compared to the Palmaz-Schatz stent. The primary success rate and incidence of major adverse cardiac events (MACE) in the first 48 hours post-stenting is comparable to that for large vessel stenting. Pascual Figal et al.\(^5\) studied 234 patients with 300 stents, of which 84 stents were implanted in 79 lesions located in small vessels. They found the procedural success rate without any in-hospital complication to be 94\% in both the <3.0 mm and ≥3.0 mm reference vessel groups. However, the long-term outcome in the small coronary vessel group was worse; subacute thrombosis was higher (3.8\% v. 0\%; \(p=0.006\)) and event-free survival was less (69\% v. 87\%; \(p<0.001\)).

Subacute thrombosis: Earlier studies reported the rate...
of subacute thrombosis to be higher with stents placed in small coronary vessels as compared with those in larger vessels.\textsuperscript{4,5} Karrillon et al.\textsuperscript{6} in the large French multicenter registry (n=2900) found the stent thrombosis rate to be 10% for vessels with a reference diameter of ≤2.5 mm, 2.5% for those between 2.5 and 3.5 mm and 1% for those ≥3.5 mm (p<0.001). With improvement in technique, availability of stents especially designed for smaller vessels and better antiplatelet regimens, subacute thrombosis is no longer an important problem, especially for sizes between 2.5 and 3.0 mm.\textsuperscript{6-10} Moussa et al.\textsuperscript{4} found the rate to be 0.6% following stenting of both small and large vessels, while Lau et al.\textsuperscript{8} found it to be 0.5% in 197 consecutive Asian patients undergoing small vessel stenting.

**Restenosis:** Higher clinical and angiographic restenosis rates are a major concern of small vessel stenting. The exact reason for this higher risk is not known. Several explanations have been suggested, such as greater late luminal loss, higher balloon-to-artery ratio and increased plaque burden. Hoffmann et al.\textsuperscript{11} demonstrated that the degree of intimal hyperplasia is relatively constant and independent of stent size. Thus, there is greater encroachment on the lumen by intimal hyperplasia if a stent is placed into a small coronary vessel as compared with stents implanted into larger vessels. The same volume of neointimal thickness is more likely to reduce the lumen by more than 50% in smaller arteries than in larger arteries. As balloon angioplasty in small vessels leads to a higher restenosis rate than that in larger arteries, stents designed to ameliorate restenosis could have a greater relative impact if applicable to smaller vessels.

Earlier studies had shown that there was an inverse relationship between vessel size and in-stent restenosis rates. Akiyama et al.\textsuperscript{4} in a study of 1298 patients, found the restenosis rate to be 20% in vessels ≥3.0 mm in diameter while it was 33% in vessels <3.0 mm in diameter. Independent predictors of freedom from restenosis were found to be larger baseline reference diameter, larger post-procedure minimal stent cross-sectional area and shorter lesions. At long-term clinical follow-up, patients with small vessels had a lower rate of event-free survival (63% v. 71%; p=0.007). Elezi et al.\textsuperscript{12} in a study of 2602 patients also found the restenosis rates to be 39%, 28% and 20% for vessels sizes <2.8 mm, 2.8–3.2 mm and >3.2 mm, respectively. The restenosis rate is influenced by the complexity of lesions treated and by the presence of diabetes mellitus. Within the subgroup of patients with small vessel disease, the restenosis rate was 30% if there was no additional risk factor and 54% in patients with diabetes mellitus and complex lesions. Wong et al.\textsuperscript{13} found the restenosis rate after stenting of small coronary arteries to be about 35% on pooling of available data.

**Non-randomized Trials of Small Vessel Stenting**

Many operators had started stenting even the lesions in small coronary arteries soon after stents had become commercially available. Chan et al.\textsuperscript{14} reported the use of intracoronary stents for treatment of acute or threatened closure in small coronary arteries (<3.0 mm diameter) as early as 1995. They used 2.0 or 2.5 mm Flex-Stents in 42 such patients. The procedural success rate was 95% with a primary clinical success rate (freedom from myocardial infarction, coronary artery bypass surgery or death) of 90%. Subacute stent thrombosis occurred in 2.4%. Clinical follow-up at a mean of 14.8±7.6 months revealed recurrence of angina in 53% with angiographic restenosis in 66%. They concluded that intracoronary stenting is an effective and safe nonsurgical alternative for the treatment of acute or threatened closure for this subset of patients. However, the data do indicate that stenting in small coronary arteries carries a significant risk of subacute thrombosis as well as relatively high restenosis rates. The feasibility and safety of provisional small vessel stenting has also been demonstrated by Moer et al.\textsuperscript{15} They studied patients who had undergone stent implantation following suboptimal results of balloon angioplasty in vessels with a diameter of <3 mm. The overall restenosis rate was found to be 22.5%.

Stents designed for larger vessels could also be deployed successfully in smaller vessels. Cohen et al.\textsuperscript{16} reported outcomes following the use of hand-crimped Palmaz-Schatz stents (designed for vessels >3.0 mm diameter) in the small coronary arteries of 117 patients. In-hospital clinical composite end-points occurred in 6.8% (death 1%, myocardial infarction 5.1% and revascularization 1%).

Studies have not only shown the safety and usefulness of stenting focal, discrete type A lesions in small vessels, but also those in complex lesions. Miketic et al.\textsuperscript{17} reported the use of high-pressure stenting in small coronary arteries (<3 mm referenced diameter) with type C lesions. They found a high procedural success rate (98.2%). The 6-month angiographic restenosis rate was 36%. It was concluded that high-pressure stenting with flexible stents is a safe and feasible option in small vessels, even in those with unfavorable lesion morphology.

As the experience with small vessel stenting increased, even vessels smaller than 2.5 mm were successfully stented. Huang et al.\textsuperscript{18} reported the outcomes of 2.5 mm stent deployment using high pressure in small coronary arteries
(<2.5 mm reference diameter; mean 2.3±0.2 mm). The clinical and/or angiographic restenosis rate on follow-up was 24%.

Two large non-randomized trials with small vessel stenting have recently been reported. Lau et al.19 reported early and long-term results in 197 consecutive patients who underwent stent implantation in 207 vessels with a diameter <3.0 mm. The procedural success rate was 97.3%, lesion severity reduced from 85±9% to 3±7%, with a subacute stent thrombosis rate of 0.5%. Survival without major target lesion-driven events was 77% and 74% at 1 and 2 years of follow-up, respectively. The 6-month angiographic restenosis rate was 30.1%. Diabetes mellitus, small vessel size and stent size <2.7 mm were found to be independent predictors of in-stent restenosis. In a similar study, Morice et al.20 reported that among 190 patients stented with 2.5 mm stents, the procedural success rate was 98%, subacute thrombosis rate was 2.6% and repeat intervention rate on follow-up was 24.5%.

Thus, a number of non-randomized trials of small vessel stenting have been reported. The initial procedural success rate ranged from 93% to 98%, subacute thrombosis rate from 0.5% to 3.8% and the restenosis rate from 21% to 36%. Adverse clinical events ranged from 11% to 26%. The initial and long-term success rates of stenting in small coronary vessels were nearly the same as those for large vessel stenting. These studies conclusively established the feasibility, safety and efficacy of small vessel stenting, especially in situations where balloon angioplasty results were suboptimal (provisional stenting). However, the real issue of whether elective stenting is better than provisional stenting could not be resolved from these studies.

**Randomized Trials of Elective Stenting versus Balloon Angioplasty**

To clarify the crucial issue of elective stenting, Savage et al.3 performed retrospective, post-hoc analysis of the STRESS I and II trials which were originally designed for lesions in coronary vessels with a reference diameter larger than 3 mm. In this trial, 331 out of 598 patients had a vessel diameter of <3 mm by quantitative coronary angiography. The data of these patients were analyzed (163 in the stent group and 168 in the balloon angioplasty only group). The procedural success rate was 100% with stenting versus 92% with angioplasty (p<0.001). Abrupt closure within 30 days occurred in 3.6% of patients in both groups. The primary end-point of 6-month binary angiographic restenosis rate was 34% with stenting versus 55% with angioplasty alone (p<0.001). The minimum luminal diameter at 6 months was larger in the stent group than in the balloon group (1.54 v. 1.27 mm; p<0.001). One-year event-free survival was 78% in the stent group versus 67% in the balloon group (p=0.019). The target lesion revascularization rate was also lower at 16.1% in the stent group as compared with 26.6% in the balloon group (p=0.015). On the whole, this analysis revealed that elective stent placement in small vessels was better than balloon angioplasty alone. However, STRESS I and II were not originally designed to test the role of stenting in small vessels and such analyses cannot replace prospective randomized controlled trials, which is the only way to answer such a question definitively. A number of such trials were thus initiated and the results of many of these are now available.21–28

Eight major prospective, randomized, controlled trials of elective stenting in small vessels involving 2687 patients have been reported (Table 1). The main end-points of interest are angiographic restenosis rate and major adverse cardiac events at follow-up. The angiographic restenosis rate at follow-up (usually 6 months) was available in 6 of these 8 studies and was found to be similar in the balloon angioplasty and the stent groups in 4 of these 6 studies. Only 2 studies (BESMART and RAP) found that elective stenting significantly reduced the angiographic restenosis rate. The average restenosis rate in the balloon angioplasty group was 37% while that in stent group was 32%. Clinical events at follow-up were found to be no different in 7 of these 8 studies. Only the SISC A study found these to be significantly reduced in the elective stenting group. In the BESMART study, the target lesion revascularization rate was reduced significantly, though there was no difference in the mortality or myocardial infarction rate. However, these trials are not exactly comparable due to a number of variables, e.g. baseline characteristics, type of lesions treated, type of stents used, antiplatelet regimen used, use of high pressure stenting, use of glycoprotein IIb/IIIa inhibitors, etc. Evaluation of individual data from these trials provides important insight into this problem.

The BESMART (BeStent in Small Arteries) trial21 is a French prospective, multicenter, randomized study that evaluated the role of stenting in de novo lesions 15 mm or less in length with vessel diameter <3.0 mm (mean 2.2 mm). Three hundred and eighty-one patients were randomized. The procedural success rates were similar in both groups, and the in-hospital rates of major adverse events did not differ significantly. Death or myocardial infarction rate at 6 months also did not differ. Target lesion revascularization at 6 months was 25% for the balloon angioplasty group versus 13% for the stent group.
The primary end-point of a 6-month angiographic restenosis rate was 49% for the balloon angioplasty group versus 23% for stent group (p=0.0001). The rate of cross-over to stenting because of suboptimal result following balloon angioplasty was high (24%).

Suwaidi et al.\(^\text{22}\) compared immediate and 1-year outcomes in 651 patients with stenosis in small coronary arteries treated with either 2.5 mm stent implantation (n=108) or 2.5 mm balloon angioplasty (n=543). Angiographic success was higher in the stent group (97% v. 90%; p=0.02). In-hospital myocardial infarction rates were comparable (4.6% v. 2.4%; p=0.2). At 1 year of follow-up, MACE was higher in the stent group (35% v. 22%; p=0.05). Amongst successfully treated patients, there was no difference at 1 year with respect to survival (3.8% v. 4.8%; p=0.37). It was concluded that stents could be deployed in small coronary arteries with high success and low in-hospital complication rates. However, stent use was not associated with improved outcome at 1 year of follow-up, compared with balloon angioplasty.

Park et al.\(^\text{23}\) randomly assigned 120 patients with lesions in small coronary arteries (de novo, nonostial lesions with reference diameter <3.0 mm) to optimal balloon angioplasty or elective stenting (7-cell NIR stent). The primary end-point was restenosis at 6 months. Optimal balloon angioplasty (residual stenosis <30%) was aimed at in all cases and cross-over to stenting was allowed. The procedure was successful in all patients. Twelve patients in the balloon angioplasty group were stented for suboptimal result or major dissection. The post-procedural lumen diameter was larger in the stent group but late loss was also greater (1.12±0.67 mm v. 0.63±0.48 mm; p<0.01). The angiographic restenosis rate was 30.9% in the angioplasty group and 35.7% in the stent group (p=NS). Clinical events during follow-up were also similar. It was concluded that optimal balloon angioplasty with provisional stenting may be a reasonable approach for these lesions.

Briguori et al.\(^\text{24}\) compared 209 patients with complex lesions (type B2 or C) in arteries <3.0 mm treated either with balloon angioplasty or elective stenting. At a mean follow-up of 20±4 months, MACE (39% in the angioplasty group v. 44% in the stent group), target lesion revascularization (33% in the angioplasty group v. 34% in the stent group) and restenosis rates (47% in the angioplasty group v. 38% in the stent group) were not statistically different in the two groups. It was concluded that elective stent implantation in small vessels with complex lesions does not improve early and late outcomes. The results are different from those of the STRESS trial as instead of focal lesions, the present study was carried out in complex lesions.

ISAR-SMART\(^\text{25}\) was a randomized trial in 404 patients comparing stenting (using MultiLink stents) with balloon angioplasty in small native coronary arteries (vessel size between 2 and 2.8 mm). All patients received abciximab, ticlopidine and aspirin. The primary end-point was 6-month angiographic restenosis rate (>50% diameter stenosis); adverse clinical events constituted secondary end-points. No significant difference was found in the two groups with respect to any of the primary or secondary end-points at follow-up: angiographic restenosis (35.7% v. 37.4%), net luminal gain (0.76±0.78 mm v. 0.76±0.63 mm), infarct-free survival (96.6% v. 97%), and target vessel revascularization (20% v. 16.5%). Angiographic restenosis at 6-month follow-up was 35.7% in the stent group versus 37.4% in the angioplasty group. It was concluded that RAP.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Reference vessel size included</th>
<th>Angiographic restenosis at follow-up</th>
<th>Clinical events at follow-up</th>
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<td></td>
<td></td>
<td></td>
<td>Balloon</td>
<td>Stent</td>
</tr>
<tr>
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<td>381</td>
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<td>NA</td>
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<tr>
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<td>&lt;3.0 mm</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Briguori(^\text{24})</td>
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<td>&lt;3.0 mm*</td>
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<td>36%</td>
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<tr>
<td>ISAR-SMART(^\text{25})</td>
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<td>37%</td>
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<tr>
<td>SISA(^\text{26})</td>
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<tr>
<td>RAP(^\text{27})</td>
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<td>37%</td>
<td>27%</td>
</tr>
<tr>
<td>SISCA(^\text{28})</td>
<td>145</td>
<td>2.1-3.0 mm</td>
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<td>NA</td>
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</tbody>
</table>

NS: not significant; NA: indicate data not available; MI: myocardial infarction; TLR: target lesion revascularization; *: type B2 and C lesions; @: values for MI and death not available
elective stenting does not reduce restenosis rates compared with the strategy of provisional stenting in small coronary arteries.

The SISA (Stenting in Small Arteries) trial was a randomized, multicenter trial in which balloon angioplasty was compared with elective stenting (using Medtronic BeStent) for lesions in vessels 2.3-2.9 mm in diameter in 351 patients. Angiographic restenosis at 6 months was the primary end-point. There was no significant reduction in this primary end-point (32.4% for balloon angioplasty v. 28% for stent group). There was a trend for less non-Q wave myocardial infarction at 6 and 12 months in the stent group, but there was no reduction in total cardiac events or re-angioplasty rates.

The RAP (Restenosis en Arterias Pequenas) trial was a multicenter, prospective randomized trial comparing elective BeStent implantation with balloon angioplasty alone in 426 patients with lesions in small vessels (2.2-2.7 mm reference diameter). Angiographic restenosis at 6 months was the primary end-point. Immediate post-procedure as well as 6-months minimum luminal diameter was higher in the stent group (1.47 mm v. 1.31 mm at 6 months; p=0.01). The restenosis rate at 6 months was less with stent implantation (27% v. 37%; p<0.05) as also the vessel occlusion rate (1.4% v. 3.7%; p<0.01). At 6 months, MACE was no different in the two groups (11% v. 14%). The results of the RAP study demonstrate that coronary artery stenting significantly reduces the rate of restenosis and vessel reocclusion in small coronary arteries.

SISCA (Stenting in Small Coronary Arteries) is a multicenter, randomized trial comparing elective stenting using the 15 mm heparin-coated BeStent and balloon angioplasty in 145 patients with lesions in the small coronary arteries (2.1-3.0 mm reference diameter). The procedural success rate was 94.6% in the stent group versus 80% in the balloon angioplasty group (p=0.008). During 6 months of follow-up, occurrence of cardiac events was significantly reduced (9.5% in stent group and 23.9% in balloon angioplasty group; p=0.025). Target lesion revascularization was required in 8% of patients in the stent group versus 25% of patients in the balloon angioplasty group. It was concluded that in small vessels, elective placement of a heparin-coated BeStent significantly improves both procedural and 6-month clinical outcomes compared with balloon angioplasty.

What conclusions can we draw from the above data? Results of most of the above studies point to provisional stenting as a better option, with stent placement only for suboptimal results or complications. Routine elective stenting was not found to have better long-term results in most of the trials. However, the data have been conflicting regarding many issues, and a number of patient and procedure-related factors could be responsible for these differences.

Role of Intravascular Ultrasound Guidance

The role of intravascular ultrasound (IVUS) in optimization of stent implantation in larger coronary arteries is well documented. Quantitative coronary angiography (QCA) has several fallacies in evaluating the “true” diameter of vessels. Intravascular ultrasound may be of significant importance in choosing the correct stent diameter and its length in small vessels. Atherosclerosis is frequently a diffuse process and the diseased vessel may be reduced in caliber along its entire length (diffusely diseased artery), giving the angiographic impression of “small” vessel disease; IVUS helps to differentiate between a “small” vessel and a diffusely diseased artery. One should also keep in mind the fact that there is a progressive decline in luminal diameter as coronary arteries course distally. This tapering is an important consideration in small vessels (especially in long lesions) in order to avoid over-dilatation of distal lesions with stents.

Ortolani et al. studied the feasibility and safety of IVUS guidance during stenting of small coronary arteries. In this pilot study, they included 14 patients who were to undergo stent implantation in small coronary arteries (mean reference vessel diameter 2.3±0.2 mm). They showed that IVUS-guided coronary stenting can be performed in small vessels with a high success rate and low incidence of in-hospital complications. However, though the initial results showed improvement with IVUS guidance, the long-term clinical and angiographic outcomes were less favorable. The 6-month angiographic restenosis rate was 30.7% and late loss in stent diameter was 1.1±0.6 mm. Akiyama et al. showed the benefit of optimal IVUS-guided stenting. The restenosis rate was 26% when optimal IVUS outcome was achieved, as compared with 37% when IVUS outcome was suboptimal.

Effect of Stent Design

The stent design may have important implications for outcome in terms of both subacute thrombosis and long-term restenosis. It is necessary to develop stents specially designed for small arteries so as to obtain an optimal radial force at a smaller diameter with a lower metal-to-vessel ratio. Caputo et al. compared the outcomes of small vessel
Treatment of In-stent Restenosis in Small Vessels

In-stent restenosis following small vessel stenting can also be treated with repeat angioplasty. Gross et al.31 studied in-stent restenosis following small vessel stenting and found that repeat angioplasty was effective in reducing restenosis rates. A number of stents specifically designed for small vessels are now becoming commercially available. These include, among others, BioDivYsio phosphorylcholine-coated stent (Biocompatibles International), Multi-Link Pixel coronary stent (Guidant Corporation) and BeStent (Medtronic).

Conclusions

Should stenting be performed routinely in all cases after angioplasty of lesions in small coronary arteries (elective stenting) or only if there is a complication after balloon angioplasty such as acute or threatened vessel closure, major dissection or suboptimal result (provisional stenting)? According to the ACC expert consensus document on coronary artery interventions, stents are recommended in small vessels if the result of balloon angioplasty is suboptimal.32 Data currently available indicate that provisional stenting may be a better option, as elective stenting has not been consistently shown to improve long-term results on follow-up. However, the situation may change with newer developments, especially the availability of stents designed specifically for small coronary arteries, routine use of glycoprotein IIb/IIIa inhibitors, introduction of effective antiplatelet regimes including clopidogrel and use of antioxidants such as probucol. In addition, early studies with drug-coated stents have shown promise in significantly reducing restenosis rates, a major concern in small vessel stenting.

References

Women now outlive men by 10 years, thanks to the dramatic (>99%) decline in obstetrical death rate over the past 100 years. Women represent 60% of those over the age of 65 years in the United States (US) and more women than men have died of cardiovascular disease (CVD) since 1984. There has been an explosive increase in the knowledge of the natural history of coronary artery disease (CAD) in women in the past decade. This is due to a combination of greater participation of women in research studies, improved medical technology, and perhaps political pressure. Among women, the lifetime risk of death from CAD is more than 10-fold greater than that from breast cancer. It is estimated that 31% of women will die from CAD; yet, about 70% of university educated women consider their risk of CAD to be <1%. They worry profoundly about breast cancer, although the risk of death from breast cancer is <3%.

This lack of concern for CAD by women and perhaps their physicians could explain why the decline of CAD in women in western countries has been only half that of men. The excess of CAD among overseas Indians has been similar or greater in women than in men, and offers a broad “window to the world” for the impending epidemic of CAD among Indian women. In this article, the term “Indian” refers not only to people of Indian origin but all those originating from the entire Indian subcontinent.

This review discusses the progress in understanding the major risk factors leading to the high rates of CAD in women, especially in India.

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Magnitude of CAD in Indian Women

CAD rates in India: Since 1960, life expectancy in India has increased by 20 years to 61 years of age. From 1960 to 1995, the prevalence of CAD in adults increased from 3% to 10% in urban Indians and from 2% to 4% in rural Indians, with women having rates similar to men. Although the prevalence of CAD in rural India is half that of urban India, this is still two-fold higher than the overall CAD rates in the US and several-fold higher than in rural China. In 1990, there were 783,000 deaths due to CAD in India and this is projected to double by the year 2015, primarily due to affluence and urbanization. Young Indians with CAD have extensive coronary atherosclerosis, with even premenopausal women having multivessel disease, a pattern rarely seen in the West.

CAD rates among overseas Indians: Although more women than men die annually from CAD, the age-adjusted standardized mortality rate (SMR) for CAD among women is about one-third that of men all over the world. This is due to a higher age (average 10 years) in women at the time of death. The excess of mortality due to CAD among overseas Indians is equal or greater in women than men. This is particularly noteworthy since smoking is rare among Indian women. In the US, Indian women have the highest CAD mortality—30% higher than Whites and 325% higher than the Chinese.

Excess CAD morbidity and mortality in women: Women have a poorer prognosis and a more severe outcome than men after myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG). Women are more likely than men to die after a first MI, and for survivors, there is a higher risk of recurrent MI, heart failure, or death. In the Framingham Heart Study (FHS), the one-year mortality following an MI was 44% in women versus 27% in men. The overall short-term and long-term CAD mortality following an MI are about 40% higher in women after adjustment for age and other risk factors. The excess in-hospital CAD mortality in women compared to men almost balances their lower prehospital mortality. Despite their
excess risk, women are only half as likely as men to receive aspirin, betablockers or thrombolytic therapy, or to be referred for coronary angiogram or revascularization procedures. This difference is rapidly disappearing in the US but not all over the world. Recently, Vaccarino et al. found that mortality from MI in women <50 years of age was double that of men and the excess mortality in women is limited to <60 years of age. This is in sharp contrast to a report from India showing lower rates of morbidity and mortality in young women and deserves greater scientific scrutiny.

**Presentation of CAD:** Although women are more likely than men to present with angina as the initial complaint, the reliability of typical angina as a sign of CAD is poor. In the FHS, only 17% of women with typical angina developed an MI compared with 44% of men. In the Coronary Artery Surgery Study (CASS), only 50% of women with typical angina had significant CAD compared with 83% of men. Whether this discrepancy is due to over-reporting of chest pain by women or under-reporting by men is unclear. Women having an MI are more likely to present with atypical chest pain (midback pain) and atypical symptoms (indigestion, nausea, vomiting and dyspnea). They present to the hospital significantly later than men, which may decrease the benefit of reperfusion therapy.

**Sudden death:** More than half of sudden deaths occur within six hours of the onset of symptoms. Early diagnosis is important, since two-thirds of women who experience sudden death have no previous symptoms of CAD, compared with about half of men. The risk factors and mechanisms of sudden coronary death differ between older and younger women. Older women who die of CAD often have dyslipidemia, with severe coronary narrowing and plaque ruptures. Young women who die of CAD are often smokers with plaque erosions and little coronary narrowing. However, most young Indian women with CAD have advanced CAD resembling that in older women.

**Coronary Risk Factors**

Women, in comparison with men, tend to have a better risk factor profile at younger ages, whereas the opposite is true at older ages. Although most risk factors for CAD are similar in men and women, gender differences have been documented, particularly for diabetes, central obesity and dyslipidemia. Among Indian women, the presence of hypertension, diabetes, low levels of high density lipoprotein (HDL) and high levels of total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), and Lp(a) are correlated with CAD. Compared with Whites, Indian men and women have a lower prevalence of hypertension, hypercholesterolemia, obesity and smoking, but a higher prevalence of high TG, low HDL, glucose intolerance and central obesity. The prevalence of most risk factors is lower in rural than in urban India with the exception of smoking/tobacco use. The higher rates of CAD in urban areas despite a low rate of tobacco use (Tobacco Paradox) underscore the critical importance of factors associated with urbanization.

**Asian Indian ethnicity:** At a given level of risk factors, compared to Americans, the CAD risk is 50% lower among southern Europeans but 50% higher among northern Europeans. Therisk of CAD among Indians is even greater than in northern Europeans at any given level and/or combination of conventional risk factors—at least double that of Americans and several-fold higher than other Asians. At any given level of TC the CAD risk varies >5-fold depending on ethnicity and level of other risk factors. Indian ethnicity has now been demonstrated to be a risk factor by itself.

**Family history:** Among women, a history of an MI or sudden death before the age of 55 in a sister is more strongly associated with risk of MI than that in a brother or parent. A family history of premature CAD in a sister is associated with a 12-fold higher risk versus 6-fold for a brother and 3-fold for a parent. Since choosing one’s parents or siblings is not an option, this topic will not be discussed further except that women with a family history of premature CAD, especially in a sister, should follow a course of action similar to the one recommended for those who had survived an MI or had coronary revascularization at a young age.

**Age:** Compared with the age group 34–44, CAD mortality among women increases 40-fold by the age of 80, when its incidence becomes identical in men and women. Women are about 10 years older than men at first manifestation of CAD, although they have a similar plaque burden. Women lose this 10-year advantage if they smoke, have diabetes, or had a premature menopause. The postmenopausal increase in the risk of CAD is related to a higher incidence of hypertension, diabetes, dyslipidemia and obesity. The steady increase in CAD mortality with age is in sharp contrast to that of breast cancer, which peaks between the ages of 40 and 50 years and declines steadily thereafter.

**Height:** Height is inversely associated with CAD in women as it is in men. In a large study involving about 2000 women, short women (<59 inches) had a 3-fold higher risk
individuals. In the 16-year data from the Nurses' Health Study (NHS), CAD mortality was 4-fold lower in lean (BMI <21) than in obese women. For Asians, the optimum BMI is <23, whereas >23 is considered overweight and >25 obese. Thus the BMI cut-off points for overweight is 2 units, and obesity 5 units lower in Asians than in Whites.

Central obesity: The distribution of fat is of equal or greater importance as the total amount of fat. Marked adverse metabolic consequences are seen with central obesity (android or apple-type) but rarely with gluteofemoral obesity (gynoid or pear-type). The waist-to-hip ratio (WHR) has been traditionally used to measure central obesity. This is a better marker for CAD death than BMI in women under 50 years of age. Because the excess fat is usually concentrated in the hip in women and the waist in men, the optimum WHR is lower in women (<0.75) than in men (<0.95).

Recently, waist circumference has been found to be a simple and better marker of central obesity than WHR. In women, the optimum waist circumference is 10 cm lower—<80 cm in women and <90 cm in men. These values are about 8–10 cm lower than that recommended for Whites and underscore the need for instituting a weight management program at much lower BMI and waist circumference in Indian men and women. At a given level of WHR or waist circumference, CAD rates are identical in men and women. It is plausible that sex differences in central obesity are the key to the gender gap in CAD.

The recognition of the significance of central obesity should not divert attention from the metabolic consequences of noncentrally obese individuals who need to reduce weight. Among Indians, as in other populations, both BMI and WHR are related to CAD risk factors in a graded manner; the maximum risk occurs in apple-shaped overweight and minimum in pear-shaped lean individuals.

Adult weight gain and weight reduction: Atherogenic risk factor clustering is common in both sexes and worsens with weight gain. Age-related increase in weight and waist circumference is greater in women than in men and is closely related with decrease in physical activity. A weight gain of even 7–11 kg after the age of 18 years has substantial health consequences, with a doubling of risk for diabetes and CAD in women. Middle-aged women who lose ≥5 kg of weight have a significantly reduced risk for diabetes. The recommended weight reduction is about 0.5 kg per week and this requires a negative caloric balance of 3500 calories equal to walking 56 km per week.

Physical activity: Physically active women have a 50% lower risk of CAD than sedentary women. Increased physical activity along with diet can prevent a rise in LDL and weight gain, especially around the waist. Daily walking for 45–60 minutes is necessary to prevent weight gain in most women. However, even walking 2 km per week produces a favorable risk factor profile, especially fibrinogen and insulin levels, and reduces the CAD risk. Home physical activity is positively related to favorable lipoprotein levels, with those engaging in heavy home physical activity having higher HDL levels. Other benefits of exercise include reduced risk of breast cancer (relative risk 0.28).

Socioeconomic status (SES) and psychosocial factors: CAD has now become a disease of the poor in rich countries and of the rich in poor countries. Women with less than a high school education have a 30%–50% higher CAD mortality than those with higher education. Depression, high hostility, low social support and low education levels are associated with CAD, after controlling for adverse health behaviors. Indians with low literacy have a higher prevalence of CAD and risk factors such as smoking and hypertension. However, differences in SES failed to explain the excess burden of CAD among Indians in the UK. Despite having a lower level of TC, Indians had a 3- to 4-fold higher odds ratio for a high-risk lipid profile, after controlling for SES, age and sex. The impact of psychosocial and behavioral factors on CAD in Indian women requires further investigation.

Paradox of healthy lifestyle and shorter lifespan in women physicians: Women physicians in the US report having generally good health habits and exceed all examined national goals for personal screening practices and other personal health behaviors. Women physicians' behaviors may provide useful standards for other women. Ironically, women physicians die an average of 10 years earlier than their male counterparts, the opposite of what happens in the general population. The suicide rate among female physicians is higher than that for male physicians and four times higher than the age-matched female population and may partially explain their lower life span despite a healthy lifestyle.
Tobacco abuse: Due to its anti-estrogenic effects, smoking quadruples the risk of MI in young premenopausal women. It is a stronger risk factor in women than in men. Over 50% of MI in middle-aged women in the US is attributable to cigarette smoking. The risk of CAD begins to decline within months of cessation of smoking and disappears within 3-5 years. The smoking cessation rates have declined more slowly in women in the US, especially younger ones than in men and parallel slower rates of decline of CAD in women. The overall rate of smoking is low among Indian women, particularly in urban areas.

Passive smoking: Although only 8% of the women in Asian countries smoke, >60% of the men are smokers. Therefore, vast numbers of women and children are exposed to environmental tobacco smoke (ETS), which increases platelet activity, accelerates atherosclerosis, reduces exercise tolerance, and increases the risk of both fatal and nonfatal cardiac events. Urgent public health measures are needed to reduce the dangers of both active and passive smoking in India.

Hypertension: Hypertension confers a 4-fold risk of CAD in women versus a 3-fold one in men. Hypertension tends to be more common in women than in men after 45 years of age (White women 60% and Black women 79%). The systolic blood pressure (BP) continues to increase disproportionately in women until the age of 80. Hypertension is closely correlated with obesity and is 6-fold higher in women with a BMI >30 versus BMI <20. Conversely, a weight reduction of 9 kg can lower systolic BP by 6 mmHg and diastolic BP by 3 mmHg in hypertensive patients.

Insulin resistance syndrome or Syndrome X: This is a precursor of diabetes and a common pathogenic mechanism for the development of CAD. This syndrome is particularly common among Indians and consists of hyperinsulinemia, atherogenic dyslipidemia, glucose intolerance, prothrombotic state, central obesity and hypertension. This is different from the cardiac syndrome X (angina with abnormal treadmill test and normal coronary angiogram), which is also more prevalent in women. It is unclear if the cardiac risk in this syndrome exceeds that of the constituent risk factors.

Diabetes mellitus: In the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), diabetes is regarded as a CAD risk equivalent. Diabetes is a stronger risk factor for CAD in women than in men, with a 3- to 7-fold higher CAD incidence and mortality compared to a 2- to 3-fold higher risk in men. Diabetes increases the risk of heart failure by 8-fold in women compared to 4-fold in men; diabetes eliminates the protective effects of estrogens and removes the normal sex difference in the prevalence of CAD. Premenopausal women with diabetes face a similar risk of developing CAD as nondiabetic men of the same age. Following an MI, diabetic women have double the rate of recurrence and shorter survival than men.

Diabetic dyslipidemia: Approximately 80% of deaths in diabetic patients are attributable to CVD, which in turn is highly correlated with dyslipidemia. Diabetic dyslipidemia consists of elevated TG, low HDL, and an increased proportion of small dense LDL. Recently, the NCEP ATP III has also recommended an LDL goal of <100 mg/dl in diabetic patients, irrespective of the presence or absence of CAD. Diabetic women with HDL ≤50 mg/dl and TG ≥100 mg/dl have high CAD mortality and should be treated aggressively. Treatment of dyslipidemia with statins in patients with both impaired fasting glucose and diabetes is highly cost-effective.

Crucial Role of Dyslipidemia

Total cholesterol (TC): Total cholesterol levels in women compared to men are about 10 mg/dl lower before the age of 45 and 10 mg/dl higher after the age of 65. A 20% difference in TC level is associated with a 50%-60% difference in CAD risk over a lifetime. The optimum TC level appears to be <160 mg/dl.

LDL: The LDL fraction of TC is a strong predictor of CAD mortality in women as well as in men. Unlike in men whose LDL levels plateau at the age of 50 years, the LDL levels in women increase steadily by an average of 2 mg/dl/year between the ages of 40 and 60 (total of 40 mg/dl). The optimum LDL level is <100 mg/dl.

HDL: Low HDL is an important risk factor even if TC and TG levels are normal. It is a stronger predictor of CAD in women than in men, especially after the age of 65; indeed, the protective effect of HDL is twice as important as the atherogenic effect of LDL. High density lipoprotein levels are about 10 mg/dl higher in premenopausal women than in men. Among women, the HDL levels vary markedly depending on the ethnicity, with Indian women having the lowest levels. The HDL level among Indian women (45 mg/dl) is about 10 mg/dl lower than in Whites (55 mg/dl) and 20 mg/dl lower than in Blacks, the Chinese and Japanese (65 mg/dl). These high levels of HDL among Black, Chinese and Japanese women also parallel their low rates of CAD, whereas the low levels of HDL in Indian women parallel their high rates of CAD.
The NCEP ATP III has classified HDL <40 mg/dl as low HDL and >60 mg/dl as high HDL. In India, 32% of urban and 18% of rural women have HDL levels <40 mg/dl. Many experts consider HDL <50 mg/dl to be low in women. In the Coronary Artery Disease in Indians (CADi) study, 70% of Indian women had HDL levels <50 mg/dl. If the level is <35 mg/dl, it confers an 8-fold higher CAD risk than an HDL of >75 mg/dl in women.45

**Total cholesterol/HDL (TC/HDL) ratio:** This ratio is now widely recognized as the single best predictor of CAD. At any given level of TC/HDL ratio, the CAD risk is virtually identical in men and women.18 Indian women worldwide have a high TC/HDL ratio by virtue of low HDL, even when TC levels are not elevated.46 The optimum TC/HDL ratio is 3 and the average ratio is 4. A TC/HDL ratio >5 appears to be a strong predictor of CAD, and is observed in 25% of industrial and 32% of urban female populations in India.18

**Triglycerides:** A high TG level is a stronger predictor of CAD in women than in men. An increase in TG level of 90 mg/dl increases the CAD risk by 75% in women versus 30% in men.47 A high TG level was significantly associated with cardiac and total mortality in a 20-year follow-up of Swedish women.48 Conversely, low TG (<97 mg/dl) and high HDL (>57 mg/dl) is associated with very low risk of CAD,49 but is uncommon among Indians. A low level of HDL often accompanies a high TG. The optimum TG level is <150 mg/dl.

**Lipid triad:** The combination of high TG, low HDL and high small dense LDL is called the lipid triad. The TG level is the principal determinant of small dense LDL, which in turn is the link between cholesterol and TG metabolism.50 The predominant form of LDL is small and dense when HDL is <40 mg/dl and TG >100 mg/dl.51 Recently, a TG/HDL ratio of >3 was found to be a simple, accurate and inexpensive predictor of small dense LDL.52 Individuals with small dense LDL have a 3-fold higher risk of CAD, which increases to 20-fold when apolipoprotein B (Apo B) and insulin levels are also raised.53 All these abnormalities are common among Indian men and women, rendering them highly susceptible to CAD.54

**Lipoprotein(a):** An elevated level of Lp(a) is a powerful risk factor for the presence and severity of premature CAD in women as well as in men. Since its pathological effects begin in infancy, Lp(a) is a stronger determinant of CAD in premenopausal than in postmenopausal women. The pathogenicity of Lp(a) is markedly influenced by other risk factors, especially low HDL, a high TC/HDL ratio, and high homocysteine levels. For example, high levels of Lp(a) increase the risk of CAD by a factor of 5 when associated with hypertension, by a factor of 7 with high TC/HDL ratio, by a factor of 8 with low HDL and by a factor of 9 with high homocysteine. The combination of all four of the above increases the risk of CAD by a factor of 122.55 Lipoprotein(a) level was a powerful predictor of mortality in the 4S study.56 Lipoprotein(a) appears to be a stronger risk factor than diabetes in young women. Indian women in the US have a higher CVD risk than their American counterparts, by virtue of central obesity, high Lp(a) levels, and an atherogenic lipid profile. Although Lp(a) levels are largely genetically determined, there is a 10% increase in Lp(a) levels in postmenopausal women. Hormone replacement therapy (HRT) reduces Lp(a) levels by an average of 20% (up to 50% in women with high Lp(a) levels). The role of Lp(a) among Indians has been reviewed recently.57

**Homocysteine:** An elevated homocysteine level is a risk factor for MI, especially among young women. After adjusting for other CVD risk factors, women with homocysteine levels ≥15.6 µmol/L have twice the risk of MI as women with homocysteine levels <10 µmol/L. The most common cause of elevated homocysteine is low folate levels, though many patients also have low levels of vitamins B6 and B12.58 Prolonged cooking of vegetables, a common practice in India, can result in the destruction of up to 90% of the B group of vitamins.59 The optimum homocysteine level is <10 µmol/L. The combination of high Lp(a) and high homocysteine levels is very common among Indians and carries a 32-fold increased risk of CAD.55 The multiplicative effects of the emerging and conventional risk factors best explain the excess burden of CAD among Indian men and women.

