Chronic Constrictive Pericarditis: Pending Issues

SS Kothari, Ambuj Roy, VK Bahl
Department of Cardiology, All India Institute of Medical Sciences, New Delhi

Chronic constrictive pericarditis (CCP) is a well characterized clinical entity. With advances in the understanding of hemodynamics, Doppler echocardiography, and cardiac cross-sectional imaging, the diagnosis of CCP has been straightforward. However, it often masquerades as chronic liver disease, cardiomyopathy, unexplained heart failure, etc. Furthermore, there is a remarkable paucity of information regarding the pathogenesis, and the optimal management of patients with CCP. In this article, we provide a brief perspective on the recent advances in CCP, and highlight the need for more evidence-based data regarding a disease that is still common in India.

Pathogenesis

The precise pathogenesis of CCP remains unknown, and is scantily investigated. CCP may result from the progression of an acute pericarditis from a dry stage through an effusive, absorptive, and constrictive phase sequentially; or it may result from a smouldering fibrosis with no previous history of an acute pericarditis (as occurs in the majority of patients). The factors responsible for the resolution of inflammation or its progression to severe fibrosis remain unknown. For example, in nearly half the patients with tubercular pericardial effusion resolution occurs without constriction, while the rest develop CCP despite adequate and similar antitubercular therapy. The virtual absence of CCP following rheumatic fever, and its low incidence in tubercular pericarditis in HIV-positive patients are noteworthy. Little research has been done to unravel the inflammatory repertoire of the pericardial tissue. The role of cytokines in tubercular pericardial effusion has been investigated recently. It appears that tubercular pericarditis is a hypersensitivity reaction to antigens such as tuberculoproteins. The increased production of interferon-gamma, tumor necrosis factor-alpha, and interleukin-1 and interleukin-2 in tubercular pericardial effusion suggest that the inflammation is orchestrated by T-helper-1 lymphocytes. T-lymphocytes and activated macrophages seem to play an important role in granuloma formation and fibrosis. However, the exact mechanism has not been elucidated. Similarly, the mechanisms of constriction in postoperative patients, in patients with collagen vascular disease, or those with the rare but interesting hereditary disease mulibreynanism remain unexplored and unexplained.

Mechanism of Fluid Retention

In general, patients with CCP retain more water and sodium than patients with myocardial disease. The ascites in CCP is out of proportion to edema, and also occurs earlier than peripheral edema, a sequence opposite to that seen with other causes of congestive heart failure (CHF). The cause of this “ascites precoex” has never been satisfactorily explained. It could simply be a reflection of very high right atrial pressures compared to other causes.

Correspondence: Professor VK Bahl, Department of Cardiology, All India Institute of Medical Sciences, New Delhi 110029

e-mail: vkbahl2002@yahoo.com
of CHF. Increased venous pressures, hypoalbuminemia resulting from protein-losing enteropathy, cardiac cirrhosis, increased capillary permeability, and impedance to lymph flow have been suggested but appear to be inadequate explanations.

The mechanisms of fluid retention in CCP have been explored in a systematic fashion in only one study. In 16 patients with untreated CCP, it was found that the magnitude and mechanisms of sodium and water retention differed somewhat from a similar congestion resulting from decreased cardiac output due to myocardial failure. For a comparable reduction in cardiac output, volume retention was higher and vascular resistance was lower in patients with CCP compared to those with myocardial disease. The activation of the renin–angiotensin–aldosterone and sympathetic systems were found to be similar in CCP and other causes of CHF. The atrial natriuretic peptide (ANP) levels in patients with CCP were five times higher than those in normal controls, but were only one-third of those seen in myocardial disease. The ANP levels in CCP are less than what might be expected on the basis of right atrial pressures alone. This may be primarily due to less distensible atria caused by the constrictive process in CCP, as ANP release is mediated by atrial stretch. The greater salt and water retention in CCP could be due to smaller increase in ANP levels. The ANP hypothesis has been suggested to explain the lack of pulmonary edema in CCP and tamponade despite very high central pressures. ANP is shown to increase capillary hydraulic conductivity, and enhance transcapillary fluid movement. To the best of our knowledge, ANP in restricted cardiomyopathy (RCM) has not been studied systematically.

Interestingly, other neurohumoral or autonomic effects may also be important. In CCP, severe autonomic dysfunction was reported in all segments of the autonomic nervous system. In contrast, autonomic dysfunction may also be important. In CCP, severe autonomic dysfunction was reported in all segments of the autonomic nervous system. In contrast, autonomic dysfunction was reported in all segments of the autonomic nervous system. In contrast, autonomic dysfunction was reported in all segments of the autonomic nervous system.

Prevention of Constrictive Pericarditis

Nonsteroidal anti-inflammatory drugs, colchicines, and steroids may reduce the chances of CCP by preventing recurrence of pericarditis. However, the data on this aspect are scanty and inconclusive. Limited information is available regarding even the commonly occurring tubercular pericarditis. The oft-quoted South African trial in 240 patients of tubercular pericarditis reported a significant reduction in the need for repeat pericardiocentesis in patients randomized to receive steroids for 11 weeks. But steroids did not reduce the need for pericardiectomy at 24 months. The study has been criticized as it did not include all-cause mortality, did not analyze data on the basis of intention-to-treat, and excluded patients not adhering to the protocol. A re-analysis of this trial by Ntsekhe et al. also did not give definite answers. In the other trial of steroids in patients with established CCP, 2 of the 53 patients (4%) treated with prednisolone and 7 of the 61 patients treated with a placebo (11%) died from pericarditis, and 11 (21%) and 18 (30%), respectively, required pericardiectomy. However, these differences were not statistically significant.

Corticosteroids could have an adverse impact on the already compromised immune status of patients with HIV and tubercular pericarditis. However, in a recent trial of 58 patients, steroids led to a significant reduction in all-cause mortality in HIV-positive patients with tubercular pericarditis on 18-month follow-up. Interestingly, a re-analysis of the trial data failed to show the benefit of steroids. Thus, there is still a need for large, multicentric, prospective controlled trials to accurately assess the benefit of adjuvant steroids in tubercular pericarditis.

Role of pericardial drainage: Usually, large effusions that are unresponsive to treatment, unexplained effusions or effusions that last for longer than 3 months warrant pericardiocentesis. Such pericardiocentesis is curative in half the cases. Whether routine drainage of pericardial effusion is helpful in preventing the occurrence of CCP has rarely been investigated. Strang et al. randomized patients with tubercular pericarditis to open drainage, or no drainage, and followed them up for up to 24 months to assess their outcome. Open pericardial drainage did not decrease mortality or improve clinical outcome at follow-up. The routine drainage of pericardial fluid in tubercular pericarditis does not seem to be useful, especially in areas with a high prevalence. It may be useful in areas where tuberculosis is an uncommon cause of pericarditis as it may help to obtain pericardial fluid for examination. In a study of 71 patients with large pericardial effusion (>2 cm on echocardiography) of different etiologies, routine drainage did not yield significant diagnostic information, and was not useful in preventing the occurrence of cardiac tamponade or CCP.

The efficacy of pericardiocentesis in preventing CCP in hemorrhagic effusion has not been tested specifically. In purulent pericarditis, adequate drainage and fibrinolytic agents seem to reduce the occurrence of CCP, but again the data are limited. In one study of 6 children with pyopericardium, instillation of intrapericardial streptokinase at a dose of 10 000 to 15 000 U/kg twice
daily for a mean of 6 days led to the resolution of pericarditis, and freedom from CCP on follow-up.29

**Diagnosis of CCP**

**Hemodynamics:** The hemodynamic criteria to diagnose CCP, viz. elevated diastolic pressures, typical pressure waveforms, and equilibration of pressure of all four chambers in diastole, have been discussed widely, yet these may not be diagnostic in individual cases. In one study, one-fourth of the patients could not be identified by these criteria of equalization of the right and left ventricular diastolic pressures within 5 mmHg, pulmonary artery systolic pressure less than 50 mmHg, and right ventricular end-diastolic pressure more than one-third of the right ventricular systolic pressure.30 Evidence of dissociation of intracardiac and intrathoracic pressures, and the presence of ventricular interdependence (i.e. reciprocal respiratory variation in right ventricular/left ventricular pressures) have improved the accuracy. Ventricular interdependence had 100% sensitivity and 95% specificity for distinguishing CCP from RCM.31 However, in real-world situations several patient-related or other factors complicate the interpretation of laboratory data. The presence of localized constriction, associated myocardial dysfunction, other valve disease, obesity, obstructive airway disease, previous infarction, and other co-morbidities may influence their measurement. For example, a disproportionately elevated pulmonary artery wedge pressure was seen in patients with mitral valve disease,32 and even evidence of ventricular interdependence was reportedly lacking in a patient with a localized constriction.33

**Doppler echocardiography:** Doppler echocardiographic parameters have been a very valuable addition to the diagnosis of CCP, and in its differentiation from RCM. The initial study that suggested a cut-off of 25% respiratory variation in mitral valve inflow velocities was based on the data from only 7 patients with CCP.34 Subsequently, a larger study found that 12% of patients did not show diagnostic changes in these echocardiographic parameters.35 Several caveats need to be considered in individual cases. For example, a very high preload may be one reason for the absence of respiratory variation,36 and a reduction in preload may be required to bring out the typical pattern, or fluid challenge may be required to diagnose patients with occult CCP.37 In addition, irregular breathing, irregular heart rate, and short diastolic periods resulting from tachycardia may cause difficulty in the interpretation of respiratory variation of Doppler velocities. The additional use of tissue Doppler imaging (TDI) may further enhance the diagnostic utility of echocardiography. Reduced mitral annular velocity on TDI was reported in RCM, whereas these parameters were normal in patients with CCP in the initial reports.38,39

**Cross-sectional imaging:** The other commonly used investigation for the diagnosis of CCP is cross-sectional imaging with computerized tomography (CT) and magnetic resonance imaging (MRI). The diagnostic hallmark of these tests is the presence of pericardial thickening with or without calcification. While a minimal amount of pericardial calcium is better detected by CT scan, MRI provides better soft tissue characterization.40 Pericardial thickening of more than 3 mm is usually taken as abnormal; the usual thickening of the pericardium being 1–2 mm. The actual thickness of the pericardium is 0.4–1 mm, and this discrepancy between MRI and pathological measurement is most likely due to a combination of volume averaging, chemical shift artifact, motion artifact, and the inclusion of a small amount of pericardial fluid in MRI measurements.41 Though commonly used, the data on the diagnostic utility of CT/MRI in CCP are not robust. In one small study of 29 patients, pericardial thickening on MRI was found to be 88% sensitive and 100% specific for detecting CCP.42

It is important to look for additional findings suggestive of CCP, such as dilated inferior vena cava (IVC), enlarged atria, tubular-shaped ventricles, ascites and pleural effusion on CT/MRI images. Myocardial tagging has also been suggested as a new method of mitral/tricuspid annular movement. As normal ventricles contract, there is a slippage between the myocardium and pericardium; however, once pericardial adhesions develop, this slippage is absent and the tag lines passing through the myocardium and pericardium are not deformed during the cardiac cycle.43 The presence of abnormal diastolic motion of the septum on cine MRI may also be a useful finding to diagnose CCP, and to distinguish it from RCM.44

Thus, no single test in isolation should be considered diagnostic of CCP.

**CCP with Normal Pericardial Thickness**

It is well known that pericardial thickening may be present without CCP; however, it is not as well recognized that CCP may occur with normal thickness of the pericardium, which was reported in 18% of 143 patients in a recently published series from the Mayo Clinic. These patients most commonly had post-surgical and post-radiation CCP.12 Their clinical characteristics were similar to patients with CCP with a thickened pericardium, and pericardiectomy
was very effective in relieving the symptoms. Microscopy of the excised pericardium was abnormal in all the patients, and included the presence of focal fibrosis, focal calcification or inflammation. Thus, pericardiectomy should not be denied to patients with typical clinical and hemodynamic features of CCP but with a normal pericardial thickness on imaging.

**Transient CCP**

It is conceivable that occasionally, the inflammatory exudates causing clinical CCP may resolve with no features of constriction on follow-up. Such an event occurred in 15% of patients with tubercular pericarditis in one report from South Korea. The resolution occurred within 2 months in the majority of patients. Perhaps transient CCP could occur even more often with purulent pericarditis. However, decisions regarding the management of these patients should be based on the overall clinical profile.

**Surgical Aspects**

Pericardiectomy is the definitive treatment for CCP but its timing, surgical approach, and preoperative stabilization need careful consideration. Various approaches to pericardiectomy, i.e. median sternotomy, lateral thoracotomy and bilateral thoracotomy with or without the use of cardiopulmonary bypass, and anterior or total removal of the pericardium have been described depending on patient population or personal preferences. The surgical mortality of pericardiectomy continues to be high, and has been generally reported to be 6%–12%. A subgroup of patients with calcific CCP had a mortality of 19% in a recent series. The negative predictors of survival after pericardiectomy include NYHA class IV, low-voltage ECG complex, markedly increased atrial pressure, associated organ failure, and post-radiation CCP.

The optimal timing of pericardiectomy is important. Pericardiectomy is unwarranted too early or too late in the course of the disease. Long-standing CCP may lead to myocardial atrophy. Medical therapy may be better in some patients with CCP having adverse risk factors in whom the surgical mortality approaches 30%–40%. In purulent pericarditis, it is important not to intervene in the subacute stage when a plane of cleavage has not developed clearly. The occurrence of low cardiac output following CCP is often a reflection of the chronicity of CCP and associated myocardial atrophy. Acute cardiac dilatation and failure following pericardiectomy may occur unpredictably and is not well characterized. Preoperative inotropes for 48 hours and preoperative digitalization are often used to reduce the chances of postoperative heart failure but their effectiveness is not clear. The improvement following pericardiectomy may be rapid but, at times, occurs over a few weeks. However, residual CCP or recurrence of CCP due to epicardial constriction remains a persistent problem. Multiple incisions into the fibrous epicardium while protecting the myocardium and coronary arteries are useful in relieving the constriction (waffle procedure). In patients with extensive calcific plaques, where large plaques do not permit the development of cleavage planes, wedge incisions that reach up to the epicardium help release constriction. More recently, ultrasonic decalcification has been used in tough calcific lesions.

**Conclusion**

CCP continues to intrigue and engage clinicians despite advances in knowledge about the disease. No single test or diagnostic finding should be considered pathognomonic of CCP. A combination of clinical and investigative results should be thoughtfully analyzed to prevent misdiagnosis. Further research is required to understand the pathogenesis, prevention, and optimal treatment of CCP.

**References**


Prudent Diet and Preventive Nutrition From Pediatrics to Geriatrics: Current Knowledge and Practical Recommendations

Enas A Enas, A Senthilkumar, Hancy Chennikkara, Marc A Bjurlin
Coronary Artery Disease in Asian Indians (CADI) Research Foundation, and University of Illinois, Chicago, USA

“A man is what he eats” (German proverb). Food provides not only the essential nutrients for life but also other bioactive compounds for the promotion of health and the prevention of disease.1–3 The results of 50 years of intensive worldwide research support the conclusion that diet is the major environmental cause of atherosclerosis and cardiovascular diseases (CVD), especially in genetically susceptible individuals.4 A high-caloric diet, combined with limited physical activity, contributes to dyslipidemia, insulin resistance, diabetes, and obesity. All these abnormalities increase the risk of CVD. Over the past few decades, the prevalence of obesity has doubled in adults, and quadrupled in teenagers in the USA. A similar pattern is emerging in India, where an epidemic of coronary artery disease (CAD) and diabetes is under way, with no signs of a downturn. Whereas the rates of CAD have declined by 60% in the US, the rates have increased by 300% in India over the past 30 years.5 The public and physicians are constantly bombarded with confusing and conflicting dietary advice. This review analyzes the important recent developments in the fields of diet and nutrition for the prevention and treatment of CVD and diabetes, with particular attention to Asian Indians.

Facts and Myths about Cholesterol, Fats, and Meats

The modern understanding of the role of nutrition in heart disease began in 1903 when Anitschkow and Chalatow found that a diet of meat, milk, and egg produced atherosclerosis in rabbits. A decade later, serum total cholesterol (TC) level was found to be the agent responsible. Contrary to common belief, the contribution of dietary cholesterol to serum TC is small (<10 mg/dl). The average adult on a western diet consumes about 300 mg of cholesterol daily, which is about the size of 3 toothpicks, and hardly 3 cal. Nonetheless, high intakes of dietary cholesterol increase the number of circulating low-density lipoprotein (LDL) particles.6 Dietary cholesterol is found only in the animal kingdom; 3 oz of beef, lamb, or pork contains 75 mg of cholesterol. Most of the cholesterol in poultry is in the skin, and some in dark meat. One cup of milk has 33 mg, 2 egg yolks have 560 mg, and 100 g of brain has 2000 mg of cholesterol. One hundred grams of shrimp contain about 150 mg of cholesterol but <1 g of saturated fat. The recommended dietary intake of cholesterol and various types of fat is given in Table 1.1,6–12 The contribution of dietary saturated fat to serum TC is very large—10 times greater than that of dietary cholesterol. Fats are substances consisting of a combination of fatty acids, which are classified as saturated (SAFA), monounsaturated (MUFA), polyunsaturated (PUFA), and transunsaturated (TRAFA), depending on the location and number of double bonds.13 It is not often appreciated that the quality of the fat is more important than the quantity of fat consumed. The National Cholesterol Education Program (NCEP) recommends an intake of total fat of 25%–35%, MUFA up to 20%, PUF A up to 10%, and SAFA <7% of the total energy14 (Table 1). Although many affluent Asian Indians consume 50% of energy from fat, the average consumption is about half this amount (20%–25% of the energy). Increasing the MUFA intake to 20%, and total fat intake to 35% of the energy appears to be appropriate for Asian Indians because of the beneficial effects on high-density lipoprotein (HDL) and triglycerides (TG). The NCEP dietary guidelines for PUF A and SAFA seem appropriate for Asian Indians without any modification.