**Diagnostic Testing and Coronary Revascularization**

**Noninvasive diagnostic testing:** Although women with resting ischemic electrocardiographic findings have an increased risk for CAD, false-positive stress tests may be seen in as high as 50% of women with chest pain.60 This is particularly true in those on HRT, which produces ST segment depression similar to a digitalis-like effect. Therefore, the accuracy of stress testing depends on the Bayesian principles.

Stress imaging, including thallium myocardial perfusion imaging, has lower sensitivity and specificity in women than in men, possibly due to smaller left ventricular chamber size, hormonal milieu, and autonomic imbalance.60,61 Estimation of coronary calcification by electron beam computerized tomography has a low sensitivity among premenopausal women.
women and its role in detection of CAD is currently evolving. Stress echocardiography appears to be superior in identifying women who require further expensive diagnostic and therapeutic interventions.

**Coronary angiography:** Of the 323 women enrolled in the pilot phase of the Women’s Ischemia Syndrome Evaluation (WISE) study, 57% had no significant CAD (34% not detectable, 23% minimal stenosis) versus 43% with significant CAD (stenosis >50%) on coronary angiogram. The contemporary common finding of “no CAD” and “extensive CAD” at coronary angiography among symptomatic women with similar presentations is similar to the CASS data reported 20 years earlier. These findings underscore the need for better use of noninvasive tests to identify women who are candidates for invasive procedures.

**PTCA:** Women who are hospitalized for CAD undergo fewer invasive procedures than men. Whether this difference represents overtreatment of men or undertreatment of women or both remains to be determined. Although women have excellent long-term prognosis after successful PTCA and stent insertion, similar to that observed in men, the procedural morbidity and mortality are 3-fold higher in women, which may be due to severity of their underlying disease rather than gender alone. Recent evidence suggests that the gender bias against aggressive intervention and treatment of CAD in women is disappearing in the West.

**CABG:** Women in general are more severely ill than men and have double the mortality following CABG. People with small body size have small coronary arteries but women have smaller coronary arteries than men despite controlling for differences in body size. Small coronary artery diameter is associated with substantially increased risk of in-hospital mortality following CABG. Thus, smaller coronary artery diameter is one explanation for the higher perioperative mortality and poorer long-term success with CABG in women. Women have less graft patency and symptom relief and higher reoperations within the initial five years following CABG. A high TG level is particularly dangerous in women who undergo CABG. Agressive lipid-lowering therapy can stabilize the vulnerable plaque and thus provide a more stable milieu for CABG to avoid the need for repeat and “3-peats.” A strategy of delayed revascularization with optimum medical therapy is advisable. Women have higher risk profiles and are older; yet, the unadjusted 5-year mortality rates in women and men undergoing CABG and PTCA are similar. This would suggest that the gender differences in mortality related to CAD do not exist, or may even be lower in women, after adjusting for age, risk factors and interventions.

**Preventive and Therapeutic Implications**

**Asymptomatic progression of CAD:** Atherosclerosis is a disease that manifests clinical symptoms only late in its development. Coronary artery disease is not a categorical event but rather a continuum of a progressive process. Sudden cardiac death may be the first symptom and such patients obviously cannot benefit from secondary prevention. Furthermore, women fare worse following an MI than men; therefore primary prevention is even more important in women.

**Comprehensive guide to risk reduction in women:** The American Heart Association recommendations can be modified to suit Indian conditions. Caloric intake should be balanced to caloric expenditure to achieve and maintain optimum BMI. Regular exercise is mandatory for both men and women. Women who have gained 5 kg of weight or 5 cm of waist should be advised by physicians to make gradual but permanent adjustments in physical activity and eating patterns. The essential ingredients and goals for risk reduction in women are given in Table 1.

**Undertreatment of dyslipidemia in women:** About 50% of women >55 years of age qualify for drug treatment under NCEP ATP III guidelines in the US. In the Heart and Estrogen/Progestin Replacement Study (HERS), only 9% met the LDL goal of <100 mg/dl. Another study found only 12% of women achieved the LDL goal compared to 31% of men. This underscores the need for a more aggressive approach to the treatment of dyslipidemia in women.

**Statins in the prevention and treatment of CAD:** Most physicians do not wait for the development of stroke to treat hypertension, or coma to treat diabetes. The benefit of dyslipidemia treatment with statins is several-fold greater than treatment of hypertension or diabetes. There is no justification to delay or deny the use of statins to treat dyslipidemia in asymptomatic women until a cardiac catastrophe. Development of angina should be considered a medical failure rather than the first indication for mechanical intervention.

**Landmark trials and benefits of statins:** Convincing evidence now exists about the substantial reduction in CAD morbidity and mortality due to lowering of lipid levels with statins in women. In the Cholesterol A and Recurrent Events (CARE) trial, the reduction in major acute coronary events
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Indian Heart J 2001; 53: 282–292

(MACE) in women (46%) was more than double that in men (20%). Other statin studies with substantial enrolment of women have also shown an impressive risk reduction (RR); 4S (827 women, RR 37%), LIPID (1508 women, RR 15%), and AFCAPS/TexCAPS (997 women, RR 46%).

Statins reduce clinical coronary events by stabilizing the vulnerable plaques, disruption of which results in MACE. In women this disruption is usually related to plaque erosion, in contrast to plaque rupture in men. Other differences in CAD between men and women are shown in Table 2. Recently, statins have been shown to increase bone density and decrease fractures, dementia and stroke, all of which provide additional benefits in women. Preliminary data also indicate a reduced risk of breast cancer among statin users.

**Table 1. Guide to CAD risk reduction for women**

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Goal(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Complete cessation</td>
</tr>
<tr>
<td></td>
<td>Avoid passive smoking</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Accumulate &gt;30 min of moderate-intensity physical activity daily</td>
</tr>
<tr>
<td></td>
<td>Women who have had recent cardiovascular events or procedures should participate in cardiac rehabilitation, a physician-guided home exercise program, or a comprehensive secondary prevention program</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Low SAFA diet (&lt;7% energy and &lt;200 mg/dl cholesterol)</td>
</tr>
<tr>
<td></td>
<td>High MUFA diet (up to 20% energy) for those with high TG and low HDL</td>
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<tr>
<td></td>
<td>Nuts up to 30 g per day</td>
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<tr>
<td></td>
<td>Total dietary fiber intake of 25–30 g/day</td>
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<tr>
<td></td>
<td>Five or more servings of fruits and vegetables per day</td>
</tr>
<tr>
<td></td>
<td>Avoid prolonged cooking of vegetables</td>
</tr>
<tr>
<td></td>
<td>Limit salt intake to 6 g/day (lower in women with high blood pressure)</td>
</tr>
<tr>
<td>Weight management</td>
<td>Achieve and maintain desirable weight (BMI &lt;23 kg/m²)</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td>Positive adaptation to stressful situations</td>
</tr>
<tr>
<td></td>
<td>Improved quality of life</td>
</tr>
<tr>
<td></td>
<td>Maintain or establish social connections</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Goal(s)</td>
</tr>
<tr>
<td>Blood pressure (BP)</td>
<td>Achieve and maintain BP &lt;140/90 mmHg (optimal &lt;120/80 mmHg)</td>
</tr>
<tr>
<td>Lipids, lipoproteins</td>
<td>LDL &lt;100 mg/dl; TC &lt;160 mg/dl; TG &lt;150 mg/dl; HDL &gt;50 mg/dl; Lp(a) &lt;20 mg/dl</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Maintain blood glucose: preprandial 80–120 mg/dl, bedtime 100–140 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Maintain HbA1c &lt;7%</td>
</tr>
<tr>
<td></td>
<td>BP &lt;130/85 mmHg</td>
</tr>
<tr>
<td>Medications</td>
<td>Goal(s)</td>
</tr>
<tr>
<td>HRT</td>
<td>Initiation or continuation of HRT in women for whom the potential benefits may exceed the risks (Lp(a) &gt;20 mg/dl; HDL &lt;50 mg/dl)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Minimize risk of adverse cardiovascular effects while preventing pregnancy. Use the lowest effective dose of estrogen/progestin</td>
</tr>
<tr>
<td>Antiplatelet agents/</td>
<td>Prevention of clinical thrombotic and embolic events in women with established CAD. Primary prevention studies are in progress</td>
</tr>
<tr>
<td>anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>To reduce the reinfarction rate, incidence of sudden death, and overall mortality in women after MI</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>To reducethemorbidity and mortality among MI survivors and patients with or without LV dysfunction</td>
</tr>
</tbody>
</table>

SAFA: saturated fatty acid; MUFA: monounsaturated fatty acid; HRT: hormone replacement therapy (Adapted from Mosca L, 1999)
those with high Lp(a) and low HDL levels or high TC/HDL ratio. The results of the AFCAPS/TexCAPS support this recommendation. There was a 46% reduction in MACE by lowering LDL levels to <110 mg/dl in low-risk asymptomatic American women (one-fourth the risk of Indian women) with no CAD or risk factors.82 Statins are highly effective in reducing the TC/HDL ratio (goal <4) in women with low HDL unresponsive to lifestyle measures.88

**Hormone replacement therapy (HRT):** More than 30 observational studies suggest a 35%-55% reduction in CAD incidence and mortality among women who receive HRT.89 However, the first two randomized clinical trials of HRT failed to demonstrate any cardiovascular benefit.90-92 In the HERS, there was a suggestion of early harm and late benefit overall. Women who were in the highest quartile of Lp(a) levels and received HRT had an impressive 54% decrease in MACE with no suggestion of early harm.93 Over 40% of Indian women have Lp(a) levels >20 mg/dl, which is associated with a high risk of CAD.93,94 The benefits of HRT may be greater in Indian women, who have substantially higher rates of CAD (3-fold) and lower rates of breast cancer (one-half)95 compared with Whites.

**Conclusions**

CAD is the leading cause of death in women. Health care providers need to be sensitive to gender differences in presentation, prognosis and responsiveness to treatment of CAD. The prognosis of women with CAD differs according to age, mode of presentation, accuracy of diagnosis, and number of risk factors and is generally more ominous in women. The failure to treat women as vigorously as men contributes to their worse outcome although the gap is narrowing rapidly in western countries.96 Doctors need to understand the risk as well as risk factors of CAD in women and the importance of prevention, diagnosis and timely intervention. Most of the modifiable risk factors such as obesity, smoking, hypertension, diabetes and dyslipidemia are the same in both sexes and should be identified and treated early. Reducing saturated fat in the diet and simultaneously increasing the consumption of fish, fruits, vegetables, nuts and fiber are the dietary ingredients for a healthy heart. Exercising regularly, maintaining an ideal BMI and waist size, quitting tobacco, controlling hypertension and diabetes can substantially reduce the risk of CAD and its complications. Health care systems need a paradigm shift that emphasizes a healthy lifestyle for young men and women.

Because of the high rate of CAD despite maximum modification of lifestyle, pharmacological therapy may be necessary in many Indians.97 The underdiagnosis and undertreatment of dyslipidemia is greater in women worldwide and appears to be worse in India.98 Use of statins for dyslipidemia should not be delayed until a cardiac catastrophe. The collective efforts of the government, professional organizations, food industry and academic community should be directed toward realizing a significant health benefit by the society. Advances in the prevention and treatment of CAD should not be denied to women.
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Mechanisms of Sudden Cardiac Death: A Review of Investigative Approaches for a Global Dilemma

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If a man will begin with certainties, he shall end in doubts; but if he is content to begin with doubts, he shall end in certainties.

— Francis Bacon (1561–1626)

Recent analyses of disease progression patterns have revealed a globally increased incidence of cardiac disease. With a burgeoning population of patients with coronary disease as well as heart failure, this translates directly into a rising incidence of sudden cardiac death (SCD). With the economic scale tipped in their favor, warning symptoms of cardiac disease may allow the industrialized world to pre-empt SCD in approximately 50% of cases. However, in the remainder, fatal arrhythmia is the first and only manifestation of SCD. Thus, SCD is a shared and indiscriminate worldwide medical catastrophe.

Diverse Etiologies but a Common Terminal Event

Despite the broad spectrum of etiologic conditions, in the overwhelming majority of cases, SCD results from a fatal cardiac arrhythmia, either ventricular tachycardia/fibrillation or severe bradycardia. As is often the case with medical therapies, effective treatment of fatal arrhythmia with electrical or pharmacologic maneuvers has long preceded the complete understanding of culprit mechanisms. The significant delay in the development of effective measures for the prevention and risk stratification of SCD can thus be attributed directly to a poor understanding of mechanisms involved in fatal arrhythmogenesis. At the close of the twentieth century, awareness of this important deficiency has focused considerable interest on the mechanisms of SCD. This review discusses selected present and future directions for research in this area.

Magnitude of the Problem

Due to significant logistic issues, there is a conspicuous lack of data regarding a directly measured population-based incidence of SCD. In the United States of America, an estimate was recently reported by the Centers for Disease Control and Prevention. In 1996, there were 452,675 estimated SCDs, accounting for 63.4% of all cardiac deaths and 0.16% of the total population. When compared with the estimated incidence in 1989, this represented a 10% increase in SCD cases. In the absence of such figures for India, extrapolation of the US data would provide a crude estimate of at least 1.6 million SCDs per year; probably an underestimate, given the relatively poor availability of out-of-hospital emergency cardiac life-support services.

Does Sudden Cardiac Death Equal Sudden Coronary Death?

The most common cause of SCD is coronary artery disease (CAD). However, culprit etiologies also include a wide variety of other disease conditions (Table 1) which, in the face of growing concerns regarding risk stratification, are receiving renewed attention. While approximately 80% of SCDs are attributed to CAD, a more accurate risk stratification for sudden death remains ineffective even in this largest subgroup. Recently, large randomized trials (e.g. AVID, MADIT, MUSTT and CIDS) have underscored our improved ability to predict risk in specific high-risk groups; however, these account for a small percentage of overall SCD. To develop new means of risk stratification for SCD, our search for risk factors must extend beyond sudden coronary death.

Prevailing Concepts of Arrhythmogenesis

In the majority of patients with SCD, the terminal arrhythmia is ventricular fibrillation. In a significant percentage of patients who present with ventricular fibrillation, it is likely that ventricular tachycardia precedes ventricular fibrillation. Ventricular tachycardia can be monomorphic (as in most cases of CAD-related SCD) or polymorphic, as in patients with the long QT syndrome. In general, all tachycardias have been attributed to one of two broad mechanisms—re-entry or triggered activity. The
phenomenon of re-entry results from conditions that cause heterogeneous patterns of action potential duration in the ventricular myocardium, e.g. heart failure or coronary ischemia. An important additional factor may be abnormal propagation of the electrical impulse through the myocardium, such as gap junction proteins or connexins. The phenomenon of triggered activity results from premature electrical potential called early after-depolarizations (EADs) or delayed after-depolarizations (DADs). Early after-depolarizations may occur during the second or third phases of the action potential and the essential prerequisite is prolongation of the action potential duration. Delayed after-depolarizations have been observed during the fourth and final phase of the monophasic action potential. While bradyarrhythmias are likely to constitute the minority, a distinct subgroup of SCD manifests with severe bradycardia as the terminal arrhythmia.

Animal Models of Sudden Cardiac Death

In attempts to understand the mechanisms of fatal arrhythmogenesis, several animal models have been utilized. Of these, the rat model of myocardial infarction (MI) and the canine pacing-induced heart failure model have been well characterized.

The rat infarct model: Myocardial infarction is induced by surgical ligation of the left coronary artery via a left thoracotomy. There is a high incidence (up to 65%) of sudden death within 48 hours of a large MI. With moderate-sized infarcts (30% of the total myocardium), acute mortality is estimated to range between 10% and 30%. Within 4–6 weeks, the animals consistently develop signs of heart failure with evidence of significant postinfarction remodelling and dilated cardiomyopathy. Multiple observations vis-a-vis hemodynamic, neurohormonal, anatomic and cellular properties point to distinct similarities between human and rat hearts in the post-MI period. In fact, beneficial interventions in the model have been directly transported to the human heart failure population with remarkable success. An important example is the survival benefit of captopril observed in this model, which led to the large clinical trials of angiotensin-converting enzyme (ACE) inhibitors and their subsequent widespread use in patients with heart failure.

Table 1. Diverse etiologies of sudden cardiac death

<table>
<thead>
<tr>
<th>Etiology</th>
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<td>Coronary artery disease</td>
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<td>Myocarditis</td>
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<tr>
<td>Drug abuse</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
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<tr>
<td>Idiopathic dilated cardiomyopathy</td>
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<tr>
<td>Arrhythmogenic right ventricular dysplasia/cardiomyopathy</td>
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<tr>
<td>Congenital cardiac syndromes (coronary anomalies, cyanotic/ non-cyanotic syndromes)</td>
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<td>Myocardial infiltrative diseases (e.g. sarcoidosis, amyloidosis)</td>
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<td>Long QT syndrome</td>
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<td>Brugada syndrome</td>
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<td>Unexplained sudden cardiac death (idiopathic polymorphic tachycardia/ventricular fibrillation)</td>
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Studies of the mechanisms of arrhythmia in this model have focused on ion channel pathophysiology as well as evidence of altered genetic expression in potentially arrhythmogenic cardiac-specific genes. Ion channel abnormalities lead to alterations in inward or outward flow of current from the cardiac myocyte, which can lead to prolongation or heterogeneity of the action potential duration. In this model, a significant decrease in the potassium transient outward current (Ito) is known to contribute to action potential prolongation. In the rat, the myocardial voltage gated K+ channel is constituted by multiple pore-forming alpha subunits. Of these, genetic expression of Kv 2.1, Kv 4.2 and Kv 4.3 subunits is decreased in postinfarct ventricular myocytes and this downregulation may account for the decrease in Ito current. El-Sherif et al. have also reported reversion of the fetal:adult isoform ratio of two other ionic currents in post-MI rat ventricular myocytes. Messenger RNA levels of the fetal isoform of the L-type Ca2+ current are significantly increased. In addition, the T-type Ca2+ current, which is normally expressed only in fetal rat ventricular myocytes, is re-expressed in postinfarct myocytes. All of these described changes in ion channel function due to altered expression of ion channel genes are likely to contribute to the genesis of after-depolarizations. It is likely that re-entry is also promoted by spatial alterations in expression of connexin 43 in the rat ventricle. Decreased expression of connexin 43 has been observed in the left ventricular endocardium, septum and right ventricle but not in the left ventricular epicardium. Also, significant downregulation occurs of connexin 43 gap junctions in myocardium remote from the infarction and these changes may occur as early as three days after MI.

Canine pacing-induced heart failure: In dogs, ventricular pacing at rapid rates (250 bpm) over a period...
of 3–5 weeks consistently results in contractile dysfunction and four-chamber dilated cardiomyopathy.14,32 As a result, significant abnormalities of cardiac repolarization occur, with an increased risk of spontaneous ventricular arrhythmias and sudden death.33 Ion channel abnormalities identified include downregulation of the transient outward potassium channel as well as the potassium inwardly rectifying channel.33 The resultant prolongation of the monophasic action potential produces a distinct vulnerability to the effects of type III antiarrhythmic agents.14,32 There is increased sensitivity to the effects of ibutilide as well as d,l-sotalol, as measured by prolongation of the action potential duration in vivo. In the case of ibutilide, there is a tendency for increased occurrence of polymorphic ventricular tachycardia, also caused by early after depolarizations.14

In general, the likelihood of successful resuscitation from ventricular fibrillation is significantly lower in patients with heart failure as well as animal models of congestive heart failure (CHF).34–36 This has long been attributed to the structural and hemodynamic aspects of ventricular remodelling in heart failure. However, a recent study in a canine model of heart failure induced with combined MI and rapid ventricular pacing, indicates that other mechanisms may be involved.37 Ventricular fibrillation induced by AC shock was quantified using a special multi-electrode device placed in the left ventricle of both heart failure and sham animals. As expected, both structural and hemodynamic deterioration was observed in the heart failure group. In addition, however, the nature of terminally induced ventricular fibrillation in heart failure was significantly different from control animals. There were fewer re-entrant ventricular fibrillation circuits in heart failure animals compared to controls. While these findings remain to be elucidated, it is clear that ventricular fibrillation occurring in heart failure may be distinct from that occurring in the absence of left ventricular dysfunction.37 Further investigations of possible unique ventricular patterns in this model may facilitate the development of more effective defibrillation therapies for the prevention and treatment of SCD in heart failure.

Transgenic and knockout mouse models: These genetically engineered animal models represent the vital link between genetics and physiology. Transgenic technology involves expression of foreign genes by the introduction of foreign DNA into fertilized mouse eggs via the process of microinjection. In contrast, the gene knockout procedure involves inactivating or “knocking out” genes in the mouse. Specific genes are isolated, inactivated and subsequently introduced into mouse embryonic stem cells. Recently, both techniques have been employed to produce distinct mouse models of SCD. In one such investigation, transgenic mice were produced that overexpressed calreticulin, a calcium-binding protein in the endoplasmic reticulum.38 These transgenic animals exhibited decreased myocardial systolic function and inward calcium current, as well as low levels of the proteins connexins 43 and 40. Clinically, these animals manifested with sinus bradycardia and prolonged atrioventricular node conduction, followed by complete heart block and sudden death. In addition, Chien et al.39 have reported that knockout mice deficient in HF-1b, a transcription factor-related protein, manifest with SCD despite having normal systolic function. Ambulatory electrocardiographic recordings in these mice revealed both ventricular tachycardia and severe bradycardia as culprit fatal arrhythmias. Interestingly, there is normal distribution of the conduction proteins connexins 43 and 40 in this model as well. Similar gene targeted mouse models are likely to enhance our understanding of mechanisms related to specific genes involved in fatal arrhythmogenesis.40 In the era of functional genomics, new techniques such as gene expression profiling with microarray technology will facilitate such investigations.41,42

Human Investigations

Autopsy series: Autopsy-based studies have contributed greatly to our understanding of the mechanisms of SCD.43–45 In the majority of SCD cases, a structural or functional abnormality can be identified, CAD being the most common.3 Other causes include drug use, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomypathy, several congenital cardiac syndromes (coronary anomalies, cyanotic/noncyanotic syndromes), myocarditis and infiltrative diseases such as sarcoidosis and amyloidosis. However, in 5%–15% of SCD patients, the culprit etiology cannot be identified.8,46–51 As a consequence, there is insufficient knowledge of both substrates and triggers of SCD in this subset. For these patients, inherited or de novo genetic defects leading to SCD need to be excluded. The list of heritable syndromes leading to SCD is growing steadily.42,53

The genetic basis of sudden cardiac death: The long QT syndrome: This inherited primary electrophysiologic disorder is characterized by prolongation of the QT interval on ECG and increased risk of sudden death due to polymorphic tachycardia.54–56 The condition is relatively rare, with an estimated incidence in the general population
of 1 in 10 000. Disease-causing mutations have been identified in five culprit genes, each encoding a cardiac ion channel or channel subunit. For the autosomal dominant form of the long QT syndrome (Romano–Ward syndrome) the genes implicated are KVLQT1 (long QT syndrome 1), HERG (long QT syndrome 2), SCN5A (long QT syndrome 3), KCNE1 (long QT syndrome 5), and KCNE2 (long QT syndrome 6).66,67 For long QT syndrome 4, a chromosomal locus has been identified but the search for a specific gene is ongoing. In the case of the autosomal recessive form associated with deafness (Jervell and Lange-Nielsen syndrome), mutations in KVLQT1 and KCNE1 have been identified. For the identification of carriers of the long QT syndrome, genetic screening remains the most important tool.59 Important issues confronting researchers include the development of cheap and effective tools for diagnosis, as well as prevention and risk stratification. Beta-blockers and implantable defibrillators remain the mainstay of therapy for the long QT syndrome.

The Brugada syndrome: This condition is characterized by an apparently normal heart, distinct ECG abnormalities and a propensity for sudden death.63 The electrocardiographic features include a right bundle branch block pattern and ST segment elevation in the right precordial leads (leads V1 through V3) but the QT interval is normal.63 In a small number of patients with a Brugada pattern ECG, structural abnormalities have been observed in the right ventricle, which has led some researchers to conclude that a “right ventricular” cardiomyopathy may form the basis for this condition.64 In general, the majority opinion would indicate that the Brugada syndrome is an inherited primary electrophysiologic disorder with autosomal dominant transmission. In affected patients, mutations have been detected in the cardiac sodium channel gene (SCN5A), which is also the gene implicated in long QT syndrome 3.65 Interestingly however, the ion channel phenotype is expressed differently. In the Brugada syndrome, there is loss of function of the cardiac sodium channel, as opposed to gain of function in long QT syndrome 3.66,67 It is likely that the syndrome of sudden unexpected nocturnal death in South-east Asian males is identical to the Brugada syndrome.68 Furthermore, a third cardiac rhythm disorder has been attributed to the SCN5A gene. Mutations in this gene were also detected in members of a family who manifested with cardiac conduction system disease or Lev-Lenegre syndrome.69

The typical ECG findings of the Brugada syndrome can be transient, but intravenous ajmaline (1 mg/kg), procainamide (10 mg/kg), or flecainide (2 mg/kg) can effectively unmask these ECG features.70 An earlier study showed that permanent or transiently induced ECG abnormalities were predictive of patients having a higher risk of sudden death.70 However, these findings have been refuted in a more recent investigation, which concluded that the only significant prognostic indicator of sudden death was the presence of prior symptoms.71 In addition, due to a low overall prevalence of mutations of the cardiac sodium channel (15%), the authors concluded that significant genetic heterogeneity may be an inherent feature of the condition. Another recent investigation also concluded that asymptomatic patients with a Brugada-type pattern on the ECG are likely to have a benign course.72 At present, the implantable defibrillator is widely accepted as the most effective treatment modality for symptomatic patients.

Idiopathic ventricular fibrillation (unexplained sudden cardiac death): In cases where there are no identifiable structural or genetic abnormalities attributable to the event, SCD may remain unexplained. These cases have also been grouped under the category of idiopathic ventricular fibrillation. Due to a relative lack of co-morbid conditions, these patients constitute a human model for the understanding of this common terminal event. Since knowledge regarding substrates and triggers of SCD in this subgroup could be applied to other subgroups such as CAD, idiopathic ventricular fibrillation is currently the subject of active investigation.

The diagnosis of this condition is by exclusion, and can be made in the absence of clinical or laboratory findings that could account for the occurrence of fatal arrhythmia.73 The first observations of patients with ventricular fibrillation, a normal baseline electrocardiogram and no structural heart disease were reported in 1987.74 Subsequently, survivors have been followed up in US as well as European registries. It is likely that idiopathic ventricular fibrillation may constitute 5%–10% of all cases of out-of-hospital cardiac arrest.73 Patients tend to be relatively young (age range 27–55 years) and both sexes are affected equally. In up to two-thirds of patients, there is no prior history of syncope,74 but risk of recurrent syncope is significant and events tend to occur in clusters. As a rule, ventricular stimulation protocols have been ineffective for the purpose of risk stratification.75–77 Clinical subtypes have been reported as well. Based on the mode of onset of the ventricular arrhythmia, some patients have been classified as short-coupled torsades de pointes.78 Ambulatory ECG recordings in these patients showed that a premature ventricular beat with a short coupling interval initiates the tachycardia, as opposed to the long QT syndrome, where the premature beat generally follows a pause. Another clinical subtype is catecholamine-dependent polymorphic
ventricular tachycardia, a condition which mainly affects children and is induced by stress, especially exercise. Recently, mutations in the human cardiac ryanodine receptor gene (hRyR2) were identified in families of patients with catecholamine-dependent polymorphic tachycardia. Thus, genetically determined abnormal intracellular calcium handling is likely to be a key pathophysiologic mechanism for the genesis of this arrhythmia. Again, while beta-blockers have proven beneficial in many cases, they have not replaced the implantable defibrillator as the therapy of choice.

There are several conditions associated with sudden death which merit further investigation. In patients with unexplained SCD, it is not uncommon to find relatively minimal or nonspecific cardiac abnormalities. In a recent analysis of cardiac pathologic findings from a relatively young (mean age 42 years) autopsy series of SCD, 29% hearts had evidence of nonspecific cardiac structural abnormalities but no clearly identifiable cause of SCD. These abnormalities included left ventricular hypertrophy, mitral valve prolapse and myocardial interstitial fibrosis. It is conceivable that in the presence of a critical trigger mechanism, even these relatively minimal abnormalities may constitute an arrhythmogenic substrate. Further investigations in this subgroup may be of high yield. Also, in subjects with an otherwise normal heart and no evidence of significant CAD or MI, coronary artery spasm cannot be ruled out as a possible etiology of ventricular fibrillation arrest. Lastly, two noncardiac conditions, seizure disorder and obesity, have strong associations with SCD. Abnormal alterations in autonomic inputs to the heart have been implicated in both conditions, but specific etiologic mechanisms are unclear.

Population-based investigations of sudden cardiac death: The importance of prospective population-based investigations was emphasized by two recently published studies of SCD. Both studies examined the occurrence of overall sudden death, one including 500 cases and the other 128 cases and the conclusions are similar. These studies provide strong evidence for aggregation of SCD in families, independent of the distribution of classic risk factors. While the latter factors have been the primary focus of preventive measures, these studies underscore the need to expand research toward chromosomal as well as other shared nongenetic risks, such as common in utero or postnatal environmental exposure. Identification of such factors will proceed only with population-based studies to identify familial clustering of SCD.

Conclusions

The significant worldwide incidence of SCD must be confronted with matching developments in prevention and risk stratification for this condition. Since fatal arrhythmia is the most common terminal event, a complete understanding of the mechanisms of arrhythmogenesis is essential. The investigative strategy will continue to include both animal studies and human investigations. In the era of functional genomics, transgenic and knockout mouse models form the crucial link between the pathophysiology and genetics of cardiac arrhythmia. Such investigations will be enhanced by the rapid development of techniques such as microarray gene expression profiling. While CAD is the most common cause of fatal arrhythmia, its prevention has not affected the incidence of SCD. In the future, it is likely that the power of CAD to predict SCD may be enhanced in combination with other, yet unexplored factors. Genetic testing in patients with ostensibly normal hearts or only nonspecific cardiac abnormalities may provide important clues. In this context, a combination of population-based studies and human molecular genetic investigations is likely to be of high yield in the search for novel mechanisms of SCD.

Acknowledgment

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Neurohumoral Activation in Percutaneous Coronary Interventions: Apropos of Ten Vasoactive Substances During and Immediately Following Coronary Rotastenting

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Background: Ischemia, left ventricular dysfunction, endothelial damage and hemodynamic changes during percutaneous coronary intervention can lead to neurohumoral activation. This may partly explain the frequent episodes of coronary spasm, hypotension and bradycardia which occur during the procedure. Rotastenting, by employing the two basic mechanisms for coronary interventions—debulking and dilatation—epitomizes percutaneous coronary interventions in general. We sought to investigate the neurohumoral changes during and immediately following coronary rotastenting.

Methods and Results: Eighteen patients undergoing elective rotablator atherectomy followed by balloon predilatation and stenting for chronic stable angina were studied. Four femoral vein blood samples were drawn from each patient at the start of the intervention (baseline), and 2 (postdebulking-2), 10 (postdebulking-10) and 60 (postdebulking-60) minutes, respectively, after the first complete passage of the rotablation burr across the whole length of lesion. Levels of 10 neurohormones, namely, endothelin-1, bradykinin, arginine vasopressin, norepinephrine, dopamine, epinephrine, angiotensin II, serum angiotensin-converting enzyme activity, atrial natriuretic peptide and kininogen were estimated in each sample. Endothelin-1 and bradykinin attained their peak levels in the postdebulking-2 samples, and the rise from 0.34±0.07 pmol/ml and 235.8±17.7 pg/ml to 0.42±0.06 pmol/ml and 337.2±41.0 pg/ml, respectively, was statistically significant (p<0.05). The level of arginine vasopressin showed a significant (p<0.05) rise from baseline (108.5±31.8 pg/ml) to postdebulking-60 samples (136.5±39.4 pg/ml). The other neurohormones did not show significant changes.

Conclusions: The results suggest a definite but differential neurohumoral activation during and immediately following rotastenting. These neurohumoral changes may have a role in untoward intra- and postprocedural vasomotor and hemodynamic effects. This study establishes the concept of neurohumoral activation during percutaneous coronary interventions. (Indian Heart J 2001; 53: 301–307)

Key Words: Rotational atherectomy, Neurohormones, Vasoactive peptides

The incidence of myocardial necrosis in patients undergoing routine percutaneous coronary interventions (PCIs) is between 30% and 40%. This suggests that microembolization is common and that many patients actually suffer some extent of measurable myocyte damage. Ischemia and left ventricular dysfunction coupled with hemodynamic changes and local endothelial injury can lead to neurohumoral, paracrine and autocrine activation during PCI. Besides this, pharmacological manipulations and constitutional accompaniments can also modulate neurohumoral milieu. Morphine, which is routinely used intraprocedurally, can stimulate the release of arginine vasopressin (AVP). While nausea and vomiting may also stimulate the release of AVP, anxiety and pain can cause sympathetic activation. Attempts have been made to study vasoactive peptides and neurohumoral parameters during coronary angioplasty and coronary artery bypass surgery. Correlation has been made between the levels of these peptides and the severity of coronary artery disease and unstable plaque mechanisms. Our group has reported the release of catecholamines during elective and primary angioplasty. Recently, the effects of rotational coronary
atherectomy on plasma levels of peripheral endothelins (ET-1), atrial natriuretic peptide (ANP) and cyclic adenosine monophosphate (cAMP) have been studied and compared with those of percutaneous transluminal coronary angioplasty (PTCA). It was found that the level of ET-1 increased less, that of ANP increased more and that of cAMP decreased more during atherectomy than during plain balloon angioplasty. None of the studies so far, however, has comprehensively studied the phenomenon of neurohumoral activation during coronary interventions.

We hypothesized that since PCIs exploit two basic mechanisms—dilatation and debulking—and since rotastenting, comprising rotablator atherectomy followed by balloon predilatation and stenting uses both these mechanisms, it can epitomize PCI in general from the viewpoint of the study of neurohumoral activation. The procedure should then embrace the composite effects of plain balloon, stenting and atherectomy, the three commonest techniques employed. Moreover, rotastenting will also include the effects, if any, of the interaction of blood elements with intra coronary metallic prostheses resulting in the release of vasoactive substances. We further hypothesized that there should be substantial neurohumoral activation during rotastenting, which may partly explain some of the cardiovascular and hemodynamic disturbances, such as repeated coronary spasms, bradycardia and hypotension, which are common during PCI. The aim of the present study was to study the whole gamut of neurohumoral, autocrine and paracrine substances in central venous blood samples during coronary rotastenting.

**Methods**

**Study population:** The study included eighteen patients with chronic stable angina referred to the Department of Cardiology, Medical University Hospital, Lübeck, in whom rotablator atherectomy followed by balloon predilatation and stenting were electively done as the intervention of choice. The exclusion criteria were acute or recent myocardial infarction, unstable angina pectoris, decompensated heart failure, total coronary artery occlusion, uncontrolled hypertension, peripheral vascular disease and significant psychiatric, neurologic, endocrine, hepatic or inflammatory disease. Patients undergoing rotational atherectomy alone or those undergoing rotastenting in whom balloon predilatation was not used before deploying a stent were also excluded from the study. All patients gave informed written consent.

**Protocol:** The patients were allowed their usual cardiac medications and routine pre- and postangioplasty orders were followed. Four femoral vein blood samples were drawn from the sheath of each patient. The first (baseline) sample was obtained at the time the venous sheath was introduced at the inception of the procedure. The second (postdebulking-2), third (postdebulking-10) and fourth (postdebulking-60) samples were drawn 2, 10 and 60 minutes, respectively, after the first complete passage of the rotablator burr across the whole length of lesion.

**Biochemical analysis:** The serum activity of angiotensin-converting enzyme (ACE) was determined by incubation with the ACE-specific tripeptide substrate o-aminobenzoyl glycyl-p-nitro-L-phenylalanyl-L-proline. Angiotensin-converting enzyme hydrolyzes the substrate, producing the highly fluorescent o-aminobenzoylglycine. Quantitative determination was performed by spectrofluorimetric detection (Shimadzu RF 551; Ex 320 nm; Em 412 nm) after separation by HPLC (Nova-Pak C18-column, 3.9×150 mm, Waters USA). Angiotensin II, bradykinin (BK) and kininogen were extracted and quantified by specific radioimmunoassays (RIA). The procedures of ethanol precipitation and solid phase extraction described by Pellacani et al. were applied in combination. Radioimmunoassays were set up as described by Menard et al. Kinin-specific antiserum was obtained after immunization of a female rabbit with albumin-coupled kallidin following the method of Shimamoto et al. The chloramine-T method was used for the preparation of [125I-Tyr8]-BK and [125I]-angiotensin II which was purified by RP-HPLC. Rabbit polyclonal anti-angiotensin II was purchased from Peninsula (Belmont, CA, USA). Bovine serum used for RIA was obtained from Sigma, Deisenhofen, Germany and was treated with fumed silica (Serva, Heidelberg, Germany). Iodine was bought from Amersham Buchler, Braunschweig, Germany. Plasma norepinephrine, dopamine and epinephrine were assayed by HPLC and electrochemical detection was done as described by Smedes et al., while commercially available ELISA kits were used to determine ET-1, N-terminal of proatrial natriuretic peptide (Biomedica GmbH-A 1210 Vienna, Austria) and AVP (Assay design, Inc. 1327 Ann Arbor, MI 48105, USA).

**Statistical analysis:** For descriptive purposes, quantitative variables are presented as mean±SEM. The means of the baseline and the subsequent samples were compared using the paired sampl test and a p value <0.05 was considered significant. Data processing and analysis were performed with SPSS software for Windows, version 7.5.
Results

Eighteen patients, 9 males and 9 females, age range 61–81 years, were included in this study (Table 1). All were on medication for more than three months with cardioactive drugs (94.4% on beta-blockers, 77.8% on ACE inhibitors, 44.4% on calcium-channel blockers and 27.8% on diuretics), besides other routine antianginal, antihypertensive and lipid-lowering drugs, as required. The mean ejection fraction was 64.4±4.0%. There was an assortment of target vessels with 11% left main stem (protected), 72% left anterior descending, 17% left circumflex and 11% right coronary arteries. The final result of intervention in all patients ranged from good to acceptable angiographically. There were no major adverse clinical events in any patient during the hospital stay.

The results are summarized in Table 2. Endothelin-1 and BK levels demonstrated a significant rise from 0.34±0.07 pmol/ml and 235.8±17.7 pg/ml, respectively, at baseline to 0.42±0.06 pmol/ml and 337.2±41.0 pg/ml, respectively, in the second (postdebulking-2) samples. The mean levels of both declined thereafter. Arginine vasopressin, however, demonstrated a different temporal pattern. A significant rise from 108.5±31.8 pg/ml to 136.5±39.4 pg/ml (p<0.05) was seen in the postdebulking-60 sample. Norepinephrine, dopamine and epinephrine (sympathetic system), angiotensin II and serum ACE activity (renin–angiotensin system), and N-terminal of proatrial natriuretic peptide showed a similar pattern of rise in plasma concentrations, with the highest mean values occurring in the last, i.e. postdebulking-60 samples, but in neither case was this rise statistically significant. Although kininogen showed a pattern of fall, with the steepest fall in the second sample, the levels did not reach statistical significance.

Discussion

Percutaneous coronary interventions may cause neurohumoral activation through a variety of mechanisms. While anxiety and pain are important accompaniments, the procedure may induce ischemia and left ventricular dysfunction, cause a drop in arterial blood pressure and mechanical endothelial damage, all of which can potentially stimulate autocrine, paracrine and endocrine systems either directly or through cardiosystemic reflexes. A distinct neurohumoral activation shown by the rise of vasoactive peptides such as ET-1, BK and AVP was the principal finding of the present study. Mediators of the sympatho-adrenergic and renin–angiotensin systems, however, showed minor, insignificant rise. A differential pattern in the rise of levels with time was also documented.

Endothelin-1 is the most potent endothelium-derived vasoconstrictor peptide identified so far. The effect is more pronounced in small-sized coronary vessels compared to large epicardial vessels. The deluge of studies on the release of ET-1 during PTCA have shown an increase in its levels. The kinetics of release have been somewhat disparate in different studies. It was found to be biphasic with an early peak occurring within the first 10 minutes and a late peak 90 minutes after PTCA, while a recent study published from our laboratory established an instantaneous elevation, with the levels gradually falling thereafter to normal within 6 hours. In another study, during reperfusion after transient (10-minute) periods of ischemia, the release of ET-1 occurred early and lasted for about 10 minutes even in the absence of endothelial damage, suggesting that hypoxia is the primary mechanism responsible for the release.
Thus, an instantaneous or early release has been noted and our data conform with these observations. We observed a significant instantaneous rise of ET-1 levels in the postdebulking-2 samples which was then followed by a fall till the levels reached the baseline in the postdebulking-60 samples (Fig. 1). This rise may be important in the context of frequent, relatively resistant spasms occurring during rotational atherectomy. The hypothesis that ET-1 plays a role in the pathogenesis of coronary spasm during PTCA has been investigated. A significant increase in the coronary sinus and arterial blood was observed immediately after PTCA. Because this increase did not occur after coronary angiography, it is unlikely to represent a nonspecific response to contrast medium or the catheterization procedure. The mechanisms that may account for the increase in ET-1 levels during PTCA include

Table 2. Mean values with SEM of plasma vein neurohormone levels at baseline, i.e. at the start of the intervention, and 2 (postdebulking-2), 10 (postdebulking-10) and 60 (postdebulking-60) minutes after the first complete passage of the burr across the whole length of the lesion, respectively, and comparison between the baseline and latter values

<table>
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<tr>
<th>Neurohormone</th>
<th>Baseline (A)</th>
<th>Postdebulking-2 (B)</th>
<th>Postdebulking-10 (C)</th>
<th>Postdebulking-60 (D)</th>
<th>p value</th>
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<tbody>
<tr>
<td></td>
<td>Mean SEM</td>
<td>Mean SEM</td>
<td>Mean SEM</td>
<td>Mean SEM</td>
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<tr>
<td>Endothelin-1 (pmol/ml)</td>
<td>0.34 0.07</td>
<td>0.42 0.06</td>
<td>0.40 0.06</td>
<td>0.34 0.06</td>
<td>0.03*</td>
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<td>Bradykinin (pg/ml)</td>
<td>235.8 17.7</td>
<td>337.2 41.0</td>
<td>306.2 31.9</td>
<td>273.3 20.7</td>
<td>0.01*</td>
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<td>Arginine vasopressin (pg/ml)</td>
<td>108.5 31.8</td>
<td>122.0 35.5</td>
<td>113.4 31.4</td>
<td>136.5 39.4</td>
<td>0.13</td>
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<td>Norepinephrine (pg/ml)</td>
<td>308.5 40.9</td>
<td>320.5 42.6</td>
<td>377.6 64.8</td>
<td>396.1 67.1</td>
<td>0.69</td>
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<tr>
<td>Dopamine (pg/ml)</td>
<td>51.8 6.6</td>
<td>55.2 8.8</td>
<td>62.3 8.7</td>
<td>62.9 7.4</td>
<td>0.59</td>
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<tr>
<td>Epinephrine (pg/ml)</td>
<td>46.1 11.9</td>
<td>37.6 5.8</td>
<td>44.7 8.9</td>
<td>66.8 17.7</td>
<td>0.48</td>
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<tr>
<td>Angiotensin II (pg/ml)</td>
<td>7.3 2.8</td>
<td>8.1 3.2</td>
<td>8.3 3.1</td>
<td>9.5 3.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Serum ACE activity (nmol/h/ml)</td>
<td>15.4 4.6</td>
<td>14.9 4.6</td>
<td>15.3 4.7</td>
<td>16.7 4.7</td>
<td>0.15</td>
</tr>
<tr>
<td>NT-proANP (fmol/ml)</td>
<td>2425.1 1456.5</td>
<td>2487.2 1478.9</td>
<td>2598.6 1542.9</td>
<td>3363.6 2076.2</td>
<td>0.19</td>
</tr>
<tr>
<td>Kininogen (pg/µl BK)</td>
<td>1528.2 139.0</td>
<td>1433.0 122.6</td>
<td>1383.0 130.8</td>
<td>1377.6 139.9</td>
<td>0.07</td>
</tr>
</tbody>
</table>

NT-proANP: N-terminal of proatrial natriuretic peptide; * significant (p<0.05)

Fig. 1. Graphic representation of the mean values of endothelin, bradykinin and arginine vasopressin. Standard error (SEM) bars have not been added to the figures in order to express the means more explicitly. Significantly high values (p<0.05) were attained at the instance of second, i.e. the postdebulking-2, samples and at all instances of endothelin and bradykinin. There is a gradual fall after this peak and while the levels reach the baseline at the end of the observation window in case of endothelin, they tend to be above the baseline in case of bradykinin. With arginine vasopressin, the significant (p<0.05) rise in mean levels is attained at the instance of the last, i.e. the postdebulking-60, sample (Pdeb stands for postdebulking).
mechanical endothelial damage, hypoxia from transient coronary occlusion, and activation of clotting factors such as thrombin, though the latter mechanism has been considered unimportant. Increased levels of ET-1 during rotastenting can be attributed to these mechanisms. It may be noted that the vasconstrictor effect of ET-1 depends strictly on extracellular Ca\(^{2+}\) concentrations, and is noncompetitively inhibited by voltage-operated calcium-channel blockade with dihydropyridine calcium antagonists. The use of intraprocedural intravenous verapamil (a phenylalkylamine and not a dihydropyridine) infusion during rotablator atherectomy, which forms the standard protocol in most centers including ours, may be questioned from this perspective. Kyriakides et al., in contradiction to our observations, did not find a change in ET-1 levels following rotational atherectomy.

Bradykinin and related kinins have a definite role in the control of vascular tone. Bradykinin induces endothelium-dependent vasodilation of large epicardial and resistance coronary arteries through nitric oxide (NO) mediation. Our study with rotastenting showed a significant instantaneous increase in the postdebulking-2 samples, following which the levels started falling (Fig. 1). The mean levels did not, however, reach the baseline till the last sampling. Kininogen levels fell correspondingly, and arguably so, as BK is its cleavage product, but though the fall was the steepest in the postdebulking-2 samples, it did not reach statistical significance. It is interesting to note that the kinetics of release of BK, a potent vasodilator and ET-1, a potent vasoconstrictor, are similar and both reach a significant instantaneous peak followed by a fall. This might suggest a counter-regulatory mechanism between the two, and also that, while all other hormones maintained a rising curve during our observation window and may be responsible for relatively long-term regulation, these two hormones are mainly involved in immediate and short-time regulation. If our assumption is substantiated, the counter-regulatory nature of BK can be exploited to counteract the untoward effects of ET-1. We have recently shown that the intracardiac availability of BK can be increased by intracoronary administration of enalaprilat. The pre- or intraprocedural administration of ACE inhibitors may be useful in this context as well as from another point of view. The role of BK in ischemic preconditioning has been extensively studied and lately, direct evidence of this beneficial effect in patients undergoing coronary angioplasty was reported. It was suggested that pretreatment with BK may be just as effective as ischemic preconditioning and could be used prophylactically to attenuate ischemia in selected patients undergoing PTCA.

The release of BK consequent upon small ischemic episodes may also explain our observation of a significant rise in its level during rotastenting.

Arginine vasopressin is a pituitary hormone that plays a central role in the regulation of free water and plasma osmolality. In addition, it is a vasoconstrictor. Its role in producing coronary vasoconstriction in nondiseased small vessels has been studied and this effect seems to be intensified after ischemia and reperfusion. Two types of AVP receptors (V1 and V2) have been identified in a variety of tissues. Regulation of free water is through the V2 receptors while V1 receptors are mainly responsible for vasoconstriction. During rotastenting, we found a significant rise in the mean postdebulking-60 levels of AVP compared to baseline (Fig. 1). In the light of the above-mentioned observations pertaining to its vasoconstrictive properties, this rise may be important from a pathophysiological standpoint. The kinetics of this rise were, however, different from the two vasoactive peptides discussed above, inasmuch as the rise was delayed rather than instantaneous. While blood pressure fluctuations are common during PCI, decrease in mean arterial and pulse pressure have been shown to increase AVP levels and the release is predominantly through baroreceptor unloading. Other mechanisms, like changes in plasma osmolality and blood volume, can also be potentially involved, as administration of radiographic contrast medium, nitroglycerine, morphine, etc. form an integral part of the procedure. The deleterious potential of AVP is evinced by the evidence that low-dose infusions which alter the levels within a physiological range are shown to cause a fall in cardiac output and increase in total peripheral vascular resistance without modifying mean arterial pressure.

The other neurohormones studied did not reach significantly high levels, even though they maintained rising curves during the study period. Thus, three observations accrue from our study. First, there is definite evidence of neurohumoral activation during PCI and the potent vasoactive peptides can explain the frequently seen abnormalities in vasomotion and cardiovascular hemodynamics during and after the procedure. Second, the kinetics of release of these peptides is different and the effects may persist beyond the immediate postprocedure period; and third, if PCI is compared to the chronic heart failure model in which there is a generalized pattern of neurohumoral activation, a differential pattern seems to be present. Several plausible explanations can be put forth for the last observation. The situation might be truly reflective of a different pathophysiological state. It is likely that
different trigger mechanisms are involved in the release of various vasoactive substances. From this perspective, an insult comprising ischemia or transient left ventricular dysfunction or both of relatively short duration, as for instance during PCI, may have an effect different from that of a long-lasting chronic insult which leads to congestive heart failure. It could also be that ischemia with reperfusion may behave differently from prolonged ischemia as during myocardial infarction. Not only this, differences may exist in the amount and component of injury, e.g. ischemic versus endothelial injury during PCI. Though there are several studies of vasoactive substances released during coronary interventions, we could not find any which dealt with a wide array of these. Almost all have reported a differential pattern of neurohumoral activation. Thus, while studying the influence of PTCA on cardiac release of ET-1, neuropeptide Y and noradrenaline, only the level of ET-1 was found to be significantly increased, and it was postulated that endothelial damage rather than ischemia was the cause of this increase. In another instance, PTCA was associated with a rise of ET-1 and ANP, but a reciprocal decrease of epinephrine and nonepinephrine levels. Differences were also found in relation to techniques of intervention, e.g. when PTCA was compared to rotational atherectomy.

**Limitations of the study:** The most striking limitation of the present study is the small cohort size. Initially, a much larger sample size was enrolled, but the rigorous exclusion criteria reduced the evaluable numbers to less than half. Second, the observation window was short. All the substances (except kininogen) that could not reach significant values had rising curves during the observation window. The third limitation is the lack of a control group against which the present changes could have been gauged in order to attribute them to have been caused by the intervention. Rotational atherectomy entails several elements, which directly or indirectly, individually or collectively, have a potential to cause neurohumoral activation. Thus, introduction of a large vascular access, application of drugs such as verapamil, nitroglycerine, morphine and volume load, etc. are unavoidable. Fourth, cardioactive drugs were not stopped for a few days before the procedure. This would have made the patients unstable, and doing a second-generation device angioplasty after destabilizing the patient would have been unjustified on ethical grounds. Fifth, no attempts have been made to evaluate the mechanisms underlying neurohumoral activation. Finally, circulating plasma concentrations of vasoactive substances does not necessarily reflect the activity of cardiac neurohumoral activation. This is particularly so in case of the sympato-adrenergic and renin–angiotensin systems.

**Clinical implications of the study:** Our study, along with several others during PTCA, offers compelling evidence of neurohumoral activation during PCI. However, attempts to study this important aspect of PCI have been at best half-hearted and disconcerted. There is a need to study this extensively, as has been done during congestive heart failure and following myocardial infarction. The fact that neurohumoral substances have independent prognostic value and that the overall prognosis can be improved by pharmacological modification of their effects, makes this field an area of great importance. The evidence that some of these peptides, especially ET-1, may have a possible role in restenosis further lends credence to the notion. Our observations are important from the angle of procedural success also. The vasoconstrictive and hemodynamic disturbances that occur during coronary interventions can possibly be managed by pharmacological modifications, e.g. by using ACE inhibitors, BK or ET-1 and V1 receptor antagonists.

**Acknowledgments**

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Coronary Stent Implantation without Lesion Predilatation (Direct Stenting): Our Experience with this Evolving Technique

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Background: Until recently, conventional intracoronary stent deployment required predilatation of the lesion with a balloon. However, “direct stenting” of the lesion without predilatation offers certain theoretical and practical advantages. We assessed the safety and feasibility of direct stenting in a select group of patients who were likely to benefit most from these advantages, namely, those with acute coronary syndromes, saphenous vein graft lesions, associated renal or left ventricular dysfunction and those requiring multivessel intervention.

Methods and Results: After direct stenting, intravascular ultrasound was used to assess the adequacy of stent expansion in 51 patients. One hundred and twenty patients with a total of 125 lesions (83.3% males, average age 54.6±12.4 years) were enrolled for direct stenting. Of these, 90% of patients had presented with acute coronary syndromes, 21.6% of patients had associated moderate-to-severe left ventricular systolic dysfunction, 6.7% of patients had associated renal dysfunction and 30.8% of patients required multivessel intervention. Angiographically visible thrombus was present in 35.2% of patients. The mean reference diameter of the lesion was 3.18±0.32 mm and mean percentage diameter stenosis was 76.4±11.2%. Almost all varieties of stents were used (8.8% bare and 91.2% mounted). Procedural success was achieved in 98.3% of patients (98.4% of lesions). In two cases, the lesion had to be predilated prior to stenting. On angiography, the need for postdilatation of the stent was apparent in 29 (23.6%) lesions. In contrast, on intravascular ultrasound evaluation done in 51 lesions after stent deployment, the need for postdilatation to optimize stent expansion was seen in 43 (84.3%) lesions. There was one instance of acute stent thrombosis and two instances of slow-flow phenomenon. There were no deaths, myocardial infarction or need for urgent bypass surgery.

Conclusions: We conclude that direct stenting is feasible and safe in selected groups of patients. Optimization of stent expansion after direct stenting may often require aggressive postdilatation. (Indian Heart J 2001; 53: 308–313)

Key Words: Stents, Coronary disease, Ultrasound

Uncit recently, conventional intracoronary stent deployment required predilatation of the lesion with a balloon before delivery of the stent to the lesion. The basic aim of this predilatation is to increase the minimum luminal diameter (MLD) of the lesion site so as to ensure a relatively safe and uncomplicated passage of the stent across the lesion. In addition, the process of predilatation allows lesion compliance to be tested and so alerts the operator to rigid, calcified lesions unresponsive to balloon/stent dilatation. The concept of direct stenting of the lesion without predilatation offers certain theoretical and practical advantages,1,2 viz. shorter procedure and fluoroscopy time, lesser cost (by dispensing with the need for a predilatation balloon), use of a smaller quantity of contrast medium (by reducing the number of check angiographic runs), reduction in the risk of major dissection and distal embolization, and possibly reduction of in-stent restenosis (by reducing vessel trauma and hence the degree of neointimal proliferation).

Besides the potential universal advantages of reduction in cost and possibly restenosis, patients who are especially likely to benefit most by direct stenting are those with acute coronary syndromes or with lesions in degenerated venous grafts in whom the risk of distal embolization of thrombotic/degenerated material is significant,3,4 patients with left ventricular or renal dysfunction in whom reduction in the amount of contrast used would be desirable, and
patients requiring multivessel or complex interventions in which the procedure and fluoroscopy time as well as the amount of contrast used are likely to exceed desirable limits. This technique, however, is not feasible in all types of coronary lesions and is generally avoided in chronic total occlusions, and in lesions with marked proximal tortuosity and extensive calcification to minimize the risk of stent malpositioning, incomplete stent expansion or stent embolization.

In this prospective observational study, we assessed the feasibility and safety of the technique of coronary stent implantation without predilatation of the lesion in a group of patients who were likely to benefit most from this strategy. In addition, we evaluated the impact of intravascular ultrasound (IVUS) assessment in guiding direct stenting.

Methods

Patient population: Between June 1999 and December 2000, direct coronary stenting without predilatation of the lesion was attempted in 125 consecutive carefully selected patients (with a total of 125 lesions). The exclusion criteria in this prospective study were lesions with: (i) extensive calcification; (ii) marked proximal tortuosity; and (iii) chronic total occlusion.

Total occlusions in a setting of acute myocardial infarction (MI) were considered for direct stenting only when Thrombolysis in Myocardial Infarction (TIMI) flow >0 was obtained after the guidewire had passed through the lesion and if the infarct-related lesion was clearly identified. High-grade stenosis (>90%) was not an exclusion criterion.

Study protocol: The procedure was performed using the femoral approach with 6 F or 7 F guiding catheters. A left Judkin’s or an extra back-up guiding catheter was used to cannulate the left anterior descending (LAD) artery; a left Judkin’s or left Amplatz 2 was used for the circumflex (LCx) artery; and a right Judkin’s or left Amplatz 1 was used for the right coronary artery (RCA). The lesion was crossed with a 0.014” floppy tip, Balance Middle Weight™ (Advanced Cardiovascular Systems Inc, Guidant, CA, USA) guidewire, and the stent was then advanced over the guidewire across the lesion. If the lesion could not be negotiated by the stent, a sustained gentle push of the stent catheter and, if necessary, deep intubation of the guiding catheter was attempted, if considered safe. If even such an attempt was unsuccessful, the stent was withdrawn and the lesion was predilated with a low-profile balloon after which the lesion was stented. Stent deployment was done under high pressure (≥12 atm) inflation. Based on angiographic and/or IVUS findings, stent deployment was optimized by predilatation of the stent with a short balloon of bigger size or at a higher pressure. Intravascular ultrasound guidance was used to assess the adequacy of stent deployment in 51 lesions, especially in the later half of the study period. Although the choice of the stent used was based on the operator’s preference, premounted lower-profile stents were preferred.

All the patients received 10 000 IU of intravenous heparin at the beginning of the procedure unless they were already on the drug prior to the procedure. The initial dose of heparin was guided by the activated clotting time (ACT) and further doses were given during the procedure to keep the ACT >300 seconds. If not already on heparin, the patients also received 500 mg ticlopidine and 325 mg aspirin just prior to the procedure. Thereafter, ticlopidine (500 mg/day) was continued for one month and aspirin (165 mg/day) was continued indefinitely. After the procedure, the sheaths were removed when the ACT fell to <160 seconds. Patients with acute MI and some of those with unstable angina—in whom it was felt necessary on the basis of clinical or angiographic features—were given low-molecular weight heparin for 48–72 hours after removal of the sheath. A bolus injection and infusion of abciximab were given electively in 24 patients. The administration of heparin in these patients was as per the EPILOG trial. Abciximab was also used for stent thrombosis and for the treatment of slow-flow phenomenon in one patient each.

Angiographic analysis and definitions: Angiographic measurements were performed using an automated computer-based system (Philips Medical Systems, Eindhoven, The Netherlands). All the angiograms were analyzed to assess lesion characteristics according to the modified American College of Cardiology/American Heart Association classification,7 the location of the target lesion, antegrade flow graded by the TIMI trial criteria8 and occurrence of the slow-flow or no-reflow phenomenon. The presence of an angiographically visible thrombus was defined as a filling defect in the vessel surrounded by the contrast medium. Occurrence of the slow-flow or no-reflow phenomenon was defined as sudden reduction of flow to TIMI 2 or TIMI ≤1, respectively, not attributable to dissection of the dilated lesion or to a spasm of the coronary artery. During hospital stay, the occurrence of major adverse coronary events (MACE) such as death, Q or non-Q wave MI, stent thrombosis, requirement of repeat revascularization by angioplasty or emergency bypass surgery was recorded. Angiographic success was defined as successful stenting of the vessel with residual stenosis <30% and TIMI flow ≥2. Clinical success was defined as angiographic success without any in-hospital MACE.
Intravascular ultrasound evaluation: Intravascular ultrasound evaluation was performed using the Ultracross™ 3.2 30 MHz coronary imaging catheter (SCIMED™ Boston Scientific Corporation, MN, USA) in 51 lesions. In most of these cases, IVUS evaluation was performed only after stent deployment to assess the adequacy of stent expansion and to detect edge dissections. The criteria for adequate stent expansion were the same as those in the MUSIC trial, i.e. in-stent minimum lumen area $\geq 90\%$ of the average reference lumen area or $\geq 100\%$ of the lumen area of the reference segment with the lowest lumen area, with in-stent lumen area of proximal stent entrance $\geq 90\%$ of the proximal reference lumen area. In addition, complete apposition of the stent over its entire length and the symmetry index were also evaluated.

Statistical analysis: Data are presented as mean±SD or percentages. The Student’s t test and Chi-square test were performed to compare continuous and categorical variables, respectively. Probability values $<0.05$ were considered significant.

Results

The baseline clinical and angiographic characteristics of patients enrolled in the study are described in Tables 1 and 2, respectively. The quantitative coronary analysis (QCA) data are depicted in Table 3. The procedure of direct stenting was successful in 98.3% of patients (98.4% of lesions). Two examples of successful direct stenting are shown in Figs 1 and 2. In two instances, the lesion could not be crossed by the stent (both stents $<18$ mm in length) because of proximal tortuosity in one and poor guiding catheter support in the other. In both these, the stent could be retrieved and there were no instances of stent embolization. The same stents were then successfully deployed after predilatation of the lesion with a balloon at a mean inflation pressure of $13.9\pm0.9$ atm. Of the 123 lesions in which direct stenting was performed, the stents were postdilated with a short balloon of bigger size and/or at a higher pressure in 54 lesions (43.9%). The decision to postdilate the stent was based on angiographic and/or IVUS findings suggestive of inadequate expansion of the stent. Angiography showed the need for postdilatation of the stent in 29 (23.6%) lesions. In contrast, on IVUS evaluation of 51 lesions, inadequate stent expansion requiring postdilatation was seen in 43 (84.3%) lesions. Of the lesions evaluated by both IVUS and angiography, the need for postdilatation of the stent based on angiographic findings alone (i.e. prior to IVUS evaluation) was apparent in only 13 (25.5%) lesions. An example of IVUS-guided

Table 1. Baseline clinical characteristics

| Age (years) | 54.6±12.4 |
| Males | 100 (83.3) |
| Clinical presentation | |
| Acute myocardial infarction | 14 (11.7) |
| Recent myocardial infarction | 55 (45.8) |
| Unstable angina | 39 (32.5) |
| Chronic stable angina | 12 (10) |
| Moderate–severe LV systolic dysfunction (LVEF <35%) | 26 (21.6) |
| Associated renal insufficiency (Serum creatinine $\geq 2$ mg%) | 8 (6.7) |
| Requiring multivessel intervention ($\geq 2$ vessels) | 37 (30.8) |
| Risk factors | |
| Hypertension | 62 (51.7) |
| Diabetes | 31 (25.8) |
| Hyperlipidemia | 54 (45) |
| Smoking | 44 (36.7) |
| Family history of CAD | 11 (9.2) |

n: 120; CAD: coronary artery disease; LV: left ventricle; LVEF: left ventricular ejection fraction Figures in parentheses are percentages

Table 2. Baseline angiographic characteristics

| Target vessel | |
| Left anterior descending artery | 52 (41.6) |
| Left circumflex artery | 23 (18.4) |
| Right coronary artery | 44 (35.2) |
| Saphenous vein graft | 6 (4.8) |
| Lesion type (ACC/AHA) | |
| A | 8 (6.4) |
| B1 | 65 (52) |
| B2 | 40 (32) |
| C | 12 (9.6) |
| Location of lesion | |
| Ostial | 4 (3.2) |
| Proximal | 46 (36.8) |
| Mid | 60 (48) |
| Distal | 15 (12) |
| Angiographically visible thrombus | 44 (35.2) |

*n = 125; ACC/AHA: American College of Cardiology/American Heart Association classification Figures in parentheses are percentages

Table 3. Quantitative coronary analysis results

| Reference vessel diameter (mm) | 3.18±0.32 | 3.28±0.41 |
| Minimum lumen diameter (mm) | 0.75±0.38 | 3.02±0.32* |
| Diameter stenosis (%) | 76.4±11.2 | 8±7* |

*p<0.01
postdilatation of the stent in which results of angiography appeared satisfactory is shown in Fig. 3.

Almost all varieties of stents were used; the most frequently used was the NIR ROYAL™ advance (Boston Scientific Corp., Ireland) in 37 (29.6%) lesions. A majority of these stents (91.2%) were premounted, and manually crimped stents were used in only 11 (8.8%) instances.

Thirty-seven (29%) stents were >18 mm in length (long stents). All of them could be negotiated and deployed without problems. TIMI grade 3 flow was achieved in all except two cases. In one of these cases, injection abciximab was used as a bail-out measure to treat the slow-flow phenomenon. No instance of extensive edge dissection requiring an additional stent was encountered. Angiographic success was obtained in all patients in whom direct stenting could be performed. There was one instance of stent thrombosis. This patient had presented with recent anterior MI (post-thrombolysis) with post-MI angina, and underwent successful direct stenting of the LAD artery. The angiographic result was good with no residual stenosis and TIMI grade 3 flow, and no angiographically visible edge dissection. He had also undergone IVUS assessment and was confirmed to have adequate stent expansion after postdilatation of the stent, and there was no edge dissection. Eleven hours after the procedure and 6 hours after removal of the sheath, he developed chest pain with ST segment elevation in the precordial leads. Repeat angiography revealed total occlusion of the stented segment, which was then redilated after administering injection abciximab. No additional stenting was done. The electrocardiogram (ECG) reverted to normal without any Q waves or residual ST segment-T wave abnormality. He received low-molecular weight heparin for 48 hours and remained asymptomatic during the subsequent hospital stay. Clinical success was thus achieved in 99.1% of patients (99.2% of lesions).

There were no in-hospital deaths or need for emergency bypass surgery and all the patients were discharged after a mean hospital stay of 2.6±0.8 days. During clinical follow-up after one month, no major adverse events were observed in any of the patients.

Discussion

This study demonstrates the feasibility and safety of the strategy of direct coronary stent implantation without predilatation of the lesion in a cohort of patients who are considered to be at high risk for coronary angioplasty, especially those with acute coronary syndromes. Although this was a nonrandomized observational study, it highlights certain important issues about this technique, viz. (i) direct stenting in acute coronary syndromes is feasible and safe; (ii) it is also feasible in patients with acute total occlusions if passage of the guidewire establishes antegrade flow sufficient to clearly identify lesion characteristics, especially the length of the lesion; and (iii) despite the use of high pressure (≥12 atm) for stent deployment, IVUS assessment suggests that stent expansion is often suboptimal and
requires optimization by redilatation at a higher pressure or with an oversized balloon.

In this study, the majority (90%) of the total of 120 patients had presented with acute coronary syndromes. The culprit coronary lesions in such patients, including those with acute MI, have complex morphological features such as baseline total occlusions, ulcerations and presence of a thrombus. Balloon angioplasty in such complicated atherosclerotic plaques is associated with a greater risk of complications such as extensive dissection, distal embolization of tissue, thrombus or atherosclerotic debris and occurrence of slow-flow or no-reflow phenomenon. This study demonstrates a procedural success rate of 98.3% and an angiographic success rate of 100% (in those patients in whom direct stenting was performed). Of note is the fact that complications were rare; in fact, there were no instances of extensive dissection/stent loss. There was only 1 (0.9%) instance of stent thrombosis and the slow-flow phenomenon was observed in only 2 (1.7%) patients. These results compare favorably with the much higher incidence of slow-flow/no-reflow phenomenon reported in patients undergoing revascularization for acute coronary syndromes. Direct stenting was thus associated with high success and low complication rates in this subset of high-risk patients, making it an ideal indication for this technique. A similar beneficial effect of direct stenting in acute coronary syndrome was recently reported by Hamon et al. with a 2.5% incidence of no-reflow phenomenon.

Another subset of patients likely to benefit from direct stenting are those undergoing angioplasty in degenerated saphenous vein grafts, in whom the friable material may embolize less when predilatation is omitted. Our series, however, had only 6 patients belonging to this category. In one of the studies assessing the feasibility of direct stenting, in addition to patients with acute coronary syndromes, those with restenotic lesions were thought to be particularly suited for direct stent implantation because these lesions are usually free from hard, resistant and fibrocalcific elements. Other potential advantages of direct stenting are reduction in ischemic time, amount of contrast agent used, procedure time, radiation exposure and cost of the procedure. Reduction of ischemic time and the amount of contrast agent used would be beneficial in patients with severe left ventricular dysfunction and unstable clinical presentation. Although we did not assess the effect of direct stenting on procedure and fluoroscopy time in this study, a beneficial effect on these parameters was previously reported by Figulla et al. A recent study by Briguori et al. also reported a reduction in procedure time by 30%, radiation exposure by 25%, use of contrast agent by 28% and cost by 41% when direct stenting was compared with conventional stent implantation with predilatation.

The cost benefit derived from direct stenting by avoiding the use of a balloon for predilatation is obvious; however, in our setting, where balloons are frequently reused, this issue may not be very important. In addition, frequent use of a balloon to optimize the final result under IVUS guidance may offset this potential advantage.

Finally, direct stenting might be helpful in reducing restenosis rates. This postulation is based on certain experimental studies. It has been observed in animal models that balloon dilatation leads to endothelial denudation and that when a stent is placed without balloon predilatation, sufficient endothelium remains within the stented segment to allow repopulation with a much reduced requirement for endothelial proliferation and migration, which is the key step in the restenotic process. It has also been observed that occurrence of dissection by balloon dilatation exposes subendothelial tissue in which platelets and macrophages accumulate. These cells get trapped by subsequent stent deployment and eventually play a key role in inducing proliferation and migration of subendothelial smooth muscle cells, which again play an instrumental role in the process of restenosis. It is likely that dissections also occur during direct stent implantation without predilatation, but in a more controlled manner, and the stent immediately seals the dissection plane, thus preventing accumulation of macrophages and platelets. This potential advantage of direct stenting, however, has not been confirmed so far by any of the ongoing studies.

One important issue regarding direct stenting which deserves attention is the adequacy of stent expansion compared with conventional stenting owing to no or less aggressive pre- and postdilatation. This issue can be confirmed by IVUS assessment. Although we did not systematically perform IVUS in all our patients, from the IVUS evaluation of 51 lesions in our study, it appears that direct stenting often leaves stents inadequately expanded. Among those patients evaluated by IVUS, the need for postdilatation to optimize stent expansion was felt in 84.3% of lesions compared to 25.5% of lesions based on angiographic evaluation alone. This has important implications since inadequately expanded stents may predispose the patient to an increased risk of stent thrombosis and restenosis. Such a discrepancy, although of lesser magnitude, between angiographic and IVUS evaluation after angioplasty and stenting, has been reported earlier with conventional stenting.

In these studies, it was found that after stent placement, angiography overestimates lumen dimensions and thus the adequacy of stent expansion. Our study, however, had too small a sample size to address this issue. The angiographic method of
determining stent expansion has the inherent limitations of one-dimensional assessment. In contrast, cross-sectional imaging by IVUS from within the lumen of the stent is a superior method of confirming adequate stent expansion and obtaining a better final result which leads to a reduced target vessel revascularization rate during follow-up.24 Our analyses of the results of IVUS evaluation suggest that direct stenting may lead to inadequate expansion of the stent in a large number of patients because of the omission of pre- and postdilatation. This raises the question of whether IVUS evaluation should be done routinely to confirm adequate stent expansion after direct stenting or whether aggressive postdilatation of the stent should be done routinely in all cases of direct stenting. Larger, multicentric studies with a control group in which IVUS evaluation is not done are warranted to confirm this observation and to answer these questions.

Study limitations: The present study is a nonrandomized one without a control group, in which all the patients underwent direct stenting; hence, comparison with a group in which routine predilatation was done is not possible. Intravascular ultrasound guidance, which was used in 51 lesions, was done randomly and not according to any predetermined angiographic criteria. Cost–benefit analysis was not done because of the frequent reuse of balloons and refurbished IVUS catheters.

Conclusions: From this nonrandomized observational study, we conclude that direct stenting without lesion predilatation appears to be safe, feasible and possibly beneficial in this selected cohort of patients. Optimization of stent deployment after direct stenting may often require postdilatation of the stent at a higher pressure or with a bigger balloon. Intravascular ultrasound helps significantly in assessing the adequacy of stent expansion and the need for subsequent aggressive postdilatation. Larger, multicentric randomized studies are warranted to confirm these observations and to further refine this evolving therapeutic strategy.

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Sapra et al. Direct Coronary Stent Implantation Indian Heart J 2001; 53: 308–313
Is Off-pump Coronary Artery Bypass Surgery Safe for Left Main Coronary Artery Stenosis?

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Background: The feasibility of off-pump coronary artery bypass surgery has been well demonstrated. The purpose of the present study was to assess the safety and efficacy of off-pump coronary artery surgery in patients with left main coronary artery disease.

Methods and Results: Between January 1997 and December 2000, 174 patients with significant left main coronary artery stenosis underwent coronary artery bypass grafting without a pump. During the same period, 991 patients who also had significant left main coronary artery stenosis underwent coronary artery surgery on a pump. The patients in the two groups were matched in preoperative variables except that those in the off-pump group were slightly older, and more required urgent surgery. Hospital mortality was 2/174 and 21/991 in the off-pump and on-pump groups, respectively (p=0.560). The incidence of perioperative myocardial infarction (1.74 v. 31%, p=0.712), atrial fibrillation (17/174 v. 157/991, p=0.050) and blood transfusion requirement (63/174 v. 476/991, p=0.050) were significantly less in the off-pump group. The intubation time (15±3 hours v. 22±4 hours, p=0.001), blood loss (365±61 ml v. 582±76 ml, p<0.001), intensive care unit stay (23±10 hours v. 36±11 hours, p<0.001) and hospital stay (6±4 days v. 9±5 days, p<0.001) were also less in the off-pump group.

Conclusions: Off-pump coronary artery bypass surgery is safe and effective for patients with left main coronary artery disease. (Indian Heart J 2001; 53: 314-318)

Key Words: Coronary disease, Surgery, Cardiopulmonary bypass

Both observational1-2 and randomized3-4 trials carried out on patients with left main coronary artery stenosis (LMCS) have shown prolonged survival of surgically treated patients compared with those treated medically. In long-term follow-up of patients listed in the Coronary Artery Surgery Study (CASS) registry, the 15-year cumulative survival of those with initial coronary artery bypass grafting (CABG) was 44% v. 31% in medically treated patients; median survival in the surgical group was 13.1 years compared with only 6.2 years in the medical group.2

Left main coronary artery stenosis has been identified as an independent predictor of postoperative morbidity and mortality after CABG by several investigators5-7 and is considered a definite indication of CABG regardless of symptomatology.

The presence of critical LMCS has been considered a relative contraindication for the off-pump coronary artery bypass (OPCAB) technique due to concerns over the well demonstrated hemodynamic changes during displacement of the heart, even though it is now being used more commonly and the results are encouraging even in high-risk and elderly patients.5-9

We analyzed our data to determine whether OPCAB can be used safely in patients with critical LMCS.

Methods

Patients with significant (>50%) LMCS operated between January 1997 and December 2000 were included in the study. Of these, 174 patients were operated without cardiopulmonary bypass (OPCAB Group) and 991 patients were operated on cardiopulmonary bypass (CCAB Group). One patient in the OPCAB Group required conversion to cardiopulmonary bypass and was excluded from the study. Preoperative and intraoperative variables, and postoperative results of the two groups were analyzed and compared. Risk assessment was done preoperatively using the Parsonnet score. Intra-aortic balloon pump (IABP) was used preoperatively in patients who were unstable and had significant ST changes.
Anesthesia and anticoagulation protocol: Patients were premedicated using morphine (0.1 mg/kg) and lorazepam (2–4 mg). Induction was achieved by midazolam (15–20 µg/kg) and fentanyl (10–100 µg/kg). Muscle relaxation was achieved by vecuronium bromide (0.10–15 mg/kg). Anesthesia was maintained by oxygen, air and incremental doses of midazolam and fentanyl. Heparin was injected in a dose of 3 mg/kg in patients operated on a pump and activated clotting time (ACT) was maintained at >400 seconds. In patients who were operated upon without a pump, the initial dose of heparin used was 1.5 mg/kg. The ACT, which was measured initially and repeated every 30 minutes, was maintained at >300 seconds. Prothamine sulphate was used in a 1:1 ratio to reverse the effect of heparin after the procedure.

A femoral arterial line was used in all the patients to insert IABP if the patient became unstable during induction of anesthesia or at a later stage before revascularization.

Hemodynamic monitoring: Hemodynamic monitoring consisted of a six-channel electrocardiogram (ECG). A combination of leads II and V5 was continuously displayed and used for ST segment trend analysis. Radial arterial pressure was monitored. A pulmonary artery catheter was used in all the patients. Recorded variables were mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), stroke volume (SV) and systemic vascular resistance (SVR). Oxygen saturation was continuously monitored with a pulse oximeter. Arterial blood gases and ACT were monitored every 20 minutes. Continuous intraoperative transesophageal echocardiographic (TEE) monitoring was done using a multiple transducer and Sonos 5500 imaging system. The parameters specifically monitored by TEE were: regional wall motion abnormalities; changes in global left ventricle (LV) function; LV filling; right atrial filling; mitral regurgitation and right ventricular outflow tract obstruction.