Saturated fatty acids, the arch villain of atherosclerosis: Excessive consumption of SAFA is the principal dietary culprit contributing to elevated serum TC level, which is the primary determinant of atherosclerosis.15,16 Differences in CAD mortality worldwide are explained by differences in SAFA intake and the resulting serum TC levels in 40 countries, except for France, Finland, and India.16–18 Intake of SAFA suppresses the LDL-receptor activity and decreases the clearance of LDL from the circulation, resulting in a marked elevation of its level.19
SAF A raises the serum TC level thrice as much as PUF A, and MUF A lowers it. For example, substitution of 20% of the daily energy intake of carbohydrate by SAF A increases the TC level by 30 mg/dl, whereas PUF A and MUF A lower it by 10 mg/dl.\textsuperscript{13} Most of this increase is due to an increase in LDL. Although some increase in HDL also occurs, it is not sufficient to offset the atherogenicity and thrombogenicity resulting from marked elevation of LDL.\textsuperscript{6,20}

Our diet contains SAF A of different chain lengths with varying atherogenic properties. According to their chain lengths, SAF A can be classified as short chain (4:0–6:0), medium chain (8:0–10:0), long chain (12:0–18:0), and very long chain (20:0–24:0) fatty acids. Stearic acid (C18:0) is desaturated to oleic acid soon after its absorption, and hence does not raise the TC level.\textsuperscript{21,22} Therefore, its use need not be restricted and, in fact, it can be recommended.\textsuperscript{23} SAF A with chain lengths of 12–16 have the most cholesterol-raising properties.\textsuperscript{24} These are lauric acid (C12:0), myristic acid (C14:0), and palmitic acid (C16:0). These 3 fatty acids account for only 25%–30% of the total dietary fat but 60%–70% of SAFAs in western diets.\textsuperscript{24} Palmitic acid is the most common fatty acid in the human diet, and the principal SAF A in both animal fats and palm oil. In a study conducted in a metabolic ward, 40% of energy as palmitic acid raised the TC by 25 mg/dl \textit{v.} 15 mg/dl with lauric acid.\textsuperscript{21} Myristic acid is the most powerful cholesterol-raising SAF A, and increases the TC level 50% more than palmitic acid. Replacement of 20% of energy from carbohydrate with myristic acid raises the blood TC level by 46 mg/dl, compared to 30 mg/dl with palmitic acid, and 20 mg/dl with lauric acid.\textsuperscript{25} Most of the rise in the TC level is due to an increase in LDL, the respective contribution from HDL being 16 mg/dl, 8 mg/d and 12 mg/dl.\textsuperscript{25} The major sources of myristic acid are butter and tropical oils (Table 2).\textsuperscript{6,20–25} The TC-raising potential of lauric acid is 33% less than that of palmitic acid, and it is the principal SAF A in coconut and palm kernel oils, both containing 48%\textsuperscript{,23–25} Coconut and palm oils are also high in myristic acid (18%), and this explains why the consumption of these oils raises the LDL level in a fashion similar to that of butter (Fig. 1).\textsuperscript{25,26} Studies in laboratory animals indicate that coconut oil increases both TG and LDL levels;\textsuperscript{6,27,28} the claim

| Table 1. Recommended daily energy intake and major sources of dietary fats\textsuperscript{16–12} |
|-----------------|-----------------|-----------------|
| **Recommended intake** | **Current intake (USA)** | **Major sources** |
| Total fat | 30%–35% (40–75 g) | 34% | Dairy products and animal flesh are the major sources of dietary fat; the former contribute more than the latter. |
| Cholesterol | <200 mg | 270 mg | Egg yolk, brain, organ meat, beef, lamb, pork, poultry (thigh and skin), shell fish, shrimp, prawn, full-fat milk (especially buffalo milk), high-fat dairy products (cream, ice cream, milk shake, cheese, curd) |
| SAF A | <7% (10–15 g) | 12% | Beef, lamb, pork, bacon, sausage, ribs, poultry with skin, butter, ghee, vanaspati (vegetable ghee), desserts, bakery products (cakes, biscuits, cookies, donut), cheese, ice cream, full-fat milk, tropical oils (coconut, palm kernel, and palm oils) |
| TRAFA | Avoid | <2% | Hard margarine, vegetable shortening, frying fats (especially those used repeatedly), bakery products (cakes, Danish pastry, donuts, crackers, rusk, biscuits, cookies, white bread), French fries, fried chicken, peanut butter, nondairy creamer, tortillas, pizza, and virtually all “crispy and crunchy foods” |
| MUFA | Up to 20% | 14% | Olive oil, canola oil, mustard oil, peanut oil, macadamia nuts, hazelnuts, pecans, peanuts, almonds, cashew nuts, pistachio nuts, avocado, dairy products, beef, lamb, mutton, poultry |
| n-6 PUF A | 7%–8% | 6%–8% | Vegetable oils (soybean, corn, safflower, sunflower, and cottonseed) |
| n-3 PUF A | 2%–3% | <1% | Fatty fish (mackerel, halibut, lake trout, herring, sardines, albacore tuna, salmon), meat, poultry, vegetables (tofu, soybeans, pinto beans, flax seeds), vegetable oils (soybean, canola), salad dressing, whole grains, and DHA-enriched egg, nuts (walnuts, butternut, flax seeds, pecans) |
that lauric acid does not raise TC is not supported by scientific data. Recent studies have shown that caprylic acid (C:8) and capric acid (C:10) raise the LDL level to about 50% that of palmitic acid, and raise the TG level. Coconut oil contains 14% of these two cholesterol-raising SAF A.

Replacing 5% of the daily energy intake of SAF A with MUFA and PUF A could reduce the risk of CAD by 42%. Since 1970, the total fat intake decreased from 42% to 34%, and SAF A from 18% to 12% in the USA, as a result of nationwide changes in dietary habits. This change in dietary fat intake is primarily responsible for the decrease in serum TC level from 220 to 200 mg/dl in the US population. This decrease in TC level is principally responsible for the dramatic reduction in CAD, during a period when the rates of obesity and diabetes doubled in Americans.

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>Chemical structure</th>
<th>Atherogenicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAFA</strong></td>
<td></td>
<td></td>
<td>Highly atherogenic and thrombogenic. Markedly increases LDL level.</td>
</tr>
<tr>
<td>Lauric acid</td>
<td>C12:0</td>
<td>†</td>
<td>Coconut oil 48%, palm oil 48%, and butter fat 3%.</td>
</tr>
<tr>
<td>Myristic acid</td>
<td>C14:0</td>
<td>†††</td>
<td>Most potent cholesterol-raising SAF A. Coconut 18%, palm kernel oil 18%, butter fat 18%, animal fats 1%-5%</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>C16:0</td>
<td>††</td>
<td>Most common and reference standard of SAF A. Palm oil 45%, butter fat 26%, beef fat 26%, mutton fat 24%, chicken fat 23%, pork fat 25%, cocoa butter 26%, coconut oil 9%, and palm kernel oil 8%.</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>C18:0</td>
<td>⇔</td>
<td>Raises HDL level without raising LDL level. Butter fat 13%, beef fat 22%, mutton fat 25%, chicken fat 6%, pork fat 12%, cocoa butter 35%, coconut oil 3%, and palm oil 4%.</td>
</tr>
<tr>
<td><strong>TRAFA</strong></td>
<td></td>
<td></td>
<td>Increases Lp(a), TG, small, dense LDL levels. Decreases HDL level; 3-fold increase in cardiac arrest.</td>
</tr>
<tr>
<td>Elaidic acid</td>
<td>C18:1 n-9 trans</td>
<td>†††</td>
<td>Fried food, crispy food, cakes, biscuits, donuts, pizza, reused frying oils.</td>
</tr>
<tr>
<td><strong>MUFA</strong></td>
<td></td>
<td></td>
<td>Significantly lowers LDL level. Raises HDL level.</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>C18:1 n-9</td>
<td>⇓</td>
<td>Butter fat 28%, beef fat 39%, mutton fat 33%, chicken fat 42%, pork fat 45%, cocoa butter 35%, coconut oil 7%, palm kernel oil 14%, and palm oil 39%.</td>
</tr>
<tr>
<td><strong>n-6 PUFA</strong></td>
<td></td>
<td></td>
<td>Lowers LDL levels.</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>C18:2 n-6</td>
<td>⇓</td>
<td>Predominant PUFA in western diets. Decreases LDL, and TG levels, blood pressure, and risk of sudden death. Increase HDL level, heart rate variability. Antiarrhythmic and antithrombogenic effects</td>
</tr>
<tr>
<td><strong>n-3 PUFA</strong></td>
<td></td>
<td></td>
<td>Decreases LDL, and TG levels, blood pressure, and risk of sudden death. Increase HDL level, heart rate variability. Antiarrhythmic and antithrombogenic effects</td>
</tr>
<tr>
<td>Alpha-linolenic acid (ALNA)</td>
<td>C18:3 n-3</td>
<td>⇔</td>
<td>Precursor to EPA and DHA. Flaxseed oil 50%, canola oil 10%, mustard oil 10%</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (EPA)</td>
<td>C20:5 n-3</td>
<td>⇔</td>
<td>Fatty fish (sardines, mackerel, salmon)</td>
</tr>
<tr>
<td>Docosahexaenoic acid (DHA)</td>
<td>C22:6 n-3</td>
<td>⇔</td>
<td>Fatty fish (sardines, mackerel, salmon)</td>
</tr>
</tbody>
</table>
Transfatty acids (TRAFA)—the hardened fat that hardens arteries fast: TRAFA is formed during the partial hydrogenation of vegetable oils, a process that converts oils into solid or semisolid fats for subsequent use in food products. This process not only improves the texture and firmness but also markedly increases the shelf-life of food by minimizing oxidative spoilage. Elaidic acid (n-9 trans 18:1) is the principal TRAFA, although several other trans isomers are also formed. Such oils are used in commercial baked goods, and for cooking in most fast-food chains in western countries. Perhaps an equally important and often neglected cause of TRAFA formation is the spontaneous hydrogenation of vegetable oils during deep-frying. Very small amounts of TRAFA are also found in beef and dairy products (Table 1).

Consumption of TRAFA has a greater adverse effect on lipoproteins than that of SAFA. Whereas both SAFA and TRAFA increase LDL levels considerably, TRAFA also decreases HDL levels, thereby increasing the TC/HDL ratio, the single best lipid-related risk factor for CAD. Replacing 9% of calories from SAFA with TRAFA results in a 20% decrease in HDL level. Other important adverse effects of TRAFA consumption include increases in lipoprotein(a) (Lp[a]), TG, and small, dense LDL levels, as well as increased platelet aggregation, endothelial dysfunction, and sudden death. TRAFA are stronger predictors of CAD and diabetes than SAFA and carbohydrates. In the Nurses’ Health Study, women in the highest versus the lowest quartile of TRAFA consumption had a 50% higher risk of CAD. It is estimated that a substitution of 2% of calories from TRAFA with MUFA and PUFA results in a 53% reduction in CAD risk—a risk double that of substitution of calories from SAFA. TRAFA consumption also markedly increases the postprandial insulin response in diabetic patients. Replacing 2% of energy from TRAFA with PUFA would lead to a 40% reduction in diabetes. SAFA calories should not be replaced by TRAFA calories: doing so is like jumping from the frying pan to the deep-fat fryer. The average consumption of TRAFA in the USA and Europe is low (<2% of energy or 11–27 g/day). However, TRAFA accounts for about 5% of fat in American diets, and 5% of fat stored in adipose tissue. Butter contains 60% SAFA, whereas stick margarine contains 16% TRAFA. The tub or soft margarine contains only 2 g of TRAFA per 15 ml. Therefore, the fat-spread of choice remains soft margarine; olive oil may be an even better substitute. Although many margarines and shortenings previously contained up to 50% of TRAFA, in most western countries, these products currently have a low TRAFA content due to recent manufacturing changes. Frying fats used in fast-food outlets still contain over 30% of TRAFA. French fries sold in these outlets provide 7–8 g of TRAFA per portion. About one-third of TRAFA in the western diet comes from French fries, fried chicken, pizza, and cookies.

The TRAFA consumption is likely to be high in Asian Indians because deep-frying is a favorite mode of cooking at home as well as in restaurants. Deep-frying is associated with spontaneous hydrogenation and TRAFA formation, and repeated re-use of oils previously used for deep-frying may further increase the TRAFA content. These practices appear to be the norm rather than the exception, and may be of enormous public health importance, especially with regard to elevated Lp(a) levels, and high rates of CAD in this population. There is an urgent need to ascertain and disseminate the TRAFA content of vanaspathi (vegetable ghee) and frying oils used in India. As of today, we are not aware of any industrial manufacturing changes aimed at lowering the TRAFA content of Indian foods, as has been done in western countries.

MUFA, the good fat that raises the good cholesterol: Diets high in MUFA (oleic acid C18:1) make LDL resistant to oxidation, restore LDL-receptor activity, and markedly lower LDL levels. Substitution of 20% of energy from carbohydrates with MUFA decreases TC by 10 mg/dl. The reduction in TC is 3-fold higher when MUFA replaces SAFA. For example, TC decreases by 40 mg/dl when 20% of energy from SAFA is replaced with MUFA. The effect on small, dense LDL is even greater. Other beneficial effects of MUFA include the favorable influence on blood pressure, endothelial activation, inflammation, and thrombogenesis. A higher intake of MUFA lowers insulin resistance and diabetes, unlike SAFA and TRAFA, which increase it. Consumption of MUFA offers the unique

**Fig. 1.** Predicted change in HDL and LDL when all fat in Dutch diet is replaced by a particular oil.
advantage of effectively lowering LDL levels without lowering HDL or raising TG levels. Individuals with low HDL levels have a high risk of CAD. Subjects with high TG, especially those with the metabolic syndrome and diabetes, are highly sensitive to the TG-raising effects of a high carbohydrate load. A high carbohydrate diet is associated with highly atherogenic, small, dense LDL particles, while high-fat diets are associated with less atherogenic, buoyant LDL particles. Thus, replacing SAFA with MUFA is more effective in preventing CAD than reducing the total fat intake, especially in Asian Indians, a population with high rates of prevalence of the metabolic syndrome and diabetes.

The NCEP III has recommended up to 20% of total calories from MUFA (Table 1). This recommendation seems particularly appropriate for Asian Indians. In Mediterranean countries, the high intake of MUFA in the form of olive oil is inversely related to CAD. The Nurses’ Health Study and other studies of almost 300,000 Americans showed that a diet rich in MUFA in the form of canola oil also reduces the risk of CAD. Contrary to common belief, energy-controlled, high-MUFA diets do not promote weight gain, and are more acceptable than low-fat diets for weight loss in obese subjects. The addition of MUFA should be at the expense of SAFA and carbohydrates. Since all fats are high in calories (9 cal/g), failure to decrease the energy from carbohydrates and SAFA would invariably result in weight gain, and mitigate most of the beneficial effects of MUFA.

Meat and dairy products, which are also rich in SAFA, provide most of the MUFA in western diets. Olive oil and canola oil are good sources of MUFA (Table 3), canola oil appears to be even better as it contains less SAFA and more PUFA, especially alpha-linolenic acid (ALNA). Mustard oil is high in MUFA but also high in erucic acid, which is known to have toxic effects on the heart. Canola oil is genetically engineered mustard oil without erucic acid. Nuts and avocado are excellent sources of MUFA and are recommended, provided the quantity is no more than 50-100 g/day. Groundnut (peanut) products are a rich source of MUFA; they are inexpensive and widely available in India.

**Table 3. MUFA, PUFA, and SAFA content (%) in 100 g of various cooking oils**

<table>
<thead>
<tr>
<th></th>
<th>MUFA</th>
<th>PUFA</th>
<th>SAFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunflower oil, high oleic (&gt;70%)</td>
<td>84</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Safflower oil, high oleic (&gt;70%)</td>
<td>75</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Olive oil</td>
<td>74</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Almond oil</td>
<td>70</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Mustard oil</td>
<td>59</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Canola oil</td>
<td>59</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>47</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Peanut oil</td>
<td>46</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>Sunflower oil, linoleic (&lt;60%)</td>
<td>45</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>40</td>
<td>42</td>
<td>14</td>
</tr>
<tr>
<td>Rice bran oil</td>
<td>39</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>Palm oil</td>
<td>37</td>
<td>9</td>
<td>49</td>
</tr>
<tr>
<td>Cocoa butter</td>
<td>33</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>Corn oil</td>
<td>24</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>23</td>
<td>58</td>
<td>14</td>
</tr>
<tr>
<td>Walnut oil</td>
<td>23</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td>Sunflower oil, linoleic (&gt;60%)</td>
<td>20</td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td>Cottonseed oil</td>
<td>18</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Safflower oil, linoleic (&gt;70%)</td>
<td>14</td>
<td>75</td>
<td>6</td>
</tr>
<tr>
<td>Palm kernel oil</td>
<td>11</td>
<td>2</td>
<td>82</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>6</td>
<td>2</td>
<td>92</td>
</tr>
</tbody>
</table>

Substituting 20% of energy from SAFA with PUFA decreases the TC level by 40 mg/dl. Most of the reduction is in LDL, and the number of apo B particles. PUFA does not raise the TG level, and sometimes lowers it. The two undesirable effects of PUFA are increased susceptibility for peroxidation, and lowering of the HDL level. HDL levels are reduced by about 1% for every 2% of MUFA or SAFA energy substituted with PUFA.

The substitution of PUFA for SAFA calories has played a major role in reducing TC levels and CAD in the USA. The CAD mortality rate declined by 60% in the past 3 decades in the USA. About a third of the decline in CAD rates is attributed to a 6%–8% decrease in the serum TC level in the population; this, in turn, was due to an increase in the consumption of PUFA from 3% to 6%, and a decrease in SAFA consumption from 16% to 12% of the energy. The importance of PUFA is further underscored by the marked differences in PUFA consumption, which parallel the 4-fold difference in CAD rates between France and Finland. Vegetable oils, such as soybean, corn, safflower, sunflower, and cottonseed, are the primary sources of n-6 PUFA (Table 1). Their average consumption in the western diet is 6%–8% of energy, (17 g/day for men, and 12 g/day for women).

Contrary to previous fears, n-6 PUFA do not antagonize the anti-inflammatory effects of n-3 PUFA nor do they raise the risks of breast, colorectal, or prostate cancer in
However, a very high n-6 PUFA to n-3 PUFA ratio may increase the thrombogenicity through increased production of arachidonic acid and thromboxane A₂. This is because linoleic and linolenic acids use the same set of enzymes for desaturation and chain elongation. An n-6 PUFA to n-3 PUFA ratio of 3:1 appears to be optimum. Japan, which has one of the highest rates of fish consumption, has recently changed the recommendation of this ratio from 4:1 to 2:1; this ratio may be advisable for vegetarians.