Technique of off-pump CABG: All procedures were performed through a median sternotomy. The left internal mammary artery (LIMA) was harvested by the standard technique using hemoclips. It was harvested as a pedicled graft in most patients. The radial artery and saphenous vein were harvested simultaneously. Patients were heparinized with a dose of 1.5 mg/kg body weight. Octopus 2, Octopus 2+ and Octopus 3 (Octopus tissue stabilization system, Medtronic Inc., Minneapolis MN) were used as the mechanical stabilizers in most of the patients. Intracoronary shunts (Baxter AnastafLO Intravascular shunt, Irvine, CA) were used in most of the patients. The oxygen blower was used to assist in anastomosis. Hemodynamic monitoring was performed using the Swan–Ganz catheter.

The left anterior descending (LAD) artery was the first coronary artery to be grafted in most cases. The right coronary artery (RCA) was normally the second artery to be grafted. The vessels on the lateral and posterior wall were grafted last. However, the sequence of grafting was individualized for a particular patient, depending on the patient’s hemodynamics. The LAD and RCA could be grafted without much displacement of the heart. For exposure of the circumflex vessels, three pericardial traction sutures were used to pull the heart vertically. The right pleura was opened in the majority of the patients and vertical pericardiotomy was performed to herniate the heart to the right of the chest under the sternum. Other maneuvers, such as the Trendelenburg position and tilting the table, were performed as required. Inotropes were used as and when necessary during surgery.

Proximal anastomosis was performed using standard techniques. Normally, proximal anastomosis was performed after every distal anastomosis.

Techniques of CABG on cardiopulmonary bypass (CPB): Standard cardiopulmonary bypass (CPB) was established using ascending aortic and two-stage venous cannulation. Patients were not actively cooled but the temperature was allowed to drift. Most patients were operated under cardiopлегic arrest, using warm blood cardioplegia, both antegrade and retrograde. Cardioplegia was repeated after every distal anastomosis. Warm blood without potassium was infused after completing all distal anastomoses, and while performing proximal anastomosis. Some patients were operated on CPB without arresting the heart. The LV vent was inserted through the right superior pulmonary vein in some patients. Hemodynamic management protocol was followed. Patients were extubated in the intensive care unit (ICU) as soon as possible, depending on their hemodynamic stability. Antibiotic therapy was continued as long as patients had central lines or chest drains (normally 24–48 hours).

Postoperative management: A standard postoperative management protocol was followed. Patients were extubated in the intensive care unit (ICU) as soon as possible, depending on their hemodynamic stability. Antibiotic therapy was continued as long as patients had central lines or chest drains (normally 24–48 hours).

Definitions: Perioperative myocardial infarction (MI) was defined as the development of new Q waves on postoperative electrocardiogram or loss of R wave progression, new left bundle branch block or new ST and T wave changes in association with increase in CPK level >40 U/L or CPK-MB/CPK ratio more than 5%. Prolonged ventilation was defined as ventilation for more than 48 hours. Mediastinitis was
defined as mediastinal collection which was positive on culture. Acute renal failure was defined as the requirement of peritoneal or hemodialysis. Total operative time was defined as the time from incision to closure of the skin.

Urgent surgery was defined as surgery undertaken within 24 hours of the angiogram. Emergency surgery was that undertaken when the patient was shifted directly to the theatre from the catheterization laboratory or if the surgery was required within a few hours of admission or of performing the angiogram.

Statistical analysis: Data are reported as mean±SD. The Chi-square test and Fisher’s exact t test were used to compare categorical variables. Unpaired Student’s t test was used to compare inter-group means. A p value of less than 0.05 was accepted as significant. Variables that are not normally distributed were compared using the Mann–Whitney test.

Results

The demographics of the group of patients are shown in Table 1. The patients were matched in terms of sex, diabetes, hypertension, smoking, history of cerebrovascular accidents (CVA), peripheral vascular disease (PVD) and obesity but the mean age was slightly higher in the OPCAB Group. The two groups were matched for the number of patients with angina, and those in NYHA functional Class III or IV but there were more patients in the OPCAB Group with chronic obstructive pulmonary disease (COPD). The number of patients with poor LV function was comparable in the two groups. There were more urgent procedures in the OPCAB Group than the CCAB Group. The Parsonnet risk score was comparable in the two groups.

The LIMA was used for grafting in the majority of patients in both the groups (Table 2). The right internal mammary artery (RIMA) was used in more patients in the OPCAB Group. The other grafts used were the radial artery and veins. The number of patients in whom the radial artery was used as one of the conduits was comparable in the two groups. The average number of grafts was slightly higher in the OPCAB Group.

Hemodynamically, the ECG showed some ST segment changes during LAD anastomosis, which returned to normal after the flow was established from the LIMA to the LAD. The MAP, SV and CI decreased during anastomosis to vessels on the lateral and posterior wall of the heart. The CVP increased while pulmonary artery pressure and PCWP did not show much rise or decreased slightly. Pacing the patient in the Trendelenburg position increased the CVP though pulmonary pressure still remained within normal limits in the majority of patients.

Intraoperatively, IABP was used in more patients in the OPCAB Group. The total operating time was significantly less in the OPCAB Group than in the CCAB Group (Table 2).

Table 1. Preoperative variables of patients with left main coronary artery stenosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OPCAB Group (n=174)</th>
<th>CCAB Group (n=991)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>62±9.8</td>
<td>59±8.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>152 (87.4)</td>
<td>891 (89.9)</td>
<td>0.379</td>
</tr>
<tr>
<td>Female (%)</td>
<td>22 (12.6)</td>
<td>100 (10.1)</td>
<td>0.379</td>
</tr>
<tr>
<td>NIDDM (%)</td>
<td>35 (20.1)</td>
<td>213 (21.5)</td>
<td>0.757</td>
</tr>
<tr>
<td>IDDM (%)</td>
<td>2 (1.1)</td>
<td>8 (0.8)</td>
<td>0.650</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>18 (10.3)</td>
<td>111 (11.2)</td>
<td>0.841</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>68 (39.1)</td>
<td>365 (36.8)</td>
<td>0.630</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>66 (37.9)</td>
<td>277 (28.0)</td>
<td>0.010</td>
</tr>
<tr>
<td>History of CVA (%)</td>
<td>6 (3.4)</td>
<td>21 (2.1)</td>
<td>0.423</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>50 (28.7)</td>
<td>252 (25.4)</td>
<td>0.410</td>
</tr>
<tr>
<td>NYHA Class III or IV (%)</td>
<td>38 (21.8)</td>
<td>158 (15.9)</td>
<td>0.071</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>15 (8.6)</td>
<td>75 (7.6)</td>
<td>0.745</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>23 (13.2)</td>
<td>132 (13.3)</td>
<td>0.932</td>
</tr>
<tr>
<td>Redo CABG (%)</td>
<td>10 (5.7)</td>
<td>61 (6.2)</td>
<td>0.971</td>
</tr>
<tr>
<td>Mean EF (mean±SD) (%)</td>
<td>42±9</td>
<td>40±8</td>
<td>0.002</td>
</tr>
<tr>
<td>EF &lt;30%</td>
<td>36 (20.7)</td>
<td>158 (15.9)</td>
<td>0.150</td>
</tr>
<tr>
<td>Preop IABP (%)</td>
<td>16 (9.2)</td>
<td>119 (12.0)</td>
<td>0.347</td>
</tr>
<tr>
<td>Urgent surgery (%)</td>
<td>91 (52.2)</td>
<td>416 (42.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>Emergency surgery (%)</td>
<td>3 (1.7)</td>
<td>16 (1.6)</td>
<td>0.826</td>
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<tr>
<td>CHF (%)</td>
<td>38 (21.8)</td>
<td>213 (21.5)</td>
<td>0.998</td>
</tr>
<tr>
<td>Parsonnet score (mean±SD)</td>
<td>8.2±6.6</td>
<td>7.6±6.2</td>
<td>0.244</td>
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</tbody>
</table>

Table 2. Intraoperative variables of patients with left main coronary artery stenosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OPCAB Group (n=174)</th>
<th>CCAB Group (n=991)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIMA (%)</td>
<td>164 (94.3)</td>
<td>933 (94.1)</td>
<td>0.904</td>
</tr>
<tr>
<td>RIMA (%)</td>
<td>15 (8.6)</td>
<td>38 (3.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>RA (%)</td>
<td>125 (71.8)</td>
<td>773 (74.0)</td>
<td>0.092</td>
</tr>
<tr>
<td>CPB time (mean±SD) (min)</td>
<td>NA</td>
<td>85±13</td>
<td>—</td>
</tr>
<tr>
<td>AoXL time (mean±SD) (min)</td>
<td>NA</td>
<td>36±8</td>
<td>—</td>
</tr>
<tr>
<td>Number of grafts (mean±SD)</td>
<td>2.9±0.8</td>
<td>3.1±0.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Total operating time (min)(mean±SD)</td>
<td>178±47</td>
<td>238±54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative IABP (%)</td>
<td>11 (6.3)</td>
<td>13 (2.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LIMA: left internal mammary artery; RIMA: right internal mammary artery; CPB: cardiopulmonary bypass; AoXL: aortic cross clamp; RA: radial artery; IABP: intra-aortic balloon pump; NA: not applicable
Postoperative complications and hospital mortality are shown in Table 3. The overall mortality was slightly less in the OPCAB Group than in the CCAB Group but this was not statistically significant. The incidence of perioperative MI was slightly lower in the OPCAB Group than in the CCAB Group though it was not statistically significant (p=0.712). Only 1 (0.6%) patient in the OPCAB Group was re-explored for bleeding while 24 (2.4%) patients in the CCAB Group required re-exploration for bleeding (p=0.158). The mean blood loss was significantly less in the OPCAB Group and a smaller number of patients required blood or blood product transfusion. The requirement of inotropes, prolonged ventilation and postoperative IABP was comparable in the two groups.

In the OPCAB Group required shorter ventilation and were extubated more quickly than the patients in the CCAB Group. None of the patients in the OPCAB Group, but 3 (0.3%) patients in the CCAB Group suffered a stroke (p=0.932). The incidence of pulmonary complications, mediastinal infection and acute renal failure was comparable in the two groups. The mean ICU stay and total hospital stay were significantly less in the OPCAB Group.

**Discussion**

Off-pump coronary bypass surgery through a median sternotomy has recently gained renewed interest for multivessel coronary revascularization.\(^{10,11}\) Results of this technique are encouraging and many reports have shown lower postoperative morbidity and cost with the OPCAB technique compared with the conventional coronary bypass technique.\(^{8,9,12}\) The OPCAB technique is now being used even in high-risk patients including the elderly and those with poor LV function.\(^{13,14,15}\)

Patients with significant LMCS present a special situation because the hemodynamic disturbances which develop during manipulation of the heart in OPCAB surgery, may not be tolerated by the patient. In our experience, LIMA-LAD anastomosis can be performed without much displacement of the heart, and the use of an intracoronary shunt to permit continued myocardial perfusion during anastomosis reduces hemodynamic disturbances to a minimum.

Left anterior descending artery grafting using LIMA via left anterior small thoracotomy without CPB has been shown to offer good early and mid-term results.\(^{16}\) Multivessel revascularization needs full sternotomy to access all the vessels of the heart. Access to the obtuse marginal and posterior descending artery needs displacement and manipulation of the heart. Various techniques have been described to access and revascularize the vessels on the lateral and inferior walls of the ventricle without compromising hemodynamics significantly.\(^{17–20}\) Cartier et al.\(^{20}\) described a technique of exposing the circumflex vessels. They used four pericardial sutures around the base of the heart and then used a pull-type mechanical stabilizer. Using this technique, they could easily access the obtuse marginal as well as the posterolateral branches while maintaining hemodynamic stability. They achieved complete revascularization in 95% of patients with one patient needing conversion to cardiopulmonary bypass. We used a combination of deep pericardial sutures, Trendelenburg position, right pleurotomy and vertical pericardiotomy near the diaphragm to expose the circumflex vessels. Octopus was used as the mechanical stabilizer.

Hospital mortality was comparable in the OPCAB and CCAB Groups, though the patients in the OPCAB Group were older and more often required urgent surgery. The majority of patients were moved out of the ICU within 24 hours and the number of patients who required ventilation for more than 48 hours was equal in both the groups, even though the incidence of COPD was higher in the OPCAB Group.

We use IABP preoperatively in patients with LMCS who have unstable angina with ST and T wave changes in the ECG or those with severely impaired LV function.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OPCAB Group</th>
<th>CCAB Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative MI (%)</td>
<td>1 (0.6)</td>
<td>14 (1.4)</td>
<td>0.712</td>
</tr>
<tr>
<td>Reoperation for bleeding (%)</td>
<td>1 (0.6)</td>
<td>24 (2.4)</td>
<td>0.158</td>
</tr>
<tr>
<td>Postoperative inotropes (%)</td>
<td>22 (12.6)</td>
<td>184 (18.6)</td>
<td>0.075</td>
</tr>
<tr>
<td>Blood loss (mean±SD)</td>
<td>365±61</td>
<td>582±76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood transfusion (%)</td>
<td>63 (36.2)</td>
<td>476 (48)</td>
<td>0.005</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>17 (9.8)</td>
<td>157 (15.8)</td>
<td>0.050</td>
</tr>
<tr>
<td>Intubation time in hours (mean±SD)</td>
<td>15±3</td>
<td>22±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prolonged ventilation (%)</td>
<td>6 (3.4)</td>
<td>73 (7.4)</td>
<td>0.083</td>
</tr>
<tr>
<td>Postop IABP (%)</td>
<td>1 (0.6)</td>
<td>12 (1.2)</td>
<td>0.730</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0 (0)</td>
<td>3 (0.3)</td>
<td>0.932</td>
</tr>
<tr>
<td>Pulmonary complications (%)</td>
<td>3 (1.7)</td>
<td>34 (3.4)</td>
<td>0.342</td>
</tr>
<tr>
<td>Mediastinitis (%)</td>
<td>1 (0.6)</td>
<td>7 (0.7)</td>
<td>0.761</td>
</tr>
<tr>
<td>Acute renal failure (%)</td>
<td>1 (0.6)</td>
<td>12 (1.2)</td>
<td>0.705</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>2 (1.1)</td>
<td>21 (2.1)</td>
<td>0.560</td>
</tr>
<tr>
<td>ICU stay in hours (mean±SD)</td>
<td>23±10</td>
<td>36±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital stay in days (mean±SD)</td>
<td>6±4</td>
<td>9±5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; IABP: intra-aortic balloon pump; ICU: intensive care unit; Postop: postoperative
Preoperatively, 9.2% and 12.0% of patients in the OPCAB and CCAB Groups, respectively, were on IABP. Preoperative use of IABP has been shown to reduce myocardial ischemia and thus improve outcome in high-risk coronary patients.21,22 Christenson et al.23 showed that preoperative use of IABP in high-risk patients including those with significant LMCS was associated with a lower incidence of low cardiac output, and a shorter intubation time and length of stay in both the ICU and hospital. The requirement of IABP intraoperatively was equal in the OPCAB and CCAB Groups in our study.

We observed lower postoperative morbidity, particularly perioperative MI, blood loss, requirement of blood or blood products and atrial fibrillation in the OPCAB Group. The ICU and hospital stay were shorter in this group. Similar observations have been reported by other workers also.24–26

Conclusions: Off-pump coronary artery surgery is a safe and effective technique in patients with significant left main coronary artery disease. The postoperative morbidity and length of ICU and hospital stay are shorter compared to patients operated on CPB. Proper monitoring of various hemodynamic parameters during surgery, including monitoring of LV wall motion by TEE, is useful. An IABP helps in patients with unstable angina and ischemic changes on ECG, and in those with severely impaired LV function.

References

Surgical Experience with Dissecting and Nondissecting Aneurysms of the Ascending Aorta

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Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi

Background: Patients who underwent replacement of the ascending aorta with a prosthetic graft for treatment of ascending aortic aneurysm and dissection between January 1992 and December 2000 were studied.

Methods and Results: Bentall’s operation, using a composite aortic valve and prosthetic graft, was performed in 82 patients (70 males). Indications for the procedure included ascending aortic aneurysm \( n = 54 \) (including 16 patients with Marfan’s syndrome); DeBakey Type I or II aortic dissection \( n = 26 \) (including 10 patients with Marfan’s syndrome) and ascending aortic aneurysm with severe aortic stenosis (bicuspid aortic valve disease) \( n = 2 \). Bentall’s procedure with the inclusion technique was performed in 72 patients and a Cabrol fistula created in 63 patients. In 10 other patients, coronary button transfer was done without a Cabrol fistula. There were 6 early deaths (7.3%) and 8 patients required re-exploration for excessive bleeding. Eighteen patients showed low cardiac output while the wound of 8 became infected. Postoperative arrhythmia and renal failure was seen in 26 and 6 patients, respectively. Four patients had pericardial effusion. Follow-up ranged from 1 month to 8 years. There were 8 late deaths, the causes of which include congestive heart failure \( n = 3 \), cerebral hemorrhage \( n = 3 \) and sudden cardiac death \( n = 2 \). Two patients reported back with dissection of the descending thoracic aorta and await surgery.

Conclusions: Bentall’s operation is a safe procedure with an acceptable mortality and morbidity. (Indian Heart J 2001; 53: 319–322)

Key Words: Surgery, Aortic aneurysm, Aortic dissection
to determine the extent of the intimal flap in case of dissection and coronary angiography was done in 68 patients. Indications for Bentall’s operation included ascending aortic aneurysm (n=54 including 16 patients with Marfan's syndrome); DeBakey Type I or II aortic dissection (n=26 including 10 patients with Marfan's syndrome) and ascending aortic aneurysm with severe aortic stenosis (bicuspid aortic valve disease) (n=2). Among patients with dissection, 10 had acute and 16 had chronic aortic dissection. Out of the 8 patients with DeBakey Type I dissection, 3 had an intimal tear involving the arch vessels. In one patient, the intimal tear had involved the right coronary ostium. Fifty-two patients had severe aortic valvular incompetence while 30 had moderate aortic regurgitation. Five patients had moderate-to-severe mitral regurgitation, 42 had left ventricular dysfunction (ejection fraction <50%) and 3 had associated coronary artery disease. Preoperatively, 15 patients were in New York Heart Association (NYHA) Class I, 28 patients were in Class II, 30 patients were in Class III and 9 patients were in Class IV. Preoperative characteristics are summarized in Table 1.

Operative considerations: The Bentall’s procedure, which involves replacement of the ascending aorta with a composite graft and reimplantation of the coronary ostia, was undertaken in 82 patients. In 72 cases, direct re-attachment of the coronary artery ostia to the opening in the composite graft was performed using the inclusion technique. In 10 patients, the coronary button technique was used for anastomoses of the coronary ostia to the prosthetic graft.

Table 1. Preoperative characteristics of patients (n=82)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>9-74</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>41±13.6</td>
</tr>
<tr>
<td>Male/Female</td>
<td>70/12</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>26 (32%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>30 (37%)</td>
</tr>
<tr>
<td>Severe</td>
<td>52 (63%)</td>
</tr>
<tr>
<td>Mitral regurgitation (moderate/severe)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Left ventricular dysfunction (EF &lt;50%)</td>
<td>42 (51%)</td>
</tr>
<tr>
<td>Ascending aortic pathology</td>
<td></td>
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<tr>
<td>Aneurysm</td>
<td>56 (68%)</td>
</tr>
<tr>
<td>Type I or II dissection</td>
<td>26 (32%)</td>
</tr>
<tr>
<td>NYHA Class III/IV</td>
<td>39 (48%)</td>
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</tbody>
</table>

Technique: In all the patients, the groin was routinely prepared for cannulation. Cardiopulmonary bypass was instituted either by cannulating the high ascending aorta or femoral artery, and single atrial, bicaval or the femoral route was used for venous cannulation. Depending upon the individual case, moderate-to-severe hypothermia was induced. Moderate systemic hypothermia (28°C) was instituted in 70 patients and severe hypothermia with total circulatory arrest in the remaining 12. After aortic cross-clamping, myocardial protection was achieved with hyperkalemic cold blood cardioplegia and topical cooling.

In the initial 72 cases, the inclusion technique with direct coronary re-attachment was performed. In these cases, the aneurysm was incised longitudinally at the center and direct coronary ostial cardioplegia given. After adequate cardioplegic arrest, the aortic valve was carefully assessed for incompetence and valve leaflets were either excised or left intact to be used as part of the buttressing material. Composite graft replacement was then carried out with the use of interrupted, pledgetted 2-0 ethibond sutures (Johnson and Johnson, Somerville, New Jersey). Either a St Jude composite graft (St Jude Medical, Brussels, Belgium) or a Medtronic composite graft (Medtronic Inc., Minneapolis, MN) was used. After completion of the suture line between the aortic annulus and the sewing ring of the prosthetic valve, holes for coronary implantation were made in the aortic graft with graft cautery. The aortic wall surrounding the coronary ostia was then sutured to these openings with continuous 5-0 polypropylene sutures. When needed, this suture line was reinforced with pledgetted mattress sutures.

The tube graft was then cut to the appropriate length and the aorta was transected as high as possible just below the aortic clamp. In the 52 cases in which there was no dissection, the grafts were directly anastomosed to the distal cut portion of the aorta. In the 26 cases in which dissection was present, the separated layers of the distal aorta were prepared with inner and outer layers of Teflon felt (Impra Inc. Tempe AZ, USA) and strip sutured with continuous 4-0 polypropylene sutures. The graft was sewn to this cuff with continuous sutures.

After completion of both proximal and distal anastomoses, the aortic wall was wrapped around the prosthesis and sutured. In 63 patients, a Cabrol shunt was created between the aneurysmal wrap and the right atrium in order to avoid the formation of a tense hematoma in the periprosthetic space.

In 10 patients, the coronary ostia were carefully excised with a button of aortic wall to serve as a Carrel patch and were anastomosed to the buttonhole made in the graft with
a 5-0 polypropylene suture. In these patients, the Bentall inclusion wrap was abandoned.

In the 12 cases of ascending aortic dissection in which the extent of involvement of the dissection flap was beyond the aortic arch, the distal anastomosis was done under total circulatory arrest after removing the aortic cross-clamp.

Three patients required hemi-arch replacement and in 1 patient the Bentall procedure was accompanied by the elephant trunk procedure. Circulatory arrest time varied between 20 and 45 minutes. In 6 cases of circulatory arrest, retrograde cerebral perfusion was performed to decrease cerebral ischemia.

Concomitant procedures included coronary artery bypass grafting (n=4), mitral valve repair (n=3) and mitral valve replacement (n=2).

Follow-up: Patients were followed up postoperatively in the outpatient department (OPD) at 1 month, 3 months, 6 months and 1 year in the first year and once a year thereafter. All the patients were given oral anticoagulants on the basis of prothrombin time and International Normalized Ratio (INR). Patients who failed to attend the OPD for a prolonged period after initial follow-up were contacted through letters and asked to come to the OPD for follow-up on specified dates. On each follow-up visit, they were evaluated clinically, echocardiographically and, when required, by computed axial tomography and magnetic resonance imaging.

Statistical analysis: Continuous or interval-related data were expressed as mean±standard deviation (SD). Categorical variables were expressed as percentages. A step-wise logistic regression analysis was performed to determine predictors of early mortality. A probability of 0.10 was a criterion for inclusion or exclusion cut-off in step-wise analysis and a final probability of 0.05 was considered significant.

Results

There were 6 early deaths (7.3%). One death occurred on postoperative day 6. This patient had preoperative renal dysfunction and developed severe acute renal failure on postoperative day 1. He was put on peritoneal dialysis but gradually developed multiorgan failure and died on postoperative day 6. Two patients, who had acute dissection and were in Class IV preoperatively, developed low output syndrome postoperatively. They died on days 10 and 12 postoperatively. One patient, whose platelet count and coagulation profile were borderline preoperatively, developed disseminated intravascular coagulation. He was re-explored on postoperative day 1 for excessive bleeding but no surgical site could account for the bleeding. Subsequently, he developed endotracheal tube bleeding on postoperative day 3 and gastrointestinal bleeding on postoperative day 4 and died on postoperative day 5. One patient died on postoperative day 22 owing to severe respiratory insufficiency. One patient died due to severe right ventricular failure on postoperative day 3. This patient had an abnormal right coronary ostium which was involved by a dissection flap. Initially, both the right and left coronary ostia were implanted in the aortic graft by direct inclusion but there was difficulty in weaning away the patient from cardiopulmonary bypass and on electrocardiogram, changes were seen in the inferior leads. We then applied a venous graft to the right coronary artery and were able to wean her away from cardiopulmonary bypass but the patient died on postoperative day 3 due to severe right ventricular failure.

A number of risk factors (Table 2) were analyzed to determine independent predictors of early death. The presence of acute dissection was the only significant predictor (p=0.03) of early death.

Eight patients (9.7%) required re-exploration for excessive bleeding. The cause was surgical in only one patient who had bled from the aorta. Eighteen patients had low cardiac output syndrome and were managed with high inotropic support. Eight patients had infected wounds and 2 of them developed mediastinitis. Postoperative arrhythmias were seen in 26 patients. Two patients, in whom atrial fibrillation persisted for more than 2 months, required prolonged amiodarone therapy. Postoperative renal insufficiency requiring peritoneal dialysis occurred in 6
patients. Four patients had pericardial effusion and required pericardial drainage. Three patients developed right-sided pleural effusion postoperatively.

**Long-term results:** The duration of follow-up for hospital survivors was from 1 month to 8 years and follow-up information was available for all. Twenty-five patients have been followed up for more than 5 years and 15 for more than 7 years.

There have been 18 late deaths among the 76 early survivors. Three patients died of cerebral hemorrhage 18–24 months postoperatively. Three patients, who had left ventricular ejection fraction ranging from 20%–25% preoperatively, died of cardiac failure. Left ventricular function deteriorated postoperatively and death occurred after 30–42 months. Two other patients died suddenly, one after 24 months and the other after 54 months. The cause of these deaths could not be determined.

No patient required reoperation for graft-related complications. There was no clinical, echocardiographic or tomographic evidence of any pseudoaneurysm formation or periprosthetic leak. Two patients who had come back with pain in the chest and showed evidence of descending thoracic aortic dissection on computed axial tomographic scan, now await surgery. No patient had flow through the Cabrol fistula on echocardiography, suggesting closure and thrombosis of the periprosthetic space. Two patients had prosthetic valve thrombosis which was treated with streptokinase. One patient had an episode of transient ischemic attack, followed by right-sided hemiparesis two years after surgery but improved on conservative treatment. Three patients had minor anticoagulant-related hemorrhages. They improved on readjustment of the anticoagulant dose. Two patients had prolonged fever which persisted for 2 months. Their blood cultures did not grow any organism and both recovered after 6 weeks of aggressive antibiotic therapy.

**Functional status of the survivors:** At the last follow-up, 49 patients (72%) were in NYHA Class I or II. Sixteen patients (23.5%) were in NYHA Class III and 3 (4.4%) in NYHA Class IV.

**Discussion**

Bentall’s operation for ascending aortic aneurysm and ascending aortic dissection gives good early and long-term results for all elective cases. Investigators have reported an operative mortality of 4%–10.5%. In our experience, the operative mortality was 7.9% which suggests that the procedure has an acceptable mortality. The major morbidity associated with this procedure was that of intraoperative and postoperative hemorrhage. However, with standardization of the technique and the availability of nonporous grafts, the incidence of bleeding has been reduced to a minimum. In our series, bleeding occurred in only 8 patients (9.7%).

The inclusion technique is safe and yields good results. However, there is a possibility of a leak from the coronary anastomotic site and formation of a pseudoaneurysm. Furthermore, coronary anastomosis is difficult with this technique if the coronary arteries are placed very low in the native aorta. As bleeding from the graft does not appear to be a major problem with the availability of nonporous grafts, we have switched over to the coronary button technique and obtained equally good results.

The entire aorta is abnormal in these patients. Hence, a strict and regular follow-up is necessary since they can develop a pseudoaneurysm/leak at the site of the operation or a dissection/aneurysm in the distal aorta. Furthermore, anticoagulation monitoring of the prosthetic valve in the composite graft is also required.

Considering the generalized involvement of the aorta in the disease process, the Bentall’s procedure appears to be a palliative one. However, dramatic improvement in symptoms and a drastic reduction in disease-related mortality makes it a valuable procedure. A low operative mortality and morbidity have added value to this procedure.

**References**

Prescribing Patterns and Cost of Antihypertensive Drugs in an Internal Medicine Clinic

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Departments of Pharmacology and Internal Medicine, Government Medical College, Chandigarh

Background: Antihypertensive agents are selected primarily for their ability to prevent morbidity and mortality related to hypertension.

Methods and Results: Prescribing trends and the cost of antihypertensive drugs were studied in 300 patients attending an internal medicine clinic. Beta-blockers were the most frequently used group of drugs (46.7%), followed by calcium-channel antagonists (34.3%) and angiotensin-converting enzyme inhibitors (30%). Diuretics were used in only 13.2% of the prescriptions. Atenolol (36%), amlodipine (29.3%) and enalapril (19%) were the most frequently used individual drugs. Propranolol, furosemide, amlodipine and atenolol were the least expensive drugs used, with annual drug acquisition costs of Rs 80, 102, 182 and 318, respectively. Benazepril (Rs 1778), diltiazem SR (Rs 1777), lisinopril (Rs 1660), prazosin (Rs 1416) and losartan (Rs 1365) were the most expensive drugs in terms of annual drug acquisition costs.

Conclusions: The results of our study emphasize the need to encourage frequent use of diuretics. Since the costs of different antihypertensives vary considerably, newer and relatively expensive antihypertensives should be prescribed only when clearly indicated. (Indian Heart J 2001; 53: 323-327)

Key Words: Hypertension, Cost–benefit analysis, Drugs

The primary goal of antihypertensive therapy is to prevent morbidity and mortality related to hypertension. Selection of antihypertensive agents should therefore be based primarily on their comparative ability to prevent these complications. Such an ability has been well established for β-adrenergic blockers and diuretics.1–3 Although a reduction in adverse cardiovascular events has also been reported recently with an angiotensin-converting enzyme inhibitor (ACEI),4 further studies are necessary to corroborate these findings. Over the last decade, there has been a dramatic increase in the use of new antihypertensives, i.e. ACEIs and calcium-channel antagonists (CCA), without convincing evidence of their ability to decrease cardiovascular morbidity and mortality in hypertension.5–9 Earlier justifications for their widespread use, which were based on their improved side-effect profile and the possibility of a better quality of life, have not withstood the test of large randomized studies. Several long-term, double-blind clinical trials have shown no consistent differences in antihypertensive efficacy, side-effects and quality of life within these four major classes of drugs.7–9 Moreover, some of the newer agents are more expensive than β-blockers and diuretics, cost being an important consideration for therapy of a chronic disease like hypertension, often requiring lifelong medication.

In view of this apparent disparity between a rational therapy for hypertension based on available scientific evidence and what is actually prescribed, we studied the pattern of use and cost of antihypertensive agents in the internal medicine clinic of a teaching hospital.

Methods
The study was conducted in the internal medicine outpatient department (OPD) of the Government Medical College and Hospital, Chandigarh. From June to November 1999, prescriptions of patients with essential hypertension were studied. Only prescriptions written by consultant doctors were included, which were collected and photocopied by team members from the internal medicine OPD. Hypertension was defined and staged according to the guidelines of the sixth report of the Joint National

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Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VI).  

The age and sex of patients, diagnosis (including hypertension and other diseases) and drugs prescribed were recorded. Brand names as well as generic names of prescribed drugs were noted. Costs of drugs were obtained from the Current Index of Medical Specialities (CIMS), Oct-Dec 1999 and the Indian Pharmaceutical Guide 1999. Drug acquisition costs (cost of buying a drug) were calculated, using the cost of the cheapest available preparation and the most commonly prescribed dosage, for each drug on a daily and annual basis. Total annual drug expenditure (money spent on buying required doses of all antihypertensives prescribed in the study population for a year) was also calculated. Drug expenditure due to a single drug was expressed as a percentage of total drug expenditure, e.g. annual drug expenditure due to atenolol was calculated as:

\[
\text{Cost of daily treatment with atenolol} \times \text{Number of prescriptions of atenolol} \times 365
\]

\[
\text{Total annual drug expenditure on antihypertensives}
\]

### Results

**Demographic profile of the study population:** A total of 300 prescriptions for essential hypertension were studied. Out of these, 173 (57.7%) patients were newly diagnosed hypertensives. Among the new cases, 45 patients had Stage I, 76 had Stage II and 47 had Stage III hypertension. Five patients had isolated systolic hypertension. The number of men (51%) and women (49%) were nearly equal. The mean age of both sexes was also nearly the same (53.4±12.7 years for men and 51.8±11.6 years for women). A total of 99 (33%) patients had one or more concurrent disease which could influence the choice of antihypertensives, including coronary artery disease (18.7%), diabetes mellitus (DM) (14.3%), bronchial asthma (2.7%), heart failure (2.7%) and gout (1 patient).

**Antihypertensives prescribed:** Thirty-five (11.7%) patients received no antihypertensive therapy. All of these had Stage I hypertension and 27 (9%) were newly diagnosed cases. Among the patients prescribed an antihypertensive, the majority (58.7%) received a single drug, while 29.7% patients were prescribed 2 or more drugs (counting a fixed-dose combination [FDC] with 2 or more ingredients as 2 or more drugs). The majority of the patients received single-ingredient preparations, with only 27 (9%) receiving an FDC.

Table 1 lists the drugs prescribed for hypertension in the study population. Beta-blockers were the most commonly prescribed drug group (46.7%, including FDCs), followed by CAs (34.3%) and ACEIs (30%). Diuretics were used in only 13.2% of the patients, mostly as part of FDCs. Atenolol (36%), amloidopine (29.3%) and enalapril (19%) were the most frequently used β-blocker, CCA and ACEI, respectively. Furosemide was the most commonly used diuretic. None of the patients received a thiazide diuretic as a single agent—thiazides were used only as part of FDCs. Of the 27 prescriptions which contained an FDC (Table 1), the majority (10) were a combination of amloidopine and atenolol or triamterene and benzthiazide(9). The remaining FDCs contained combinations of other diuretics, CCA, atenolol and lisinopril.

Various drug combinations were used (Table 2) for treating 89 (29.7%) patients. Most of these (26% of total patients) were on 2-drug combinations, while 3.3% of the patients received 3-drug combinations. Only 1 patient was prescribed 4 drugs. Thirty-five patients receiving ≥2 drugs had coronary artery disease and/or heart failure.

### Table 1. Drugs prescribed for essential hypertension in an internal medicine clinic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of prescriptions (n=300)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>140</td>
<td>46.7</td>
</tr>
<tr>
<td>Atenolol</td>
<td>108</td>
<td>36.0</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>21</td>
<td>7.0</td>
</tr>
<tr>
<td>Propranolol</td>
<td>7</td>
<td>2.3</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>Calcium-channel antagonists</td>
<td>103</td>
<td>34.3</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>88</td>
<td>29.3</td>
</tr>
<tr>
<td>Nifedipine SR</td>
<td>9</td>
<td>3.0</td>
</tr>
<tr>
<td>Diltiazem SR</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>90</td>
<td>30.0</td>
</tr>
<tr>
<td>Enalapril</td>
<td>57</td>
<td>19.0</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>15</td>
<td>5.0</td>
</tr>
<tr>
<td>Ramipril</td>
<td>14</td>
<td>4.7</td>
</tr>
<tr>
<td>Benazepril</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Diuretics and others</strong></td>
<td>48</td>
<td>16.0</td>
</tr>
<tr>
<td>Furosemide</td>
<td>16</td>
<td>5.3</td>
</tr>
<tr>
<td>Triamterene</td>
<td>10</td>
<td>3.3</td>
</tr>
<tr>
<td>Benazthiazide</td>
<td>9</td>
<td>3.0</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Amiloride</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Prazosin</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Losartan</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Fixed-dose combinations</strong></td>
<td>27</td>
<td>9.0</td>
</tr>
<tr>
<td>Triamterene+bazthiazide</td>
<td>9</td>
<td>3.0</td>
</tr>
<tr>
<td>Triamterene+furosemide</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Amiloride+hydrochlorothiazide</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Amlodipine+atenolol</td>
<td>10</td>
<td>3.3</td>
</tr>
<tr>
<td>Nifedipine+atenolol</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Chlorthalidone+atenolol</td>
<td>2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme; SR: sustained release
blocker with CCA (9.3%), β-blocker with ACEI (7.3%), and CCA with ACEI (4.3%) were the most frequently used drug combinations.

Drug treatment of newly diagnosed patients: Of the 173 (57.7%) newly diagnosed patients, 27 (15.6%) received no antihypertensive drug, 106 (61.3%) received a single drug while 40 (23.1%) received 2 drugs. Similar to the overall pattern, a β-blocker was the most commonly used drug in new cases (45.6%), followed by CCA (33.5%) and ACEI (26.6%), with only 9.2% patients being given a diuretic (Table 3). Of the 40 newly diagnosed cases receiving more than 1 antihypertensive drug, 22 had either coronary artery disease or heart failure, while 8 presented with Stage III hypertension. The drug combinations used (not shown in the table) were also similar to the overall pattern, i.e. β-blocker with ACEI (6.4%), β-blocker with CCA (5.8%) and CCA with ACEI (2.9%) were the commonly used combinations. Thirty-four patients were on 2 drugs, while 6 patients were on 3 drugs.

Drug treatment of patients with hypertension and diabetes mellitus: There were 43 patients with coexistent hypertension and Type 2 DM. Only 1 patient had diabetic nephropathy. Four patients were not on any antihypertensive drug, 21 were on a single agent and 18 patients were receiving 2 or more drugs. Angiotensin-converting enzyme inhibitors (62.8% of patients with Type 2 DM) and CCAs (39.5%) were the most commonly used drugs in this group of patients (Table 3). In 5 patients, ACEI along with CCA was used. A β-blocker was used in 10 patients—1 patient received atenolol alone while 9 patients received a β-blocker along with a CCA, ACEI or furosemide. All these patients received β1-receptor selective β-blockers, i.e. atenolol or metoprolol.

Drug treatment of patients with hypertension and bronchial asthma: There were only 8 cases with hypertension and asthma. Of these, 4 patients received a CCA, 2 received an ACEI and 1 patient each received a diuretic combination (triamterene+bendiazide) alone or with a CCA. No patient with bronchial asthma was prescribed a β-blocker.

Cost of antihypertensive drugs: Daily and annual drug acquisition costs of various antihypertensives are presented in Table 4. Propranolol and furosemide were the least expensive agents used, followed by amlodipine and atenolol. Benazepril, diltiazem, lisinopril, prazosin and losartan were the most expensive drugs, with the annual drug cost nearly (or exceeding) 20 times that of propranolol. A total of Rs 179,402 was spent in 1 year on drug acquisition for 300 patients of hypertension in the clinic.