**Fish, a tasty way to prevent sudden death:** Fish do not die from myocardial infarction (MI), and populations that consume large amounts of marine foods have a low prevalence of CVD death. Replacing high-fat meat with fish is also associated with a decreased risk of CAD. The results of several large studies show that one or two fish meals per week are associated with a 30%–50% reduction in sudden death. In a meta-analysis of 11 prospective studies involving 116 764 individuals, fish consumption was inversely related to CAD death. This report suggests that 40–60 g/day of fish consumption is optimal, and results in a 40%–60% risk reduction. Greater intake has no additional benefits, and suggests a threshold effect. The amount of n-3 PUFA necessary for cardioprotection is surprisingly low. The current recommendation is to take 2–3 fish meals per week (200–300 g/week of fish). A less

<table>
<thead>
<tr>
<th>Table 4. Omega-3 fatty acids and CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decrease the risk of ventricular fibrillation and sudden death</td>
</tr>
<tr>
<td>• Favorably alter cardiac ion channel function and action potential</td>
</tr>
<tr>
<td>• Decrease the ventricular fibrillation threshold</td>
</tr>
<tr>
<td>• Increase heart rate variability</td>
</tr>
<tr>
<td>• Decrease the risk of stroke and MI</td>
</tr>
<tr>
<td>• Decrease platelet reactivity, aggregability, and the risk of thrombosis</td>
</tr>
<tr>
<td>• Reduce monocyte reactivity</td>
</tr>
<tr>
<td>• Reduce inflammatory cytokines and response</td>
</tr>
<tr>
<td>• Improve endothelial function</td>
</tr>
<tr>
<td>• Reduce the expression of vascular adhesion molecules</td>
</tr>
<tr>
<td>• Markedly lower the TG and remnant lipoprotein levels</td>
</tr>
<tr>
<td>• Decrease the growth of atherosclerotic plaques</td>
</tr>
<tr>
<td>• Decrease homocysteine levels</td>
</tr>
<tr>
<td>• Improve insulin sensitivity and reduce the risk of diabetes</td>
</tr>
<tr>
<td>• Slightly lower blood pressure</td>
</tr>
</tbody>
</table>

Both plant-based (ALNA), and fish-based (EPA and DHA) supplements have shown benefits in secondary prevention. In one such trial of 605 French men recovering from an MI, there was a 70% reduction in total and cardiac death during a follow-up of 27 months in those who received an experimental “Mediterranean diet” using canola oil-based margarine, enriched with n-3 PUFA. Frying fish is associated with an even greater loss of EPA and DHA, and may be particularly harmful if fried in SAFAs. The current intake of DHA and EPA is only 200 mg/day, and needs to be increased 5-fold to meet the dietary goals.
The current intake of n-3 PUFA in the US is 1600 mg/day or 0.7% of the calories, which is about half the recommendation.11 Fish is more beneficial than fish oil, but the latter may be required in most patients with CAD to obtain the required amount of n-3 PUFA.90 Patients with CAD should consume about 1800 mg/day of n-3 PUFA (DHA and EPA) as the best insurance against sudden death.

Alpha-Linoleic acid (ALNA)—the n-3 PUFA of the plant kingdom: There is no DHA and EHA in a vegetarian diet. Vegetarians derive their n-3 PUFA almost exclusively from ALNA, which is also the major type of n-3 PUFA in omnivores.138 There is increasing evidence for the cardioprotective effects of ALNA, albeit less than EPA and DHA.139 In a large study involving 43,700 men, increased intake of ALNA reduced the risk of MI by 60%.64 A similar risk reduction was also observed in the Nurses’ Health Study and Multiple Risk Factor Intervention Trial (MRFIT).93,140 Some vegetable oils are high in ALNA (flaxseed oil 50%, canola oil 10%, mustard oil 10%, soybean oil 7%) while others are low (groundnut oil <0.5%).141 Walnuts are a rich source of ALNA; small concentrations are found in green leafy vegetables, corn oil, almonds, hazelnuts, cereals, pulses, millets, and spices.78,142 Walnuts and canola oil account for most of the ALNA in the western diets.78,101 The recommended intake of ALNA is 2% of energy but the current intake in the USA is 0.6% of energy.11,74

ALNA is readily converted to EPA, and more slowly to DHA; the latter being the major component of phospholipid membranes of the brain and retina.78 The beneficial effects of ALNA are less than half that of DHA and EPA, because the conversion of ALNA to the more active longer-chain metabolites is inefficient: <5%–10% for EPA, and 2%–5% for DHA.90,141,142 This explains why vegetarians have lower levels of n-3 PUFA than omnivores, and also higher platelet aggregability.77 Since the biological effects of plant n-3 PUFA are significantly lower than marine n-3 PUFA, the requirements may be higher (3% of energy) for vegetarians than for nonvegetarians.9,74,77

Protein: Americans eat 80–90 g/day of protein, which is twice the daily requirement, and most of this comes from meat, which is also high in SAFA. Up to 25% of daily energy from protein (but not more than 100 g/day) is permissible if the major source of protein is plant-based. Nuts are important sources of plant protein along with soy, bran, beans, and legumes. Substituting protein for carbohydrates increases HDL and lowers TG levels.144,145 In a meta-analysis of 38 controlled human clinical trials, consumption of soy protein (47 g/day) was associated with a significant 13% decrease in LDL, 10% decrease in TG, and a 2% increase in HDL levels.146 This led to FDA approval for the use of food labels for the health claim that soy protein can reduce the risk of heart disease.

Meat: Although meat contains a significant amount of SAFA, almost half the SAFA is stearic acid, which does not raise TC levels. In addition, meat contains up to 45% of cholesterol-lowering MUFAs. Furthermore, lean meat has much less SAFA than fatty cuts of meat (Table 5).6,147 Lean beef is an excellent source of protein and MUFAs, and has less SAFA than chicken (dark meat); 6 oz of lean beef contains 3.0 g of SAFA v. a chicken thigh which contains 5.2 g of SAFA (the term loin or round signifies lean meat whereas prime or rib signifies fat cuts with very high SAFA in the USA). Chicken and lean beef (not fatty meat) have similar effects on plasma lipoproteins, and are interchangeable in a healthy diet.30,148,149

Glycemic Load: A Potent Predictor of the Metabolic Syndrome and Diabetes

The source, nature, and amount of carbohydrates have a profound influence on postprandial glycemia, which in turn is directly associated with the risk of CAD in patients with diabetes.6,150,151 Foods containing the same amount of carbohydrate (carbohydrate exchange) may have up to a 5-fold difference in glycemic impact, depending on the differences in the digestion and absorption.152,153 The glycemic index is an extension of the fiber hypothesis, and was proposed in 1981 as a physiological system for the classification of carbohydrate-containing foods.154,155
Carbohydrates classified by glycemic index, in contrast to its traditional classification as either simple or complex, is a better predictor of CAD in epidemiological studies. The glycemic index is a scientific measure of the glycemic response to various foods, and is obtained from published food tables. The hierarchy of the glycemic index begins with beans, lentils, rice, spaghetti, potatoes, white bread (with refined flour), and refined grain cereals. A high glycemic index indicates a lower quality of carbohydrate associated with low HDL levels, and low rates of satiety. Fruits, nonstarchy vegetables, parboiled rice, and legumes have a low glycemic index. The glycemic index of potato is 102%, white bread 100%, whereas that of apple is 55%, and broccoli 13%. Glycemia observed after consuming dried peas is only one-third that of an equivalent amount of potatoes. Since peas are also high in fiber, their consumption needs to be encouraged, especially in patients with diabetes.

Glycemic load is the product of the glycemic value of the food and its carbohydrate content (per serving) divided by 100. For example, carrot has a high glycemic index but a low glycemic load (Table 6). The overall daily dietary glycemic load is calculated by adding the glycemic loads of all the different foods consumed in a given day. Accordingly, the glycemic load can be decreased by reducing the amount of carbohydrate intake and/or by consuming foods with a low glycemic index. In addition to the quality and quantity of carbohydrates consumed, the glycemic load also represents diet-induced insulin demand. PAI-1 levels are significantly increased with high glycemic load, and decreased with low glycemic load.

Dietary carbohydrates drive TG much more than dietary fat. A high glycemic load produces only mild increments in TG levels in individuals with normal TG levels but marked elevation in those with fasting lipemia and/or obesity. A low HDL level is a strong risk factor for CAD, even when the TC level is not elevated. In a prospective study of 75,521 women followed up for 10 years, those in the highest quintile of glycemic load had double the risk of CAD after adjustment for age, smoking status, total energy intake, and other risk factors (p<0.0001).

More importantly, a glycemic load promotes diabetes, especially in those with insulin resistance. (Fig. 2) This is particularly true for refined carbohydrates, sweets, white bread, and potatoes. Thus, a high glycemic load may be considered a risk factor of equal importance as high SAFA diet in precipitating diabetes. A low glycemic load can reduce insulin secretion in patients

<table>
<thead>
<tr>
<th>Table 6. Glycemic index of common foods162,161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic index</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Basmati rice</td>
</tr>
<tr>
<td>Brown rice (South India)</td>
</tr>
<tr>
<td>Parboiled rice (Canada)</td>
</tr>
<tr>
<td>White rice (Uncle Ben’s)</td>
</tr>
<tr>
<td>Curry rice (Japan)</td>
</tr>
<tr>
<td>Jasmine rice</td>
</tr>
<tr>
<td>White bread</td>
</tr>
<tr>
<td>Uppuma</td>
</tr>
<tr>
<td>Upittu</td>
</tr>
<tr>
<td>Chapati</td>
</tr>
<tr>
<td>Dosa</td>
</tr>
<tr>
<td>Idli</td>
</tr>
<tr>
<td>Poori</td>
</tr>
<tr>
<td>Pongal</td>
</tr>
<tr>
<td>Millet/ragi</td>
</tr>
<tr>
<td>barley</td>
</tr>
<tr>
<td>tapioca</td>
</tr>
<tr>
<td>Kellogg’s cornflakes</td>
</tr>
<tr>
<td>Milk, full-fat</td>
</tr>
<tr>
<td>Yogurt</td>
</tr>
<tr>
<td>Orange juice (reconstituted USA)</td>
</tr>
<tr>
<td>Pineapple</td>
</tr>
<tr>
<td>Plums</td>
</tr>
<tr>
<td>Prunes</td>
</tr>
<tr>
<td>Raisins</td>
</tr>
<tr>
<td>Cantaloupe</td>
</tr>
<tr>
<td>Plantain, green</td>
</tr>
<tr>
<td>Banana, unripe</td>
</tr>
<tr>
<td>Banana</td>
</tr>
<tr>
<td>Strawberry jam</td>
</tr>
<tr>
<td>Laddu</td>
</tr>
<tr>
<td>Black-eyed beans</td>
</tr>
<tr>
<td>Chickpeas</td>
</tr>
<tr>
<td>Kidney beans (rajmah)</td>
</tr>
<tr>
<td>Lentils</td>
</tr>
<tr>
<td>Lima beans</td>
</tr>
<tr>
<td>Pinto beans</td>
</tr>
<tr>
<td>Soy beans</td>
</tr>
<tr>
<td>Sweet corn</td>
</tr>
<tr>
<td>Green peas</td>
</tr>
<tr>
<td>Carrot</td>
</tr>
<tr>
<td>Beet root</td>
</tr>
<tr>
<td>Potato</td>
</tr>
<tr>
<td>Split peas</td>
</tr>
<tr>
<td>Snicker bar</td>
</tr>
<tr>
<td>Pizza Hut supreme pan pizza</td>
</tr>
<tr>
<td>Coca Cola</td>
</tr>
<tr>
<td>Instant noodles</td>
</tr>
<tr>
<td>Macaroni</td>
</tr>
<tr>
<td>Spaghetti</td>
</tr>
</tbody>
</table>
with type 2 diabetes, decrease insulin requirements in type 1 diabetes, and improve glycemic control in both types of diabetes. The incremental benefit from low glycemic load is similar to that offered by pharmacological agents that also target postprandial hyperglycemia, such as alpha-glycosidase inhibitors.185,186 The benefit of low glycemic load on the development of diabetes is similar to MUF A, PUF A, whole grains, fiber, fruits, and vegetables.

Whole Grains: The Foundation of Healthy Food

Whole grains have been the staple food worldwide for centuries, especially among vegetarians.187,188 Whole grain and legume consumption not only decreases blood sugar and insulin resistance but also prevents the development of diabetes, particularly in people with the metabolic syndrome.185,186 Whole-grain products are a good source of fiber, minerals, as well as several vitamins, including vitamins B and E. In a 12-year follow-up of 42,898 men, the risk of developing diabetes was 42% lower in those with the highest intake of whole grains. The risk was reduced by 52% in those who also engaged in physical activity, and 87% in those who also had a low BMI.189 The risk reduction was attributed to higher intakes of cereal fiber and magnesium. Intake of whole-grain cereal is inversely associated with hypertension, CAD, stroke, and CVD mortality190,191 (Table 7).192–206 In another study, 25%–30% reduction in stroke was observed with the intake of whole grains—similar in magnitude to that of statins.206–208 In sharp contrast, intake of refined grains increases the risk of diabetes, stroke and CVD.192,205–212 These prospective data highlight the importance of distinguishing whole-grain from refined-grain cereals in the prevention of CVD and diabetes.209 Efforts should be made to replace refined-grain with whole-grain foods.189

Fig. 2. Risk of diabetes in 65,173 US women during 6 years of follow-up: influence of glycemic load and fiber

Table 7. CVD risk reduction demonstrated with selected food groups192–206

<table>
<thead>
<tr>
<th>Author</th>
<th>CVD risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits and vegetables</td>
<td>(15%–48%)</td>
</tr>
<tr>
<td>Bazzano et al.192</td>
<td>25</td>
</tr>
<tr>
<td>Liu et al.193</td>
<td>15</td>
</tr>
<tr>
<td>Joshipura et al.194</td>
<td>30</td>
</tr>
<tr>
<td>Joshipura et al.195</td>
<td>20</td>
</tr>
<tr>
<td>Gaziano et al.196</td>
<td>48</td>
</tr>
<tr>
<td>Knekt et al.197</td>
<td>35</td>
</tr>
<tr>
<td>Nuts (19%–48%)</td>
<td></td>
</tr>
<tr>
<td>Albert et al.198</td>
<td>48</td>
</tr>
<tr>
<td>Ellsworth et al.199</td>
<td>19</td>
</tr>
<tr>
<td>Hu et al.200</td>
<td>35</td>
</tr>
<tr>
<td>Fraser et al.201</td>
<td>38</td>
</tr>
<tr>
<td>Fraser et al.202</td>
<td>40</td>
</tr>
<tr>
<td>Jiang et al.203</td>
<td>21 (diabetes)</td>
</tr>
<tr>
<td>Whole grains (32%–44%)</td>
<td></td>
</tr>
<tr>
<td>Jacobs et al.204</td>
<td>33</td>
</tr>
<tr>
<td>Fraser et al.205</td>
<td>44</td>
</tr>
<tr>
<td>Liu et al.206</td>
<td>32</td>
</tr>
<tr>
<td>Liu et al.206</td>
<td>32 (stroke)</td>
</tr>
</tbody>
</table>

A whole-grain food includes all the edible parts of the grain: the bran, the germ, and the endosperm.213 Grinding or milling, using modern technology, leads to the loss of many beneficial micronutrients, antioxidants, minerals, phytochemicals, fiber, and much of the germ.214 As a result, refined grain products are devoid of most vitamins and essential fatty acids, and contain more starch.215 Because of the loss of bran and pulverization of the endosperm, refined grains are digested and absorbed rapidly, resulting in a large increase in the levels of blood sugar and insulin.215 The common grains consumed in the West include wheat, oats, rye, rice, barley, and corn.215 In the USA, rye bread is an important source of whole grain consumption, and results in a lower glucose response than white bread.152,212 Whole-grain, ready-to-eat cereal contains >25% whole grain content by weight.189 The recommended intake is at least 6 servings of grain (but not more than 11) with at least 3 being whole grains. The current intake of whole grains is less than half a serving/day or 15% of the grain intake. Only 2% of the 150 lb of wheat flour consumed per capita in the USA is whole-grain flour.216 Commonly consumed refined grain foods include white rice (idli, dosa), refined wheat and flour (white bread), pancakes, cakes, sweet rolls, English muffins, muffins, waffles, rolls, biscuits, pizza, and refined-grain ready-to-eat breakfast cereal, and their use should be minimized.
Nuts: A Wholesome Food and Powerhouse of Healthy Fats and Nutrients

Extensive studies during the past decade have transformed the image of nuts from fattening snacks to a wholesome and heart-healthy food to be consumed daily. Nuts are rich sources of protein, antioxidants, fiber, vitamins and minerals (especially potassium and magnesium). Nuts yield 5%–10% fiber, and 12%–25% protein. The consumption of nuts is also associated with a reduced risk of CAD in several studies. Yet, nuts are not generally recommended as snacks because of their high fat content. Although nuts contain 45%–80% fat, most of the fats are the highly beneficial MUFA and PUFA (Table 8).

Nuts, particularly almonds, significantly improve lipid profiles because of the high fiber and MUFA component. The dose–response effects of almonds were compared with low-SAFAs (<5% energy), whole-wheat muffins used as the control diet in a randomized crossover study involving 27 dyslipidemic men and women. Three isoenergetic supplements each (mean 423 kcal/day; 22% of energy) were consumed for 1 month. The supplement consisted of full-dose almonds (73 g/day), half-dose almonds plus half-dose muffins, and full-dose muffins. Full-dose almonds produced a highly significant decrease in the Lp(a) level (8%), LDL:HDL ratio (8%), and oxidized LDL (14%) compared to the control diet. A 9% decrease in the LDL level occurred with 73 g/day of almonds, and a 4% decrease with 37 g/day (handful) of almonds. This result translates to a 1% reduction in LDL for every 7 g/day of almonds, and is consistent with other studies. More importantly, there was no difference in body weight between the almond and muffin diet.

Fruits and Vegetables, the Natural Way to Consume Antioxidants and Flavonoids

Fruits and vegetables are rich in a myriad of nutrients and phytochemicals, including fiber, vitamins B and C, antioxidants, potassium, and flavonoids. Phytochemicals are bioactive nonnutrient plant

<table>
<thead>
<tr>
<th>Nuts</th>
<th>Calories per 100 g</th>
<th>Fat content per 100 g</th>
<th>MUFA</th>
<th>PUFA</th>
<th>SAFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macadamia nuts</td>
<td>718</td>
<td>76</td>
<td>59</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Hazelnuts</td>
<td>646</td>
<td>62</td>
<td>47</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Pecans</td>
<td>710</td>
<td>74</td>
<td>44</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Almonds</td>
<td>597</td>
<td>53</td>
<td>34</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Cashew nuts</td>
<td>574</td>
<td>46</td>
<td>27</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Pistachio nuts</td>
<td>570</td>
<td>46</td>
<td>24</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Walnuts</td>
<td>607</td>
<td>57</td>
<td>13</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Flax seed</td>
<td>492</td>
<td>34</td>
<td>7</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Coconut meat, creamed</td>
<td>684</td>
<td>69</td>
<td>3</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>Coconut meat, sweetened, shredded</td>
<td>501</td>
<td>35</td>
<td>2</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Fruits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avocados, California</td>
<td>177</td>
<td>17</td>
<td>11</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Olives</td>
<td>115</td>
<td>11</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Avocados, Florida</td>
<td>112</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
compounds linked to a reduced risk of chronic diseases. Fruits and vegetables decrease blood pressure, homocysteine, and cancer, especially that of the GI tract.\textsuperscript{211,215,216} Since fruits and vegetables are rich in potassium, their liberal intake is recommended for the prevention and treatment of hypertension.\textsuperscript{217} Good sources of potassium include bananas, oranges, beans, fish, and dairy products. While you can get an overdose of potassium from pills, you cannot get an overdose of potassium from food. Moreover, dietary supplements do not have the health benefits associated with a diet rich in fruits and vegetables. For example, the antioxidant value of 100 g of apple is equivalent to 1500 mg of vitamin C.\textsuperscript{3}

Several large studies, including one comprising 84 000 women and 42 000 men, have shown a significant inverse association between the consumption of fruits and vegetables and CVD mortality.\textsuperscript{190,194,195} (Table 8). The relationship is particularly strong with vitamin C-rich fruits, green leafy vegetables, and carotenoid vegetables (carrots, broccoli, spinach, lettuce, tomatoes, and yellow squash).\textsuperscript{192–196,238,239} Consuming fruits and vegetables (3 times/day compared with <1 time/day was associated with a 27% lower incidence of stroke, a 42% lower stroke mortality, a 24% lower CAD mortality, a 27% lower CVD mortality, and a 15% lower all-cause mortality after adjustment for standard CVD risk factors.\textsuperscript{192} In sharp contrast, consumption of potatoes and French fries increase the risk of CAD and stroke.\textsuperscript{152,215}

The landmark study of the Dietary Approaches to Stop Hypertension (DASH)\textsuperscript{240} has yielded tremendous insights into the benefits of increased intakes of various types of fruits and vegetables. The DASH diet is rich in vegetables, fruits, and low-fat dairy products (9 servings of fruits and vegetable combined per day).\textsuperscript{240} As compared with the control diet with a high sodium, the DASH diet with a low sodium intake led to a decrease in systolic blood pressure of 7 mmHg in normotensive individuals, and 11.5 mmHg in hypertensive individuals. The benefits of the DASH diet on lipoprotein levels were equally spectacular, with an 11 mg/dl decrease in LDL and a 4 mg/dl increase in HDL levels without significant effects on TG levels. Men had a greater reduction in LDL level than women, with no difference between Whites and Blacks. These results suggest that the DASH diet is likely to reduce the risk of CAD and can be recommended as an overall eating plan.\textsuperscript{241} The current intake of fruits and vegetables is 3 servings/day each in the USA; only 23% consume the recommended 5 servings/day each.\textsuperscript{242} The DASH diet is feasible in the real world, unlike the array of drastic diets which are impossible to continue for more than a few months.\textsuperscript{240}

**Flavonoids:** Flavonoids are secondary metabolites that plants use to attract pollinators, repel predators, and to color flowers, leaves, and fruits.\textsuperscript{243} Important biological effects of flavonoids include the scavenging of oxygen-derived free radicals, inhibition of LDL oxidation, increase in HDL levels, and protection against CVD and several chronic diseases.\textsuperscript{244–246} The beneficial effects of these natural products on health were known long before the discovery of flavonoids. The major sources of flavonoids are vegetables (onions, kale, broccoli), fruits (apples, grapes, berries), olive oil, and beverages such as tea and wine.\textsuperscript{244,248,249} Other sources include grains, bark, roots, stems, and flowers. Flavonoids present in red wine could be partly responsible for the low CAD mortality seen in red wine drinkers (“French Paradox”). Red wine is the major source of flavonoid in France and Italy (40%), onions and apples in Finland, and olive oil in Greece.\textsuperscript{250} The strong taste of extra-virgin olive oil is partly caused by the abundance of flavonoids.

**Antioxidants:** Oxidative modification of LDL accelerates atherosclerosis whereas dietary antioxidants prevent LDL oxidation. These antioxidants include vitamin C, vitamin E, beta-carotene, selenium, flavonoids, magnesium, and MUFA.\textsuperscript{251} It is worth emphasizing that vitamin pills are no substitute for a healthy diet. Although an earlier study suggested some benefits from antioxidant vitamin supplementation, several subsequent studies involving more than 100 000 patients have consistently failed to demonstrate any benefit. More recent studies suggest that possible harm may outweigh the benefit of these vitamins.\textsuperscript{252–254} In a recent study, the use of vitamins E and C reduced the lipid-lowering efficacy of statins and niacin by 50%. More importantly, the clinical event reduction was lowered from 90% to 60%.\textsuperscript{255} The current scientific evidence does not support any protective role of vitamins E, C, and beta-carotene supplements; their use only creates a diversion away from proven therapies.\textsuperscript{256} The US Preventive Service Task Force (USPSTF) recommends against the use of beta-carotene supplements.\textsuperscript{257} It is worth noting that the oxidative modification of LDL continues to be relevant, and people should obtain their antioxidant vitamins from food sources. (However, folic acid fortification is recommended in women who are pregnant or might become pregnant.)

**Non-nutritive Food Adjuncts**

**Fiber:** The term dietary fiber was coined to describe the plant cell wall removed during the refining process.\textsuperscript{258} Dietary fiber improves coagulation, fibrinolysis, insulin
sensitivity, LDL, and blood pressure levels. Fiber is particularly concentrated in bran. Insoluble fiber shortens the intestinal transit, resulting in less time for carbohydrate absorption. Soluble (viscous) fiber, such as beta-glucan, which is found in oat bran, delays gastric emptying, and slows the absorption and digestion of carbohydrates. These processes lead to a slower release of glucose into the circulation, resulting in a reduced demand for insulin. An intake of 16 g of total fiber is associated with a 12% decrease in CAD risk. FDA has permitted cardiovascular health claims to be made by the industry for 2 viscous fibers, beta-glucan and psyllium. Psyllium supplementation significantly lowers TC and LDL levels; it is safe and well tolerated.

The benefit of whole grains appears to be mediated primarily through the greater intake of fiber, and is greater with cereal fiber than vegetable or fruit fiber.

Approximately one-fourth of the fiber provided by cereal sources is water soluble. Cereal fiber consumption is associated with a 21% lower risk of incident CVD, and 30% lower risk of diabetes. Cereal fiber consumption may reduce the risk of CVD via the substitution effect, replacing the intake of other foods having potentially detrimental effects. In addition to cereal grains, legumes are also excellent sources of water-soluble dietary fiber. Half a cup of cooked beans contains, on an average, 6 g of total fiber and 2 g of soluble fiber.

The current ADA recommendation for a healthy diet is to consume 25 g/day of fiber with about one-third from soluble fiber. In one study, type 2 diabetics consuming 50 g/day of fiber (25 g soluble, 25 g insoluble) lowered the blood sugar by 13 mg/dl, plasma TC by 7%, and TG levels by 10%. Thus, a high intake of dietary fiber, above the level recommended by the ADA, particularly of the soluble type, improves glycemic control, insulin levels, and plasma lipid concentrations in patients with type 2 diabetes.

Plants sterols and stanols: Plant sterols and stanols are structural analogues of cholesterol. Low-fat plant stanol-containing margarines lower plasma LDL levels (by as much as 12%) in those with hypercholesterolemia by suppressing cholesterol absorption. In one randomized controlled study, the reduction in LDL with such supplements was similar to 20 mg of lovastatin (30% with statin vs. 28.6% with diet). Various plant supplements have been shown to reduce LDL by 40% (Table 9).

<table>
<thead>
<tr>
<th>Decrease in LDL(%)</th>
<th>SAFA intake</th>
<th>&lt;7%</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary cholesterol intake</td>
<td>&lt;200 mg</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>5 kg</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Plant sterols/stanols</td>
<td>1–3 g/day</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Soy protein</td>
<td>25 g/day</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Nuts (almonds)</td>
<td>50 g/day</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Viscous fiber intake</td>
<td>5–10 g/day</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total LDL reduction</td>
<td>Full portfolio</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Dried aromatic parts of plants, generally the seeds, berries, roots, pods, and sometimes leaves, that mainly grow in tropical countries. Common spices include turmeric, paprika, saffron, cinnamon, nutmeg, red and black pepper. In contrast, herbs used in cooking are typically composed of leaves and stems.

Caffeine: Caffeine is found in coffee, tea, soft drinks, chocolate, and some nuts. Finland has one of the highest rates of per capita coffee drinking (13 kg/year). In a prospective study of 20,179 Finnish adults, coffee drinking was not associated with an increased risk of MI. However, consumption of large quantities of boiled unfiltered coffee raises cholesterol and homocysteine levels. In an experiment involving 10 volunteers, who consumed the equivalent lipid content of 6–7 cups of boiled unfiltered coffee daily for 6 weeks, the LDL levels increased by 33 mg/dl. These data suggest that daily consumption of 1–2 cups of coffee is safe with no particular health benefits or risks.

Tea: Tea, the most widely consumed beverage in the world other than water, has been associated with lower cardiovascular risk. Unlike coffee, tea consumption is associated with a substantial reduction in LDL levels. Tea is rich in flavonoids. Green tea contains catechins, whereas black tea, formed from the polymerization of catechins, contains theaflavins. In one recent study, theaflavin-enriched green tea extract reduced the LDL level by 16%. Tea is the major source of flavonoid intake in Japan (>80%); the Japanese consume an estimated 7 cups/day of tea compared to half a cup/day in the USA. Adding milk to tea, as is common in the UK and India, abolishes the beneficial effect of tea.

Alcohol: Moderate intake of alcohol (one drink a day for women and 2 drinks a day for men) may decrease the risk of CAD. Recently, it has been shown that only one drink per week is enough to provide cardiac protection (45 ml of spirits or 350 ml of beer or 120 ml of wine); the...
cardioprotection is similar for beer, wine, whiskey, brandy, vodka, rum, and drinks in equivalent amounts. More than 2 drinks per day does not provide any additional protection and, in fact, the net effect may be harmful until the age of 45 years in men and 55 years in women.431 Like carbohydrates, consumption of large quantities of alcohol raises TG levels. Other dangers of excessive alcohol consumption includes alcohol dependence, liver disease, high blood pressure, obesity, stroke, traffic accidents, spousal abuse, suicide, and breast and other cancers. Given these risks, the American Heart Association cautions people against increasing their alcohol intake or starting to drink if they do not already do so.

Weight Gain and Weight Loss Diets

Excess calories and obesity: Diets of any type containing more energy than needed or expended will lead to obesity and dyslipidemia. A calorie is a caloric whether it comes from carbohydrates, fat, or protein. Excess calories of any kind will eventually be converted by insulin to body fat. A common misconception is that dietary fat of any kind is fattening, while low-fat and high-protein diets have slimming properties. It is absolutely vital that both physicians and the public understand that it is the excess calories and not diet composition that causes weight gain. There is no evidence of weight gain with a high MUFA diet, compared with a high carbohydrate diet, under isoenergetic conditions. Obesity is not only a reflection of overnutrition but also an important contributor to the mass dyslipidemia seen in India and western countries. Obesity in general is accompanied by the increased production of apo B and a decrease in the HDL levels. Humans have a limited capacity to store energy as carbohydrates. When carbohydrate intake exceeds storage and oxidation capacities, the excess is converted to fat by de novo lipogenesis that leads to high TG levels. This process is increased several-fold in people with the metabolic syndrome which, if left untreated, leads to overt diabetes (25-fold risk). Body fatness and not lean body mass is the principal determinant of diabetes and prediabetes. At a given BMI, Asian Indians have 7%–10% higher body fat; accordingly, BMI <23 is termed optimum; BMI 23–25 overweight, and >25 obese in Asian Indians. Likewise, the optimum waist circumference is lower in Asian Indians than Whites with a cut-off <90 cm in men and <80 cm in women. Although obesity and dyslipidemia are uncommon in less affluent societies, some individuals may be excessively sensitive to caloric excess.

Fast foods rapidly produce plaques. The average American gained 9 lb in the past decade. A third of vegetable taken in the USA are either French fries or potato chips. In one study, overweight subjects who consumed fairly large amounts of sucrose (28% of energy), mostly as beverages, had increased energy intake, body weight, fat mass, and blood pressure after 10 weeks. These effects were not observed in a similar group of subjects who consumed artificial sweeteners. Restricting the dietary cholesterol can achieve a 3% reduction in TC level, whereas losing weight from trimming extra calories can reduce LDL by 5% to 20%.

Weight loss: The recipe for effective weight loss is a combination of motivation, physical activity and caloric restriction; maintenance of weight loss is a balance between caloric intake, and physical activity, with life-long adherence. Each pound of body fat contains 3500 cal. Therefore, a person who consumes 500 cal less than he spends each day can lose 1 lb of fat a week. Any higher weight loss is due to a more severe caloric restriction or water loss rather than fat loss. The minimum caloric intake in a medically unsupervised weight loss diet is 1500 cal/day for men, and 1200 cal/day for women. Superior long-term participation and adherence is observed in a high-fat diet rather than a low-fat diet (35% vs. 20%), especially in western cultures. The greater success rate is due to higher palatability of the high-fat diet provided by mixed nuts and lean meat. Furthermore, the long-term outcome of a reduced-fat diet consumed ad libitum for weight control is dismal. In one study, compared with the control group, weight decreased in the reduced-fat diet group significantly by 3 kg in 1 year but diminished to an insignificant 1 kg by 5 years. Until more information becomes available, “the prudent diet,” which is a balanced diet, is the one to follow for young and old alike.

Very low fat diet: Some experts have argued for a very low-fat diet (<10%). Since these diets are not high-protein diets (like the Atkins diet), they are in reality very high in carbohydrate. High-carbohydrate diets (the Macrobiotic diet) increase insulin resistance and induce the metabolic syndrome. In controlled trials, low-fat, high-carbohydrate diets decreased HDL levels. Replacing 10% of energy from SAF A with carbohydrate lowers the HDL levels by 5 mg/dl, even when the carbohydrate consumed is complex. There is also a marked increase in TG level, which makes LDL small, dense, and more dangerous. The effect is strongest when carbohydrates replace SAF A but is also seen when carbohydrates replace MUFA and PUFA. The effect is seen
in both short- and long-term trials, and is therefore not a transient phenomenon. Therefore, replacement of SAFA must be achieved through increasing MUFA and not by carbohydrates. The adverse effects of high-carbohydrate diets (high glycemic load) in the metabolic syndrome and diabetes have not received due attention, especially in the Indian literature. The recommended carbohydrate intake is <50% of calories in people with the metabolic syndrome or diabetes (NCEP).

The allure and dangers of very low-carbohydrate, high-protein diets: High-protein diets that are extremely low in carbohydrates are touted as a new strategy for successful weight loss by many. Most such diets contain <10% carbohydrates, 25%–35% protein, and 55%–65% fat. Because the protein is provided mainly by animal sources, these diets are high in SAFA and cholesterol. Thus, these diets are truly high-fat diets masquerading as high-protein diets. Advocates of this diet often promote serious misconceptions about carbohydrates, insulin resistance, ketosis, and fat burning as the mechanisms of action for weight loss. To avoid excess load on the kidneys, the total protein intake should not exceed 100 g/day. More importantly, the body has an obligatory requirement for glucose of about 100 g/day, largely determined by the metabolic demands of the brain.

In randomized studies, the extent of weight loss was small (4 kg), and adherence to the diet was low. In one study, although a low-carbohydrate diet produced a 4% greater weight loss at 6 months than did the conventional diet, the differences did not persist at 1 year. Furthermore, adherence was poor, and attrition was high in both the high- and low-carbohydrate groups. Longer and larger studies are required to determine the long-term safety and efficacy of low-carbohydrate, high-protein, high-fat diets. Two recent studies have provided insight into high-protein diets; the initial weight loss is due to fluid loss and ketosis-induced appetite suppression. The monotony of this diet also results in involuntary caloric restriction.

The beneficial effects on blood lipids and insulin resistance are due to the weight loss, and not the change in caloric composition. Such diets increase LDL, but decrease TG levels, in sharp contrast to high-carbohydrate diets, which increase TG, and decrease HDL levels. Although these diets may not be harmful for most healthy people over a short period of time, there are no long-term scientific studies to support their overall efficacy and safety. Markedly atherogenic profiles have also been reported in children with ketogenic diets. At 6 months, the high-fat ketogenic diet significantly increased plasma LDL levels by 50 mg/dl, triglycerides 58 mg/dl, apo B 49 mg/dl, and non-HDL cholesterol 63 mg/dl. The mean HDL-cholesterol levels decreased significantly. These lipid abnormalities in children are more than likely to translate into a high risk of heart disease as young adults.

High-protein diets also do not provide the variety of foods needed to continue the diet on a long-term basis. High-protein diets are not recommended, and are perhaps dangerous because they restrict most healthful foods that provide essential nutrients, especially fruits and vegetables. Individuals who follow these diets are therefore at risk for compromised vitamin and mineral intake, as well as potential cardiac, renal, bone, and liver abnormalities overall. The consumption of a very low-carbohydrate diet for 6 weeks delivers a high acid load to the kidney, increases the risk of stone formation, decreases body calcium, and may increase the risk of bone loss and fractures. A high-protein diet is the ultimate antithesis of the prudent diet. It is important to realize that diets are not for 6 weeks, 6 months or 6 years, but for a lifetime. Although most quick-fix diets have a short-term success rate >90%, the long-term failure rate is 100%.