### Table 2. Drugs combinations used in treatment of hypertension

<table>
<thead>
<tr>
<th>Drug combinations*</th>
<th>Number of prescriptions (n=300)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-drug combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker+CCA</td>
<td>28</td>
<td>9.3</td>
</tr>
<tr>
<td>β-blocker+ACEI</td>
<td>22</td>
<td>7.3</td>
</tr>
<tr>
<td>β-blocker+dihydrate</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>β-blocker+losartan</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>CCA+ACEI</td>
<td>13</td>
<td>4.3</td>
</tr>
<tr>
<td>CCA+dihydrate</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>CCA+losartan</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>CCA+prazosin</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>ACEI+dihydrate</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Losartan+dihydrate</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>K-sparing+loop/thiazide diuretic</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>3-drug combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker+dihydrate**</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>CCA+2 diuretics**</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>ACEI+2 diuretics**</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Diuretic+ACEI+β-blocker</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>CCA+ACEI+β-blocker</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>4-drug combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker+dihydrate**</td>
<td>1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*including fixed-dose combination; **K-sparing+loop/thiazide diuretics; CCA: calcium-channel antagonist; ACEI: angiotensin-converting enzyme inhibitor

### Table 3. Antihypertensives prescribed in newly diagnosed cases and patients with concomitant diabetes mellitus

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Number of prescriptions</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cases (n=173)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>79 (3 carvedilol)</td>
<td>45.6</td>
</tr>
<tr>
<td>Calcium-channel antagonist</td>
<td>58</td>
<td>33.5</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>46 (10 ramipril, 5 lisinopril, 2 benazepril)</td>
<td>26.6</td>
</tr>
<tr>
<td>Diuretic</td>
<td>16</td>
<td>9.2</td>
</tr>
<tr>
<td>Losartan</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine+atenolol</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Amlodipine+lisinopril</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Nifedipine+atenolol</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Amiloride+hydrochlorothiazide</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Furosemide+triamterene</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Patients with DM (n=43)</td>
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<td></td>
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<tr>
<td>Single drug</td>
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<td></td>
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<tr>
<td>ACE inhibitor</td>
<td>27</td>
<td>62.8</td>
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<tr>
<td>Calcium-channel antagonist</td>
<td>17</td>
<td>39.5</td>
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<tr>
<td>β-blocker</td>
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<td>23.2</td>
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<tr>
<td>Diuretic</td>
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<td>9.3</td>
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<tr>
<td>Losartan</td>
<td>3</td>
<td>7.0</td>
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<tr>
<td>Prazosin</td>
<td>1</td>
<td>2.3</td>
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<tr>
<td>Fixed-dose combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine+atenolol</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Amlodipine+lisinopril</td>
<td>1</td>
<td>2.3</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme
Discussion

In India, hypertension (blood pressure >140/90 mmHg) is present in 25%–30% of urban and 10%–15% of rural adults\(^1\) while Stage II and high levels of hypertension (>160/100 mmHg) are present in 12%–15% of urban and 5%–7% of rural adults. These figures increase with age and prevalence rates of up to 51.8% have been reported in an elderly Indian population.\(^1\) There is thus little doubt that hypertension is no longer a disease of the developed world alone. It is, therefore, important to lay stress on the optimal management of hypertension by making the best use of the drugs available to us.

In our study of 300 prescriptions for hypertension, we observed that a majority (58.7%) contained a single antihypertensive. Another 11.7% of the patients were managed without drug treatment. Of the remaining 29.7% who received combination therapy, 12.7% had concomitant heart failure or coronary artery disease, which could be additional indications for some of the drugs used for the treatment of hypertension. Thus, only a small percentage of patients were on combination therapy for the treatment of hypertension alone, as compared to 49.2% of patients receiving 2 or more drugs in a study reported by Lee et al.\(^1\) from Hong Kong.

The JNC VI\(^1\) report states that in the absence of compelling or specific indications for another drug, a diuretic or β-blocker should be chosen as initial therapy for hypertension. These recommendations are seconded by the British Hypertension Society.\(^1\) Despite these guidelines, diuretics were prescribed in only 13.2% of the prescriptions in our clinic, compared to 24% in Hong Kong\(^1\) and 26.5% in a study from Bangalore (South India).\(^1\) However, the use of β-blockers (46.7% of the prescriptions) was only slightly less than that reported from Hong Kong (51%) and much higher than that reported from Bangalore (19%).

Angiotensin-converting enzyme inhibitors and CCAs together made up 63.3% of the prescriptions. This percentage was higher than expected from the number of patients (33%) with concurrent diseases which are indications for either of these drug groups or contraindications for diuretics or β-blockers, i.e. Type 2 DM, heart failure, coronary artery disease, bronchial asthma and gout. This propensity to use ACEIs and CCAs is in keeping with the trend of increasing use of these drugs, accompanied by a decreasing utilization of β-blockers and diuretics, even in developed countries.\(^1,6\)

Some choices of individual drugs within the drug groups used need comment. Although thiazide diuretics are preferred over loop diuretics for hypertension, furosemide was more commonly used (in 40% of diuretic prescriptions). Of these, 4 patients had congestive heart failure which could explain the use of furosemide. Fewer patients (27.5% of diuretic prescriptions) received a thiazide diuretic, that too only as an FDC.

The use of some newer drugs such as carvedilol, ramipril, losartan and benazepril (in 40 patients of whom 20 were newly diagnosed) which are much more expensive than the prototypes (atenolol/enalapril) without significant clinical advantage over them,\(^1\) can probably be ascribed to aggressive marketing of these agents, often combined with the prescriber’s desire to keep up with the latest trends. Similarly, losartan, which should be used only if an ACEI is indicated but not tolerated,\(^9\) was used in 6 patients, 4 of whom were newly diagnosed.

Beta-blockers are by and large not recommended in DM,\(^9\) because of their possible adverse effects on glucose metabolism. In fact, a recent large cohort study has reported

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**Table 4. Drug acquisition (daily and annual) costs of different antihypertensives prescribed in the clinic**

<table>
<thead>
<tr>
<th>Drug/combination</th>
<th>Daily dose</th>
<th>Drug acquisition cost (Indian Rupees)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Per day</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50 mg o.d.</td>
<td>0.87</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50 mg b.d.</td>
<td>1.38</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg o.d.</td>
<td>0.22</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>12.5 mg o.d.</td>
<td>2.50</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5 mg o.d.</td>
<td>1.12</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 mg o.d.</td>
<td>3.60</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10 mg o.d.</td>
<td>4.55</td>
</tr>
<tr>
<td>Benazepril</td>
<td>10 mg o.d.</td>
<td>4.90</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5 mg o.d.</td>
<td>0.50</td>
</tr>
<tr>
<td>Nifedipine SR</td>
<td>20 mg b.d.</td>
<td>1.98</td>
</tr>
<tr>
<td>Diltiazem SR</td>
<td>90 mg b.d.</td>
<td>4.84</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg b.d.</td>
<td>0.28</td>
</tr>
<tr>
<td>Indapamide</td>
<td>1.25 mg o.d.</td>
<td>1.20</td>
</tr>
<tr>
<td>Losartan</td>
<td>50 mg o.d.</td>
<td>3.74</td>
</tr>
<tr>
<td>Prazosin</td>
<td>1 mg b.d.</td>
<td>3.88</td>
</tr>
<tr>
<td>Triamterene+benzthiazide</td>
<td>1 tab o.d.</td>
<td>2.05</td>
</tr>
<tr>
<td>Triamterene+furosemide</td>
<td>1 tab o.d.</td>
<td>1.85</td>
</tr>
<tr>
<td>Atenolol+amlodipine</td>
<td>1 tab o.d.</td>
<td>1.50</td>
</tr>
<tr>
<td>Atenolol+nifedipine SR</td>
<td>1 tab o.d.</td>
<td>1.97</td>
</tr>
<tr>
<td>Atenolol+hydrochlorothiazide</td>
<td>1 tab o.d.</td>
<td>1.21</td>
</tr>
<tr>
<td>Amlodipine+chlorthalidone</td>
<td>1 tab o.d.</td>
<td>1.90</td>
</tr>
<tr>
<td>Amlodipine+lisinopril</td>
<td>1 tab o.d.</td>
<td>3.28</td>
</tr>
</tbody>
</table>

Although β-blockers constituted 46.7% of the prescriptions, they were responsible for only 24.9% of the total annual drug expenditure. Similarly, CCAs made up 34.3% of the prescriptions but only 16% of the expenditure. However, ACEIs were advised in 30% of the prescriptions but were responsible for 39.2% of the annual drug expenditure. Drug expenditure due to diuretics was not calculated separately since these were used mostly in FDCs.
a 28% increase in the risk of DM in non-diabetic hypertensives treated with β-blockers. 19 On the other hand, β-blockers have shown long-term protective effects against cardiovascular disease in hypertensive patients, including those with DM. 20 In our study, β-selective blockers were prescribed in 10 (23.2%) patients with DM. We found that β-blockers, though used in 46.7% of the patients, accounted for only 24.9% of the annual drug expenditure because of their low cost. Their low cost, in addition to proven efficacy, cannot be ignored in a developing country like ours. Calcium-channel antagonists also showed this favorable picture (34.3% of prescriptions and 16% of drug expenditure). Angiotensin-converting enzyme inhibitors, on the other hand, accounted for 39.2% of drug expenditure but were prescribed for only 30% of the patients. Drug costs for diuretics could not be calculated separately since they were used mostly as FDCs, but furosemide was one of the least expensive single agents used.

Conclusions: In our study of drug prescribing patterns for hypertension in an internal medicine clinic, we found that most patients were being treated with single drugs. Although β-blockers were the most frequently prescribed antihypertensive agents, diuretics were prescribed sparingly. Calcium-channel antagonists and ACEIs were prescribed for a number of patients, many more than can be explained by the presence of concurrent diseases which are either indications for these drugs or contraindications for β-blockers or diuretics. Newer and more expensive drugs, e.g. benazepril, ramipril, carvedilol and losartan, were advised in a significant number of prescriptions, which added to the cost of drug treatment. Perhaps more serious consideration of available scientific evidence should go into writing a prescription for hypertension, especially in a developing country, to avoid unnecessary and expensive treatment.

Acknowledgments

The authors wish to thank Dr Arvinderpal Singh, Dr Rishi Kad, Dr Sanjeev Bhagat and Dr Spinder Gill for their invaluable help in collecting data for this study.

References

Serous Fluid Leakage Following Modified Blalock-Taussig Operation Using PTFE Grafts

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Background: Serous fluid leakage is an unusual but often devastating complication following the placement of a modified Blalock-Taussig shunt using a polytetrafluoroethylene graft.

Method and Results: Between September 1994 and September 1999, out of 268 patients undergoing a modified Blalock-Taussig shunt using polytetrafluoroethylene grafts, 10 developed massive pleural effusion or seroma due to a leak from the surface of the shunt. The age of the patients ranged from 9 days to 7 years. There were 7 males and 3 females. Nine patients presented with respiratory distress between 2 and 12 weeks of shunt surgery and one presented with sudden cardiac arrest. The shunt was patent in all the patients. Initial management was conservative, i.e. by pharmacological means and tube thoracostomy. Reoperation was undertaken in 9 patients when conservative treatment failed. All patients survived except one who had a cardiac arrest before any intervention could be carried out.

Conclusions: Patients with serous effusion have significant morbidity and mortality and often require reoperation. The initial management remains conservative but, if unsuccessful, re-exploration can be undertaken as it proved to be uniformly successful in our experience. (Indian Heart J 2001; 53: 328–331)

Key Words: Shunts, Congenital heart defects, Pleural effusion

Methods

Between September 1994 and September 1999, 10 patients who underwent a BT shunt were diagnosed to have massive pleural effusion. The patients included 7 males and 3 females with ages ranging from 9 days to 7 years and had a mean weight of 9.6 kg. During this period, 268 modified BT operations were performed using PTFE grafts for a variety of cyanotic congenital heart defects (Table 1). All PTFE grafts were Gore-Tex vascular grafts (WL Gore & Associates, Inc.) with an internal diameter of 4–6 mm.

Nine patients (#1–9, Table 1) presented with respiratory distress between 2 and 12 weeks of shunt surgery and chest X-ray showed signs of pleural effusion. A chest tube was inserted in all the patients to drain the pleural fluid which was found to be clear and acellular. Biochemical analysis of the fluid was consistent with serum, but the total protein and glucose contents were lower than the normal serum values. Cultures for pathogenic organisms were negative in repeated samples. A continuous murmur of the shunt flow could be heard and Doppler echocardiographic evaluation confirmed the patency of the shunt in all the patients. They were treated with digitalis and diuretics, but a decision for re-exploration was taken as there was continuous drainage through the chest tube.

All patients were managed with either orotracheal or nasotracheal general anesthesia, which was induced with intravenous ketamine 1.5–2 mg/kg and vecuronium.
0.1 mg/kg. An arterial line and a central venous cannula were inserted in the nonshunted side. Maintenance of anesthesia was achieved with O₃/N₂O and isoflurane 0.6%–1%. Incremental morphine was given as an analgesic. Induction of general anesthesia was well tolerated with minimal changes in blood pressure and heart rate. Dopamine (5–10 µg/kg/min) was administered for 1–2 days as and when needed to maintain adequate cardiac output. Each patient received broad spectrum antimicrobial drugs from pre-incision till the thoracic catheter was removed.

Re-exploration confirmed the diagnosis of a perigraft serous effusion. There were no lymphatic leaks or distended lymphatic vessels. The shunt was found to be patent in all the patients. The seroma was cleared away. It was dull grey, semi-translucent and oozed continuously. Out of 9 patients, topical thrombin was used in 3 patients and in 3 other patients topical fibrin glue was used.

One patient (#4, Table 1), who had received a 5 mm graft earlier, also showed features of congestive heart failure due to overshunting. The 5 mm graft was replaced with a 4 mm graft, though this had nothing to do with the management of the seroma. Two patients underwent open reparative surgery (#1 and 9, Table 1). Patient #1, who underwent a right-sided BT shunt for tricuspid atresia with pulmonary atresia, was readmitted with respiratory distress 2 weeks after he was discharged. Pharmacological management and tube thoracostomy failed to reduce the pleural effusion/seroma, hence, a decision for reoperation was made. A bidirectional Glenn along with PDA ligation and takedown of the BT shunt was performed. Another patient (#9), in whom a BT shunt was performed for tricuspid atresia with pulmonary atresia, was readmitted with respiratory distress 2 weeks after he was discharged. Considering the suitable morphology, total correction of tetralogy of Fallot was undertaken. In all these patients, recovery after reoperation was uneventful, and the patients were discharged after 10–14 days.

In addition to these 9 patients, one patient (#10, Table 1), who had undergone a BT shunt, developed sudden cardiac arrest on day 9 postoperatively. The cause was cardiac

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Sex</th>
<th>Congenital defect(s)</th>
<th>Operation (modified BT shunt)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>1 year</td>
<td>7</td>
<td>M</td>
<td>TA, PA, ASD, PDA</td>
<td>Right</td>
<td>Bidirectional Glenn</td>
</tr>
<tr>
<td>#2</td>
<td>5 years</td>
<td>14</td>
<td>F</td>
<td>TGV, PS, SV</td>
<td>Left</td>
<td>Topical thrombin</td>
</tr>
<tr>
<td>#3</td>
<td>3 years</td>
<td>10</td>
<td>F</td>
<td>SV, Common AV valve, PA, TAPVC</td>
<td>Left</td>
<td>Topical fibrin glue</td>
</tr>
<tr>
<td>#4</td>
<td>1 month</td>
<td>3</td>
<td>M</td>
<td>Large VSD, PA</td>
<td>Right</td>
<td>Re-do PTFE graft</td>
</tr>
<tr>
<td>#5</td>
<td>3 months</td>
<td>6</td>
<td>M</td>
<td>TA</td>
<td>Right</td>
<td>Topical thrombin</td>
</tr>
<tr>
<td>#6</td>
<td>5 years</td>
<td>14</td>
<td>M</td>
<td>TA</td>
<td>Right</td>
<td>Topical fibrin glue</td>
</tr>
<tr>
<td>#7</td>
<td>7 years</td>
<td>20</td>
<td>M</td>
<td>TA, PA</td>
<td>Right</td>
<td>Topical thrombin</td>
</tr>
<tr>
<td>#8</td>
<td>3 years</td>
<td>9</td>
<td>F</td>
<td>TOF, RAA</td>
<td>Left</td>
<td>Topical fibrin glue</td>
</tr>
<tr>
<td>#9</td>
<td>4 years</td>
<td>10</td>
<td>M</td>
<td>TOF</td>
<td>Right</td>
<td>Total correction</td>
</tr>
<tr>
<td>#10</td>
<td>9 days</td>
<td>3.5</td>
<td>M</td>
<td>VSD, PA, RAA</td>
<td>Right</td>
<td>—</td>
</tr>
</tbody>
</table>

TA: tricuspid atresia; PA: pulmonary atresia; ASD: atrial septal defect; PDA: patent ductus arteriosus; TGV: transposition of great vessels; PS: pulmonary stenosis; SV: single ventricle; TAPVC: total anomalous pulmonary venous connection; RAA: right aortic arch; TOF: tetralogy of Fallot; BT Shunt: Blalock-Taussig shunt

**Fig. 1.** Chest X-ray showing large serous pleural effusion on the right side
Discussion

In spite of a trend towards early corrective surgery for infants and small children with complex cyanotic congenital heart diseases, systemic-to-pulmonary artery shunts continue to be necessary for initial palliation. Excessive serous fluid leakage constitutes a rare complication following the insertion of a vascular prosthesis. LeBlanc et al. reported this complication after a modified PTFE BT shunt. The incidence of this complication in the setting of PTFE aortopulmonary shunt is unclear.

We performed 268 BT shunts using PTFE tubular grafts between September 1994 and September 1999. Ten patients (3.7%) required reoperation for persistent serous leakage. Maitland et al. and Noyez et al. had a reoperation rate of 2.3% and 2.5%, respectively. In a previous study by LeBlanc et al., serous fluid complications occurred in 20% of the patients. Leakage may occur as soon as the prosthesis has been implanted. In our series, presentation of serous leakage occurred between 2 and 12 weeks after the initial shunt procedure. According to another study, patients who underwent reoperation did so within 90 days of the initial operation. The mechanism of this leakage is unknown. Plasma leakage may occur due to wetting the graft with organic solvents such as antiseptics, excessive manipulation with blood, an initial high blood flow through the graft or forcing irrigating solutions through the wall. Despite avoiding these factors, we have encountered several patients in whom excessive leakage of serous fluid persisted for several days following graft insertion. It is difficult to evaluate the incidence of serous fluid leakage in the patient population under study. Persistent serous leak is usually managed adequately by thoracocentesis but in our experience it did not prove to be sufficient. However, when drainage does not diminish, reoperation is indicated.

All patients with a serous leak presented with marked respiratory distress. One patient (Table 1) had a cardiac arrest due to tamponade following a massive pleural effusion. Large pleural effusions clearly impair gas exchange and attenuate cardiac output. Recent findings suggest that effusions can impair right ventricular relaxation, effectively resulting in a state of "thoracic tamponade". However, the mechanisms of impairment of gas exchange are incompletely understood. One of the reports suggests that improvement in lung mechanics and oxygenation occur after aspiration of unilateral pleural effusion in humans. The current recommendation is that a large pleural effusion should be drained before induction of anesthesia because it can restrict lung expansion and drainage will enhance ventilation, whereas others suggest that drainage of pleural effusion should be done a day before the operation to avoid re-expansion pulmonary edema. However, this was not the problem with our patients as they had already undergone pleural drainage for a prolonged period.

Induction of general anesthesia was achieved with careful titration of intravenous agents. Volatile anesthetics are known to inhibit hypoxic pulmonary vasoconstriction (HPV), which in turn impairs oxygenation. Isoflurane was used during maintenance as, among all the volatile anesthetics, it causes the least inhibition of HPV. Chest X-rays were taken daily to ensure lung expansion and to check for any pneumothorax or residual effusion.

Postoperative serous ultrafiltration through the graft wall has been successfully treated by evacuating seroma from around the graft, replacing the graft with the same or another type of graft, replacing the graft material at the ultrafiltration site, drainage of perigraft fluid, using fibrin glue and topical thrombin to "preclot" the graft in situ and, finally, monitoring the patient closely over a period of time. We also had good results with combinations of these techniques.

Conclusions: We conclude that serous fluid leakage is an unusual but often devastating complication of a modified BT shunt using a PTFE graft. Patients with serous effusion have significant morbidity and mortality and often require reoperation. As these patients present late after being discharged, they should undergo frequent chest X-rays so that the effusion can be diagnosed at the earliest. The initial management remains conservative but, if this is not successful, one should not hesitate to carry out re-exploration, as it proved to be uniformly successful in our experience.

References

Lipid Abnormalities in Coronary Heart Disease: A Population-based Case-Control Study

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Background: We performed a case-control study to estimate lipid-cholesterol fractions in patients with coronary heart disease and compared them with population-based controls.

Methods and Results: A total of 635 newly diagnosed patients with coronary heart disease (518 males and 117 females) and 632 subjects (346 males and 286 females) obtained from an ongoing urban coronary heart disease risk factor epidemiological study were evaluated. Age-specific lipid values (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, and total:high-density lipoprotein cholesterol ratio) were compared using the t-test. Age-adjusted prevalence of dyslipidemia as defined by the US National Cholesterol Education Program was compared using the Chi-square test. In all the age groups, and in both males and females, levels of total and low-density lipoprotein cholesterol were not significantly different. In males, the high-density lipoprotein cholesterol (mg/dl) was significantly lower in patients with coronary heart disease as compared to controls in the age groups 30–39 years (35.1±11 v. 43.7±9), 40–49 years (39.0±10 v. 47.1±8), 50–59 years (38.9±11 v. 43.8±9) and 60–69 years (38.6±11, v. 42.8±7) (p<0.05). In females, high-density lipoprotein cholesterol was less in the age groups 30–39 years (30.2±9 v. 40.7±9), 50–59 years (39.7±12 v. 44.7±8) and 60–69 years (35.6±11 v. 42.2±9). The level of triglycerides was significantly higher in male patients in the age groups 40–49 years (195.3±6 v. 152.8±7), 50–59 years (176.7±6 v. 162.9±8), 60–69 years (175.5±9 v. 148.1±6) and >70 years (159.8±62 v. 100.0±22); and in female patients in the age group 30–39 years (170.8±20 v. 149.9±9) (p<0.05). The total:high-density lipoprotein cholesterol ratio was significantly higher in all age groups in male as well as female patients with coronary heart disease (p<0.05).

Conclusions: An age-adjusted case-control comparison showed that the prevalence of hypertension, diabetes, high total cholesterol (>200 mg/dl) (males 48.8% v. 20.2%; females 59.8% v. 33.4%) and high low-density lipoprotein cholesterol (>130 mg/dl) (males 42.1% v. 15.0%; females 52.1% v. 31.0%) was significantly more in cases than in controls. The prevalence of low high-density lipoprotein cholesterol (<35 mg/dl) (males 39.6% v. 6.2%; females 39.3% v. 9.5%), high total:high-density lipoprotein ratio (>5.0) and high triglycerides (>200 mg/dl; males 39.6% v. 10.2%; females 17.1% v. 11.9%) was also significantly higher in cases (p<0.05). (Indian Heart J 2001; 53: 332-336)

Key Words: Lipids, Coronary disease, Population
levels of HDL-cholesterol have also been reported.\textsuperscript{1,9,11,13} Epidemiological studies within India have shown that in urban subjects, who show a three-fold greater prevalence of CHD compared to rural subjects, levels of total- and LDL-cholesterol and triglycerides are higher while there is no significant difference in HDL-cholesterol levels.\textsuperscript{14,15} Most of the CHD case–control studies within India have been performed in tertiary-care hospitals and used hospital-based controls. These subjects are neither appropriate cases nor controls, as has been commented upon previously.\textsuperscript{16} To remove this possible bias, we performed a case–control comparison of lipid levels using cases presenting to a charitable hospital and population-based controls obtained from an ongoing epidemiological study.

**Methods**

Successive patients presenting to this charitable hospital between 1997 and 1999 were enrolled in the study. These patients were all newly diagnosed as having CHD according to the criteria reported previously\textsuperscript{17} and were either survivors of a recent myocardial infarction (>28 days old) or had classical angina pectoris confirmed either by a positive stress test or coronary angiogram. Of the 750 patients seen during this period, 635 (84.7%) patients with CHD (518 males and 117 females) were found to be eligible. History of risk factors such as smoking, hypertension and diabetes was obtained and fasting blood glucose and lipid levels were determined. The methodology of determination and standardization of lipid levels has been described in earlier studies.\textsuperscript{18}

Controls were obtained from an ongoing population-based epidemiological study in Jaipur. The recruitment strategy was similar to that reported in a previous study.\textsuperscript{19} In brief, individuals from randomly selected locations (municipal wards) in the city were recruited using the stratified random sampling technique. Population proportionate adults ≥20 years of age according to the voters' lists were examined by a house-to-house survey in these locations. In each location, 500 subjects were contacted for examination. Subjects in two of the six locations that have been covered so far have been included in the present study. History of coronary risk factors was obtained and a physical examination and fasting blood analysis for lipids and glucose was performed. Serum lipid levels in 632 of the 1000 eligible subjects (345 males and 286 females) were available (response rate 63.2%).

**Statistical analysis:** Numerical variables are reported as mean ±1SD. Case-control comparison was performed using the Chi-square test for categorical variables and unpaired t-test for continuous variables. Comparison in lipid levels at various age groups was done using the t-test. Age distribution was significant in both the patient and control populations, hence an age-adjusted comparison was performed after matching controls with cases using the indirect method of age-standardization as described by Rao and Richards.\textsuperscript{20} A p value of <0.05 was considered significant.

**Results**

We studied 635 cases (518 males and 117 females) and 632 controls (346 males and 286 females) within an age range of 20–75 years. Age-group distribution and cholesterol, lipoprotein and triglyceride values are shown in Table 1. In all the age groups, and in both males and females, the levels of total- and LDL-cholesterol were not significantly different, although there was a trend towards higher LDL-cholesterol in cases.

In males, the level of HDL-cholesterol (mg/dl) was significantly lower in patients with CHD compared to controls in the age groups 30–39 years (35.1±11 v. 43.7±9), 40–49 years (39.0±10 v. 47.1±8), 50–59 years (38.9±11 v. 43.8±9) and 60–69 years (38.6±11 v. 42.8±7), (p<0.05). In females, HDL-cholesterol was less in the age groups 30–39 years (30.2±9 v. 40.7±9), 50–59 years (39.7±12 v. 44.7±8) and 60–69 years (35.6±11 v. 42.2±9). The level of triglycerides was significantly higher in male patients in the age groups 40–49 years (195.3±96 v. 152.8±78), 50–59 years (176.7±76 v. 162.9±97), 60–69 years (175.5±93 v. 148.1±65) and >70 years (159.8±62 v. 100.0±22); and in female patients at 30–39 years (170.8±20 v. 149.9±9) (p<0.05). Total: HDL-cholesterol ratio was significantly higher in all age groups in male as well as female patients with CHD (p<0.05).

Age-adjusted case–control comparison of risk factors (Table 2) showed that prevalence of smoking (current or previous tobacco use) was similar in cases as compared with controls in both males (24.3% v. 21.2%) and females (2.6% v. 10.6%). The prevalence of hypertension either in known hypertensives on drug therapy or patients with a current blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic on repeated measurements, as well as prevalence of diabetes, were significantly higher in cases than in controls.

In cases as compared to controls, the prevalence of high total cholesterol (≥200 mg/dl) (males 48.8% v. 20.2%; females 59.8% v. 33.4%), high LDL-cholesterol (≥130 mg/ dl) (males 42.1% v. 15.0%; females 52.1% v. 31.0%), and
low HDL-cholesterol (<35 mg/dl) (males 39.6% v. 6.2%; females 39.3% v. 9.5%) was significantly higher (p<0.01). High total:HDL-cholesterol ratio (>5.0) was significantly higher in both males (56.9% v. 10.4%) and females (51.3% v. 16.7%) (p>0.01). The prevalence of borderline-high triglycerides (150–199 mg/dl: males 53.9% v. 9.1%; females 37.6% v. 8.8%) as well as high triglycerides (≥200 mg/dl: males 39.6% v. 10.2%; females 17.1% v. 11.9%) was also significantly higher in cases (p<0.05) as compared to controls.

**Discussion**

This case-control study shows that low HDL-cholesterol, high total:HDL-cholesterol and high triglyceride levels, apart from high total- and LDL-cholesterol, are important lipid abnormalities in Indian patients with CHD. These lipid abnormalities are similar to those reported in emigrant Indians in Britain and the USA. 

Case-control studies within India have reported high total- and LDL-cholesterol and triglyceride levels in patients suffering from CHD, while low HDL-cholesterol was reported in only a few studies. Kumar et al. from Chandigarh, Misra et al. from Madras, Wasir et al., Vashist et al. and Bahl et al. from Delhi, Sahi et al. from Bombay and Krishnaswamy from Vellore reported that total cholesterol levels were 20–40% more in patients with CHD compared to hospital-based controls (p<0.05). Vashist et al. from Delhi studied 702 clinically documented CHD cases and 186 normal healthy controls and reported that...
Gupta et al. Lipid Abnormalities in Coronary Heart Disease

controls. Prevalence of hypertension and diabetes was significantly higher in both male and female cases. Unlike some recent Indian and international studies, we found that lipid profile abnormalities in Indian patients with CHD are similar to many other ethnic groups characterized by mixed dyslipidemia (increased levels of LDL and triglycerides and low HDL). A high prevalence of diabetes in cases with CHD explains the diabetic dyslipidemia characterized by low HDL and high triglycerides. Diabetes is a major risk factor in emigrant Indians with CHD and this study highlights its importance. One drawback of the present study is that we did not measure small-dense LDL which is an important lipid abnormality in Asian Indians settled in the USA.

Studies have reported increasing total- and LDL-cholesterol and triglyceride levels in Indian urban subjects, associated with increasing prevalence of CHD. Dietary and lifestyle-related coronary risk factors could thus be important in accelerating the CHD epidemic in India but more studies are needed. The importance of LDL-cholesterol, total-HDL-cholesterol ratio, triglycerides, HDL-cholesterol and small-dense LDL particles should be confirmed by well-designed Indian prospective studies.

### Table 2. Age-adjusted coronary risk factor prevalence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases (n=518)</th>
<th>Controls (n=346)</th>
<th>Cases (n=117)</th>
<th>Controls (n=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (current/previous)</td>
<td>126 (24.3)</td>
<td>73 (21.2)</td>
<td>3 (2.6)</td>
<td>10 (10.6)</td>
</tr>
<tr>
<td>Hypertension (BP ≥140/90 mmHg)</td>
<td>176 (34.0)*</td>
<td>43 (12.4)</td>
<td>35 (29.9)*</td>
<td>41 (14.3)</td>
</tr>
<tr>
<td>Diabetes (fasting glucose &gt;126 mg/dl)</td>
<td>104 (20.1)</td>
<td>11 (3.1)</td>
<td>29 (24.8)*</td>
<td>14 (4.8)</td>
</tr>
<tr>
<td>Cholesterol (≥200 mg/dl)</td>
<td>235 (48.8)*</td>
<td>70 (20.2)</td>
<td>70 (59.8)*</td>
<td>95 (33.4)</td>
</tr>
<tr>
<td>LDL-cholesterol (&lt;35 mg/dl)</td>
<td>166 (32.0)*</td>
<td>52 (15.0)</td>
<td>30 (25.6)*</td>
<td>36 (12.7)</td>
</tr>
<tr>
<td>Total-HDL ≥5.0</td>
<td>218 (42.1)*</td>
<td>52 (15.0)</td>
<td>61 (52.1)*</td>
<td>89 (31.0)</td>
</tr>
<tr>
<td>Triglycerides (150–199 mg/dl)</td>
<td>205 (39.6)*</td>
<td>21 (6.2)</td>
<td>46 (39.3)*</td>
<td>27 (9.5)</td>
</tr>
<tr>
<td>(≥200 mg/dl)</td>
<td>295 (56.9)*</td>
<td>36 (10.4)</td>
<td>60 (51.3)*</td>
<td>48 (16.7)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages

* Significant difference p<0.05

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Transcatheter Fenestration of a Total Cavopulmonary Connection Baffle

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Surgical management of patients with cardiac malformations characterized by a functionally single ventricle is based upon the concept that systemic venous blood can be made to pass through healthy mature lungs without the assistance of a ventricular pump.1 The staging of univentricular repair has been associated with a significant reduction in perioperative mortality and morbidity.2 Introducing a right-to-left shunt at the atrial level by the creation of a fenestration3 or adjustable atrial septal defect (ASD)4 preserves cardiac output and oxygen delivery despite some degree of systemic arterial desaturation. We report a case of postoperative recurrent pleural effusion after total cavopulmonary connection (TCPC), in which transcatheter TCPC baffle fenestration was carried out to reduce venous congestion.

Case Report

A cardiac murmur was detected at birth in a 4-year-old boy weighing 12 kg. He had cyanosis since the age of two years (no cyanotic spells) with recurrent lower respiratory tract infection not requiring hospitalization. A color Doppler study done at that time showed transposition of the great arteries with a large, nonrestrictive, sub-pulmonic ventricular septal defect (VSD) and severe valvar pulmonary stenosis (PS) (peak systolic gradient [PSG] 87 mmHg). Cardiac catheterization performed prior to intracardiac repair revealed equalization of the systolic pressures in the left ventricle (LV) and right ventricle (RV) (110 mmHg). The RV and LV end-diastolic pressures (EDP) were 8 mmHg and 6 mmHg, respectively, and the pulmonary venous wedge pressure was 32/17 mmHg with a mean of 24 mmHg (the pulmonary artery could not be entered). There was no pressure gradient between the left and right atria. Angiography confirmed the findings of the color Doppler study. In addition, the pulmonary arteries were confluent and not distorted. The sizes of the right and left pulmonary arteries were 9 mm and 8 mm, respectively. Basal saturation of the ascending aorta was 79% at the time of catheterization.

Though the patient was suitable for a biventricular repair, our surgeons decided to perform TCPC with a pericardial baffle due to the inherent problems of conduits in this age group (i.e. nonavailability of conduit, need for replacement at a later date and complexity of surgery). A lateral tunnel, which was not fenestrated, was created with a pericardial patch. The ASD was left untouched during the procedure. The surgery was uneventful and the child recovered from bypass after TCPC. The immediate post-bypass central venous pressure was 12 cm of water. The child had repeatedly accumulating, large (500 ml per day) bilateral pleural effusion which was treated by chest tube drainage. The large amount of the effusion resulted in hypoproteinemia (total protein 3.6 g%, albumin 1.6 g%) with progressive edema of the feet, despite vigorous diuretic therapy. In view of a high lymphocyte count and protein content in the pleural fluid, the child was put on antitubercular therapy (ATT). However, despite ATT, the pleural effusion persisted.

On examination, the patient had a heart rate of 110 beats/min, BP of 100/70 mmHg, grade 3/4 clubbing, mildly dusky appearance and generalized edema, with an ejection systolic murmur (Grade II/VI) at the left parasternal border and bilateral pleural effusion. The hemoglobin was 13.7 g%.
with an oxygen saturation of 95%. Chest X-ray showed a cardiothoracic ratio of 55% with pulmonary venous congestion and moderate bilateral pleural effusion. A transthoracic echocardiogram showed a dilated and congested inferior vena cava (IVC) suggestive of high venous pressure; there was no obstruction between the baffle and the pulmonary artery. A provisional diagnosis of postoperative high intra-atrial baffle pressure with systemic venous congestion was made, which was refractory to medical (diuretic) therapy.

Three weeks postoperatively, cardiac catheterization was performed to assess the hemodynamics of the pulmonary artery and pericardial baffle. A raised pericardial baffle and IVC pressure (mean pressure 24 mmHg) but normal pulmonary artery pressure (mean pressure 22 mmHg) were recorded. There was no pull-back gradient from the pulmonary artery to the pericardial baffle. The left ventricular EDP was 8 mmHg at the time of catheterization. Pericardial baffle angiography (Fig. 1) through the IVC showed opacification of the baffle and pulmonary arteries with no narrowing or obstruction.

In view of raised intra-baffle pressure, fenestration of the pericardial baffle was planned. The baffle was punctured with a Brockenbrough trans-septal needle which was passed into the left atrium. A double length 0.021 guidewire was exchanged over a Mullin’s dilator and kept in the left superior pulmonary vein. Serial dilatation of the pericardial baffle (up to 15 mm) was done using a Tyshak II balloon over the guidewire (Fig. 2). After balloon dilatation, there was a significant reduction in the elevated intrapericardial baffle and IVC pressure (mean pressure 10 mmHg); there was no gradient between the left atrium and pericardial baffle and the saturation fell to 87% after fenestration. A widely patent fenestration in the baffle was demonstrated on check angiography at the end of the procedure (Fig. 3).

Clinically, edema and pleural effusion started subsiding rapidly. The quantity of pleural fluid drained was 300 ml after 24 hours and 150 ml on days 2 and 3. The drain was removed after 5 days. The child was discharged on ATT and diuretics. The ESR was 80 mm in the first hour. As per our chest physician’s advice, ATT was continued.

At one-year follow-up, the child was totally asymptomatic with no evidence of pleural effusion or a congestive state. The basal saturation was 89%; color Doppler studies showed a normally functioning shunt between the superior vena cava (SVC) and baffle to the pulmonary artery. The pericardial baffle fenestration (7 mm, nonrestrictive) was patent with right-to-left shunt (Fig. 4). A diagnostic catheterization has been planned at a later date.

**Discussion**

Fenestration of the pericardial baffle increases the number of candidates suitable for the Fontan procedure, although the exact inclusion criteria for these patients are not well defined. Despite the reduction in early mortality, significant postoperative morbidity in the form of effusions (pleural and pericardial effusions and ascites) continues to be common in patients undergoing definitive surgical management of cardiac malformations with one effective
ventricle. The benefit of fenestration is likely to be greatest in the early postoperative period when the patient may experience increased pulmonary vascular resistance and decreased ventricular function due to the effects of a cardiopulmonary bypass, aortic cross-clamping and positive pressure ventilation.

However, with an extracardiac conduit, fenestration need not be performed initially. The requirement for fenestration should be assessed after cardiopulmonary bypass when the hemodynamic status can be evaluated accurately. If required, the fenestration can be made and revised easily at this stage without a bypass.

In our patient, the baffle was intracardiac and in view of the high-risk repeat surgery on a cardiopulmonary bypass, we decided to create a transcatheter fenestration of the TCPC baffle. The pericardial lateral tunnel baffle was dilated with serial balloon inflations of up to 15 mm, after puncturing the baffle with a Brockenbrough trans-septal needle. Perforation of the baffle wall was very difficult in view of the fact that the anatomy was distorted and there was no anatomical landmark. Hence, it was performed using contrast injections frequently to delineate the baffle anatomy. Post-procedure effusion reduced significantly and the pleural drain was removed. The child improved and is asymptomatic after 1-year follow-up. There was a weight gain of 4 kg over 1 year. At the time of follow-up, arterial oxygen saturation was 92%. Few de novo transcatheter fenestration of baffle have been reported in the literature. This case of transcatheter fenestration of TCPC baffle is probably the first of its kind in India.