Healthy and Contaminated Vegetarian Diets

Omnivores or nonvegetarians outnumber vegetarians 10 to 1 in western cultures. Vegetarians include vegans who do not consume any animal products, ovo-vegetarians who consume egg, lacto-vegetarians who consume milk, ovo-lacto-vegetarians who consume egg and milk, and semi-lacto-vegetarians who eat small amounts of meat (<1 time/week). Ironically, most self-defined vegetarians in western countries consume red meat and poultry, albeit infrequently, and in very small quantities. In a recent survey, only 1% of self-reported vegetarians did not eat meat in the USA, whereas about 6% of Americans who do not consume any meat did not identify themselves as vegetarians. Western vegetarians generally consume a healthier diet than omnivores; healthy foods such as soy, nuts, legumes and vegetables replace meat. They generally have twice the fish consumption of nonvegetarians. This is not the case with Indian vegetarians who shun fish. US vegetarians eat more whole-grain products, dark green and deep yellow vegetables, whole-wheat bread, brown rice, soy milk, tofu, meat substitutes, legumes, lentils, garbanzos, walnuts, and pecans. However, they eat the same amount of food as omnivores (1000 kg/year) but are usually thinner. A healthy vegetarian diet is characterized by more frequent
Vegetarians eat about two-thirds of SAF A, and one-half of cholesterol as omnivores; vegans consume one-half of SAF A and no cholesterol. Moreover, cholesterol levels among western vegetarians are 15–25 mg/dl lower than omnivores. Vegans have very low levels of LDL. Nuts, viscous fibers (from oats and barley), soy proteins, and plant sterols in vegetarian diets improve serum lipid levels. Furthermore, substituting soy or other vegetable proteins for animal proteins reduces the risk of developing nephropathy in type 2 diabetes.

With the exception of tropical oils, calories from plant sources are negatively correlated with CAD mortality, whereas calories from animal sources are positively correlated. Olive oil, fresh fruits, and vegetables are protective against heart disease, and seem to play a greater role in the French paradox than wine. Greater consumption of whole milk and other animal products were important contributors to Finland having the highest rates of CAD. In a prospective study of 4671 vegetarians were important contributors to Finland having the highest consumption of whole milk and other animal products. In the CADI study, Asian Indian physicians in the USA followed a heart-healthy diet, with 32% energy from total fat, and 8% from SAF A, which is the recommendation by the NCEP. This phenomenon is due to contaminated vegetarianism, wherein vegetarians manage to consume excessive amounts of SAF A and TRAF A. In the CADI study, Asian Indian physicians in the USA followed a heart-healthy diet, with 32% energy from total fat, and 8% from SAF A, which is the recommendation by the NCEP. This phenomenon is due to contaminated vegetarianism, wherein vegetarians manage to consume excessive amounts of SAF A and TRAF A. In the CADI study, Asian Indian physicians in the USA followed a heart-healthy diet, with 32% energy from total fat, and 8% from SAF A, which is the recommendation by the NCEP. This phenomenon is due to contaminated vegetarianism, wherein vegetarians manage to consume excessive amounts of SAF A and TRAF A. In the CADI study, Asian Indian physicians in the USA followed a heart-healthy diet, with 32% energy from total fat, and 8% from SAF A, which is the recommendation by the NCEP. This phenomenon is due to contaminated vegetarianism, wherein vegetarians manage to consume excessive amounts of SAF A and TRAF A. In the CADI study, Asian Indian physicians in the USA followed a heart-healthy diet, with 32% energy from total fat, and 8% from SAF A, which is the recommendation by the NCEP.
its preparation by prolonged heating of butter.\textsuperscript{162–164} Liberal dietary exposure to cholesterol oxides from \textit{ghee} is a likely contributor to the high frequency of CAD among Asian Indians.\textsuperscript{164} There are conflicting data on the risk of heart disease with \textit{ghee}.\textsuperscript{165,166} We are unaware of any biological explanation as to why Asian Indians can be immune to the unfavorable effects of butter and/or \textit{ghee}. In addition to milk \textit{ghee}, vegetable \textit{ghee} (\textit{vanaspathi}) is also immensely popular in Indian cooking, which exerts similar adverse effects through its high TRAF\textsubscript{A} content.

\textbf{Tropical oils:} The term tropical oils refers to coconut, palm kernel, and palm oils. These oils contain a very high percentage of SAFA, unlike other vegetable oils such as rapeseed oil (mustard oil), sesame oil, and rice bran oil, which are low in SAFA and high in MUFA (Table 3). Tropical oils are more atherogenic and thrombogenic than mutton and beef fat; the latter contains <5% myristic acid compared to 18% in coconut and palm kernel oils.\textsuperscript{104} In fact, these oils contain more TC-raising SAFA than animal fats—coconut oil 89%, palm kernel oil 71%, and palm oil 46% compared to <30% for butter fat, beef fat, pork fat, and chicken fat (Table 5).\textsuperscript{6,147} Tropical oils account for <2% of energy (<4 g/day) in the USA, but 25% or more in many other countries.\textsuperscript{147,167} Tropical oils are also found in commercially baked cakes, biscuits, cookies, and “snack foods”. In Mauritius, a regulated change in the SAFA content by substituting soybean oil for palm oil resulted in a dramatic 32 mg/dl fall in TC level, and underscores the crucial role of cooking oils in population levels of TC.\textsuperscript{168}

\textbf{Coconut oil:} Coconut oil contains mostly cholesterol-raising SAFA (8% caprylic, 6% capric, 45% lauric, 17% myristic, and 8% palmitic acid).\textsuperscript{169–171} Rabbits fed a commercial chow diet containing 0.5% cholesterol and 14% coconut oil developed more severe dyslipidemia and atherosclerosis than rabbits fed the same diet containing olive oil instead of coconut oil. The average plasma TC level was 2-fold, and TG level 20-fold higher in the coconut oil-fed rabbits than in the olive oil-fed rabbits.\textsuperscript{28} Cox et al.\textsuperscript{169,170} have reported the cholesterol-raising effects of coconut oil to be similar to that of butter. In a comparative study of diets rich in beef fat versus coconut oil, the plasma TC, LDL, and HDL responses were lower with beef fat than coconut oil, commensurate with the lower proportion of cholesterol-raising SAFA in beef (29%) than coconut oil (89%)\textsuperscript{171} (Table 5). A Malaysian study in which 22% of the energy intake was substituted with coconut oil found an increase of 40 mg/dl in TC, 29 mg/dl in LDL, 36 mg/dl in TG, and 4 mg/dl in HDL levels.\textsuperscript{172} The impact on LDL and HDL by using various fats as the sole source of fat in a Dutch population is shown in Fig. 1. Note the marked increase in LDL in contrast to HDL with the use of coconut oil.

Kerala, renowned for the universal and liberal consumption of coconut milk and oil, not only has the highest level of TC in India, but also the highest rate of CAD.\textsuperscript{173} The proportion of subjects with high TC (\textgreater{}239 mg/dl) in Kerala is almost double that of the USA. (32% v. 18%).\textsuperscript{174} This is in sharp contrast to the Japanese among whom only 6% have high TC.\textsuperscript{175} In Sri Lanka, which also has a very high rate of CAD, about 80% of the fat in the habitual diet comes from coconut.\textsuperscript{134,374,176}

Consumers need to be educated about the atherogenic and antiatherogenic effects of various cooking oils, as well as animal and vegetable \textit{ghee}. There is little awareness, and even controversy, about the atherogenic effects of certain foods and oils, especially in regions where the production, sale, and consumption of such oils have a profound impact on the regional economy.

\textbf{Prudent Diet for All Ages and the Entire Population}

The traditional Mediterranean diet is characterized by abundant plant foods (vegetables, breads, pastas, beans, nuts, and seeds). Fresh fruit is the typical daily dessert, and olive oil is used as the principal source of fat. Dairy products (principally cheese and yogurt), fish, and poultry are consumed in low-to-moderate amounts. Red meat and egg are consumed in low amounts (0–4 eggs weekly). Wine is consumed in low-to-moderate amounts, normally with meals. This diet is typically high in total fat (35%–45%) but low in SAFA (7%–8% of energy). Greater adherence to the traditional Mediterranean diet is associated with a significant reduction in total mortality.\textsuperscript{177} The 6 beneficial components of this diet have recently been elucidated. They are vegetables, legumes, whole-grain cereal, fish, fruit, and nuts, which form the basis for the “prudent diet”\textsuperscript{177} (Table 10).\textsuperscript{199–203,225–227,231–236}

According to the new paradigm, dietary pattern rather than individual nutrients appears to be more important. Recent research suggests the existence of a food synergy in which the beneficial effects of healthy foods are magnified when several different types of foods are consumed.\textsuperscript{213} Hu et al. have developed the concept of “prudent diet” (modified from the Mediterranean diet).\textsuperscript{10,178–180} The “prudent diet” has a higher intake of vegetables, fruits, legumes, whole grains, fish, and poultry, whereas the “western diet” is characterized by a higher intake of red meat, processed meat, refined grains, sweets, desserts, French fries, and
high-fat dairy products. The "prudent diet" is associated with a 24% decreased risk of CVD compared to a 46% increased risk with the western diet.

Consumers are bombarded on a daily basis with the Babel of nutritional breakthroughs. Food companies adverzite their products, nutrition researchers publicize their latest results, and the media are more interested in a controversial story than in scientific facts. Trivial reports are often publicized as major breakthroughs by the media, and cause confusion among consumers. It is difficult for most journalists and consumers to tell the difference between a major research finding and a trivial report.

The dangers of the current western diet and the contaminated vegetarian diet, and the remarkable benefits of the prudent diet need to be disseminated among cardiologists, physicians, and the public. This diet can be sustained lifelong but needs to be adapted to Indian ingredients and cooking methods. Several countries have developed dietary guidelines to reduce nutritional information anarchy. The Indian consensus on the prudent diet should incorporate scientific facts, and the cultural preferences appropriate for different parts of India. Such information needs to be adopted by the scientific community, and adapted by the food industry.

**Current Knowledge on Preventive and Therapeutic Nutrition**

Randomized, controlled clinical trials, meta-analysis, and systematic reviews are considered the ultimate tests of the benefits of therapeutic interventions. Such reviews have shown a 24% reduction in major coronary events in dietary trials lasting >2 years. The TC/HDL ratio is the single best lipid predictor of CVD. This ratio is determined by 3 partly opposing dietary factors—the proportion of energy from SAF A, which raises TC; the proportion of energy from total fat, which raises HDL; and the excess in total energy intake, which produces obesity and secondarily lowers HDL. The greatest reduction in CVD risk is achieved by LDL-lowering by reducing SAF A intake. Decreasing SAF A intake is best accomplished by reducing the intake of high-fat dairy products, and increasing fiber-rich foods. A diet incorporating lean beef, skinless chicken, and fatty fish has been shown to improve the lipid profile by 5%–10.

The preferred replacement for SAF A is MUFA or PUFA.
and not carbohydrates (Table 11). Replacing SAF A with carbohydrates decreases the LDL levels but makes LDL small, dense, and more dangerous by increasing the TG levels.30 Substituting carbohydrates with MUFA decreases the LDL level, and increases the HDL level. PUFA and MUFA increase insulin sensitivity, and decrease the risk of type 2 diabetes.45,384–386 Substantial evidence indicates that diets using MUFA and PUFA as the predominant form of dietary fat, an abundance of fruits and vegetables, and adequate n-3 fatty acids can offer significant protection against CAD, stroke and diabetes (Table 8). Adequate consumption of fruits and vegetables provides most of the necessary antioxidants, and are preferable to dietary supplements in the form of pills. Replacing a high glycemic with a low glycemic index, and reducing the glycemic load can reduce the risk of diabetes.161

Nuts, once deemed unhealthy because of their high fat content, have become an important part of diets designed to control weight, lower blood pressure and cholesterol, and achieve secondary prevention of CAD, besides adding variety, texture and flavor to dishes.145,211,215,387 Unless a beneficial effect is clearly demonstrated by well-designed scientific studies, the liberal use of butter, ghee, palm oil, and coconut (oil and milk) should be discouraged. However, in diets with a negligible intake of fish, meat, milk, and dairy fat, the modest use (<7% of energy) of such oils may be preferable to no fat at all.

**Practical Recommendations**

Better food habits can help reduce the risk of diabetes, MI, stroke, and death. A healthy eating plan means choosing the right foods to eat, and preparing them in a healthy way. A healthy diet involves a decrease in the use of refined grains, tropical oils, egg yolks, animal, dairy, and hydrogenated fats, and an increase in the consumption of whole grains, vegetables, nuts, legumes, and fruits.7 Increasing the MUFA intake up to 20% of energy, as a replacement for SAF A and carbohydrates, may help prevent and treat the metabolic syndrome, diabetes, and CVD. Such a strategy can also significantly reduce the need for lipid-optimizing drugs. Since meat contains one-third MUFA and one-third cholesterol–neutral stearic acid, its consumption can also be incorporated into a healthy diet, provided lean cuts are used, and the quantity limited to 150 g/day.6

Practical recommendations on diet are given in Table 12.

**Table 11. Summary of current knowledge on diet**

- Quality of fat is more important than the quantity of fat consumed.
- SAF A is the principal determinant of elevated LDL levels. Reduction in energy intake from SAF A is the cornerstone of dietary modification. Dairy products provide more SAF A than meat, even in western diets.
- Contrary to common belief, MUFA and PUFA can significantly lower LDL levels. Replacement of 20% of energy from SAF A with MUFA or PUFA decreases TC level by 40 mg/dl.
- The atherogenicity and thrombogenicity of tropical oils are several times higher than meat.
- Increase in LDL level from lean meat is no higher than chicken, and need not be eliminated from a healthy diet.
- n-3 PUFA found in fatty fish is antithrombotic, antiarrhythmic, and prevents sudden death.
- The adverse effects from TRAF A consumption are greater than those from SAF A, because of increase in LDL and Lp(a) levels, and decrease in HDL level.
- Both quality (glycemic index) and quantity (glycemic load) of carbohydrates are important determinants of insulin resistance and the metabolic syndrome. A high glycemic index or load portends an inferior quality of carbohydrates.
- Although carbohydrates do not raise LDL levels, a high glycemic load is the major determinant of postprandial lipemia.
- Vegetarian diet is unhealthy if it contains large amounts of SAF A and TRAF A.
- Nuts, fruits, vegetables and whole grains can each reduce the risk of CVD by 15%–45%.
- Nuts are wholesome and nutritious food.
- The risk from alcohol outweighs the benefit in men <45 years and women <55 years of age.
- Drinking coffee does not increase the risk of heart disease but consumption of large amounts of unfiltered coffee can increase TC levels.
- Tea is rich in antioxidants and flavonoids, and is associated with a reduced risk of CAD; however, most of the beneficial effects are neutralized with the addition of milk.
- A calorie is a calorie, whether derived from carbohydrates, protein or fat.
- Obesity is a reflection of overnutrition (caloric excess), and a major cause of dyslipidemia.
- Caloric excess, irrespective of the composition of food, can raise LDL and lower HDL levels as a secondary effect of obesity.
- Weight reduction seen in high protein diets is due to the involuntary caloric restriction from the monotony of the diet rather than the diet composition.
Table 12. Dietary recommendations

- A minimum carbohydrate intake of 100 g/day is necessary but should not exceed more than 300 g/day.
- Indians with or predisposed to the metabolic syndrome and diabetes should limit carbohydrate intake to <50% of energy.
- Most carbohydrate calories should be from whole grains and low glycemic index foods. A total fat intake of 30%–35% is preferable to a very high carbohydrate diet.
- Reduce SAF A intake to <7% of the daily energy (10 g for women and 15 g for men), and cholesterol intake to <200 mg/day.
- Substitute excess SAF A and carbohydrate calories with MUFA (≤20%) and PUFA (≤10%).
- Substitute full-fat with low-fat milk and dairy products.
- Choose lean meat or skinless poultry, and limit the amount to <150 g/day.
- Minimize the intake of TRAF A by avoiding fried or crispy foods.
- Use cooking oils with beneficial effects on lipids and avoid deep-frying, especially with previously used oils.
- Consume 2–3 fish meals (200–300 g) per week; avoid frying to maintain the benefits.
- Those who are unable to consume fish may take the equivalent of 1 g/day of EPA and DHA (3 g of fish oil); 2 g/day is needed for those with heart disease or high TG.
- Protein intake, up to 25% of energy, is permissible if most of the protein is from plant sources.
- Control caloric intake to achieve and maintain optimum weight and waistline.
- Increase physical activity to >60 min every day.
- Reduce intake of salt to <6 g/day.
- Eat a variety of foods, including whole grains, nuts, legumes, fruits, and vegetables.
- Consume nuts, up to 60 g/day, as a substitute for unhealthy foods.
- Increase intake of fruits to ≥5 servings/day (500 g/day), and use whole fruits instead of juices.
- Increase intake of vegetables to ≥5 servings/day (500 g/day), and avoid prolonged cooking of vegetables.
- Limit alcohol intake to 1–6 drinks/week.

Conclusions

People eat specific foods because of their taste, easy availability and affordability, but are often unaware of the health benefits and risks. Dietary modifications remain the cornerstone of both the treatment and prevention of diabetes and CVD, the twin epidemics of the twenty-first century.234,388–391 A prudent diet together with regular physical activity, avoidance of smoking, and maintenance of a healthy body weight may prevent the majority of diabetes and CVD in the Indian population.30 Aggressive dietary interventions may reduce CVD events to a similar magnitude as that achieved with statins. Compared with medical or surgical interventions, nutritional intervention is low-risk, low-cost, and readily available.259 A variety of whole grains, not refined grains, as well as various types of fruits and vegetables should be the main form of carbohydrates.242 Prolonged cooking of vegetables should be avoided. It is important to realize that the vegetarian diet is healthy only when it is low in SAF A, and the predominant energy is from foods with a low glycemic index.215 The best way to counter the perils of contaminated vegetarianism is by substituting full-fat dairy products with low-fat dairy products. Cooking oils containing high SAF A should be replaced with those containing high MUFA. Deep-frying, especially with previously used oils, should be discouraged. Nuts are healthy, wholesome foods, and their use should be encouraged as a replacement for unhealthy calories.

A diet rich in fish has multiple benefits, including raising HDL, and lowering TG levels, and preventing sudden death.381 Consumption of fish is preferable to taking a large number of fish oil capsules. There is increasing evidence that dietary and lifestyle modifications begun in childhood are likely to have benefits later in life.392 Therefore, these dietary guidelines are applicable to all Asian Indians >2 years of age, and not just those with diabetes or heart disease.

References

3. Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr 2003; 78 (Suppl): 517S–520S
26. Mann JI. The role of nutritional modifications in the prevention of macrovascular complications of diabetes. *Diabetes* 1997; 46 (Suppl); S125–S130


63. Hu FB, Willett WC. Diet and coronary heart disease: findings from the Nurses’ Health Study and Health Professionals’ Follow-up Study. *J Nutr Health Aging* 2001; 5: 132–138


74. Simopoulos AP. Leaf A, Salem N. Workshop on the essentials of and recommended dietary intakes for n-6 and n-3 fatty acids. Bethesda, MD: National Institutes of Health; 1999


80. Gerster H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? *Int J Vitam Nutr Res* 1998; 68: 159–173


114. Leaf A. The electrophysiologic basis for the antiarrhythmic and pro-arrhythmic effects of n-3 polyunsaturated fatty acids: heart and brain. Lipids 2001; 36 (Suppl): S107–S110


120. Lemaitre RN, King IB, Mozaffarian D, Fuller LH, Tracy RP, Siscovick DS. n-3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr 2003; 77: 319–325


166. Wolfer TM, Mehling C. Long-term effect of varying the source or amount of dietary carbohydrate on postprandial plasma glucose, insulin, triacylglycerol, and free fatty acid concentrations in subjects with impaired glucose tolerance. Am J Clin Nutr 2003; 77: 612–621


169. Jarvi AE, Karlstrom BE, Granfeldt YE, Bjorck IE, Asp NG, Vessby
Enas et al. Prudent Diet and Preventive Nutrition


334 Enas et al. Prudent Diet and Preventive Nutrition

Indian Heart J 2003; 55: 310–338

disease mortality in the oldest-old. The Adventist Health Study. Arch
Intern Med 1997; 157: 2249–2258

and peanut butter consumption and risk of type 2 diabetes in
women. JAMA 2002; 288: 2495–2500

204. Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake
may reduce the risk of ischemic heart disease death in
postmenopausal women: the Iowa Women's Health Study. Am J

Whole-grain consumption and risk of coronary heart disease:
results from the Nurses’ Health Study. Am J Clin Nutr 1999; 70:
412–419

Whole grain consumption and risk of ischemic stroke in women: a
prospective study. JAMA 2000; 284: 1534–1540

207. Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake
may reduce the risk of ischemic heart disease death in
postmenopausal women: the Iowa Women’s Health Study. Am J

208. Jacobs DR Jr, Meyer HE, Sovio K. Reduced mortality among whole
grain bread eaters in men and women in the Norwegian County

209. Liu S, Sesso HD, Manson JE, Willett WC, Buring JE. Is intake of
breakfast cereals related to total and cause-specific mortality in

Carbohydrates, dietary fiber, and incident type 2 diabetes in older

211. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks
FM, et al. A clinical trial of the effects of dietary patterns on blood
336: 1117–1124

212. Montonen J, Knekt P, Jarvinen R, Aromaa A, Reunanen A, Whole-
grain and fiber intake and the incidence of type 2 diabetes. Am J
Clin Nutr 2003; 77: 622–629

213. Jacobs DR Jr, Stufken LM. Foods, nutrients, and dietary patterns as
exposures in research: a framework for food synergy. Am J Clin
Nutr 2003; 78 (Suppl): 508S–518S


215. Hu FB. Plant-based foods and prevention of cardiovascular disease:

216. Cleveland LE, Mosleh AF, Albertson AM, Goldman JD. Dietary

Effectiveness of a low-fat vegetarian diet in altering serum lipids in
healthy premenopausal women. Am J Cardiol 2000; 85: 969–972


risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein (a), homocysteine, and pulmonary nitric oxide: a
randomized, controlled, crossover trial. Circulation 2002; 106:
1327–1332

220. Spiller GA, Jenkins DA, Bosello O, Gates JE, Craven LN, Bruce B.
Nuts and plasma lipids: an almond-based diet lowers LDL-C while

221. Abbey M, Noakes M, Belling GB, Nestel PJ. Partial replacement of
saturated fatty acids with almonds or walnuts lowers total plasma
cholesterol and low-density-lipoprotein cholesterol. Am J Clin
Nutr 1994; 59: 995–999

78 (Suppl): 647S–650S

223. Almario RU, Vonghavaravat V, Wong R, Kasmir-Karakas SE. Effects of
walnut consumption on plasma fatty acids and lipoproteins in
women with combined hyperlipidemia. Am J Clin Nutr 2001; 74:
72–79

224. Curb JD, Wargowskie G, Dobbs JC, Abbott RD, Huang B. Serum lipid
effects of a high-monounsaturated fat diet based on macadamia

225. Sabate J, Fraser GE, Burke K, Knutsen SF, Bennett H, Lindsted KD.
Effects of walnuts on serum lipid levels and blood pressure in

226. Edwards K, Kwaw I, Matud J, Kurta I. Effect of pistachio nuts on
serum lipid levels in patients with moderate hypercholesterolemia.

227. Morgan WA, Clayshulte BJ. Pecans lower low-density lipoprotein
cholesterol in people with normal lipid levels. J Am Diet Assoc 2000;
100: 312–318

228. O’Byrne DJ, Knauf DA, Shramek RB. Low fat-monounsaturated rich diets containing high-oleic peanuts improve serum lipoprotein
profiles. Lipids 1997; 32: 687–695

Substituting walnuts for monounsaturated fat improves the serum
lipid profile of hypercholesterolemic men and women. A randomized

230. Rajaram S, Burke K, Connell B, Myint T, Sabate J. A monounsaturated fatty acid-rich pecan-enriched diet favorably alters the serum
lipid profile of healthy men and women. J Nutr 2001; 131: 2275–2279

231. Garg A, Bonanome A, Grundy SM, Zhang ZJ, Unger RH. Comparision of a high-carbohydrate diet with a high-
omounsaturated-fat diet in patients with non-insulin-dependent

59: 103–111

233. Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC. Effect of
diets enriched in almonds on insulin action and serum lipids in
adults with normal glucose tolerance or type 2 diabetes. Am J Clin
Nutr 2002; 76: 1000–1006

234. van Dam WM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary

235. Appel LJ, Miller ER 3rd, Jee SH, Stolzenberg-Solomon R, Lin PH,
Erlinger T, et al. Effect of dietary patterns on serum homocysteine:
results of a randomized, controlled feeding study. Circulation 2000;
102: 852–857

236. Key TJ, Allen NE, Spencer EA, Travis RC. The effect of diet on risk

randomized controlled clinical trials. JAMA 1997; 277: 1624–1632

238. Gillman MW, Cupples L, Gagnon D. Protective effects of fruits and
vegetables on development of stroke in men. JAMA 1995; 273:
1113–1117


240. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D,
et al; DASH-Sodium Collaborative Research Group. Effects on blood
pressure of reduced dietary sodium and the Dietary Approaches
to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative

241. Obarzanek E, Sacks FM, Vollmer WM, Bray GA, Miller ER 3rd, Lin
PH, et al; DASH-Research Group Effects on blood lipids of a blood
Dietary protein and soluble fiber reduce ambulatory blood pressure in treated hypertensives. *Hypertension* 2001; 38: 821–826


279. Blair SN, Capuzzi DM, Gottlieb SO, Nguyen T, Morgan JM, Cater NB. Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol...


338. Thompson JA, May WA, Paulose MM, Peterson RJ, Chang SS. Chemical reactions involved in the deep-fat frying of foods. VII.


360. Thompson JA, May WA, Paulose MM, Peterson RJ, Chang SS. Chemical reactions involved in the deep-fat frying of foods. VII.

Enas et al. Prudent Diet and Preventive Nutrition 337


Simmons D, Williams R. Dietary practices among Europeans and different South Asian groups in Coventry. Br J Nutr 1997; 78: 5–14


Vertical Displacement of the Precordial Leads Alters Electrocardiographic Morphology

Fatimah Lateef, Narayan Nimbkar, Zhuang Kun Da, Foo Rui Min
Department of Emergency Medicine, Singapore General Hospital, Singapore, Uniformed Services University of Health Sciences Bethesda, Maryland, USA; National University of Singapore

**Background:** The present study was undertaken to assess whether the vertical displacement of electrodes affects the waveforms of precordial leads.

**Methods and Results:** Two hundred forty healthy, adult volunteers had a standard 12-lead electrocardiogram, a 12-lead electrocardiogram with the precordial leads displaced 2 cm cranially, and another with the precordial leads displaced 2 cm caudally from the standard positions. All the three sets of electrocardiograms were visually compared, and changes noted. One hundred twenty male and 120 female volunteers, 20–68 years of age, were analyzed. Fifty-four males (45.0%) and 2 females (1.7%) showed no difference between the 3 sets of electrocardiograms, while 66 males (55.0%) and 118 females (98.3%) had some changes. R wave amplitude changes were noted in 63 male (52.5%) and 111 female (92.5%) volunteers; S wave amplitude changes were seen in 59 males (49.2%) and 99 females (82.5%); T wave changes in 5 males (4.2%) and 3 females (2.5%); ST segment changes in 1 male (0.8%) and none of the females; and QRS morphologic changes in 1 male (0.8%) and 12 females (10.0%).

**Conclusions:** Precordial electrocardiographic waveform changes were seen with the vertical displacement of the precordial leads. This will have implications on the interpretation of serial electrocardiograms. Healthcare providers should take into consideration this deviation when interpreting serial ECGs. *(Indian Heart J 2003; 55: 339–343)*

**Key Words:** Electrocardiography, Precordial leads, Lead placement

Electrocardiography (ECG), introduced by Einthoven in 1902, is the graphical display of electrical potential differences of an electric field originating in the heart and recorded on the body surface. It represents a unique technology that is safe, simple, and reproducible.¹ Accurate ECG interpretation assumes that technical standards are adhered to during the acquisition and recording of tracings. A number of technical factors may alter the quality of recorded ECG. Some of these are patient-related, some are operator dependent, and others relate to the equipment utilized for recording.²

The exact placement of electrodes for ECG depends on the interpretation and skill of the person performing it (e.g. nurses, technicians, medical students). Placement of precordial electrodes for the recording of a 12-lead ECG is subject to variation. Technical variability represents the largest source of error for variations in the amplitude and waveform of the chest lead ECG. Precordial leads are commonly placed either too high, too low or horizontally displaced from their anatomically defined sites. Persons recording ECGs should ensure that the chest leads are placed in the proper positions, and electrodes have good skin contact to minimize artefacts. Incorrect placement may lead to false diagnosis of infarction or cause alterations in the ECG interpretation.³,⁴ In practice, the effect of the displacement on individual ECGs is unknown.

The present study was done to assess if vertical displacement of electrodes affects the waveform of precordial leads of the ECG in healthy adult volunteers.

**Methods**

This was a clinical experimental investigation. Following ECGs in supine position were performed in healthy, adult volunteers, with no history of ischemic heart disease (IHD).

(i) a standard 12-lead ECG with the usual accepted, surface precordial lead placement;

---

**Correspondence:** Fatimah Lateef, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608. e-mail: gaejal@sgh.com.sg
(ii) a 12-lead ECG, as in (i), but with all the precordial leads (i.e. V1 to V6) shifted 2.0 cm cranially; and
(iii) a 12-lead ECG as in (i), but with all the precordial leads shifted 2.0 cm caudally.

Measurements were done with a standard ruler. All the three ECGs for each volunteer were visually compared, and the differences documented (e.g. R and S wave amplitude changes, changes in the QRS morphology, ST segment changes, T wave morphology and appearance/disappearance of Q waves). T wave changes refer to either an upright, inverted or flattened T wave. ST segment changes may represent an isoelectric ST segment, or ST elevation, or depression. The morphological changes would refer to changes such as the appearance of a bundle branch block pattern.

The standard 12-lead ECG for each person was used as the control against which the other two ECGs, which had deliberate alterations in the positions of the precordial leads, were compared. When the tracings with the displaced electrodes did not resemble the standard ECG tracings, the variations were confirmed by repeating the tracings.

The study was approved by the hospital ethics committee.

**Results**

There were a total of 240 volunteers, 20–68 years of age. One hundred and twenty were males and 120 females. Fifty-four males (45.0%) and 2 females (1.7%) showed no differences when their three sets of ECGs were compared, while 66 males (55.0%) and 118 females (98.3%) had some changes noted. R wave amplitude changes were noted in 63 male (52.5%) and 111 female (92.5%) volunteers; S wave changes in 59 males (49.2%) and 99 females (82.5%) (Figs 1a–c); T wave changes in 5 males (4.2%) and 3 females (2.5%) (Fig. 2a–c); ST segment changes in 1 male (0.8%) and none of the females; and QRS morphological changes in 1 male (0.8%) and 12 females (10.0%) (Figs 2a–e) (Table 1). There was no Q wave appearance or disappearance noted in the group studied. Table 1 demonstrates the confidence intervals at p=0.01.

R and S wave changes were mainly amplitude changes (i.e. the height of the R wave and depth of the S wave). The range of R wave amplitude change was from +3 mm to +15 mm (positive indicates above the isoelectric baseline), while that for S was –2 mm to –15 mm (negative indicates below the isoelectric baseline) (Figs 1a–c). All the volunteers who had S wave changes also had R wave changes.

Analysis of the changes showed that these were commonest in leads V1, V2, and V3, irrespective of whether the displacement was cranial or caudal (Tables 2 and 3).

Changes were not observed in the remaining precordial leads, namely leads V4, V5, and V6.

As the volunteers did not have any history of cardiovascular problems, none of them presented with any cardiorespiratory symptoms. There was one volunteer who was detected to have left ventricular hypertrophy on ECG, which was repeated for reconfirmation. She was subsequently offered assessment by a cardiologist as an outpatient.

**Discussion**

There are numerous potential clinical uses of the 12-lead ECG.
Lateef et al. Displacement of the Precordial Leads and ECG

Table 1. Changes observed when comparing the 3 electrocardiograms

<table>
<thead>
<tr>
<th>Changes observed</th>
<th>Number of males (%)</th>
<th>Number of females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>54 (45.0)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>CI: 33.87–56.65</td>
<td>CI: 0.33–8.07</td>
<td></td>
</tr>
<tr>
<td>Changes</td>
<td>66 (55.0)</td>
<td>118 (98.3)</td>
</tr>
<tr>
<td>CI: 43.35–66.13</td>
<td>CI: 91.3–99.67</td>
<td></td>
</tr>
<tr>
<td>R wave amplitude</td>
<td>63 (52.5)</td>
<td>111 (92.5)</td>
</tr>
<tr>
<td>CI: 40.94–63.80</td>
<td>CI: 83.85–96.70</td>
<td></td>
</tr>
<tr>
<td>S wave amplitude</td>
<td>59 (49.2)</td>
<td>99 (82.5)</td>
</tr>
<tr>
<td>CI: 37.77–60.65</td>
<td>CI: 71.93–89.66</td>
<td></td>
</tr>
<tr>
<td>T wave</td>
<td>5 (4.2)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>QRS morphological</td>
<td>1 (0.8)</td>
<td>12 (10.0)</td>
</tr>
<tr>
<td>ST segment</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

CI: confidence interval

Note: Some patients had more than one category of change (e.g. patient A had both R wave and S wave amplitude changes), therefore, the total number of changes may be more than the number of volunteers. For male volunteers, T wave, QRS morphology, and ST segment changes when taken together, the CI at p=0.01 was 33.87%–56.65%. For female volunteers, the CI at p=0.01 was 6.64%–22.29%.

Table 2. Detailed changes among male volunteers

<table>
<thead>
<tr>
<th>Changes</th>
<th>Leads</th>
<th>Cranial displacement</th>
<th>Caudal displacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>R wave</td>
<td>(V_1)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>(V_2)</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>(V_3)</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>S wave</td>
<td>(V_1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(V_2)</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>(V_3)</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>T wave</td>
<td>(V_1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(V_2)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(V_3)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>QRS complex</td>
<td>(V_1)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ST segment</td>
<td>(V_1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(V_2)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(V_3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Some volunteers showed changes in more than one lead, and also changes in either one or both of the cranial and caudal displacement leads. For these reasons, the numbers may not tally, and may be more than the total number of male volunteers.

ECG. The ECG may reflect changes associated with primary and secondary myocardial processes, metabolic and electrolyte abnormalities, as well as toxic or therapeutic effects of drugs or devices. ECGs are composed of a number of waveforms, each with its own sensitivity and specificity,
Table 3. Detailed changes among female volunteers

<table>
<thead>
<tr>
<th>Changes</th>
<th>Leads</th>
<th>Cranial displacement</th>
<th>Caudal displacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>R wave</td>
<td>V₁</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>V₂</td>
<td>56</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>V₃</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>S wave</td>
<td>V₁</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V₂</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>V₃</td>
<td>71</td>
<td>64</td>
</tr>
<tr>
<td>T wave</td>
<td>V₁</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>V₂</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>V₃</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>QRS complex</td>
<td>V₁</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V₂</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>V₃</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Some volunteers showed changes in more than one lead, and also changes in either one or both of the cranial and caudal displacement leads. For these reasons, the numbers may not tally, and may be more than the total number of female volunteers.

and each influenced by a variety of pathologic and pathophysiologic factors. For example, although ST segment and T wave changes are the commonest and most sensitive, these changes are also the least specific.3–5

There is continuing uncertainty about standardized procedures for the placement of ECG chest electrodes. Technical variability represents the largest source of error for short-term variations in amplitude and waveforms of the chest lead ECG. There is uncertainty about locating the mid-clavicular line and, thus, the position of V₄, particularly in obese persons, and females. Appropriate selection of the position for chest leads may help in removing the inconsistencies in ECG interpretation and selection criteria for therapy, thus improving comparability of treatment results.6

Amplitude changes are not uncommon. Previous studies on modified positions of the limb leads have shown considerable amplitude and waveform changes in the frontal plane ECG.7,8

The R wave (QRS complex) reflects the depolarization phase of the ventricles. It has been shown that in those with coronary artery disease/ischemic heart disease, there is often poor progression of the R wave as one moves across the precordial leads and approaches V₆.9

As for extrasystoles, Michaelides et al.10 in a study using angiographic confirmation, showed that the R wave of the extrasystoles is positively correlated with the number of obstructed coronary arteries, Barnhill et al.11 studied R and S waves (terminal portion of the QRS complex) in patients with myocardial infarction (MI), and concluded that these were commonly affected, and very sensitive to changes and variations.

Feldman et al.,12 in a study that examined R wave amplitude and left ventricle chamber size, concluded that there is a direct and dynamic correlation between the two factors. Chamber size and distance from the left ventricle to leads V₄ and V₆ were major determinants of the R wave amplitude. R and S wave amplitudes are also important in diagnostic criteria such as left ventricular hypertrophy (LVH).