References

Brief Report

**Spontaneous Resolution of Intramyocardial Hematoma of the Left Ventricle**

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Intramyocardial hematoma of the left ventricle (LV) is a rare entity, usually described after acute myocardial infarction and is considered to be an incomplete form of cardiac rupture.\(^1\)\(^,\)\(^2\) It has occasionally been described secondary to chest trauma.\(^3\) Diagnosis is made by two-dimensional echocardiography in cases where it is suspected during life. We describe a case of intramyocardial hematoma, occurring in a patient without any obvious evidence of acute myocardial infarction or trauma, which resolved spontaneously.

**Case Report**

A 40-year-old male presented to the emergency room with sudden onset of dyspnea at rest, which had begun 24 hours earlier. There was no history of chest pain or trauma to the chest wall. There was no suggestion of any viral illness in the preceding fortnight. The patient was a chronic smoker. He had no other known risk factors for coronary disease. On examination, the patient was dyspneic and tachypneic. The heart rate was 120/min, the extremities were cold and clammy, and blood pressure was not recordable. The neck veins were full but the jugular venous pressure could not be ascertained. On auscultation, there was a left ventricular third heart sound and bilateral crepitations over the lung fields, extending into the upper third. He was intubated and ventilated mechanically and an infusion of dopamine was started. The electrocardiogram (ECG) revealed normal sinus rhythm, left axis deviation and right bundle branch block with 2 mm ST segment elevation in leads I, aVL and V\(_2\)–V\(_6\). There were Q waves from leads V\(_2\) to V\(_6\). A diagnosis of acute extensive anterior myocardial infarction was made, and the patient was admitted to the coronary care unit. A bedside echocardiogram revealed a dilated LV showing akinesia of the middle and apical part of the septum and anterior wall with an ejection fraction of 25%. The basal segments of the LV showed good contractility. In addition, there was a 2×2 cm cyst-like structure within the myocardium at the LV apex and adjoining anterolateral wall (Fig. 1). No Doppler signals could be obtained in this cyst-like space and no communication with the main cavity of the LV could be demonstrated. The creatine kinase (CK) was elevated to 213 IU/ml and its MB isoform was 49 IU/ml (the normal value in our laboratory is <6% of the total CK). A diagnosis of intramyocardial hematoma, probably secondary to an acute myocardial infarction, was made. The patient improved with supportive therapy and could be weaned off the ventilator and inotropic support after two days. However, the initial ST segment elevation persisted and there was no evolution of the changes on serial ECGs. The serum levels of lactic dehydrogenase (LDH) and aspartate aminotransferase (AST) were normal. Also, a technetium pyrophosphate scan, done three days after admission, was negative for acute infarction, and there was no diffuse uptake to suggest myocarditis. As the nature of the intramyocardial lesion was not clear, further investigations were performed. A contrast-
enhanced computerized tomography (CT) scan demonstrated a hypodense filling defect at the apex and adjoining anterolateral wall of the LV (Fig. 2a). Magnetic resonance imaging (MRI) of the chest was also done to further define this cyst-like space (Figs 3a, b and c). The space was hyperintense on T1-weighted images and remained hyperintense after fat suppression. Gradient echo T2-weighted sequences showed hyperintensity in this region, suggesting clotted blood. Coronary angiography did not show any evidence of atherosclerotic disease. The LV angiogram showed a dilated, poorly contracting LV with an akinetic and partially dyskinetic anterolateral wall and apex. Only the basal segments showed good contractility. The global LV ejection fraction was 20%.

The patient was managed with standard oral decongestive therapy. Oral carvedilol was initiated before discharge. Repeat echocardiography performed two weeks later showed a decrease in the size of the hematoma. By 4 weeks, the hematoma had resolved completely and could not be detected by echocardiography or CT scan (Fig. 2b).

Discussion

Most of the cases of intramyocardial hematoma reported in the literature have occurred secondary to acute myocardial infarction. The cause of intramyocardial hematoma in our patient is not entirely clear. The strongest evidence for acute myocardial infarction is provided by the characteristic wall motion abnormality of a left anterior territory infarction considered in the light of the temporal course of the illness. But the cardiac enzyme levels do not suggest a large infarction. The diagnosis of acute myocardial infarction is, therefore, difficult to substantiate, especially as the coronary arteries were normal at angiography.

Cases of spontaneous intramyocardial hematomas have been reported in the literature. One such case involving the interatrial septum communicated with the noncoronary sinus producing complete heart block. The diagnosis was made at autopsy in this case. Another case presented as a large intramural hematoma in the right ventricle.

A series of 15 cases of intramyocardial dissecting hematomas, compiled from the literature, was published by Pliam et al. in 1993. Eight of these hematomas were diagnosed postmortem (all cases published before 1977). Of the remaining 7, the diagnosis was made by two-dimensional echocardiography in 4 cases, ventriculography in 1 case and at the time of surgery in the other 2 cases. Two-dimensional echocardiography is an excellent bedside tool...
modality for the diagnosis of intramyocardial hematoma and is better than the LV angiogram, particularly if the hematoma does not communicate with the LV cavity, as was seen in our case. In addition to echocardiography, which suggested the diagnosis in our case, we used CT scan and MRI to further characterize the lesion. We were able to determine the nature of the contents of the intramyocardial lesion using a standard MRI algorithm. The size and extent of the lesion was delineated accurately by CT scan. These investigations can, therefore, be of help in difficult cases.

In the series by Pliam et al., 5 of the 7 cases with a diagnosis of hematoma during life required surgery for the evacuation of the hematoma and coronary artery bypass grafting (CABG). One patient, who was managed medically, expired and another showed spontaneous resolution. The case reported by Kanemoto et al. showed spontaneous disappearance after six months of a hematoma in the ventricular septum in a patient with acute inferior myocardial infarction. We did not contemplate surgery because of the rapid improvement in the patient’s condition and the absence of significant coronary artery disease. We observed spontaneous resolution of the hematoma over a period of 4 weeks.

References
Intravascular Ultrasound-guided Angioplasty and Stenting in a Case of Transplant Coronary Artery Disease

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Atherosclerosis of the coronary arteries is the leading cause of death after the first year following cardiac transplantation. In our center, we have performed 8 cardiac transplants since the inception of the transplant program in 1995. The prevalence of transplant coronary artheriopathy is approximately 30%-50% at 5 years post-transplantation. Allograft vasculopathy in cardiac transplant recipients has been described previously. Angiographic evidence of transplant coronary artery disease (CAD) is evident in at least 50% of patients at 5 years following cardiac transplant and up to 92% have intimal thickening on intravascular ultrasound (IVUS) at the end of 4 years. Intravascular ultrasound can provide excellent quantitative information on the plaque cross-sectional area, which is not available by angiographic imaging. Keogh et al. reported decreased survival in untreated patients with significant lesions in the proximal and mid-portions of the epicardial vessels. Retransplantation and coronary artery bypass grafting have been used, with disappointing results, in an attempt to reduce ischemia-related morbidity and mortality in this patient population. Hence, percutaneous revascularization procedures, when indicated, are a rational way of dealing with post-transplant CAD under IVUS guidance. Coronary artery stenting has an advantage over balloon angioplasty due to its lower restenosis rates and ability to resolve lesion disruption. Intravascular ultrasound is a useful tool in assessing the intrastent dimension along the segment of artery where a stent has been used. We report the case of a patient who developed post-transplant CAD and required a balloon angioplasty with stent implantation in the right coronary artery. Pre-procedure IVUS was used to study the coronary arteries which helped in optimal stent deployment.

Case Report
A 49-year-old female, who underwent an orthotopic cardiac transplant six years earlier for dilated cardiomyopathy, presented to us with functional Class II dyspnea. She was optimally immunosuppressed with azathioprine, cyclosporine and prednisolone. The age of the donor at the time of surgery was 18 years. Echocardiography showed moderate left ventricular dysfunction. Ischemic coronary artery disease and multiple episodes of acute tissue rejection, previously treated with methylprednisolone and OKT3, were the factors that contributed to left ventricular dysfunction in this patient. A trans-jugular myocardial biopsy showed changes of ischemic vacuolation. Angiographically, the left main (LM), left anterior descending (LAD) and the circumflex (CX) arteries were free of disease. An IVUS pull-back through the LAD showed the LAD and LM to have intimal hyperplasia with calcification but no flow-limiting disease (Fig. 1). There was a discrete 90% lesion in the dominant proximal right coronary artery (RCA) which was confirmed on IVUS (Fig. 3).

In view of the discrete significant stenosis, the patient was subjected to coronary angioplasty. The RCA was engaged with a 7 F Judkin right guiding catheter and the stenosis in the proximal RCA crossed with a 0.14 ACS Hi-torque floppy wire. Direct stenting with a 3.5×12 mm Medtronic AVE S 670 stent at 11 atm was done. The minimum luminal diameter (MLD) and luminal area were 3 mm and 8.1 mm², respectively, after direct stenting.

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Key Words: Stents, Transplantation, Coronary disease
view of the residual plaque burden seen on the IVUS study, intrastent dilatation was done with a 3.5×10 mm balloon at 16 atm. The final IVUS study showed an MLD of 3.2 mm and a stent luminal area of 9.9 mm². The post-PTCA stent implantation angiogram (Fig. 4) showed a well deployed stent in the proximal RCA with no residual stenosis and a TIMI-3 antegrade flow. The post-PTCA IVUS image (Fig. 5) also showed a well deployed stent in the proximal RCA. The patient had an uncomplicated postoperative course and was discharged 2 days after the procedure. She is to undergo a stress thallium test at 6 months and an elective coronary angiography at 1 year post-procedure.

Fig. 1. IVUS image of the LAD artery reveals mild intimal plaque with calcification.

Fig. 2. Pre-PTCA right coronary angiogram which shows 90% stenosis in the proximal RCA.

Fig. 3. Pre-PTCA IVUS imaging which shows fibrous atheroma in the proximal RCA.

Fig. 4. Post-PTCA stent implantation image which shows a well deployed stent in the proximal RCA.

Fig. 5. Post-PTCA IVUS image which shows a well deployed stent in the proximal RCA.
Discussion

The development of CAD has been associated with reduced survival as compared to heart transplant recipients without the disease. The incidence, as seen on coronary angiography, is 18% at 1 year and up to 50% at 5 years following transplantation. Intravascular ultrasound studies have shown that the incidence of post-transplant CAD may be as high as 80% at 1 year, 79% in the second and third years and 92% in the fourth year. Most of the patients present with congestive heart failure, acute myocardial infarction and sudden death but with no pain as the transplanted heart is denervated. It was previously assumed that post-transplant CAD is more diffuse, concentric and distal in nature, but IVUS studies have confirmed the presence of proximal focal and noncircumferential plaques in addition to the diffuse distal disease. Proximal segments of the large coronary arteries are most frequently involved, containing focal, noncircumferential obstructions that resemble nontransplant coronary atherosclerosis. Diffuse concentric narrowing is more common in the middle and distal segments of the epicardial vessels. Though balloon angioplasty and stenting have been reported to be successful in selected patients with transplant CAD, restenosis remains a major problem. Christensen et al. have shown that the loss in percent area stenosis at late follow-up correlated significantly with percent area stenosis immediately after angioplasty and with gain in percent area stenosis during the procedure. Optimizing the results of angioplasty and stenting will go a long way in reducing restenosis and IVUS can be used as a tool for achieving this. However, there are some technical limitations to the use of IVUS in transplant CAD. Its safety in vessels of diameter less than 2 mm is debatable. In addition, acute angulation of the origin of the vessel and proximal tortuosity may create difficulties in tracking the IVUS catheter.

Information derived from angiography is often limited to providing an accurate assessment with regard to vessel size, plaque calcification or stent deployment. Use of vascular dimensions with the help of IVUS may assist in the optimal choice of balloon size. Intravascular ultrasound imaging after stent insertion is useful in documenting satisfactory stent expansion. It is an important and novel method for the establishment of proper stent placement, and guidance with IVUS imaging may be superior to angiography. Intravascular ultrasound guidance can reduce the rate of subacute thrombosis and restenosis after intracoronary stent implantation.

The current report of endovascular stent placement under IVUS guidance in this post cardiac transplantation patient suggests the feasibility of coronary artery stenting in patients who have undergone cardiac transplantation. Hence, we conclude that IVUS is a valuable tool in defining transplant CAD and in assessing the results of angioplasty and stent implantation. In view of its potential uses, imaging with IVUS should be routinely recommended in transplant recipient patients who require coronary angioplasty, coronary artery stenting or both for allograft atherosclerosis.

References

Ross Procedure in an Infant

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The Ross procedure, first described in 1967, involves replacement of a diseased aortic valve with a pulmonary autograft and placement of a pulmonary or aortic homograft between the right ventricle and pulmonary artery. After the Ross procedure, there is no need for anticoagulation, and the autograft has proved to be durable and to grow in proportion to somatic growth.1 Although aortic valve homografts have excellent postoperative hemodynamics, do not require anticoagulation and are associated with a low risk of thromboembolism, these homografts have limited durability and do not grow.2 Thus a pulmonary autograft is the most attractive alternative to mechanical, porcine and homograft valves in the treatment of aortic valve disease in children. We report a 4-month-old patient with congenital aortic stenosis who had an excellent outcome following treatment with the Ross procedure. To the best of our knowledge, this is the youngest patient to have undergone a successful Ross procedure in the Indian subcontinent. (Indian Heart J 2001; 53: 346–347)

Key Words: Valves, Aortic stenosis, Congenital heart defects

Case Report

A 4-month-old male child was admitted with a history of progressive respiratory distress. He was diagnosed to have a heart ailment at birth and had a history of repeated hospitalization for respiratory distress. He weighed 3.2 kg and had a grade 4/6 systolic murmur at the base. The electrocardiogram revealed normal sinus rhythm with biventricular hypertrophy. Chest X-ray revealed cardiomegaly with a cardiothoracic ratio of 0.7. A bicuspid aortic valve with severe aortic stenosis was seen on transthoracic echocardiography, with a maximum gradient of 75 mmHg. The aortic annulus measured 6.8 mm. There was grade II/IV aortic regurgitation (jet area 2.4 cm²) and mild tricuspid regurgitation (TR). In view of the associated aortic regurgitation, balloon valvotomy was not considered as an option.

The child underwent a Ross procedure using the root replacement technique. Cardiopulmonary bypass (CPB) was instituted using aortic, bicaval cannulation and the body temperature was brought down to 32°C. Antegrade cold blood cardioplegia was used for myocardial protection. The technique involves assessment of the aortic and pulmonary valves followed by excision of the aortic valve. A pulmonary autograft was harvested and implanted in the aortic position as a mini root, using continuous sutures. The left and right coronary arteries were reimplanted as a button and the aorta was re-anastomosed. The right ventricular outflow tract was reconstructed using a 14 mm size cryopreserved pulmonary homograft. The child was weaned away from CPB on minimal inotropic support. In the ICU, the child remained hemodynamically stable. Respiratory efforts were inadequate initially and the child was extubated on the seventh day. Thereafter, his recovery was uneventful. The postoperative transthoracic echocardiogram revealed grade I/IV aortic regurgitation and mild pulmonary regurgitation with good biventricular function. There was no significant gradient across the autograft (Fig. 1). The child was discharged on the fourteenth postoperative day and is being followed up regularly. At one-year follow-up, the patient is doing well and has mild aortic regurgitation.

Discussion

Treating aortic stenosis in children is a challenge. Though
valve repair is the ideal procedure, not all valves are amenable to repair. Replacement with a prosthetic valve is avoided due to the small size of the annulus, need for redo surgery as the child grows and the requirement for anticoagulation. Aortic valve replacement with a homograft does not require anticoagulation but has a limited life span and does not grow with the child, thus necessitating redo surgical procedures.²

The Ross procedure using a pulmonary autograft seems to be the ideal alternative for aortic valve replacement in children. The procedure does not require anticoagulation, the valve has excellent hemodynamics, is durable and has been shown to grow with the child, thus reducing the chances of reoperation.¹ Despite all the obvious advantages of using a pulmonary autograft, the use of the Ross procedure in the initial period was tardy. This was due to the following reasons: (i) technical difficulty in children; (ii) concern regarding the fate of the autograft in the systemic position; (iii) doubt regarding the growth of the autograft in keeping with the child's somatic growth.

Ever since the procedure was first described, various surgeons have reported their results.¹⁻³ Hospital mortality is comparable in all the series. At 17 years, freedom from intrinsic tissue degeneration was 100% for the pulmonary autograft group versus 24%–51% in the homograft group.³ Patient survival was also significantly better with the Ross procedure.

Stelzer et al.⁶ modified the Ross procedure and introduced the root replacement technique. This led to increasing use of the procedure and today it is the most commonly used technique. Recently, Elkins⁷ reported the results in 328 patients. The age of the patients ranged between 10 days and 62 years. One hundred and twenty patients were less than 16 years old. The operative survival was 95.4% with an actuarial survival of 89±5% at 8 years.

Marino et al.⁵ have reported their results of the Ross procedure in children. The age range was 6 days to 34.8 years (median 10.8 years), and the operative mortality was 1.5%. They concluded that for small children the Ross procedure has low morbidity and mortality. A similar conclusion can be drawn from the reviews of Reddy et al.⁹

One concern with this procedure has been the ability of the pulmonary valve to withstand systemic pressure. Ross et al.¹⁰ reviewed their results in 1992 and concluded that there was no evidence of primary tissue degeneration in the autograft. Further, they have shown that the autograft not only withstands the systemic pressure but also grows with the patient, making it an ideal operation for children.¹⁰

The fact that the autograft is capable of growing has been shown experimentally by Krietmann et al.¹¹ and has been confirmed clinically.³,⁴

Conclusions: The present literature suggests that the Ross procedure is perhaps the ideal alternative for aortic valve replacement in children, and has an acceptable mortality and morbidity. The autograft does not require anticoagulation and has been shown to grow with the child's somatic growth.

References


Fig. 1. Postoperative echocardiogram showing good result
Aortoarteritis Presenting with Hypoparathyroidism

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Brief Report

Clinical manifestations of aortoarteritis (Takayasu's arteritis) are varied, depending on the involved segment of the aorta and its branches. A case of a young Indian woman with aortoarteritis presenting primarily with hypoparathyroidism is reported. Aortogram showed total occlusion of the arch arteries. To the best of our knowledge, the occurrence of hypoparathyroidism in aortoarteritis has not been reported. Possible mechanisms of such an involvement are discussed. (Indian Heart J 2001; 53: 348-349)

Key Words: Aortoarteritis, Takayasu's arteritis, Hypoparathyroidism

Aortoarteritis is a nonspecific inflammatory arteriopathy involving the aorta, its major branches and sometimes the pulmonary arteries. Involvement of the arch vessels is common. Stenosis and occlusion of the subclavian, carotid and vertebral arteries in various combinations are responsible for the multiplicity of cerebral and visual disturbances. However, its association with hypoparathyroidism has not been reported. We report the case of a young Indian woman who presented with hypoparathyroidism and aortoarteritis.

Case Report

A 25-year-old female presented with a history of generalized bone pain, episodes of muscle cramps and carpopedal spasm, along with decreased visual acuity for the last eighteen months. The patient had a history of one short episode of syncope. She also had constitutional symptoms with low-grade intermittent fever and loss of appetite and weight for the same duration of time. There was no history of pulmonary tuberculosis or neck surgery.

On physical examination, she had mild pallor and jugular venous pulsations were normal. Carotid and upper limb pulses were not palpable while lower limb pulsations could be well palpated. Blood pressure in the lower limbs was 150/80 mmHg and no bruit was audible. Examination of the cardiovascular system, chest, abdomen and central nervous system did not reveal any abnormality. Chvostek's sign and Trousseau's sign were present. Both eyes had an immature cataract and the vision was 6/60. A clinical diagnosis of aortoarteritis with hypoparathyroidism was made.

Her hematological parameters revealed a raised ESR (130 mm fall in the first hour) while the total and differential leucocyte counts were normal. Biochemical parameters such as liver and kidney functions, and serum electrolytes were within normal limits. The level of serum phosphorus was high (6.6 mg/dl) while serum calcium (4.6 mg/dl) and serum parathormone (8.2 ng/dl) levels were low. The Mantoux test was positive (16×16 mm). The electrocardiograph (ECG), chest X-ray, skull X-ray, and X-ray of the hands, feet and pelvis were normal. Echocardiography was also normal, and a peripheral Doppler study revealed involvement of the carotid and subclavian arteries. The lower limb arteries were normal.

Diagnostic angiogram was done via the right femoral artery under local anesthesia. An arch aortogram revealed total occlusion of both the common carotid and both the subclavian arteries. Late frames showed collateral circulation to the vertebral arteries (Fig. 1). An abdominal aortogram revealed normal renal arteries and aorta. Pulmonary artery angiogram revealed normal pulmonary arteries. A diagnosis of Type 1 aortoarteritis with hypoparathyroidism was made and the patient was started on steroids (in view of activity), oral calcium gluconate and calciferol (Vitamin D₃) and put on regular follow-up. A follow-up angiographic re-study done after five years showed that all the arch arteries continued to be occluded while the abdominal aorta and its branches were spared. Serum parathormone (7.2 ng/dl) and serum calcium (6.1 mg/dl) levels continued to be low.

Discussion

Signs and symptoms in patients with Takayasu’s arteritis
of our knowledge, it has not been described in patients with aortoarteritis. Hypoparathyroidism in this case could be because of the compromised vascular supply to the parathyroids or a common autoimmune process involving them. A chance association of idiopathic hypoparathyroidism cannot be ruled out. Rare cases of ulcerative colitis with Takayasu’s aortitis have been reported and common immunological mechanisms have been postulated but not proved. An immunological study from India of 50 patients with aortoarteritis did not find any role of an autoimmune mechanism in aortoarteritis. Interestingly, the patient’s symptoms improved following medical treatment with steroids, calcium and vitamin D₃, but angiographic improvement on adequate, long-term steroids, as reported by some workers, was not seen in this case. No improvement of arterial obstruction has been reported in other studies. Kerr et al. reported a relapse in half the patients who had initially achieved remission on steroids.

References

2. Ishikawa K. Patterns of symptoms and prognosis in occlusive thrombocapathia (Takayasu’s disease) J Am Coll Cardiol 1986; 8: 1041–1046

(aortoarteritis), a disease of worldwide distribution and geographic variations, can show considerable clinical variation with regard to severity, duration and quality. The onset of the disease is often insidious and it progresses at a variable rate from the active inflammatory phase to the chronic, sclerotic phase with intimal hyperplasia, medial degeneration and adventitial fibrosis. Stenotic lesions are more common than aneurysms. The narrowing starts near the orifice of the artery and extends for a variable distance; progressive narrowing leads to occlusion with ischemic symptoms. In such an extreme form of brachiocephalic arteritis, all or most of the arch vessels are occluded and the entire circulation to the brain is provided through collateral vessels. Peculiarly, this case presented with symptoms of hypoparathyroidism.

Hypoparathyroidism is most commonly seen following surgery for thyroid disorders, hyperparathyroidism and radical dissection of the neck for cancer. Very rarely, it follows X-ray irradiation of the neck or massive radioactive iodine administration for cancer of the thyroid. To the best of our knowledge, it has not been described in patients with aortoarteritis. Hypoparathyroidism in this case could be because of the compromised vascular supply to the parathyroids or a common autoimmune process involving them. A chance association of idiopathic hypoparathyroidism cannot be ruled out. Rare cases of ulcerative colitis with Takayasu’s aortitis have been reported and common immunological mechanisms have been postulated but not proved. An immunological study from India of 50 patients with aortoarteritis did not find any role of an autoimmune mechanism in aortoarteritis. Interestingly, the patient’s symptoms improved following medical treatment with steroids, calcium and vitamin D₃, but angiographic improvement on adequate, long-term steroids, as reported by some workers, was not seen in this case. No improvement of arterial obstruction has been reported in other studies. Kerr et al. reported a relapse in half the patients who had initially achieved remission on steroids.

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Infective Endocarditis due to an Unusual Serotype of Salmonella

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Salmonellae are a rare cause of infective endocarditis. We report a case in which Salmonella enterica serotype Worthington was isolated from a case of endocarditis. The isolate was resistant to ampicillin, gentamicin, amikacin and chloramphenicol and sensitive to ciprofloxacin and cefotaxime. (Indian Heart J 2001; 53: 350-351)

Key Words: Infection, Endocarditis, Heart diseases

Endocarditis due to nontyphoidal Salmonella is a rare clinical entity and is associated with a high mortality rate. Approximately 75% of cases suffering from this condition have an underlying cardiac abnormality such as rheumatic heart disease and congenital heart defects. We report a case where an unusual serotype of Salmonella was isolated from a case of infective endocarditis in a patient with a predisposing valvular abnormality.

Case Report
A 21-year-old woman was admitted with complaints of fever, anorexia and general weakness of 15 days' duration. The patient had been suffering from aortic stenosis with mitral valve prolapse for 10 years. There was no history of cough, breathlessness, hemoptysis and palpitations. On examination, the patient was found to be febrile (101°F). There was no edema, cyanosis, clubbing or icterus. Her blood pressure was 110/80 mmHg, jugular venous pressure was normal and bilateral carotid thrill was present. An early systolic click and an aortic ejection murmur radiating to both the carotids could be auscultated at the aortic area and at the apex. Respiratory system, central nervous system and per abdomen examination were normal. Hematological investigations revealed a normocytic, normochromic anemia (Hb 8.5 g%), a total leukocyte count of 12 000/mm³, a normal platelet count (200×10⁹/L) and an ESR of 65 mm at the end of one hour. The patient's serum was positive for rheumatoid factor but other immunological manifestations such as Roth spots and Osler nodes were absent. Urinalysis was normal. A provisional diagnosis of aortic stenosis with infective endocarditis was made. Echocardiography did not reveal any vegetation. Three blood samples were collected at 4-hour intervals for bacterial culture and sensitivity on the day of admission. Empirical therapy with intravenous crystalline penicillin and gentamicin was administered pending culture and sensitivity reports. On the 3rd day of admission, a brief high-pitched diastolic murmur was heard on auscultation and repeat echocardiography revealed aortic stenosis with regurgitation. This was associated with a fall in peripheral blood pressure (90/60 mmHg) and a positive hepatojugular reflex indicating the onset of congestive cardiac failure, for which drug therapy with digitalis was started. Blood cultures were repeated on the 7th and 14th day of admission. In the latter part of the patient's stay in hospital, serial stool cultures were also carried out.

Blood and stool samples were processed as per standard microbiological methods. The bacterial isolate was identified with the help of biochemical reactions and antibiotic sensitivity was determined with the help of the Kirby–Bauer disk diffusion method. Salmonellae were isolated from all three blood samples collected on the day of admission. The isolate was found to be resistant to ampicillin, gentamicin, amikacin and chloramphenicol, and sensitive to ciprofloxacin and cefotaxime. After the sensitivity report was obtained, the patient was treated with intravenous cefotaxime and ciprofloxacin. This led to an improvement in the patient's clinical condition and follow-up blood cultures did not reveal any bacterial growth. None of the stool cultures revealed Salmonella.
The isolate was sent for confirmation to the National Salmonella and Escherichia Centre, Research and Development Division at the Central Research Institute, Kasauli where it was identified as Salmonella enterica serotype Worthington.

**Discussion**

Infective endocarditis commonly occurs in the setting of a prior valvular abnormality and is characterized by fever and systemic complaints such as anorexia, weakness, myalgia and arthralgia. Aerobic Gram-negative bacilli including Salmonella, Proteus, Pseudomonas and Klebsiella are rare causes of bacterial endocarditis, accounting for 1.3%–4.8% of cases.4

In the present case, the patient had a consistently positive blood culture, a predisposing cardiac ailment, fever, a positive test for rheumatoid factor and a raised ESR, all of which pointed towards a diagnosis of infective endocarditis. Cardiac vegetations were not detected by echocardiography. However, the sensitivity of echocardiography to the detection of cardiac vegetations has been found to be in the range of 60%–65%.4

Salmonelae have a predilection for involving previously diseased cardiac valves. Valvular perforation, atrial thrombi, myocarditis and pericarditis are common complications of Salmonella endocarditis and these events are associated with grave prognosis.4 In this case, the appearance of a new murmur and signs of congestive heart failure indicated deteriorating cardiac function.

The common serotypes of Salmonella that have been implicated as causative agents of endocarditis include choleraesuis, typhimurium and enteritidis.4 Amongst the infrequent Salmonella serotypes, Schneider et al.5 reported a case of Salmonella endocarditis due to serotype Thompson. In a study on salmonellosis in patients with neoplastic diseases, Wolfe et al.6 reported a case of endocarditis due to serotype Derby. In a review of endocarditis caused by nontyphoidal Salmonella,5 case reports implicating serotypes Fayed, Sendai, Dublin, Oranienburg, Infantis and Minnesota have been described. In this review, only 3 out of 22 cases of Salmonella endocarditis had a favorable outcome.

Endocarditis due to Salmonella is usually associated with an apparent focus in the gastrointestinal tract.5 However, despite serial stool cultures on selective media, we could not isolate Salmonella from any of the samples.

Serotype Worthington is an uncommon pathogen. It has been previously incriminated as a cause of neonatal septicemia and meningitis.7 However, to our knowledge, this is the first report of endocarditis caused by this serotype. In the present case, the organism was found to be resistant to commonly used antibiotics such as ampicillin, gentamicin and chloramphenicol. Resistance to multiple antibiotics has been increasing in isolates of nontyphoidal Salmonella and this is one of the important causes of the poor prognosis associated with Salmonella endocarditis.5 In other cases in which serotype Worthington has been isolated, the organism was found to be sensitive only to ciprofloxacin and a combination of amoxycillin–clavulanic acid.7 Infection of endocardium with multidrug-resistant Salmonella is associated with grave prognosis.4 In our patient, close monitoring and intensive therapy with cefotaxime and ciprofloxacin led to a favorable microbiological response and clinical improvement in the congestive cardiac failure. Although further monitoring for valvular dysfunction and cardiac failure was warranted, the patient was discharged after 17 days against medical advice. At discharge, she was advised to undergo consultation for prophylaxis of endocarditis before any surgical intervention. Surgical management for valvular heart disease was not planned due to economic reasons.

**Acknowledgments**

We would like to acknowledge the assistance rendered by the Central Research Institute, Kasauli in identification of the Salmonella serotype and the Dean, B.J. Medical College and Sassoon Hospitals, Pune for providing the necessary facilities.

**References**

Absent Coronary Venous Sinus: A Rare Anomaly

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A 42-year-old man, presenting with dyspnea on exertion and ST segment depression on treadmill test, was found to have absent coronary venous sinus on coronary angiography. We report this case of isolated congenital absence of coronary venous sinus because of its rarity. (Indian Heart J 2001; 53: 352–353)

Key Words: Congenital heart defects, Atrium, Coronary sinus

Abnormalities of the coronary venous system are rare congenital anomalies. We report a case of isolated congenital absence of the coronary venous sinus without associated structural abnormalities.

Case Report
A 42-year-old man presented with complaints of exertional dyspnea of 2 years’ duration and occasional giddiness. The dyspnea was not progressive and there was no paroxysmal nocturnal dyspnea or orthopnea. There was very few episodes of giddy spells and none of them was associated with syncope or presyncope. The patient was normotensive, non-diabetic and a nonsmoker, and had no other symptoms. Clinical examination revealed a normally disposed individual with a normal pulse, blood pressure and heart sounds with no cardiac murmurs. There was no pedal edema and the neck veins were normal.

The chest X-ray was normal and electrocardiography revealed an incomplete right bundle branch block. The echocardiograph showed a normal-sized heart with good ventricular function. The situs was normal and the intra- and infrahepatic portions of the inferior vena cava were normally visualized. The pulmonary veins drained normally into the left atrium, while the interatrial and ventricular septum were intact. A treadmill exercise test showed horizontal ST segment depression in the inferolateral leads at 7 METS. A 24-hour ambulatory electrocardiogram was normal. There was no systemic desaturation and an oximetry run did not reveal any significant oxygen step-up at any level. Coronary angiography was carried out to rule out coronary artery disease. It revealed normal epicardial coronary arteries with a normal branching pattern (Fig. 1). The contrast from the coronaries during the venous phase emptied into the left ventricle through multiple small fistulous connections giving a unique striate appearance (Fig. 2). However, the coronary veins and the coronary sinus were not visualized during the venous phase (Fig. 3). A contrast injection was given into the left brachial vein to rule out associated anomalies. The left brachial, subclavian and the innominate veins were anatomically normal, but there was no left superior vena cava (SVC). The patient was advised conservative management and showed no clinical deterioration at follow-up after 3 months.

Discussion
Abnormalities of the coronary sinus are rare congenital anomalies and the accumulated literature on this interesting entity is meagre and limited to isolated case
reports. The abnormalities include complete absence, hypoplasia, atresia—either whole or ostial—and partial or complete unroofing. There may be several anomalies associated with any of the above.

Foale et al. reported a case of isolated congenital absence of the coronary sinus with the cardiac veins draining separately into the left and right atria, in whom stenosis of an anomalous vein had produced a continuous murmur. Defects commonly associated with an absent coronary sinus include atrial septal defect (ASD), persistent left SVC and abnormalities of systemic and pulmonary venous drainage. Sheikhzadeh et al. reported the case of a 20-year-old woman with an absent coronary sinus associated with a large ASD and a persistent left SVC draining into the left atrium. The patient underwent successful surgical correction with improvement in hemodynamics. Fujimura et al. reported the case of a 27-year-old male with Raghib's syndrome, characterized by abnormal drainage of the left SVC into the left atrium, ASD and absent coronary sinus. The patient had an associated cor triatriatum, and was diagnosed during a surgical procedure for the primary cardiac disease. The coronary sinus may be partially or completely unroofed producing a coronary sinus type of ASD with significant left-to-right shunting. Several such cases have been reported with associated mild systemic desaturation due to an abnormal connection of the left SVC to the left atrium. Coronary sinus defect has also been described with tricuspid atresia.

Multiple coronary–cameral fistulous connections, through which the blood empties into one of the cardiac chambers, are well known in patients with coronary sinus abnormalities. In our patient, the flow through these fistulous connections produced a peculiar striated appearance in the wall of the left ventricle. Additionally, the abnormality of the venous system was present in isolation without any of the associated conditions described above. The physiological effect of this abnormality on the patient was not studied. Whether it could lead to myocardial ischemia due to tissue hypoxia whenever the left ventricular diastolic pressure rises due to any cause, is a moot question.

The diagnosis of an absent coronary sinus requires careful observation of the structure during coronary angiography. A diligent search should be made for associated defects and the physiology of the coronary blood flow studied in detail. The natural history is unknown.

References

Newer Antiarrhythmic Drugs

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In the 1970s and early 1980s, the target or models used in drug development were based on the suppression of premature ventricular contractions (PVCs) recorded in animal models or in patients with PVCs after myocardial infarction (MI). More recently, drug development has evolved in two general areas: amiodarone analogues and agents that block one or more components of the delayed rectifier potassium channel (Table 1). The remarkable clinical efficacy of amiodarone in the treatment of a wide variety of arrhythmias has led to the search for a new class III drug with a better safety profile. Interestingly, almost all the drugs in this new wave of development resemble sotalol more than amiodarone, both chemically and electrophysiologically. They can be grouped chemically based on the fact that they contain a methane sulfonamide moiety.

Table 1. Mechanism of action of newer antiarrhythmic drugs on K+ channels

<table>
<thead>
<tr>
<th>Ibutilide</th>
<th>Dofetilide</th>
<th>Azimilide</th>
<th>Dronedarone</th>
<th>Tedisamil</th>
<th>Trecetilide</th>
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<td>$I_{KS}$ inhibits</td>
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<td>$I_{Ks}$ activates</td>
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At least nine potassium channels have been identified, and it is being recognized that most antiarrhythmic drugs that prolong repolarization have overlapping specificity for different groups of channels. A great deal of effort has been expended in developing agents that are selective for the more discrete ion currents that contribute to repolarization. In atrial tissue, the candidate currents are the transient outward current ($I_{TO}$) and the ultra-rapid component of $I_{K}$ ($I_{KUR}$). In the ventricles, the major repolarizing currents are $I_{K}$ (composed of slow and rapid component, $I_{KS}$ and $I_{Ks}$) and the outwardly rectifying component of $I_{K}$, a current termed the inward rectifier. Of these currents, pharmaceutical companies have focused primarily on developing drugs to block $I_{KS}$ and $I_{Ks}$. Yet, at this point, there is no evidence that a selective effect on either of these components will provide any clinical advantages.

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The transient outward current is prominent in atrial tissue, and specific agents could be developed to block this current and, therefore, be selectively useful in treating atrial and supraventricular arrhythmias. Furthermore, the potassium channel that is activated by the low cellular concentration of adenosine triphosphate (ATP), called $I_{KATP}$, has been proposed as a target for drugs that would be selective in treating arrhythmias occurring during ischemia. All these concepts are appealing, but are complicated by species and tissue differences in the ion channels that are responsible for normal electrophysiology, and a poor understanding of how they are altered by age, gender and disease, especially acute ischemia or reperfusion. It is also important to recognize that actions on other channels may indirectly prolong the cardiac action potential. Another important aspect of these drugs has been the association between prolongation of the action potential duration (APD) and the risk of torsade de pointes (TdP). This association suggests that any antiarrhythmic benefit from an effect on refractoriness must be weighed against the risk of TdP that may result from increasing the APD.

Ibutilide

In 1991, the methane sulfonamide derivative ibutilide was reported to have highly potent class III activity. Ibutilide is a potent inhibitor of $I_{Ks}$ (EC$_{50}$ 20 nM), and displaces $H$-dofetilide binding ($K$ = 16 nM) to the $I_{Kr}$ channel. The precise contribution of $I_{Kr}$ blockade versus inward current enhancement to ibutilide's electrophysiological actions is uncertain.

Ibutilide is effective against the induction of re-entrant ventricular tachycardia (VT) in dogs studied 24 hours after coronary artery occlusion and is relatively ineffective against spontaneous automatic arrhythmias. It prevents ventricular fibrillation (VF) in a hypoxic rabbit heart model, and decreases the energy required for ventricular defibrillation in anesthetized dogs. Ibutilide has less proarrhythmic potential than other class III drugs in a rabbit model of TdP. It increases the QT and QTC intervals in humans, without altering the PR and QRS duration, as expected for class III drugs. The drug produces small hemodynamic changes, not significantly different from those occurring with a placebo.
Ibutilide has been introduced as an intravenous agent for the termination of re-entrant atrial tachyarrhythmias. Termination efficacy is dose related, and is maximal at 0.0015 mg/kg. The drug is usually given as a 10-minute infusion, with an initial dose of 1 mg followed by a second dose of 0.5 to 1 mg, if necessary. The most significant potential adverse effect of ibutilide is polymorphic VT in association with excess QT prolongation. Heart failure, female sex, non-White race and a slower heart rate are all associated with a greater risk of polymorphic VT.

**Cardioversion for atrial fibrillation**: In some patients, atrial fibrillation (AF) cannot be converted to sinus rhythm (SR) with external cardioversion. Pretreatment with ibutilide can be useful in these patients. Ibutilide probably decreases the atrial defibrillation threshold (DFT), as was recently observed by Oral et al. in a study at the University of Michigan. One hundred consecutive patients with AF were examined in a prospective trial in which patients were randomly assigned to undergo DC cardioversion with or without pretreatment with 1 mg of intravenous (IV) ibutilide. Cardioversion terminated AF in 36 out of 50 patients (72%) who were not receiving ibutilide. In patients receiving ibutilide, AF was terminated acutely by ibutilide alone in 10 patients (20%) while the other 40 (80%) were all successfully converted to SR with transthoracic cardioversion (100% compared with 72% of patients not receiving ibutilide; p>0.001). When the energy requirement for atrial defibrillation was examined in the patients initially assigned to ibutilide pretreatment rather than no pretreatment, ibutilide significantly reduced the amount of energy required for cardioversion to SR from 228±93 J to 166±80 J (p>0.001).

This important study shows that ibutilide significantly reduces atrial DFTs and can lead to successful transthoracic cardioversion to SR in patients in whom transthoracic cardioversion would otherwise have failed. Wesley et al. evaluated ibutilide-induced reduction in ventricular DFTs in a canine model and hypothesized that the effect was secondary to the prolongation of repolarization without changes in ventricular conduction. However, the mechanism responsible for reducing DFTs has not been fully determined.

**Dofetilide**

Dofetilide has been approved by the cardiorenal panel of the US Food and Drug Administration (FDA) and is expected to be clinically available in the next few months. It is being developed for the treatment of life-threatening ventricular arrhythmias and for the prevention of recurrent AF or atrial flutter (AFL). It is one of the methane sulfonamide compounds that has relative selectivity at 10 to 30 nM for blocking the rapidly activating component of the delayed rectifier potassium current, $I_{Kr}$. At these concentrations, it does not block $I_{ks}$ or $I_{kr}$ nor does it affect the sodium or calcium currents. This yields a selective effect on the QT interval of the surface ECG. In clinical electrophysiological studies (EPS), it has been found to prolong the QT interval with little effect on QT dispersion, and no effect on conduction parameters (PA, AH, HV, PR or ORS intervals), sinus cycle length, or sinus node recovery.

Dofetilide, like most other potassium-channel blockers, is metabolized predominantly by the CYP 3A4 family. It is therefore likely to interact with drugs such as erythromycin or ketoconazole. Kobayashi et al. evaluated the clinical and electrophysiological effects of IV dofetilide in patients with paroxysmal AF of recent onset (<7 days) and paroxysmal supraventricular tachycardia (PSVT). They administered 2.5–5 µg/kg of dofetilide for the termination of arrhythmias; and for the EPS, they administered 3.0 µg/kg as a loading dose, followed subsequently by 2 µg/kg IV over 45 minutes as a maintenance dose. Dofetilide proportionately lengthened the effective refractory period (ERP) of the atrium, ventricle and the accessory pathways (AP) without slowing intracardiac conduction.

Falk et al. reported a placebo-controlled study of the safety and efficacy of a single bolus dose of IV dofetilide for the termination of sustained AF or AFL. Ninety-one patients with sustained AF (75 patients) or AFL (16 patients) were entered into a double-blind, randomized, multicenter study of one or two doses of dofetilide (4 or 8 µg/kg body weight) or placebo. Dofetilide effectively terminated the arrhythmia in 31% of patients receiving 8 µg/kg and in 12.5% of those receiving 4 µg/kg compared to zero conversion after placebo (p<0.01). Although the number of patients with AFL was small, this group had a greater response to dofetilide (54%) compared to those with AF (14.5%, p<0.001).

Echt et al. evaluated the efficacy of dofetilide in patients with life-threatening sustained VT or VF using a novel placebo-controlled, dose-ranging protocol. The study was designed to define the range of effective doses and to evaluate the clinical electrophysiology of IV dofetilide in patients in whom sustained VT and VF was reproducibly inducible at baseline EPS. The initial 4 patients received low doses that were increased in the subsequent groups of 4 patients if there were no adverse effects. In each group of 4 patients, 1 patient was randomly assigned to placebo (double blind). Twenty-four patients were studied at six incremental loading and infusion regimens. Dofetilide (0.1–8.0 ng/ml in plasma) produced a concentration-
related increase in the QT=0.79 (p<0.001), QTc=0.60 (p=0.02), RR=0.62 (p<0.02), and right ventricular ERP (cycle length 600 ms; r=0.68, p=0.04). Placebo infusion produced no changes in any of these measurements. Sustained VT or VF was no longer inducible in 1 of the 6 patients receiving placebo and 8 of 18 patients receiving dofetilide (4–13 seconds non-sustained ventricular tachycardia [NSVT] was induced in 4 of these 8 patients). One patient developed TdP at a high concentration (5.3 ng/ml).

Bashir et al.21 for the Dofetilide Arrhythmia Study Group21 reported a multicenter open trial of dofetilide in patients with sustained VT. These investigators evaluated the acute electrophysiological effects, antiarrhythmic efficacy and safety of different doses of IV dofetilide in 50 patients with sustained monomorphic VT inducible by EPS, who had previously been unsuccessfully treated with 0 to 7 (median 3) other drugs. Dofetilide was administered over 60 minutes at doses of 1.5, 3, 6, 9 and 15 µg/kg. Doses of 3–15 µg/kg prolonged the QTc interval by 13.4%–14.2%, the ventricular ERP by 7.9%–20.6%, and the ventricular functional refractory period (FRP) by 7.3%–25%. The corresponding plasma dofetilide concentrations ranged from 1.45±0.52 to 6.48±1.31 ng/ml. The investigators failed to see any evidence of reverse use dependence. At these dosages, IV dofetilide suppressed or slowed inducible VT in 17 of 41 patients (41%) compared with 0 of 9 patients receiving the lower electrophysiologically inactive dose of 1.5 µg/kg. The response rate was fairly uniform among the groups receiving 3–15 µg/kg.

In humans with ejection fractions (EF) of 20%–30%, dofetilide has been shown to be essentially devoid of significant hemodynamic effects.22 Its effect on mortality in patients with CHF or those at high risk after MI were prospectively evaluated in the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) trials,23,24 which randomly assigned patients to placebo or dofetilide. Entry criteria included a cardiac index less than 1.2 (which corresponds to a left ventricular ejection fraction [LVEF] of 35% or less) and an acute MI (n=1510) within the past 2 to 7 days (MI trials), or recent new or worsened CHF (n=1518; CHF trial). Placebo or dofetilide administration was initiated during a 3-day hospitalization, and patients were evaluated for QT interval prolongation and TdP. After one year of follow-up, the overall mortality rate was 22% in the MI study and 27% in the CHF study, and mortality did not differ in the dofetilide and placebo groups. In both studies, dofetilide recipients had a greater conversion rate from AF to SR. In the CHF trial, the development of new onset AF was also significantly reduced.23,24 Dofetilide is renally excreted and the dosage of the drug must be adjusted as per the renal function. In the DIAMOND-CHF trials,26 dofetilide was stopped most commonly because of QT interval prolongation (2% vs. 0.4% for placebo), which usually occurred on the second day of medication. Torsade de pointes was seen in 25 patients (3.2%); 76% of the episodes occurred during the first three days after dose initiation and two of them were fatal.

The results of the DIAMOND-MI trials are markedly different from those of the Survival with Oral d-Sotalol (SWORD) trial.26 In the SWORD trial, d-sotalol was associated with an increased mortality rate (5.7% compared with 3.1%; p<0.01). This is of interest because dofetilide and d-sotalol exert similar electrophysiological actions; both are I_Kr blockers (although d-sotalol also blocks I_k and possibly I_to). The different results probably stem from several factors and are due, in part, to the fact that the DIAMOND trial enrolled a much sicker patient cohort (mortality rate in the placebo group: 22% in the DIAMOND trial and 3% in the SWORD trial). Patients in the SWORD trial were at a low risk for death, and the use of an antiarrhythmic drug that can cause TdP subjected them to a proarrhythmic risk with little likelihood of decreasing arrhythmic events. In addition, the SWORD trial, unlike the DIAMOND-MI trial, started antiarrhythmic therapy on an outpatient basis. Thus, patients who had excessive QT interval prolongation or short runs of TdP were more likely to be identified and have the study drug discontinued in the DIAMOND-MI trial.

In the SAFIRE trial,27 325 patients with persistent AF (lasting 14 days to 7 months) were randomly assigned to receive placebo or one of three dofetilide regimens: 125 µg, 250 µg, or 300 µg twice daily. Patients were hospitalized and blinded administration of the drug started. If the patients did not convert to SR within 3 days, they were electrically converted to SR, and only those patients who were successfully converted continued in the study. Of note, 67% of patients had structural heart disease and 40% had CHF. After 6 months of follow-up, 62% of the patients receiving the highest dosage (500 µg every 12 hours) of dofetilide and 36% of placebo recipients remained in SR (p<0.05). Of interest is the fact that 32% of patients receiving the highest dosage and 1% of placebo recipients were converted to SR pharmaceutically. Patients who maintained SR had fewer arrhythmic symptoms than patients who had a recurrence of AF (35% and 48%, respectively; p<0.05). This shows that maintenance of SR is significantly associated with symptom reduction. The incidence of TdP in this study was 0.6%.

In a related investigation, the European and Australian Multicenter Evaluative Research on Atrial Fibrillation...
Dofetilide (EMERALD) study—randomly assigned patients after cardioversion to receive placebo or one of the three regimens of dofetilide: 125 µg, 250 µg, or 500 µg twice daily. All dosages of dofetilide significantly increased the number of patients in SR, and a dose-response curve was seen, with the greatest benefit at the highest dose. After 6 months of follow-up, 71% of patients receiving the 500 µg of dofetilide and 26% of placebo recipients remained in SR (p<0.001). The incidence of TdP was 0.75%. Maintenance of SR was shown to improve the quality of life and exercise capacity.39

In summary, these studies show that dofetilide, a pure I_{Kr} blocker, prolongs atrial repolarization and prevents recurrent AF. It seems to have an acceptable safety profile in patients with heart failure and in those after MI.

Azimilide

Azimilide (NE-10064) blocks the slowly activating (I_{KS}) and rapidly activating (I_{Kr}) components of the delayed rectifier potassium current, which distinguishes it from most other potassium channel blockers such as sotalol and dofetilide, which block only I_{Kr}. Azimilide is being tested for its ability to delay the time to recurrence of AF, AFL and PSVT in patients with and without structural heart disease. Azimilide is also being studied for its ability to prevent sudden cardiac death (SCD) in high-risk patients after MI. Preclinical and clinical studies indicate that azimilide prolongs the cardiac refractory period in a dose-dependent manner, as manifested by an increase in APD, QTc interval, and ERP.30 Azimilide does not effect the PR or QRS intervals and has minimal hemodynamic effects on blood pressure and heart rate. In preclinical experiments, its effects appear to be rate independent and are maintained under ischemic or hypoxic conditions. As with other drugs that prolong cardiac refractoriness, azimilide has been demonstrated to suppress supraventricular arrhythmias effectively (>85%) in a variety of dog models. It also suppresses complex ventricular arrhythmias in infarcted dogs and decreased mortality in an SCD model.30

The safety and efficacy of azimilide in preventing recurrent AF, AFL and PSVT was assessed in more than 1000 patients randomly assigned to receive placebo or escalating doses of oral azimilide for 6–9 months.31–33 In these studies, almost all patients received azimilide on an outpatient basis. In the preliminary data33 on the first 367 patients with AF or AFL randomly assigned to placebo (n=87); azimilide 50 mg/day (n=99); or azimilide 100–125 mg/day (n=181), a significant increase was shown at the higher dose level, in the median time to the development of arrhythmia (60 days compared to 17 days; p<0.005). In a combined analysis32 of three trials of AF and AFL that examined 906 patients, azimilide significantly prolonged the hazard ratio for recurrence of arrhythmia when it was given at a dosage of 100 mg/day (hazard ratio 1.32; p=0.02) and 125 mg/day (hazard ratio 1.81; p<0.01). However, in a fourth study evaluating the 125 mg/day dose, azimilide did not significantly reduce the recurrence of AF.32

The effect of azimilide was also evaluated in 133 patients with PSVT. Fifty patients received placebo and 83 received azimilide, which significantly prolonged the arrhythmia-free interval (hazard ratio 2.4 for azimilide 100 mg/day; p=0.01).34 The overall incidence of TdP in the PSVT studies has been less than 0.8%, and the incidence of all serious adverse events in the AF trials was not significantly increased compared with the placebo (6.4% for placebo compared with 8.5% for azimilide; p=ns). The incidence of other side-effects was low. An early reversible neutropenia was observed in approximately 0.39% of patients. The risk of death31 was 0.77 (95% CI: 0.2–3.1; p=ns) in patients with SVT who were receiving azimilide compared with patients receiving placebo; thus mortality was not increased in azimilide recipients.

The Azimilide Post-Infarct Survival Evaluation (ALIVE) trial designed by Camm et al.35 will examine the potential of azimilide for improving survival in post-MI patients at high risk of SCD. It is a double-blind, placebo-controlled, multinational trial that uses LVEF and heart rate variability (HRV) as predictors to target a post-MI patient population at high risk of SCD. The major inclusion criteria for the study are adult patients of either gender with an LVEF of 15% to 35% who have had a recent MI (6–21 days). Additional stratification will be based on the patients’ HRV. Exclusion criteria include factors that may predispose a patient to nonarrhythmic death or to low risk of SCD caused by arrhythmia. Sample size is based on the assumption that all-cause mortality rates (the primary end-point) at one-year in placebo patients at high risk for SCD are 15% and that azimilide will decrease the all-cause mortality by at least 45% in these patients. The trial consists of three groups—patients receiving 75 mg azimilide orally each day, patients receiving 100 mg azimilide orally each day, and patients receiving placebo. No dose adjustment for age, gender, renal or hepatic failure, or the concomitant use of digoxin and warfarin are necessary with azimilide. Enrollment for the trial is expected to continue for 24 months, and treatment is scheduled to be administered for a one-year follow-up period. The similarity of the two dosages chosen and the lack of dose individualization are the two potential drawbacks of this trial.

In summary, azimilide has unique electrophysiological
Dronedarone

Dronedarone is an experimental agent that has multiple electrophysiological actions, including all four Vaughan Williams class effects.36 Thus, it is similar to amiodarone. However, it does not have the iodine moiety of amiodarone, therefore there may be lesser side-effects. It has been shown to have antiadrenergic effects37,38 and to prolong atrial and ventricular refractory periods, atrioventricular node conduction, and the paced QRS complex;39 these effects are consistent with class I drug-induced slowing of ventricular conduction. In a recent study,40 acute electrophysiological effects of IV dronedarone were studied in a canine model with complete chronic AV block (a model with high sensitivity for acquired TdP). The IV dronedarone did not result in short-term class III effects; on the contrary, it showed a dose-dependent decrease in ventricular repolarization parameters including the QT interval, whereas the ventricular ERP (VERP) remained the same, thus increasing the VERP/QT ratio. Dronedarone suppressed spontaneous and pacing-induced TdP, early afterdepolarizations (EADs) and premature beats in this study.

In another study,41 the effects of oral dronedarone were compared with amiodarone in rabbit heart after 3 weeks of therapy with two different dosages. The main findings of this study indicate that despite the lack of iodine from the molecule, the major electrophysiological properties of dronedarone were similar to those of amiodarone. During short-term superfusion, dronedarone shortened the APD, as reported for amiodarone,42 but reduced the ventricular V_max. In contrast, after 3 weeks of oral administration of both drugs, there was significant slowing of the sinus frequency in vivo and in vitro associated with a significant prolongation of ventricular APD. In the sinus node, the slowing of the rate after long-term treatment was due to the depression of phase 4 depolarization and lengthening of the APD. Both drugs produced comparable degrees of depression of V_max as an index of inhibition of the ventricular myocardial sodium channel activity. The effects of dronedarone were more potent than those of amiodarone, despite deletion of iodine from its molecular structure. Whether these effects will translate into a less toxic and at least as effective drug as amiodarone remains to be seen.

**Tedisamil**

Tedisamil differs from other class III antiarrhythmic agents in that it blocks I_{TO} in addition to I_{Ks}.43-45 Tedisamil has been shown to reduce the incidence of VF and AF in experimental studies.44 Clinically, it produces bradycardia, presumably via a direct action on the sinus node APD, and prolongs the QT interval without affecting QRS or QT intervals.46 Reverse-frequency dependency has been seen with this agent,46 which is currently undergoing evaluation in humans for the treatment of AF and AFL.

**Trecetilide**

Trecetilide, a congener of ibutilide, is being evaluated in both IV and oral preparations for the termination and prevention of AF and AFL. In addition to blocking I_{Kr}, it seems to prolong repolarization through other mechanisms that are still being delineated. It also significantly prolongs the action potential in animals and repolarization in humans without exerting other electrophysiological effects.

**Conclusions**

Class III agents are being increasingly used as prophylaxis in patients who have AF and AFL, and for the reduction of supraventricular tachyarrhythmias after cardiac surgery. In addition to terminating AF and AFL, ibutilide significantly reduces human atrial defibrillation thresholds and increases the percentage of patients who can be cardioverted from AF to SR. Apart from SVTs, in patients with ventricular arrhythmias and implantable cardioverter-defibrillators (ICDs), class III agents are being increasingly used as an adjuvant therapy to decrease the frequency of ICD discharges. FDA has approved dofetilide for clinical use. Azimilide, which seems to be devoid of frequency-dependent effects on repolarization, is being actively investigated for the prophylaxis of AF and AFL. Dronedarone, tedisamil and trecetilide are now being studied to determine their usefulness in the treatment of patients with cardiac arrhythmias. Experimental studies are in progress to identify pharmacological agents that will selectively prolong repolarization in the atria without exerting electrophysiological effects in the ventricles.47-49
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Treatment of Hypertension in Patients with Diabetes Mellitus

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We are in the midst of a worldwide epidemic of Type 2 diabetes mellitus, the major brunt of which will fall upon developing countries. In the next 25 years, the burden of diabetes mellitus is predicted to double in India, with the number of cases increasing from 22.9 million to 57.2 million. The cause of this is multifactorial and includes an ageing population, increasing obesity, a sedentary lifestyle and genetic background. The genetic factor is of particular importance in the Indian population because of a high prevalence of the metabolic syndrome or the syndrome of insulin resistance. Although there is substantial ethnic heterogeneity in the prevalence of atherosclerosis and its risk factors, immigrants of South Asian origin have a high cardiovascular mortality rate. An increased prevalence of diabetes mellitus will undoubtedly increase the cardiovascular disease burden which has also reached epidemic proportions and is likely to grow with time. By the time most cardiologists see patients with diabetes, macrovascular disease has already been established. Hypertension is very common at this stage of the disease and its management is the subject of the present review.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure regards diabetes mellitus as a “vascular disease equivalent” in the management of hypertension. This is because patients with diabetes mellitus have as high a rate of cardiovascular events as that seen in patients with established coronary artery disease. The goal of treatment of hypertension in patients with diabetes is the prevention of morbidity and mortality due to microvascular and macrovascular complications. This is particularly relevant to India because the probability of adults dying from noncommunicable diseases, predominantly cardiovascular, is greater in India than in established market economies. Hypertension is an important risk factor for the development of vascular complications of diabetes mellitus, and results from recent trials show that lowering blood pressure (BP) in patients with diabetes mellitus is more cost-effective than tight blood glucose control, and beneficial results are apparent earlier.

Emerging data on the treatment of hypertension in patients with Type 2 diabetes and the proliferation of new antihypertensive drugs warrants a closer examination of the drug therapy and target BP in these patients. Major studies that involve patients with Type 2 diabetes mellitus or as subgroups are summarized in Table 1 and discussed in greater detail below.

Evidence for Aggressive BP Control

Evidence for aggressive BP control comes from two large outcome studies—the United Kingdom Prospective Diabetes Study-38 and -36 and the Hypertension Optimal Treatment trial.

In the United Kingdom Prospective Diabetic Study-38 (UKPDS), patients with Type 2 diabetes were randomized to tight control and less tight control: <150/85 mmHg (n=758) and <180/105 mmHg (n=390), respectively. At follow-up over 8.4 years, the group with aggressive BP control achieved an average BP of 144/82 mmHg compared to 154/87 mmHg in the group with less tight control. Despite a modest difference of 10/5 mmHg, the difference in outcomes of microvascular and macrovascular complications of diabetes was dramatic. Those assigned to tight control showed a 24% reduction for any end-points related to diabetes, 32% for deaths related to diabetes, 44% for stroke, and 37% for microvascular disease. In comparison, intensive blood glucose control decreased the risk of diabetes-related end-points by 12% and microvascular disease by 25%. Therefore, good control of BP was found to be more rewarding than control of diabetes.

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The maximum experience with an ACE inhibitor has come to us from the Heart Outcomes Prevention Evaluation (HOPE) study. The criteria for inclusion in this trial are listed in Table 1 (under the heading “Study Population”). Patients with diabetes mellitus (n=3577) had at least one other cardiovascular risk factor, such as hypertension, high levels of serum total cholesterol, low high-density lipoprotein (HDL) levels, cigarette smoking or documented microalbuminuria. Ramipril was started at a dose of 2.5 mg/day for the first week, 5 mg/day for the next three weeks and then escalated to a dose of 10 mg/day. Angiotensin-converting enzyme inhibitor therapy resulted in a 25% overall reduction in the rates of death, myocardial infarction and stroke, the primary end-points of the study in patients with diabetes mellitus. The overall trial results reported a 22% reduction in relative risk of the primary end-point. Thus, the subgroup of patients with diabetes derived at least as much benefit in reduction of cardiovascular events and deaths as those without diabetes. This trial demonstrates that ACE inhibitors not only improve the survival of patients with heart failure, asymptomatic left ventricular dysfunction and myocardial infarction, and reduce the rate of fall in renal function in those with nephropathy, but also benefit those with diabetes and hypertension. The cardiovascular protection afforded by ramipril could not be accounted for by BP reduction alone and occurred in the presence or absence of a history of hypertension, cardiovascular disease or microalbuminuria. A sub-study demonstrated prevention of nephropathy and reduced progression of carotid atherosclerosis with ramipril therapy. Also, the drug was well tolerated and provided as much cardiovascular protection in patients with renal failure. These data provide strong support for the use of ACE inhibitors in high-risk patients with diabetes mellitus, even in those without hypertension, for the prevention of cardiovascular and microvascular events. Of note is the fact that these drugs cannot be used during pregnancy and can cause hypotension and renal failure, particularly in patients with renal artery stenosis, heart failure or those on diuretics. Also, in predisposed patients such as those with renal
failure, these drugs can cause hyperkalemia. Thus, it is important to monitor BP, serum creatinine and potassium levels within a week or two of starting therapy or escalating the dose.

Equally impressive protection with ACE inhibitor-based therapy comes from the Captopril Prevention Project (CAPPP) Randomized Trial.\cite{27} In this study, 10,985 hypertensive patients, 5\% of whom were diabetics, were enrolled to either captopril (50 mg in one or two divided doses) or conventional therapy (thiazides or beta-blockers) to compare their efficacy in preventing myocardial infarction, stroke or cardiovascular death.\cite{27} Eligible patients had to have a diastolic BP of $\geq 100$ mmHg on two occasions and a step-care approach was used to reduce this pressure to at least 90 mmHg. The average age of diabetics was about 55 years and they had an average BP of 163/97 mmHg. In the overall trial, there was no difference in the primary outcome between the two treatments. However, results in the diabetic subpopulation showed that the composite primary end-point was 41\% less common in those treated with captopril (RR 0.59, $p=0.019$). Myocardial infarction was reduced by 66\% ($p=0.002$), cardiovascular events by 33\% ($p=0.030$) and total mortality by 46\% ($p=0.034$). Although the overall systolic BP was higher in the captopril group, those randomized to captopril or conventional therapy in the diabetic cohort had similar baseline BPs. Also, the BP was slightly but significantly higher in the captopril group throughout the trial. Despite poorer BP control and once-daily dosage in 48\% of the patients, the protective effect of captopril was remarkable in the diabetic cohort. These findings further support the nonhemodynamic benefits of ACE inhibitors.\cite{28}

Two smaller trials also support the evidence of the cardiovascular protection provided by ACE inhibitors in patients with diabetes and hypertension. The Appropriate BP Control in Diabetes (ABC) trial\cite{29} was a single-center, randomized, controlled trial comparing the effects of moderate control of BP (80–89 mmHg) with those of intensive control (target diastolic BP $<75$ mmHg) on the incidence and progression of complications of diabetes. In each of the two groups, patients received enalapril or nisoldipine, a long-acting dihydropyridine calcium-channel blocker. Four hundred and seventy patients participated in the trial and the primary end-point was the rate of change of creatinine clearance measured every six months. Cardiovascular end-points were secondary outcomes. The trial was halted early at 67 months of the study by the Data and Safety Monitoring Committee who observed a significant difference in the rate of cardiovascular events between the subgroups of patients treated with the study drugs in the hypertensive cohort of the study. Patients had an almost identical control of BP, diabetes and serum lipid levels through the 5 years of the study; however, 25 episodes of myocardial infarction were seen in the nisoldipine group and 5 in the enalapril group. The risk ratio was 5.5 (95\% CI: 2.1–14.6) and 7.0 after adjustment for baseline variables. The study demonstrates the cardiovascular protection afforded by ACE inhibitors in diabetic patients as compared to a long-acting calcium-channel blocker.

**Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET)**\cite{30} was an open-label trial of 380 hypertensive patients with Type 2 diabetes assigned to fosinopril (20 mg/day) or amlodipine (10 mg/day) and followed for up to 3.5 years. If BP was not controlled by one drug, the other was added, such that at the end of the trial approximately one-third of the patients in each group were on fosinopril or amlodipine, or both. The trial was designed to assess comparability of lipid levels and glucose control, but like the ABCD trial, cardiovascular outcomes were secondary end-points. In this trial as well, there were more cardiovascular events in the amlodipine group than the fosinopril group. The combined risk of acute myocardial infarction, stroke or angina requiring hospitalization was 14/189 vs. 27/191 in the fosinopril and amlodipine groups, respectively (hazards ratio 0.49, 95\% CI: 0.26–0.95). This was despite greater BP reduction (–19 mmHg systolic) in the amlodipine group compared to the fosinopril (–13 mmHg systolic) group. In crude analyses, according to post-randomization treatment given to control BP, the patients who received fosinopril only (n=131), amlodipine only (n=141), and a combination of fosinopril plus amlodipine (n=108) experienced 10, 27 and 4 major vascular events, respectively. The study was not powered to measure the benefit of combination therapy against monotherapy; however, compared with the use of amlodipine only, the risk of major vascular events was significantly decreased with the use of fosinopril only and with the combination treatment (hazards ratio 0.37, 95\% CI: 0.18–0.77, $p=0.008$ and hazards ratio 0.17, 95\% CI: 0.06–0.50, $p=0.001$, respectively).

**Trials Reporting Older Antihypertensive-based Therapy**

Other antihypertensive agents are effective in preventing cardiovascular outcomes in patients with Type 2 diabetes mellitus. The UKPDS trial, which used predominantly older antihypertensive agents for treating patients with diabetes and hypertension, has already been discussed. Three other trials using older agents are discussed below.
Antihypertensive and Lipid-lowering therapy to reduce Heart-attack (ALLHAT) trial: Since alpha-blockers are metabolically favorable and do not perturb dyslipidemia in diabetics, they were recommended for these patients. However, the alpha-blocker arm of the Antihypertensive and Lipid-lowering therapy to reduce Heart-attack (ALLHAT) trial\textsuperscript{32} comparing four drugs—chlorthalidone, lisinopril, doxazosin, and amlodipine—has been halted. This was because the doxazosin group, as compared to that given chlorthalidone, had a 19% higher risk of stroke, 25% higher risk of combined cardiovascular disease, double the risk of CHF, 16% higher risk of angina and 15% higher risk of coronary revascularization.\textsuperscript{33} These risks were also increased in the diabetic subpopulation of the trial and were similar to the non-diabetic population. This trial also confirms the increased risk of cardiovascular events in patients with diabetes; in this study, the risk was increased by 24% (12%–38%), and that of heart failure by 114% (76%–159%) compared to non-diabetics with hypertension and one coronary risk factor. In the ALLHAT trial, the favorable effect of chlorthalidone was demonstrated despite a fall in potassium and increase in fasting glucose levels, and a smaller decline in cholesterol compared to that in the doxazosin group.

**Systolic Hypertension in the Elderly Program (SHEP) trial:** In the Systolic Hypertension in the Elderly Program trial,\textsuperscript{34} 12% of the 4736 patients studied were diabetics and were randomized to either a diuretic or beta-blocker-based regimen compared to a group given a placebo to evaluate cardiovascular end-points. Placebo-corrected fall in BP was 9.8/2.2 mmHg. There was improvement in all cardiovascular end-points (34% reduction) and coronary events (56% reduction). However, there was statistically insignificant reduction in total mortality (−26%, 95% CI: −54–18) and strokes (−22%, 95% CI: −55–34%). These results represent the most compelling evidence that diuretics or beta-blockers are effective in reducing hypertension-related complications even in a diabetic population.

**Swedish Trial in Old Patients with Hypertension-2 (STOP-2) trial:** The primary objective of this randomized controlled open-label trial was to compare fatal cardiovascular events with calcium-channel blockers (felodipine, isradipine) and ACE inhibitors (benazepril, lisinopril), with conventional agents (diuretics or beta-blockers) in older hypertensives (age 70–84 years).\textsuperscript{35} Eleven percent of the 6614 patients were diabetics. The primary outcome of diabetics did not differ among the three groups, suggesting that all these agents are equally efficacious.

**Trials Reporting Calcium-Channel Blockers-based Therapy**

**Long-acting dihydropyridine calcium-channel blockers:** The diabetic subgroup of the HOT trial used felodipine, a long-acting dihydropyridine calcium-channel blocker, as first-line therapy for treatment of hypertension. It was found to confer cardiovascular protection. This has already been discussed. Three other trials using long-acting dihydropyridine calcium-channel blockers are discussed below.

**Systolic Hypertension in Europe (Syst-Eur) and Systolic Hypertension in China (Syst-China) trials:** Both these trials tested the utility of nitrendipine-based therapy in preventing strokes in older patients with isolated systolic hypertension. Other cardiovascular events were also recorded as secondary end-points. The study groups of these trials included 10% and 4% of patients with diabetes mellitus, respectively.

In the diabetic subgroup (n=492) of the Syst-Eur trial,\textsuperscript{36} BP was reduced by an average of 8.6/3.9 mmHg after a median follow-up of 2 years. In the treated diabetic group, after adjustment for confounding variables, strokes were reduced by 73%, all cardiovascular end-points by 69% and all combined cardiac events by 63%. Total mortality was reduced by 55% and cardiovascular mortality by 76%. These benefits were larger than those seen in the non-diabetic subgroup. For example, in the non-diabetic subgroup, there was a 38% reduction in strokes and a 38% reduction in combined cardiovascular events.

In the diabetic subgroup (n=98) of the Syst-China trial,\textsuperscript{37} placebo-corrected blood pressure reduction was 6/4.7 mmHg at 2 years. There were trends in reduction of cardiovascular and total mortality, strokes and cardiac events. Due to the small number of subjects, only total cardiovascular end-points reached statistical significance (risk reduction 74%, p=0.03).

**Intervention as a Goal in Hypertension Treatment (INSIGHT):** This study asked the question: Does long-acting nifedipine (GITS) reduce cardiovascular mortality in a high-risk hypertensive population compared to those treated by a diuretic-based therapy?\textsuperscript{23} The primary end-points were cardiovascular death, stroke, myocardial infarction and congestive heart failure. Nifedipine was given to 3157 patients and 3164 patients received a hydrochlorothiazide (HCTZ)/amiloride combination. A step-care approach was used to reduce BP to <140/90 mmHg or cause a fall of at
least 20/10 mmHg. The overall rate of primary outcome was 18.2 events/1000 patient-years in the nifedipine group and 16.5/1000 patient-years in the diuretic group (risk ratio 1.11, p=0.34). There were 1302 diabetics in the study who required additional treatment compared to nondiabetics for an equivalent fall in BP. The relative risk of primary outcome was increased 1.47-fold with the presence of diabetes. Amongst the diabetics, 8.3% in the nifedipine group and 8.4% in the diuretic group had events—there was no significant difference between the groups. Thus, the trial results suggest that long-acting dihydropyridine calcium-channel blockers were not damaging in patients with diabetes mellitus when compared to diuretics.

**Nondihydropyridine Calcium-Channel Blockers**

The Nordic Diltiazem Study (NORDIL): The Nordic Diltiazem Study (NORDIL) evaluated the role of diltiazem, compared to older antihypertensive drugs, diuretics or beta-blockers in reducing cardiovascular morbidity and mortality. It was an open-label, prospective randomized study with blinded evaluation of endpoints in 5410 patients receiving diltiazem and 5471 patients receiving older antihypertensive drugs. A step-care approach was used to reduce diastolic BP to <90 mmHg. In this trial, 727 patients were diabetics. Combined cardiovascular events were similar in the two groups; however, strokes occurred less in the diltiazem group (relative risk 0.8, p=0.04). The diabetic subgroup had an almost two-fold higher cardiovascular event rate but there were no differences between diltiazem and diuretic/beta-blocker-based regimens in cardiovascular outcomes.

**Conclusions**

In patients with diabetes, the target BP must be lower than that for the general hypertensive population. The Joint National Committee (JNC) VI guidelines call for a target BP of <130/85 mmHg in diabetics. Based on data from the HOT study, UKPDS and other trials, a target BP of <130/80 mmHg in patients with diabetes and hypertension has been suggested by the National Kidney Foundation to prevent cardiovascular and microvascular complications. Analysis of observational data from the UKPDS cohort suggests no threshold effect and a continuous reduction in cardiovascular events with fall in systolic BP. The lowest cardiovascular event rate was seen in diabetic patients with a systolic BP of <120 mmHg. Thus, target BP in patients with diabetes mellitus with hypertension may need to be revised to <120/80 mmHg. In patients with overt proteinuria of at least 1 g/day or more in a population of largely non-diabetic patients, a mean arterial pressure of <92 mmHg (BP <125/75 mmHg) was associated with the best preservation of renal function. Therefore, proteinuric patients, especially those with diabetes mellitus, need aggressive BP control. Those with microalbuminuria may also benefit from similar BP reduction. Should BP in diabetics be lowered to below normotensive levels? Large randomized trials are needed to answer this question.

Angiotensin-converting enzyme inhibitors should be used as first-line agents in patients with diabetes and hypertension. The cost-effectiveness of ACE inhibitors as first-line agents for all patients with diabetes has also been confirmed. But, as emphasized above, reaching the target BP is even more important. Interestingly, both the HOPE and CAPP trials show less incidence of recent diabetes in those randomized to the ACE inhibitor. In patients who are intolerant to ACE inhibitors, for instance due to cough, angiotensin-receptor (AT1) blockers are a logical second choice. In fact, these guidelines may soon change and emerging data suggest that AT1 blockers may be as valuable as ACE inhibitors, at least in preventing microvascular complications. Two large trials, the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Type II Diabetic Nephropathy Trial (IDNT), designed to demonstrate renal protection in patients with Type 2 diabetes, showed a similar benefit of about 28% reduction in death, dialysis or transplantation, or doubling of serum creatinine with AT1 receptor blockade. Other trials to assess the outcome with angiotensin-II receptor blocking agents are ongoing. The protective effects of ACE inhibitors are out of proportion to those conferred by BP reduction alone. For example, the difference between the placebo and ACE inhibitor arms of the HOPE trial was only 3/2 mmHg in favor of the ACE inhibitor; this magnitude of BP reduction would not be sufficient to explain a 22% overall reduction in the rates of death, myocardial infarction and strokes. Thus, this trial lends support to the nonhemodynamic effects of these agents in laboratory animals, which show reduction in tissue fibrosis, cell proliferation, hypertension and vascular injury and improvement in fibrinolysis and endothelial function.