The morphology of the ECG depicts the resultant electrical vector in 3 dimensions, with time being the fourth dimension. Hence, it is natural that the morphology of the ECG is known to be affected by the position of the heart, position of the unipolar leads in relation to the heart, as well as the pathway between the heart and unipolar electrodes. For example, with alteration in position of the precordial electrodes, the current may have to pass through a different, more circuitous route, if there is nonconductive tissue encountered along the more direct pathway. Other factors that have been shown to affect ECG morphology include body position,13 and age.14 There have been some studies on ethnicity, and its effect on ECGs.15–16 However, most of these studies are small and may be applicable to the local, ethnic population only.

It has often been thought that with changes in the placement of leads, there will be ST segment alterations affecting our interpretation of MI (i.e. ST segment elevation), especially when comparing serial ECGs.17 In this study, there was only one male patient (0.8%) in whom ST segment change was noted. This assumption may not be as common as previously thought.

There is intra-individual precordial voltage variation in serial ECGs. It is necessary to improve reproducibility and precision in the performance of ECGs. There is also a need to emphasize how electrode placement is taught to nurses, as well as their accountability for this duty.18,19

A new device known as the precordial ECG BELT, using a 6-lead precordial application, has been used in studies to compare its accuracy with standard precordial lead application. Results have indicated disagreement between the two methods.20 The most obvious weakness of the ECG BELT was the inability to obtain a reading with a stable baseline. The findings suggest that the ECG BELT is not adequate for clinical application in its current form.20

Another alternative may be a device with less surface connections, such as the EASI ECG. This device uses only 5 surface connections to derive the 12-lead ECG. Perhaps with less connections, there would be less placement error and
variations. The EASI system has been favorably compared with the standard 12-lead ECG.

Therefore, to reduce inconsistencies, the practice of marking precordial lead positions for short-term serial ECGs should be encouraged. Physicians should also be more cognizant of ECG changes caused by precordial lead displacement when comparing serial ECGs.

This study has shown that variations do exist among normal individuals. It is the first time this has been proven objectively on normal individuals. This suggests the need for standardization, or the use of a device to assist in lead placement, which can ensure accuracy, reproducibility, and objectivity.

References

1. Einthoven W. [Weiteresinber das elektrokardiogramm]. Arch Gesamte Physiol 1908; 172: 517–520
Calcification is closely associated with atheromatous plaque, and is a recognized marker for coronary artery disease. Until recently, it was believed that calcium present in the atheromatous plaques is in the form of calcium phosphate, precipitated in a passive manner. However, recent findings indicate that calcification is an active process and calcium is deposited as hydroxyapatite, similar to that in active bone formation. It is known that the amount of calcium in the coronary arteries is better correlated with the amount of atherosclerosis in different individuals and, to a lesser extent, with the segments of the coronary tree in the same individual. It is not known whether the quantity of calcium tracks the quantity of atherosclerosis over time in the same individual. There are numerous articles on the correlation of coronary calcium with angiographically proven coronary artery disease (CAD); however, there are no such large studies from India. This study was aimed at using helical computed tomography (CT) scan for calculating coronary calcium scores (CCSs) in the Indian population.
Methods
The study included 388 consecutive patients who underwent coronary calcium scoring as well as coronary angiography. These included patients who had presented with either typical symptoms suggestive of ischemic heart disease (with or without a positive stress test), or atypical symptoms with a positive stress test for reversible myocardial ischemia, putting these patients into a pretest probability of intermediate-to-high risk category. All the patients underwent detailed clinical evaluation, biochemical tests, coronary calcium scoring, and coronary angiography. Biochemical tests included fasting and post-prandial blood sugar, and fasting lipid profile.

Assessment of CCSs was done by using a high-speed CT scanner (GE CT/i scanner). Scores were computer generated using an advanced software “smart-score calcium” adapting a modification based on Agatston Score. Total CCSs thus obtained were correlated with the presence or absence of significant CAD. Significant CAD was defined as ≥70% stenosis of at least one of the major epicardial coronary arteries on coronary angiography. Informed consent was obtained from the entire patient population enrolled in the study. The study was approved by the hospital ethics committee.

Statistical analysis: The data obtained were maintained on a Microsoft excel spreadsheet. The differences in various parameters between the different groups were assessed by using Chi-square and t tests, as indicated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for different risk scores were calculated. A p value <0.05 was considered significant. All the statistical analyses were done on SPSS 10.0 for Windows.

Results
A total of 388 consecutive patients underwent coronary calcium scoring and coronary angiograms to rule out significant CAD. Three hundred twenty-five patients (83.8%) were male while 63 (16.2%) were female. The mean age of the patients was 52.3±11.3 years (range 15–78 years). Out of these patients, 76.2% were less than 60 years of age, and 23.8% were more than 60 years of age. For the purpose of analysis, patients were divided into four groups according to CCS: 0, 1–100, 101–400, and >400. There was no statistically significant difference in the prevalence of various conventional cardiovascular risk factors in different calcium score groups (Tables 1 and 2).

The presence or absence of significant CAD on coronary angiography in different calcium score groups is presented in Table 3. Sensitivity, specificity, PPV, and NPV for the prediction of significant CAD were calculated for three different calcium scores, namely >0, >100, and >400 (Table 4). All the 72 patients who had CCS>400 had abnormal angiograms, yielding a sensitivity of 23.1%, specificity 100%, PPV 100%, and NPV 24.1%. Two hundred thirty-six patients with CCS>100 had abnormal angiograms, with only 4 patients having normal angiogram (sensitivity 75.6%, specificity 94.7%, PPV 98.3%, and NPV 51.3%). Out of 314 patients who had

Table 1. Incidence of various risk factors in relation to the calcium score

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Calcium score</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤100 (n=148)</td>
<td>101–400 (n=168)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.2±10.7</td>
<td>51.3±10.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>86.5</td>
<td>80.4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>12.5</td>
<td>11.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>3.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>11.5</td>
<td>11.1</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>5.4</td>
<td>3.7</td>
</tr>
</tbody>
</table>

ns: not statistically significant

Table 2. Correlation of calcium score with lipid profile

<table>
<thead>
<tr>
<th>Lipid profile (mg/dl)</th>
<th>Calcium score</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤100 (n=148)</td>
<td>101–400 (n=168)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>204±45</td>
<td>220±57</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>220±47</td>
<td>181±41</td>
</tr>
<tr>
<td>High-density lipoproteins</td>
<td>42±11</td>
<td>44±9</td>
</tr>
<tr>
<td>Low-density lipoproteins</td>
<td>125±37</td>
<td>142±47</td>
</tr>
<tr>
<td>Very low-density lipoprotein</td>
<td>40±9</td>
<td>34±8</td>
</tr>
</tbody>
</table>

ns: not statistically significant

Table 3. Coronary calcium score correlation with coronary angiography findings

<table>
<thead>
<tr>
<th>Calcium scores</th>
<th>Abnormal angiogram</th>
<th>Normal angiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;400 (n=72)</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>101–400 (n=168)</td>
<td>164</td>
<td>4</td>
</tr>
<tr>
<td>1–100 (n=74)</td>
<td>62</td>
<td>12</td>
</tr>
<tr>
<td>0 (n=74)</td>
<td>14</td>
<td>60</td>
</tr>
</tbody>
</table>
CCSs >0, 298 were found to have abnormal angiograms while 16 patients had normal angiograms (sensitivity 95.5%, specificity 78.9%, PPV 94.9%, and NPV 81.1%).

**Discussion**

Quantification of calcium in the coronary arteries has been shown to reflect the total atherosclerotic plaque burden. This quantification can be determined in a straightforward manner by using advanced high-speed CT scans including helical CT scans, multi-slice CT scans, and electron-beam CT (EBCT) scans. In several studies, detection and quantification of coronary artery calcification with EBCT in suspected CAD patients has been compared with widely available conventional helical CT scan. Although images of the heart from conventional CT scans may suffer from cardiac motion artifacts, calcium scoring with spiral or multi-slice CT scanners has the potential to identify patients with CAD with an accuracy similar to that of EBCT scan. Protocols with prospective or retrospective electrocardiography triggering can be used, which appear to yield results similar to Agatston CCS with EBCT scans, despite technical differences.

Calcification is not found in normal coronary arteries. The atherosclerotic process starts in the second decade of life, when calcium deposition begins. The calcium deposition increases with age, and with progression of atherosclerotic lesions. Coronary artery calcification is temporally related to vascular inflammation and the demise of lipid-laden macrophages. The exact mechanism is unclear, and may be due to the deposition of extracellular calcium from dying cells, or the formation of bone-like structure by calcifying cells. Since calcium is deposited only in the atherosclerotic plaques and not in the normal vessels, and since atherosclerosis is a diffuse process, a high coronary calcium burden reflects the presence of more extensive coronary atherosclerosis (Fig. 1). Hence, higher CCSs are associated with the presence of significant CAD and future risk of adverse coronary events. Moreover, contrary to popular belief, coronary calcium deposition may represent a type of plaque instability, namely plaque rupture. It was earlier believed that calcified areas are unlikely to be associated with the sites of plaque rupture. However, the stiffened calcific area can induce stress at the junction of the calcified and noncalcified sections, which is a common site of plaque rupture. Burke et al. found that, contrary to expectations, the degree of calcification was greatest for acute and healed plaque ruptures, and least for plaque erosion. It has been suggested that the presence of calcium within a heterogeneous, fat-laden plaque renders the plaque more susceptible to stress cracking, as compared to a plaque that contains no calcium.

However, calcium deposition as detected by coronary calcium scoring does not correlate with the site and severity of luminal narrowing on coronary angiography. The observation that coronary plaque burden is poorly correlated with luminal narrowing has been confirmed by studies using intravascular ultrasound (IVUS), and can be explained by the process of vascular remodeling. As the atherosclerotic plaque accumulates in the coronary artery wall, there is an outward remodeling leading to the preservation of luminal size. However, the likelihood of plaque rupture leading to acute MI is not decreased and may even be increased. Thus, the apparent lower specificity of CCS for angiographic obstruction in some studies may in fact be due to the inability of angiography to detect extraluminal plaque. However, an increased CCS would mean the likelihood of significant CAD elsewhere or at another site.

Our data also suggest that in symptomatic patients, the mere presence of calcium is a very sensitive index for the presence of significant CAD somewhere in the coronary arteries. Any CCS >0 has a high sensitivity and reasonably good specificity, with good PPV to predict the presence of obstructive CAD. There have been numerous studies that...
have proved coronary calcium scoring to be an excellent predictor of the presence of angiographically proven obstructive CAD, and future risk of adverse cardiovascular events. In a large study conducted by Budoff et al., in 710 symptomatic subjects with a mean age of 56 years, comparing EBCT scan with coronary angiography, the sensitivity, specificity, and NPV were 95%, 44%, and 84%, respectively. Breen et al. and Kaufmann et al. demonstrated the relationship between CCS and coronary artery lumen obstruction as assessed by coronary angiography. Kaufmann et al. studied 160 symptomatic individuals 23–59 years of age and compared CCS with coronary artery stenosis. Sensitivity, specificity, and accuracy ranged from 81% to 86%. Several other groups have confirmed the association of increased CCS with increased presence and severity of CAD.

He et al. studied nearly 400 asymptomatic patients using EBCT scan and SPECT, and showed that none of the patients with a CCS <10 had an abnormal SPECT. Out of these, 2.6% of patients with CCS 10–100, 11.3% with a CCS of 101–399, and 46% with CCS>400 had a SPECT showing ischemia. This high sensitivity and low specificity probably relates to the fact that only 20% of the atherosclerotic plaque is calcified. However, the absence of calcification seems to indicate a lack of significant luminal stenosis.

In the Rotterdam Coronary Calcification Study, a strong and graded association was found between coronary calcification and MI. In a similar study of patients with suspected CAD, CT scan showed a 65% sensitivity, and 87% specificity for coronary artery calcification. According to the American Heart Association Expert Consensus document on the use of EBCT for the diagnosis and prognosis of CAD, a meta-analysis of the relationship between CAD and calcium prevalence in patients undergoing EBCT and cardiac catheterization to determine the diagnostic accuracy of EBCT in catheterized patients demonstrated a high sensitivity of EBCT for CAD, a much lower specificity and an overall predictive accuracy of 70% in typical CAD patient populations. The test has proven to have a predictive accuracy approximately equivalent to the alternative methods for diagnosing CAD, but was not found to be superior to alternative noninvasive tests such as SPECT imaging. A positive calcium score might be valuable in determining whether a patient who appears to be at intermediate risk of CAD is actually at high risk. Conversely, a low or absent calcium score may also prove useful in determining a low likelihood of developing CAD. The absence of coronary calcification identifies patients with false-positive exercise treadmill testing, and the two can be combined to obtain complementary information. A negative (<0) calcification generally excludes obstructive CAD. Hence, this technique can be used to evaluate patients with atypical chest pain. If the CCS is zero, the source of pain is unlikely to be due to CAD. If the CCS is very high (>400), the chances of the presence of obstructive CAD are steep.

Since coronary calcium scoring is a screening tool, a technique that has a very high sensitivity for the prediction of obstructive CAD is desirable. In our study, which involved intermediate-to-high risk patients, a CCS >0 had a very high sensitivity for obstructive CAD with fairly high specificity. There was a progressive increase in PPV with increasing CCS, suggesting that high CCSs are increasingly associated with obstructive CAD. Thus, a CCS of zero may be used to obviate the need for coronary angiography in intermediate-risk patients and in selected high-risk patients, when coronary angiography is not the preferred method due to concomitant co-morbid conditions (such as renal dysfunction, terminal illnesses, etc.). In such patients, a high CCS, particularly >400, virtually confirms the presence of significant CAD, and can help in devising further management strategies.

**Limitations:** Our study suffered from certain limitations. It involved only those individuals who were at intermediate-to-high risk of having significant CAD. Patients at low risk of CAD could not be included because of obvious ethical reasons. Hence, there was a definite selection bias that could not have been avoided.

**References**

Prehospital Delay in Patients Hospitalized With Acute Myocardial Infarction in the Emergency Unit of a North Indian Tertiary Care Hospital

S Malhotra, M Gupta, KK Chandra, A Grover, P Pandhi
Departments of Pharmacology and Cardiology, Post Graduate Institute of Medical Education and Research, Chandigarh

Background: Prompt treatment of patients presenting with acute myocardial infarction decreases the incidence of death from early arrhythmia, and maximizes the potential benefit of thrombolytic therapy. Prehospital delay has been identified as a major obstacle to the widespread use of thrombolytic therapy. The aim of the present study was to examine the extent of, and factors associated with, delay in seeking medical care (usually thrombolytic therapy) in patients with acute myocardial infarction.

Methods and Results: The study was conducted in patients visiting the medical emergency unit of the Nehru Hospital, Post Graduate Institute of Medical Education and Research, Chandigarh. A total of 104 patients diagnosed with acute myocardial infarction were interviewed using a pre-designed proforma. Pain-to-door, and door-to-drug times, were the main outcome measures. The corrected mean (SEM) and median (range) pain-to-door times were 8.5 (0.8) hours and 5.2 (0.5–24) hours, respectively. Out of 104 patients, 38 did not receive thrombolytic therapy. In those who did not receive thrombolytic therapy, prior therapy at local health centers, lack of knowledge of symptoms, and transportation problems were the main reasons for hospital delay. The mean (SEM) and median (range) of door-to-drug times were 1.2 (0.1) hours and 1 (0.2–3.5) hours, respectively.

Key Words: Prehospital delay, Thrombolytic therapy, Acute myocardial infarction

Acute myocardial infarction (AMI) results from prolonged myocardial ischemia, precipitated in most cases by an occlusive coronary thrombus at the site of a pre-existing atherosclerotic plaque. It is a major cause of mortality and morbidity in the general population. Currently, the prevalence of coronary artery disease (CAD) in the age group of 40–50 years in urban India is 4-fold higher than in the United States \(10\% \text{ v.} 2.5\%\).

Numerous studies have demonstrated the benefits of thrombolytic therapy for patients with evolving AMI. \(^2\) Thus attention has shifted towards efforts to increase the use of this therapy. However, the benefits of thrombolytic therapy are greater in the first few hours after the onset of symptoms. \(^3\) Hence, patient-associated delay in the recognition of symptoms of heart attack has been identified as a major obstacle to the widespread use of thrombolytic therapy. \(^4\) The duration of prehospital delay includes the time required to recognize the symptoms, decision to seek care, arrange transportation, travel to the hospital, and the time required for diagnosis. \(^5\)

A large number of factors have been attributed to prehospital delay; these include sociodemographic, behavioral, clinical, and situational constraints. \(^5\) The aim of the present study was to examine the extent of, and factors associated with, delay in seeking medical care (usually thrombolytic therapy) in patients with AMI.

Methods

The study was conducted in patients presenting with AMI admitted to the medical emergency or coronary care unit of the Nehru Hospital, Post Graduate Institute of Medical Education and Research, Chandigarh from December 2001 to June 2002. One hundred four consecutive patients of MI were interviewed using a pre-designed proforma. The chief constituents of the questionnaire included the demographic characteristics of the patient, nature and time of onset of symptoms, pre-existing illness and treatment

Correspondence: Dr (Mrs) P Pandhi, Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012. e-mail: ppandhi17@hotmail.com
received, and any previous knowledge about symptoms of heart attack. The patients were then asked about the time at which they presented to the emergency unit and received medical care. The main outcome measures included: (i) pain-to-door time (time interval between the onset of symptoms suggestive of AMI and arrival in the emergency unit); and (ii) door-to-drug time (time interval between arrival in the emergency unit and administration of thrombolytic therapy).

Statistical analysis: The data were expressed as mean (±SEM) and median. To examine the differences between different delay groups for continuous variables, t tests and analysis of variance (ANOVA) were used. A value of \( p<0.05 \) was considered statistically significant.

Results

Of the 104 consecutive MI patients studied, 66 received thrombolytic therapy. We initially examined the association between demographic and clinical factors, and duration of prehospital delay (Table 1). The average and median delay times increased with advancing age. Men did not experience significant delay as compared to women. Also, delay was not significant in patients with respect to the location and type of MI. Patients with a history of angina exhibited prolonged delay compared with patients without angina (13.4 v. 3.2 hours). However, patients with a history of diabetes and hypertension did not experience significant delays as compared with patients without these conditions. Patients seeking treatment from local physicians delayed longer than those who came straightaway to the emergency unit (16.1 v. 6 hours) (Fig. 1). We also found that patients who did not know the symptoms of heart attack delayed longer than those who had a good knowledge (Fig. 1).