The target BP being lower in hypertensive diabetics, these patients require the use of multiple agents over a period of time as demonstrated by the UKPDS. Furthermore, it may be harder to reduce BP in patients with diabetes. These data suggest that more than two-thirds of patients will need two or more agents to reach the target BP. Which second-line agent should be used? Diuretics or long-acting calcium-
### Table 1. Large randomized trials reporting outcomes in patients with diabetes mellitus and hypertension

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**ACE inhibitor-based trials**

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<th></th>
<th>Total number of patients randomized</th>
<th>Diabetic patients</th>
<th>% with diabetes</th>
<th>Primary aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Outcomes Prevention Evaluation Trial (HOPE) diabetes subgroup</td>
<td>9541</td>
<td>3577</td>
<td>37%</td>
<td>Evaluate the role of ACE inhibitor, ramipril, or addition of vitamin E on outcomes in patients with high risk for cardiovascular events</td>
</tr>
<tr>
<td>The Captopril Prevention Project (CAPPP) trial</td>
<td>10 985</td>
<td>572</td>
<td>5%</td>
<td>Compare the effects of ACE inhibition and conventional therapy on cardiovascular morbidity and mortality in patients with hypertension</td>
</tr>
</tbody>
</table>

**Older antihypertensive agents-based trials**

<table>
<thead>
<tr>
<th></th>
<th>Total number of patients randomized</th>
<th>Diabetic patients</th>
<th>% with diabetes</th>
<th>Primary aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate Blood Pressure Control in Diabetes (ABCD) trial</td>
<td>470</td>
<td>470</td>
<td>100%</td>
<td>Evaluate the role of BP control in patients with Type 2 diabetes with enalapril or nisoldipine on renal function</td>
</tr>
<tr>
<td>Fosinopril v. Amlodipine Cardiovascular Events Trial (FACET)</td>
<td>380</td>
<td>380</td>
<td>100%</td>
<td>Assess the role of fosinopril or amlodipine on lipid and glucose control in patients with hypertension and diabetes</td>
</tr>
</tbody>
</table>

**Calcium-channel blocker-based trials**

<table>
<thead>
<tr>
<th></th>
<th>Total number of patients randomized</th>
<th>Diabetic patients</th>
<th>% with diabetes</th>
<th>Primary aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Hypertension in Elderly Program (SHEP) trial</td>
<td>4736</td>
<td>583</td>
<td>12%</td>
<td>Test the role of diuretic-based regimens to prevent cardiovascular events in elderly Americans with ISH</td>
</tr>
<tr>
<td>Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study</td>
<td>6614</td>
<td>719</td>
<td>11%</td>
<td>Compare the effects of ACE inhibition and calcium-channel blockers to conventional therapy on cardiovascular morbidity and mortality in elderly patients with hypertension</td>
</tr>
<tr>
<td>Systolic Hypertension in Europe Trial (Syst-Eur)</td>
<td>4695</td>
<td>492</td>
<td>10%</td>
<td>Test the role of nitrendipine-based therapy to prevent stroke in elderly Europeans with ISH</td>
</tr>
<tr>
<td>Systolic Hypertension in China Trial (Syst-China)</td>
<td>2394</td>
<td>98</td>
<td>4%</td>
<td>Evaluate the role of nitrendipine-based therapy to prevent stroke in older Chinese with ISH</td>
</tr>
<tr>
<td>Intervention as a Goal in Hypertension Treatment (INSIGHT)</td>
<td>6575</td>
<td>1302</td>
<td>20%</td>
<td>Compare the reduction in cardiovascular morbidity and mortality with long-acting nifedipine compared to diuretic (HCTZ-amiloride)-based therapy</td>
</tr>
<tr>
<td>The Nordic Diltiazem Study (NORDIL)</td>
<td>10 881</td>
<td>727</td>
<td>7%</td>
<td>Compare the reduction in cardiovascular morbidity and mortality with diltiazem compared to diuretics and beta-blockers</td>
</tr>
<tr>
<td>Study population</td>
<td>Study design</td>
<td>Outcomes evaluated</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Age 25–65 years, diabetes and hypertension</td>
<td>RCT, BP goal &lt;180/105 mmHg (n=390) or &lt;150/85 mmHg (n=758). Latter group randomized to atenolol or captopril</td>
<td>First clinical end-point related to diabetes: sudden death, death from hypo- or hyperglycaemia, or macrovascular or cardiovascular complications</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age 50–80 years, essential hypertension</td>
<td>Patients randomized to 3 different DBPts, &lt;80 mmHg, &lt;85 mmHg or &lt;90 mmHg (n=6264 in each group). Half in each group received aspirin 75 mg once daily. Step-care approach with felodipine as first-line drug</td>
<td>All MI, strokes and cardiovascular deaths counted</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age &gt;55 years, previous cardiovascular event or diabetes and one risk factor (smoking, microalbuminuria, hypertension, high TC, low HDL)</td>
<td>DBRCT, ramipril (n=1808) or placebo (n=1769). Not a blood pressure reduction trial. Half the patients in each group randomized to vitamin E or placebo</td>
<td>Composite outcome of stroke, MI or death from cardiovascular cause</td>
<td>19, 20</td>
<td></td>
</tr>
<tr>
<td>Age 25–66 years, treated or untreated primary hypertension if diastolic BP was 100 mmHg or more on two separate occasions. Patients with secondary hypertension, renal failure or those needing beta-blockers excluded</td>
<td>PROBE, captopril (n=5492) or thiazide/beta-blocker (n=5493)-based therapy. Step-care approach to lower DBP to 90 mmHg or less. Initial therapy was with captopril 50 mg/day in one or two doses, atenolol/metoprolol 50–100 mg/day in single dose or HCTZ 25 mg/day or bendrofluazide 2.5 mg/day</td>
<td>Composite end-point of stroke, MI and cardiovascular deaths</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age 40–75 years, Type 2 diabetes, diastolic BP &gt;80 mmHg, on no antihypertensive medications. Patients with hypertension (DBP &gt;90 mmHg) reported here</td>
<td>DBRCT, enalapril (n=235) or nisoldipine (n=225). Factorial 2×2 design. Agressive BP control (DBP &lt;75 mmHg) or less aggressive BP control (DBP 80–89 mmHg). Follow-up mean of 6.1 years</td>
<td>Renal function measured every 6 months with creatinine clearance. Cardiovascular outcomes counted for secondary aim</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Hypertensive Type 2 diabetics, patients with pre-existing cardiovascular or renal disease excluded</td>
<td>Open-label trial with 380 hypertensive diabetics randomly assigned to fosinopril (20 mg/day) or amlopidine (110 mg/day) and followed up for up to 3.5 years. If BP not controlled, another study drug was added. Thus, 58 patients in the fosinopril group and 50 patients in amlopipine group received both drugs</td>
<td>Lipid profiles and HbA1c assessed. Cardiovascular outcomes counted for secondary aim</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Age &gt;55 years, hypertension plus one other cardiovascular risk factor (previous MI, stroke, LVH, Type 2 diabetes, smoking, low HDL)</td>
<td>DBRCT, active control. Present data limited to 24 335 patients randomized to receive either CTD (12.5–25 mg o.d.) (n=15 268) or doxazosin (2–6 mg q.d.), for a planned follow-up of 4–8 years. BP target &lt;140/90 mmHg with the least dose of the study drug. Step 2 agent (atenolol 25–100 mg/day, reserpine 0.05–0.2 mg/day, clonidine 0.1–0.3 mg/day). Step 3 drug (hydralazine 25–100 mg b.d.)</td>
<td>Composite outcome of fatal CHD and nonfatal MI. Secondary outcomes: 1. all-cause mortality, 2. combined CHD (CHD death, nonfatal MI), revascularization, hospitalization (angina), stroke, 3. combined CVD: CHD death, nonfatal MI, stroke, revascularization, angina, CHF, PVD</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Elderly, ISH</td>
<td>DBRCT. Placebo vs. chlorthalidone (12.5–25 mg q.d.) + atenolol (25–50 mg q.d.) or reserpine (0.05–0.1 mg q.d.) to reduce systolic BP to &lt;160 mmHg or by least 20 mmHg for those with BP &gt;160–179 mmHg</td>
<td>5-year rates of major cardiovascular events, strokes, fatal and nonfatal MI, major CHD events and total mortality</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Age 70–84 years, BP 180/105 mmHg or higher.</td>
<td>PROBE, enalapril or lisinopril 10 mg/day (n=2205) or thiazide/beta-blocker (n=2213) or feldopidine or isradipine 2.5 mg (n=2195)-based therapy. Step-care approach to lower BP &lt;160/95 mmHg</td>
<td>Composite end-point: fatal stroke, MI and cardiovascular deaths</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Elderly, ISH</td>
<td>DBRCT, placebo (n=2297) or nitrendipine (n=2398)-based therapy. If BP not controlled, HCTZ 25–25 mg/day or enalapril (5–20 mg/day) or both were added. BP was reduced by at least 20 mmHg systolic to &lt;150 mmHg</td>
<td>Stroke. Other cardiovascular events were also recorded as secondary objectives</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Elderly, ISH</td>
<td>DBRCT, placebo (n=1141) or nitrendipine (n=1123)-based therapy. If BP not controlled, HCTZ 25–25 mg/day or enalapril (5–20 mg/day) or both were added. BP was reduced by at least 20 mmHg systolic to &lt;150 mmHg</td>
<td>Strokes. Other cardiovascular events were also recorded as secondary objectives</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Age 55–80 years, SBP &gt; or =150 and DBP &gt; or =95 SBP = or &gt; 160 mmHg after a 4-week placebo run-in</td>
<td>DBRCT, niludipine 30 mm q.d. (n=3289) v. HCTZ-amiloride (n=3126). Target BP &lt;140/90 mmHg or fall of at least 20/10 mmHg. Step-care approach to lower BP</td>
<td>Composite end-point: cardiovascular death, strokes, MI, CHF</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Age 50–69 years, DBP &gt; or =100 mmHg x2</td>
<td>PROBE, diltiazem or thiazide/beta-blocker-based therapy. Step-care approach to lower DBP to &lt;90 mmHg</td>
<td>Composite end-point: strokes, MI and cardiovascular deaths</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>
channel blockers would be a logical second choice because of the synergistic BP reduction seen with ACE inhibitors and their safety in the diabetic population as noted in trials.\textsuperscript{44} My first choice is the addition of a diuretic. Short-acting dihydropyridine calcium-channel blockers, such as nifedipine, that may cause a sudden and unpredictable drop in BP and increase mortality, should not be used.\textsuperscript{45} The UKPDS and SHEP studies have shown the benefit of beta-blockers which should be included in the regimen of any patient with coronary artery disease. However, alpha-blockers should be used as a last resort because they compare unfavorably with diuretics. In patients with renal disease, loop diuretics may be required to reduce sodium and volume overload, and improve BP control.\textsuperscript{46} Physicians should not hesitate to use combination therapy to improve patient compliance, and patient participation should be encouraged through simple programs such as home BP monitoring.\textsuperscript{47} Attention to other modifiable risk factors such as dyslipidemia, hyperglycemia and atherosclerosis (aspirin use) is important. Trials that reduce homocysteine with folic acid and vitamins B\textsubscript{6} and B\textsubscript{12} are still being carried out (Table 2).

Finally, the importance of diabetes prevention cannot be overemphasized. In a recent study, a program of regular exercise, weight loss and dietary control (restricting total and saturated fat, and increasing dietary fiber) was effective in reducing the risk of developing diabetes mellitus by 58% and volume overload, and improve BP control.\textsuperscript{46} Physicians should not hesitate to use combination therapy to improve patient compliance, and patient participation should be encouraged through simple programs such as home BP monitoring.\textsuperscript{47} Attention to other modifiable risk factors such as dyslipidemia, hyperglycemia and atherosclerosis (aspirin use) is important. Trials that reduce homocysteine with folic acid and vitamins B\textsubscript{6} and B\textsubscript{12} are still being carried out (Table 2).

Table 2. Management of hypertension in diabetes mellitus

<table>
<thead>
<tr>
<th>Target BP</th>
<th>&lt;130/80 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>If proteinuria &gt;1 g/day target BP</td>
<td>&lt;125/75 mmHg</td>
</tr>
<tr>
<td>There is no threshold limit of benefit, the lower the BP the less the cardiovascular mortality</td>
<td></td>
</tr>
<tr>
<td>Agent of choice: ACE inhibitors</td>
<td></td>
</tr>
<tr>
<td>If BP not at goal, add low-dose HCTZ (6.25-12.5 mg/day)</td>
<td></td>
</tr>
<tr>
<td>If BP not at goal, titrate up ACE inhibitor</td>
<td></td>
</tr>
<tr>
<td>If BP not at goal, increase diuretic dose (maximum dose 25 mg HCTZ, if patient has no renal failure)</td>
<td></td>
</tr>
<tr>
<td>A 3d third agent, beta-blockers preferred due to cardioprotective effect</td>
<td></td>
</tr>
<tr>
<td>A 4th fourth agent, long-acting calcium-channel blockers</td>
<td></td>
</tr>
<tr>
<td>If still not at goal; assess compliance, dietary sodium intake, renal function</td>
<td></td>
</tr>
<tr>
<td>A stress and treat: atherosclerosis (aspirin), dyslipidemia (goal LDL &lt;100 mg/dL) and glucose</td>
<td></td>
</tr>
<tr>
<td>Folic acid, vitamin B\textsubscript{6} and vitamin B\textsubscript{12} for reducing homocysteine</td>
<td></td>
</tr>
</tbody>
</table>

HCTZ: hydrochlorothiazide

low-fat dairy products, such as the "DASH diet",\textsuperscript{49} adopted with the aid of a dietitian, are also useful in reducing blood pressure, the public health benefits of which can be substantial. As we strive to maximize the value of our resources, these nonpharmacologic interventions can be of particular value in the care of patients with diabetes mellitus and hypertension.

References

1. www.who.int/ncd/dia/databases


Several techniques are used for the introduction of a permanent pacing lead. These are cephalic venotomy, intrathoracic subclavian venepuncture (ISV) and extrathoracic subclavian venepuncture (ESV).

The most widely used technique is ISV, first introduced by Littleford et al. in 1979. However, this procedure is expensive since it requires a percutaneous lead introducer (PLI) and lead wastage could occur due to lead fracture or insulation damage due to the crush syndrome, or entry of the lead at an acute angle into the subclavian vein. It is also associated with a small but significant percentage of serious complications such as pneumothorax, hemothorax and brachial plexus injury.

These shortcomings led to a renewal of interest in the older procedure of cephalic venotomy. Though an old technique, it still remains the easiest, safest and most economical of the three procedures. Unfortunately, cephalic venotomy fails in 15% of patients due to absence or extreme slenderness of the vein, or due to an inadvertent tear of the vein during the introduction of the lead. This calls for an alternative approach.

In 1993, Magney et al. introduced the technique of ESV, which is easier and safer than ISV. In this procedure, the subclavian vein is entered more laterally than in the ISV technique.

Technique of extrathoracic subclavian venepuncture (ESV)

First, body landmarks are identified: (i) the coracoid process; (ii) the middle of the sternal angle; and (iii) the medial and lateral ends (i.e. acromioclavicular joint and sternoclavicular joint) of the clavicle. For ESV, the entry point of the needle is the junction of the medial two-third and lateral one-third of the line joining the coracoid process of the scapula and the mid-point of the sternal angle. The target point is the junction between the medial one-third and lateral two-third of the clavicle, which is the site where the subclavian vein (SV) enters the thorax crossing the first rib (Fig. 1). For venepuncture, the needle is directed from the entry point to below and behind the target point on the clavicle. The entry and target points are marked on the skin by superficial abrasions, preferably before antiseptic dressing and draping, when the patient is in a supine position on the table. Using the needle (18 G) of the PLI, ESV is accomplished either before or after making an incision for the pacemaker pocket (Fig. 2). In the former situation, the pacemaker pocket is made by an incision starting from the entry point and extending up to the deltopectoral groove laterally, 2 cm below and parallel to the clavicle. At the time of venepuncture, the patient is put in the Trendelenburg position (to dilate the subclavian vein) and the needle is advanced from the entry point to the under-surface of the clavicle behind the target point or a little (1–2 cm) below it. If the puncture is not successful, the needle is withdrawn, landmarks verified and the

Fig. 1. Relationships between the extrathoracic subclavian vein, clavicle, first rib, and the soft tissues of the costoclavicular region. The two lines identify anatomical landmarks.

Cp: coracoid process; E: needle entry point; L: lateral border of the clavicle; M : medial border of the clavicle; Sa: sternal angle; T: target point
procedure repeated without moving the needle sideways so as to avoid vascular injury. If the venepuncture is successful, a guidewire is introduced through the needle up to the right atrium under fluoroscopic control. The Trendelenburg position is then reversed to avoid bleeding. The lead is inserted by substituting the guidewire with the sheath of the PLI in the usual manner. If two leads are to be inserted, a second guidewire is inserted before peeling off the sheath.

The technique of ESV described above is the anatomic blind method. We have successfully used this technique in 102 cases of pacemaker implantation in the last 18 months. Other methods using echocardiography, fluoroscopy and contrast guidance have also been reported. At times we took the help of fluoroscopy to visualize the relationships between the needle path, rib and clavicle if initial attempts at the anatomic blind method failed.

**Discussion**

For inserting a lead during the implantation of a pacemaker, ESV is an easy and safe procedure. The success rate of this technique (>90%) is higher than that for ISV and it is free from major complications such as pneumothorax, hemothorax and brachial plexus injury. The only complication encountered by us was an inadvertent puncture of the subclavian artery in 2 cases (out of 102), without any major adverse outcome. The safety of this procedure is explained by the relationships between the extrathoracic portion of the subclavian vein and surrounding vital structures. At the site of the puncture, the first rib protects the underlying apex of the lung and the subclavian artery behind the vein. The major lymphatics, other blood vessels and nerves are medial to the path of the venepuncture needle. In difficult cases, i.e. in obese patients and those with a deformed chest wall anatomy, one can use fluoroscopy to determine the relationship between the first rib and the needle path. Even in the hands of the inexperienced, complications are remarkably few. Fracture or insulation damage of the lead is rare. This is due to the fact that the lead is not entrapped in the subclavius muscle or costoclavicular ligament and is thus protected from the mechanical stress of certain shoulder girdle movements.

**Conclusions:** Extrathoracic subclavian venepuncture is a safe and effective technique of inserting one or two permanent pacing leads either through the classic pacemaker pocket or before making the pocket. Proper localization of bony landmarks is an important prerequisite for successful ESV. The failure rate and incidence of complications with the ESV are less than that with the ISV technique. Moreover, ESV is not only simpler and therefore preferable to ISV, but long-term lead-related complications are also less.

**References**

1. Littleford PO, Parsonnet V, Spector SD. Method for the rapid and atraumatic insertion of permanent endocardial pacemaker electrodes through the subclavian vein. Am J Cardiol 1979; 43: 980–982
Extensive Arterial Calcification in Aortoarteritis

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Sri Sathya Sai Institute of Higher Medical Sciences, Prashanthi Gram, Anantapur, Andhra Pradesh

Fig. 1. Extensive calcification of the brachial artery

Fig. 2. Calcification of carotid and subclavian arteries

Fig. 3. Calcification of celiac trunk and left femoral artery

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A 33-year-old male presented with a history of painless progressive swellings in both elbows, the upper portion of the neck, popliteal fossae and the left groin. He was a known hypertensive for the past 10 years. He had symptoms of crural vascular claudication for the past one year but on examination there were no ischemic changes. He gave no history of syncope, dizziness, post-prandial abdominal discomfort, tuberculosis or syphilis. On evaluation, the swellings were vascular in origin; pulsations were absent in the carotid, brachial, popliteal and femoral arteries bilaterally. The blood pressure could not be recorded in any of the four limbs. There was no parathyroid enlargement. On investigation, the hemoglobin level was 9.2 g%, total leukocyte count was 6800/cmm, differential leukocyte count showed 59% polymorphs, 38% lymphocytes, 3% eosinophils and the ESR showed a 5 mm fall in the first hour. Urinalysis showed a 2+ proteinuria and no abnormal sediments. The serum creatinine level was 1.9 mg%, blood urea 40 mg% and blood sugar 99 mg%. Serum total proteins were 7.8 g%, albumin:globulin ratio 5.3:2.5, serum sodium 140 mEq/L, serum potassium 4.4 mEq/L, serum calcium 9.3 mg% and serum phosphate 2.7 mg%. The fundus showed Grade II hypertensive retinopathy. Plain X-rays showed extensive calcified arteries with large mass formation in the brachials (Fig. 1), carotids, subclavians (Fig. 2), left femoral (Fig. 3) and abdominal visceral arteries. Echocardiography showed concentric left ventricular hypertrophy with mild mitral regurgitation. Ultrasound of the kidneys revealed a contracted right kidney with loss of cortico-medullary differentiation and a normal-sized left kidney with calcification at its hilum. In view of these findings, a diagnosis of aortoarteritis with significant arterial calcification was made.

Aortoarteritis is a chronic panarteritis of the large elastic arteries. Though this disease has a worldwide distribution, it is common in South-East Asia and rare in European and North American countries. Aortoarteritis is a chronic disorder of the great arteries resulting in diminished caliber and insufficient blood flow to the areas supplied by these vessels. Initial descriptions were recorded by Davy (1839), Broadbent (1875), Turp (1901) and Takayasu (1908). Etiologically, though tuberculosis and syphilis were suspected initially, autoimmunological and genetic abnormalities with specific HLA associations (A9, A10, B5, B40, BW2) are presently under consideration. Pathologically, it is a panarteritis of the large elastic arteries with mononuclear and giant cell infiltration of all the layers of the arterial wall. Additional findings include intimal proliferation, fibrosis, disruption of the elastic lamina, aneurysm formation and calcification. In a study by Jain et al., calcification was reported in the abdominal aorta in 0.4% and in the arch of the aorta in 3.2% of cases. The point of interest in this patient was the finding of unusual, extensive, dense and nodular calcification of all the major arteries.

References
Randomized, Single-blind, Placebo-controlled Pilot Study of Catheter-based Myocardial Gene Transfer for Therapeutic Angiogenesis Using Left Ventricular Electromechanical Mapping in Patients with Chronic Myocardial Ischemia

Vale PR et al. Circulation 2001; 103: 2138–2143

Summary

In this pilot study by Jeffery Isner and his group, 6 patients of drug refractory, end-stage coronary artery disease (CAD), unsuitable for angioplasty or coronary artery bypass grafting (CABG) were randomized (1:1) to receive catheter-based myocardial gene transfer of naked plasmid DNA encoding vascular endothelial growth factor-2 (ph VEGF-2) or placebo (mock procedure) into ischemic myocardium. Patients received 6 injections of ph VEGF-2 (total dose 200 µg) or placebo by a steerable, deflectable 8 F catheter incorporating a 27-gauge needle advanced percutaneously to the left ventricular myocardium. Injections were guided by NOGA left ventricular electromechanical mapping. Patients in the placebo arm became eligible for crossover into the gene therapy group if they had no clinical improvement 90 days after the mock procedure. Catheter injections (n=36) were well tolerated and there were no complications as a result of the procedure. Patients in the gene therapy group experienced reduced angina (36.2±2.3 v. 3.5±71.2 episodes/week) and reduced nitroglycerin (NTG) consumption (33.8±2.3 v. 4.1±1.5 tablets/week) after gene delivery and the effect persisted for at least 360 days. Electromechanical mapping also demonstrated a reduction in the mean area of ischemia (10.2±3.5 v. 2.8±1.6 cm², p=0.04) and improved myocardial perfusion by SPECT sestamibi scanning for up to 90 days. In contrast, in patients randomized to the placebo arm, clinical improvement was not sustained beyond 30 days. Similarly, patients in the placebo arm demonstrated no improvement in electromechanically obtained mean area of ischemia (9.9±6.7 v. 9.6±6.3 cm²) at 90 days and no improvement in SPECT myocardial perfusion. In fact, all 3 patients randomized to the placebo group crossed over to the gene therapy group as per the provision made in the protocol of the trial. This trial demonstrates the feasibility, safety and potential efficacy of percutaneous myocardial gene transfer to human left ventricular myocardium.

Comments

The number of patients with end-stage CAD is continuously increasing, with some of the western reports quoting the prevalence to be as high as 30%. However, these patients pose a therapeutic dilemma. They are drug refractory and their lesions are unsuitable for conventional therapy such as angioplasty or CABG. Several emerging therapies have been tried in this situation with variable results. Initially, transmyocardial laser revascularization was found to provide clinical benefits in terms of relief of angina and decrease in NTG consumption, but this therapy failed to show improvement when objective hard end-points such as improvement in thallium images were taken into consideration. Recently, the DIRECT trial, a randomized, placebo-controlled trial, showed no advantage in the laser group. In this context, angiogenic gene therapy has consistently shown improvement in objective parameters of ischemia on radionuclide imaging and electromechanical mapping in animal models and in human subjects. This is the first randomized, placebo-controlled pilot study which has shown both subjective and objective improvement in ischemia after delivery of the plasmid VEGF-2 gene to ischemic myocardium as compared to no improvement in the placebo group. However, there are several limitations of the present study. First of all, the sample size is too small and the primary end-point of the study was safety and feasibility of gene delivery, not efficacy. Second, VEGF is associated with capillary angiogenesis (i.e. capillary collaterals less than 15 µ in size) and not arterial collaterals (approximately 100 µ in size), and therefore the dramatic and sustained improvement in the VEGF gene therapy group seems remarkable. Recently, it has been realized that arteriogenesis rather than angiogenesis should be the goal of this therapy and therefore therapy with the VEGF gene alone may be inadequate. Finally, in this study, patients but not the physicians were blinded to the treatment and therefore a possibility of bias exists. This report suggests that it is feasible to replace currently employed operative approaches with catheter-based techniques for gene therapy.
STAT was a randomized trial comparing the efficacy of primary stenting with that of accelerated tissue plasminogen activator (t-PA) in patients presenting with acute ST elevation myocardial infarction (AMI). One hundred and twenty-three Canadian patients presenting with AMI were randomized to primary stenting (n=62) or thrombolysis (n=61). Exclusion criteria for enrollment in the study were cardiogenic shock, active bleeding, history of stroke, previous coronary artery bypass grafting (CABG), renal failure and percutaneous transluminal coronary angioplasty (PTCA) within the preceding 6 months. Immediate angiography was performed in 61 patients assigned to primary stenting and based on the angiographic picture, stents could be successfully deployed in 50 patients (81%). Plain balloon angioplasty was performed in 2 patients. Four had primary CABG for left main coronary artery stenosis or triple vessel disease (TVD) and the remaining 5 were treated with medical therapy (diffuse disease or <70% stenosis in infarct-related artery [IRA]). Abciximab was given to only 12 patients (19.4%). An average of 1.3 stents were implanted per patient, at a mean pressure of 14.2±2.3 atm. A residual diameter stenosis <50% was achieved in all stented patients. Patients in the thrombolysis group received accelerated t-PA and heparin. Unscheduled angiography was performed in 39 patients (63.9%) in the t-PA group for unabated chest pain associated with ST segment elevation, or deteriorating hemodynamic status. The primary end-point of the study was the composite of death, reinfarction, stroke or repeat target vessel revascularization (TVR) for ischemia at six months. The event rates for the stent versus the t-PA group were as follows: mortality 4.8% v. 3.3%, reinfarction 6.6% v. 16.4%, stroke 1.6% v. 4.9%, (no statistically significant difference). However, repeat TVR for ischemia was statistically lower in the stent group (14.5% v. 49.2%, p<0.001). Overall, the primary end-point at six months was significantly reduced in the stent group as compared to the t-PA group (24.2% v. 55.7%, p<0.001).

Thrombolytic therapy is widely used for AMI despite continuing controversy about its clinical effectiveness. Historically, the use of intravenous thrombolytic therapy has resulted in a 13%–50% decline in short-term mortality, depending upon the time of initiation of therapy. Primary angioplasty is better in establishing vessel patency and in achieving grade 3 TIMI flow (an important consideration for subsequent prognosis). Concerns with primary angioplasty are delay in administering treatment and higher cost. Trials comparing primary PTCA with t-PA, such as PAMI and GUSTO-IIB, have shown that PTCA reduces death, reinfarction or stroke at 30 days but not at 6 months. This loss of benefit has been presumed to be due to re-occlusion and restenosis. In this context, primary stenting may provide several clinical benefits over plain balloon angioplasty, namely better immediate result, bigger minimum luminal diameter (MLD) and lower rate of restenosis. Indeed, randomized trials comparing primary PTCA with primary stenting, as in the stent-PAMI and STENTIM-2 studies, have shown reduction in the 6-month, composite end-point of death, reinfarction, stroke or repeat TVR, as well as reduced restenosis rates with stenting. However, in these studies randomization was performed only after angiography and therefore may not represent the actual clinical situation. In the present study, randomization was performed at the outset and patients enrolled on an intention-to-treat basis. This study has shown that a policy of primary stenting is clearly superior to accelerated t-PA. However, the study has several limitations. Because of the small sample size, the effect of primary stenting on mortality could not be addressed. In fact, mortality was slightly higher in the primary stenting group (4.8% v. 3.3%). Out of 218 patients presenting with AMI, only 123 could be randomized due to various reasons. Furthermore, the crossover rate from the t-PA to the angioplasty group was 11.5%. The routine use of abciximab was discouraged early in the trial; as a result only 12 patients (19.4%) received this therapy in the stent group. Several studies have shown that concomitant use of abciximab in high-risk situations such as AMI leads to better myocardial salvage and a better clinical outcome.
Novel Dosing Regimen of Eptifibatide in Planned Coronary Stent Implantation (ESPRIT): A Randomized Placebo-controlled Study

Summary

The ESPRIT was a double-blind, randomized, placebo-controlled trial conducted at 92 centers in the USA and Canada to test the efficacy of a new dosing regimen of the glycoprotein (Gp) IIb/IIIa inhibitor—eptifibatide—in 2064 low-risk patients undergoing percutaneous coronary interventions (PCIs) with elective stent implantation. Of noted was the fact that all patients with accepted indications for these drugs were excluded, i.e. fresh myocardial infarction within 24 hours and unstable angina needing PCI. Other exclusion criteria were PCI within the previous 90 days, previous stent implantation at the site, treatment with a Gp IIb/IIIa inhibitor or a thienopyridine within the last 30 days, and any history suggestive of a bleeding diathesis or recent stroke. The other important aspect was the use of a novel dosing strategy of two boluses of 180 µg/kg given 10 min apart and an infusion of 2 µg/kg/min for 18–24 hours, so as to achieve &gt;80% inhibition of platelet Gp IIb/IIIa receptor. The primary end-point was a composite of death, myocardial infarction, urgent target vessel revascularization and contain-out Gp IIb/IIIa inhibitor therapy within 48 hours. The secondary end-point was the composite of death, myocardial infarction and urgent target vessel revascularization at 30 days. Heparin was given in a dose of 60 U/kg (not exceeding 6000 U) to achieve an activated clotting time (ACT) of 200–300 seconds. Any stent design was allowed as per operator preference (over 20 types), though no Palmaz–Schatz stents were used. A bail-out strategy was also provided for patients with abrupt closure, no-reflow and coronary thrombosis, where the study drug was discontinued and open-labelled eptifibatide was given. Almost all patients received a thienopyridine (97%) as well as stents (96.2% in the treated group and 98.2% in the placebo group). Though total mortality was not different (0.1% vs. 0.2%), the 43% reduction in the end-points of death or myocardial infarction at 48 hours (5.5% vs. 9.2%, p=0.0013) and the 40% reduction in the primary end-point (6.6% vs. 10.5%, p=0.0015) in the eptifibatide group led to the premature termination of the trial by the data and safety monitoring board. The benefit was found to be consistent to the same degree at 30 days, and occurred irrespective of baseline variables such as age, weight, sex, diabetes and disease presentation. The rate of major bleeding was higher (1.1% vs. 0.4%, p=0.027), and 2 cases of severe thrombocytopenia occurred in the treated group. Investigators concluded that routine pretreatment with eptifibatide substantially reduces ischaemic complications in coronary stent intervention.

Comments

The results of this study are concordant with the available data on the Gp IIb/IIIa inhibitor abciximab, in the EPISTENT, EPIC and EPiLOG studies, though this is the first time such salutary benefits have been reported with eptifibatide. This may stress the point that the real determinant of outcome following PCI is perhaps the degree of platelet inhibition achieved (&gt;80%), and not the type of Gp IIb/IIIa inhibitor used. The reduction in the secondary end-point at 30 days is similar to the observed benefit in EPISTENT (10.5% to 6.9%, in ESPRIT v. 8.9% to 5.2% in EPISTENT). This is despite the fact that the ESPRIT patients were a low-risk PCI population in whom abciximab is generally not used, compared with the high-risk patients included in EPISTENT. In addition, bail-out use of eptifibatide would have lowered the event-rate in the placebo group of ESPRIT, thus narrowing the difference between the two groups. In contrast, previous studies (IMPACT-II), with a conventional dose of eptifibatide in which only approximately 50%–60% inhibition of platelet aggregation was achieved, could not duplicate the benefits seen with abciximab. This highlights the importance of optimal platelet inhibition in routine elective PCI utilizing stents. One factor that could have increased events in the placebo group was the use of a low dose of heparin (60 U/kg), but the event rates in the placebo group were not different in the lowest versus highest tertiles of ACT. However, major bleeding was higher in the highest tertile of ACT in the eptifibatide group, thus leading the investigators to suggest a target ACT of 200–250 seconds, when this drug is used in the recommended dose. The incidence of thrombocytopenia was lower (0.2%) in this study, compared to the 0.7% reported with abciximab. The Gp IIb/IIIa inhibitors are the only therapeutic modality thus far to have decreased the incidence of fatal and non-fatal myocardial infarction and repeat target vessel revascularization, an outcome that was not seen even with the use of stents.

These findings support the use of Gp IIb/IIIa inhibitors in patients undergoing PCI, whether elective or high-risk. Cost constraints have thus far militated against their routine use, at least in countries like India. The cost advantage of eptifibatide over abciximab, while preserving the therapeutic utility, may help in increasing its use during routine PCI in our country.
Stable Ventricular Tachycardia is not a Benign Rhythm: Insights from the AVID Registry

Rait M H et al.  Circulation 2001; 103: 244–252

Summary

The Antiarrhythmics versus Implantable Defibrillators (AVID) trial showed significantly reduced mortality with implantable cardioverter-defibrillator (ICD) in patients with unstable ventricular tachycardia (VT), i.e. patients with VT having syncope, left ventricular ejection fraction (LVEF) \(< 0.40\%\), and angina or significant hemodynamic compromise during VT. Patients with sustained, stable VT were not included in the trial because the risk of arrhythmic death in this group was thought to be too low. However, these patients were enrolled in the AVID registry and their clinical characteristics and discharge treatments were recorded. Mortality data were obtained through the National Death Index. Thus, in the AVID registry, two groups of patients were available for comparison—440 patients with stable VT and 1029 patients with unstable VT. The group with stable VT had a higher LVEF, less congestive heart failure, were less likely to be smokers, and more likely to have a history of previous VT or to be on antiarrhythmic therapy at the time of the index arrhythmia. Patients with stable VT were less likely to receive an ICD, were more likely to receive antiarrhythmic drug therapy without an ICD, were more likely to receive no specific antiarrhythmic therapy and were more likely to have catheter ablation for VT.

The stable VT patients tended to have a higher mortality (33.6\% v. 27.6\%) at 3 years with a relative risk (RR) of death of 1.22 (p=0.07). The most important interaction was found between \(\beta\)-blocker therapy and type of VT. The mortality was similar in both types of VT not on \(\beta\)-blockers, but there was significant mortality reduction in the unstable VT but not in stable VT patients given \(\beta\)-blockers. The investigators concluded that stable VT is not a low-risk arrhythmia and that ICD implantation may reduce mortality in this group of patients.

Comments

This is a retrospective analysis of a non-randomized group of patients with VT of different etiologies and presentations. Thus, this strong conclusion of increased risk of stable VT has been derived from a heterogeneous group of patients. In the end, the authors have also commented that ICD “may decrease mortality in patients presenting with stable VT”. It is acceptable that patients with structural heart disease and left ventricular dysfunction are at increased risk of malignant ventricular arrhythmias. The conclusions drawn from the study should be seen in their proper perspective. There are several limitations of these observational data. The patients were not randomized, there was no correction for baseline differences in the 2 groups at entry and therapy was not randomly assigned or planned, but left to physician preference. In 1993, Olson et al. showed that mortality due to sudden death was identical in 122 patients with tolerated versus nontolerated VT at 19.5 months (25\% v. 24\%), and that the single best predictor of mortality was LVEF. In the present study also, mortality correlated significantly with LVEF (p<0.001 for LVEF >0.25\%), as it did in the main AVID trial. A meta-analysis of the 3 large secondary prevention trials of ICD versus amiodarone (AVID, CIDS and CASH) showed that the survival benefit of 28\% in the ICD arm (p=0.0006) that was achieved by reduction of sudden death by 50\%, led to a net improvement in survival of only 4.4 months over 6 years of follow-up. So even in the groups with established benefit of ICD, the actual survival benefit in real terms is not impressive. Though it would now be unethical to withhold ICD therapy in the subgroups dealt with in these large trials, this is definitely not the status for patients covered by the AVID registry, and as such, the conclusions of this paper should be read with all the shortcomings of the data in mind.
Calendar of Conferences

July 29–Aug 10, 2001, 27th 10-Day Seminar on the Epidemiology and Prevention of Cardiovascular Diseases, Granlibakken Conference Centre, Tahoe, CA
Contact: David C Goff Jr, Seminar Director, c/o American Heart Association, 7272 Greenville Avenue, Dallas, Texas 75231, USA
Fax: 1 214 373 3406

September 1-5, 2001, XXIII Congress of the European Society of Cardiology, Stockholm, Sweden
Contact: European Congress Organization (ECOR), The European Heart House, Stockholm, Sweden
Fax: 33 4 9294 7620
e-mail: scientific@escardio.org

October 3-6, 2001, 13th Asia-Pacific Congress of Cardiology, Manila, Philippines
Contact: Dr Noe A Babilonia, Chairman, Organizing Committee, 13th APCC, Suite 1108, 11th Floor, East Tower, PSE Centre, Exchange Road, Ortigas Commercial Complex, Pasig City, Manila 1605, Philippines
Fax: 632 634 7441

October 5-7, 2001, 8th Annual Conference of Indian College of Cardiology, Bhubaneswar, India
Contact: Professor HN Mishra, Organizing Secretary, Manavilas Lane, Ice Factory Road, College Square, Cuttack 753 003, Orissa
e-mail: hnmishra@doctor.com
or
Dr Rajeev Lochan, Chairman, Scientific Committee, Apollo Hospitals, Mathura Road, New Delhi 110 044
e-mail: Rajeev@india-web.net

October 13-16, 2001, VII Asian-Pacific Symposium on Cardiac Pacing and Electrophysiology, Beijing, China
Contact: Dr Hu Da Yi, Secretary-General, VII APSPE, Beijing Red Cross Chaoyang Hospital, 8 Baijiazhang Road, Chaoyang District, Beijing 100020, People's Republic of China
Fax: 86 10 6593 7858
e-mail: heart@bme-cspe.org

November 11-14, 2001, 74th Scientific Session, American Heart Association, Anaheim, California, USA
Contact: American Heart Association, 7320, Greenville Avenue, Dallas, Texas 75231, USA
Fax: 1 214 373 3406

December 6-9, 2001, 53rd Annual Conference of Cardiological Society of India, Hyderabad, India
Contact: Professor P Krishnam Raju, Organizing Secretary, Care Hospital, D. No. 6-3-248/1, Former Hotel Bhaskara Palace, Road No. 1, Banjara Hills, Hyderabad 34
Fax: 040-6668888
e-mail: drkrishnamraju@hotmail.com
or
Dr Anjan Lal Dutta, Chairman, Scientific Committee, Indian Heart House, P-60, C.I.T. Road, Scheme VII M, Kankurgachi, Calcutta 700 054
Fax: (033) 355 6308
e-mail: csi-cal2.vsnl.net.in

February 8-10, 2002, VIth World Congress of Echocardiography and Vascular Ultrasound, New Delhi, India
Contact: Dr (Col) SK Parashar, Secretary General, C-144, Sarita Vihar, New Delhi 110044,
Fax: 6942222
e-mail: parashar@del6.vsnl.net.in

March 17-20, 2002, 51st Annual Scientific Sessions, American College of Cardiology, Atlanta, Georgia, USA
Contact: American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814, USA
Fax: 1 301 897 9745

May 5–9, 2002, XIV World Congress of Cardiology, Sydney, Australia
Contact: The Congress Secretariat, QVB Post Office Locked Bag Q4002, Sydney, NSW 1230, Australia
Fax: 61 2 9290 2400
e-mail: wcc@icms.com.au

July 17-21, 2002, 14th Asean Congress of Cardiology, Kuala Lumpur, Malaysia
Contact: Dr David KL Quek, Chairman, Organizing Committee, c/o Letter Box 1, 15th Floor, Menara Merais, 1 Jalan Petaling Jaya 46300, Selangor, Malaysia
Fax: 60 3757 8363

August 31–September 4, 2002, XXIV Congress of the European Society of Cardiology, Berlin, Germany
Contact: European Society of Cardiology (ECOR), B.P.174, Sophia Antipolis Cedex F-06903, France
Fax: 33 49244 7601