Pain–door–drug times: The mean (SEM) and median (range) pain-to-door times were 13 (2.1) hours and 5.2 (0.5–12) hours, respectively. The corrected (delay equals 24 hours for those delaying 24 hours or more) mean (SEM), and median (range) pain-to-door times were 8.5 (0.8) hours and 5.2 (0.5–24) hours, respectively (Fig. 2).

The mean (SEM) and median (range) of door-to-drug times were 1.2 (0.1) hours and 1 (0.2–3.5) hours, respectively (Table 2).

Prehospital delay was the cause for 30 of the 38 patients (79%) not receiving any thrombolytic therapy. In the remaining 8 patients, the causes for not receiving thrombolysis were: unaffordability of urokinase (3), unaffordability of streptokinase (1), associated contraindications for thrombolysis (2), and already received thrombolysis (2) (Fig. 3). Prior therapy at local healthcare services, lack of knowledge of symptoms, and transportation problems were the main reasons for prehospital delay in nonthrombolyzed patients.
Discussion

This study describes prehospital delay times for the sample of patients admitted to the emergency unit of our institute for the evaluation of suspected AMI from December 2001 to June 2002. In this study population, the overall median delay time was 5.2 hours, and door-to-drug time was 1 hour. A review of the data from studies published between 1969 and 1987 shows that the median prehospital delay for patients with AMI ranged from 2.5 to 7 hours. These differing delay times are likely attributable to varying demographic and clinical characteristics of the samples under study, definitions of symptom onset time used, and period during which the study was conducted. In our study, delays were not significant with respect to age and sex. In
Table 2. Duration of prehospital delay and timing of administration of thrombolytic therapy in patients with acute myocardial infarction

<table>
<thead>
<tr>
<th>Pain-to-door time, Duration of prehospital delay (hours)</th>
<th>n</th>
<th>Door-to-drug times (hours)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>6</td>
<td>0.8</td>
<td>1.0 (0.3)</td>
</tr>
<tr>
<td>1–1.9</td>
<td>16</td>
<td>0.8</td>
<td>0.1 (0.1)</td>
</tr>
<tr>
<td>2–3.9</td>
<td>16</td>
<td>0.7</td>
<td>1.2 (0.2)</td>
</tr>
<tr>
<td>4–5.9</td>
<td>10</td>
<td>1.4</td>
<td>1.4 (0.2)</td>
</tr>
<tr>
<td>6–11.9</td>
<td>16</td>
<td>1</td>
<td>1.4 (0.3)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>2</td>
<td>1.5</td>
<td>1.5 (0.5)</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>1</td>
<td>1.2 (0.1)</td>
</tr>
</tbody>
</table>

*p value denotes the comparison of mean door-to-drug times in the various groups of patients with different durations of prehospital delay.

In contrast, earlier studies suggested that older individuals took longer to access medical care than younger individuals. This might be due to the still prevalent joint behavior of patients with collapse, pain or pathological breathlessness after MI is at an instinctive level, though to some extent, it may be culturally related.

In contrast to previous studies, the day of the week and time of presentation did not affect the prehospital time. Prehospital delay was significantly higher in patients (9.9 v. 5.2 hours, p=0.002) who had visited a local practitioner than those who came straightaway to the emergency unit of the hospital. While the reasons for such a practice may be speculative, we suggest that this delay in time can be reduced if there is a 24-hour ambulance service with a hotline and facilities for facsimile transmission of ECG. Such an ambulance can quickly transport patients directly to the tertiary-care center if necessary. Secondly, general practitioners can be formally trained to administer streptokinase themselves, and deal with the complications arising from streptokinase therapy.

In the present study, out of 104 patients, 66 were thrombolysed. Also, prehospital delay was significantly longer in the nonthrombolysed patients (corrected mean 15 hours v. 4.6 hours). There is overwhelming evidence of the beneficial effects provided by reperfusion strategies in patients with AMI. Although various contraindications to the administration of thrombolytic therapy presently exist, including prolonged prehospital delay, thrombolytic therapy is underutilized in the management of AMI.

Findings from the Worcester Heart Attack Study show that patients who delayed for more than 6 hours were 6.5 times less likely to receive thrombolytic agents compared to patients who arrived within 1 hour of the onset of AMI. In the present study, out of 38 nonthrombolysed patients, 30 presented to the hospital after 6 hours; the remaining either could not afford thrombolytic therapy or were already thrombolysed. Another aspect of prehospital delay highlighted by our study is knowledge regarding heart attack symptoms. Patients who knew about the symptoms of heart attack delayed less than those who were ignorant (2.9 v. 11.9 hours). Thus, educational approaches are essential to reduce the extent of patient delay, and to enhance widespread use of time-dependent management strategies in patients hospitalized with AMI.

Hospital-associated delays in administering thrombolytic therapy: In our study, mean and median door-to-drug times in thrombolysed patients were 1.2 (0.1) hours and 1 (0.2–3.5) hours, respectively. However, a previous study suggests an association of increasing delays in thrombolytic therapy with increasing duration of prehospital delay. The National Heart Attack Alert Program has appropriately called attention to reduction of door-to-drug times. However, a few studies have examined the relationship between the extent of prehospital and hospital delay with thrombolytic therapy.

Limitations of the study: There are several limitations of the present study. The effect of prehospital delay on disease outcomes was not studied. Patients who died of AMI outside the hospital and those with silent MI were not studied. Appropriate caveats need to be planned for the interpretation of study findings, since different delay patterns may have existed in patients with poorly defined time of onset of symptoms. The number of patients included in the study was also small. However, our data...
are representative of a typical tertiary care hospital and, therefore, such data can be generalized to other hospitals as well.

In conclusion, prehospital delay is the main reason for not receiving thrombolytic therapy. The main factors contributing to prehospital delay are: poor knowledge of symptoms, prior treatment from local practitioners, and unavailability of rapid transport facilities. Target educational efforts, and provision of rapid transportation facilities can help reduce the excessive case fatality rates attributed to prehospital delay.

References
Mitral Valve Repair for Nonrheumatic Mitral Regurgitation

Swapnadeep Roy, Shiv Kumar Choudhary, Arkalgud Sampath Kumar
Department of Cardiothoracic and Vascular Surgery, All India Institute of Medical Sciences, New Delhi

**Background:** We studied the results of mitral valve repair in patients with severe mitral regurgitation of nonrheumatic etiology.

**Methods and Results:** Between January 1988 and April 2002, 116 patients, of which 59 were male and 57 female, with severe mitral regurgitation of nonrheumatic etiology underwent mitral valve repair using a variety of techniques. Their mean age was 26.4 years (range 2–67 years). The cause of mitral regurgitation was congenital in 56 patients, myxomatous in 44, infective endocarditis in 7, and ischemic in 9. Ninety patients were in preoperative New York Heart Association class III, and 26 in class IV. Reparative procedures included posterior teflon felt collar annuloplasty (modified Cooley’s) in 80 patients, chordal shortening in 37, cusp excision in 34, cleft closure in 8, chordal transfer in 6, and neochordae in 3. The early mortality was 3.4% (4 patients). Follow-up ranged from 1 to 167 months (mean 47 months), and was 95% complete. There were 2 late deaths (1.7%). Six patients (5.2%) underwent reoperation for severe mitral regurgitation post-repair. Of the remaining 104 patients, 90 (86.5%) had no or trivial mitral regurgitation at the last follow-up. Actuarial, reoperation-free, and event-free survival at 130 months was 93%±3.6%, 89.9%±6%, and 69.7%±13.7%, respectively. Ninety-two patients (88.5%) were in New York Heart Association class I at the last follow-up.

**Conclusions:** Mitral valve repair in nonrheumatic mitral regurgitation patients provides satisfactory results with current surgical techniques, and is the preferred option in this subset of patients. *(Indian Heart J 2003; 55: 354–357)*

**Key Words:** Mitral regurgitation, Mitral valve repair, Valvular heart disease

Surgical treatment of severe mitral regurgitation (MR) currently involves either mitral valve (MV) repair or replacement (mechanical prosthesis/bioprosthesis). Although valve replacement has been the widely accepted modality, there are numerous complications associated with this procedure such as thrombosis, thromboembolism, anticoagulant-related hemorrhage, and bioprosthetic degeneration over a period of 7–15 years, necessitating a second surgical procedure. Therefore, repair as the preferred option, whenever possible, is gaining popularity among cardiac surgeons.

The etiology of the MR may be rheumatic or nonrheumatic. In the latter category, there are numerous causes such as congenital (often associated with atrial septal defect), myxomatous degeneration, ischemic, and infective. While the results of repair for rheumatic valve disease often have a late phase of deterioration due to progression of the rheumatic valvulitis, the reported results of repair in nonrheumatic cases have generally been more satisfactory. We report our experience with repair in this subset of patients.

**Methods**

From January 1988 to April 2002, 116 patients with severe MR of nonrheumatic etiology underwent MV repair. The age range of the patients was 2–67 years (mean age 26.4 years). Of these patients, 59 were males (50.8%), and 57 females (49.2%). The causes of nonrheumatic MR were congenital in 56 patients (47.4%), myxomatous degeneration with cusp prolapse in 44 (37.9%), infective endocarditis in 7 (6%), and ischemic in 9 (7.7%). Six of the patients had a primum ASD (partial atrioventricular septal defect), and 46 had a secundum ASD. An isolated cleft MV was responsible for the MR in 4 patients. In patients with myxomatous degeneration, there was cusp prolapse with chordal elongation/rupture, predominantly in the posterior...
mitral leaflet. In the ischemic category, we included patients with chronic ischemia only, in whom the MR was due to papillary muscle dysfunction or chordal elongation/rupture. Associated annular dilatation was present in all these patients due to left ventricular dilatation. In patients with infective endocarditis, there were primarily localized areas of leaflet destruction, and repair was undertaken only after an adequate course of antibiotics (at least 2 weeks).

Seventy-four patients (63.8%) were in sinus rhythm preoperatively, and 42 in atrial fibrillation (36.2%). The predominant presenting symptom was dyspnea on exertion. Ninety patients were in New York Heart Association (NYHA) class III, and 26 were in class IV.

Preoperative transthoracic echocardiography was performed in all the patients. Cardiac catheterization and coronary arteriography were performed in patients above 40 years of age, or if there was a suspicion of associated aortic valve disease, or coronary artery disease. The severity of MR was assessed by echocardiography and/or angiography.

**Surgical technique:** After induction of general anesthesia, transesophageal echocardiography (TEE) was performed in all the patients after 1994. Intraoperatively, the surgical approach was either a mid-sternotomy (n=100) or a right anterolateral thoracotomy (n=16). The latter approach was primarily used for cosmetic reasons in young females. Before 1996, moderately hypothermic (32°C) cardiopulmonary bypass (CPB), and since 1996, normothermic perfusion was used in all the patients. Cold-blood cardioplegia and topical ice-slush was used for the protection of the myocardium. Bicaval cannulation was used in all the patients. The MV was exposed through a standard incision in the left atrial wall behind the interatrial groove. In patients with an ASD, the approach was through the right atrium. After assessing the morphology, a variety of reparative techniques were utilized, as described earlier. The adequacy of repair was confirmed by injecting saline into the left ventricular cavity and observing the coaptation of the leaflets. At the end of the procedure after discontinuing CPB, TEE was performed in all the patients treated after 1994 to confirm the adequacy of repair.

The various procedures utilized for the MV repair are as follows: (i) posterior teflon felt collar annuloplasty (modified Cooley’s) in 80 patients (68.9%); (ii) chordal shortening in 37 (31.9%); (iii) cusp excision (quadrangular resection of posterior mitral leaflet) in 34 (29.3%); (iv) cleft closure in 8 (6.9%); (v) chordal transfer in 6 (5.2%); and (vi) neochordae in 3 (2.6%).

Associated procedures performed in these patients included the following: (i) aortic valve replacement (prosthetic) in 8 (primarily for aortic regurgitation); (ii) aortic valvuloplasty in 15; (iii) closure of atrial septal defect in 52; (iv) coronary artery bypass grafting in 5 (3 of the other 4 patients with ischemic MR had prior successful angioplasty of the diseased target vessels; the remaining patient had scarred myocardium with no reuptake on thallium scan).

Follow-up ranged from 1 to 168 months (mean 47 months). The follow-up was 95% complete. At each follow-up visit, a transthoracic echocardiogram (TTE) was performed in all these patients to assess the status of the MV repair, besides looking for any associated lesions. Statistical analysis was performed using SPSS software on a Windows operating system. Kaplan–Meier survival estimates were derived for this group of patients.

**Results**

All the patients survived the operation. The mean bypass time was 51 min (range 28–70 min), and the mean aortic cross-clamp time was 37 min (range 21–58 min). The mean intensive care unit stay was 2 days (range 1–6 days), and the mean postoperative ventilation was for a period of 8 hours (range 6–72 hours). The mean postoperative stay was 5 days (range 4–9 days).

Early mortality (30-day) was seen in 4 patients (3.4%). In 1 patient, the cause of death was persistent low output following the repair (preoperatively the patient was in congestive heart failure unresponsive to medical management). The second patient developed acute renal failure in the immediate postoperative period and succumbed. Two other patients died of persistent intractable ventricular arrhythmias.

In the surviving patients, a pre-discharge TTE was performed to evaluate the status of the MV repair. In all the 112 patients, there was no or mild MR that correlated well with the TEE, performed at the end of operation in the operating room.

There were 2 late deaths (1.7%). Both patients had developed severe left ventricular dysfunction secondary to severe MR and succumbed before reoperation. Six patients (5.2%) underwent reoperation for severe MR. Of these patients, 5 had congestive heart failure, and the sixth patient was in NYHA class III prior to reoperation. In 5 of the 6 patients, the cause of failure of the original repair was due to suture dehiscence of the annuloplasty, or those used for chordal shortening. In one of them, there was progression of the original myxomatous degeneration with chordal rupture of originally uninvolved chordae. All the
Of the 104 late survivors, 92 (86.5%) are in NYHA class I, and 12 in NYHA class II at the last follow-up. Eighty patients (76.9%) are in sinus rhythm, while the rest are in chronic atrial fibrillation (AF) (all of them were also in AF preoperatively). One of the 104 late survivors (0.9%) had a thromboembolic complication (the patient was in AF postoperatively). There were no other complications. Of those who were reoperated, all have improved to NYHA class II status.

At the last follow-up, 90 of the 104 surviving patients have no or trivial MR on echocardiography, 6 have mild MR, and 8 have moderate-to-severe MR.

The actuarial, reoperation-free, and event-free survival in the group of operative survivors at 130 months was 93%±3.6%, 89.9%±6%, and 69.7%±13.6%, respectively (Kaplan–Meir estimates). Freedom from thromboembolic events at 108 months was 98.6% (Figs 1–3).

Discussion

In India, rheumatic heart disease remains the predominant cause of MR. However, MR due to nonrheumatic causes is not uncommon.

Repair of the MV has gradually become widely accepted, ever since it was popularized by Carpentier.7 For non-rheumatic severe MR, repair of the MV has shown excellent long-term durability. The Carpentier group6–8 has reported a 15-year actuarial survival of 72.4%, with freedom from reoperation at 15 years being 92.7%. This group predominantly used a prosthetic ring in most of their annuloplasty procedures. Galloway et al.9 reported on their results with Carpentier-type MV reconstructions with an operative mortality of 5%, and a 5-year freedom from reoperation rate of 94.4%. Actuarial freedom from thromboembolic complications was 93.9% at 15 years, and 96.5% were free from anticoagulant-related hemorrhage. Similar results have been reported by other groups also. Overall, the results are better than those reported with prosthetic MV replacement.10

Our results compare favorably with other reports in the literature. Our 10-year survival of about 93% with a reoperation-free rate of 89% is comparable to most reported series. Functional rehabilitation and the absence of medication are marked advantages. Preservation of left ventricular function is another advantage.

Conclusion: Repair of the MV rather than its replacement should be the procedure of choice in patients with non-rheumatic MR.
Acknowledgments

The authors acknowledge the help provided by the residents of the department for the excellent record-keeping that greatly facilitated the analysis of results. We would also like to thank Mr Rajbir of the Department of Biostatistics, for the statistical analysis.

References


Prevalence of Left Atrial Thrombus in Rheumatic Mitral Stenosis With Atrial Fibrillation and its Response to Anticoagulation: A Transesophageal Echocardiographic Study

J Srimannarayana, RS Varma, S Satheesh, R Anilkumar, J Balachander
Department of Cardiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry

Background: The frequency of occurrence of left atrial thrombi, and the effect of anticoagulation in patients with rheumatic mitral stenosis and atrial fibrillation is not well established. This study was conducted to evaluate the occurrence of left atrial body and left atrial appendage clots in patients with rheumatic mitral stenosis and atrial fibrillation, and to document the effect of long-term anticoagulation on clot dissolution.

Methods and Results: Consecutive patients with severe rheumatic mitral stenosis and atrial fibrillation were assessed by transesophageal echocardiography. Those with left atrial body or left atrial appendage clots were anticoagulated with oral nicoumalone. Transesophageal echocardiography was then repeated in patients on anticoagulation who were on regular follow-up, and in whom percutaneous transvenous mitral commissurotomy could be considered. Of the 490 patients studied, 163 had left atrial body or left atrial appendage clots. A repeat transesophageal echocardiographic examination was done in 50 patients who had optimal anticoagulation for a period of 6 months. Only 2 of the 17 patients who had left atrial body clots had successful clot dissolution after long-term anticoagulation, while the left atrial appendage clots disappeared in 31 of 33 patients (p<0.001).

Conclusions: Left atrial clots are present in a third of patients with severe rheumatic mitral stenosis and atrial fibrillation. Isolated left atrial appendage clots in patients with rheumatic mitral stenosis and atrial fibrillation can disappear with long-term anticoagulation, while thrombi that extend into the left atrial body may persist despite optimal anticoagulation. (Indian Heart J 2003; 55: 358–361)

Key Words: Rheumatic mitral stenosis, Left atrial thrombi, Echocardiography
No clots were detected on repeat TEE in 31 out of 33 patients (93.9%) with isolated LA appendage clots (Figs 1 and 2). These 31 patients underwent PTMC successfully. Only 2 out of 17 patients (11.8%) with a previous LA body clot had no detectable clots. Patients with persistent LA clots were referred for an open mitral valvotomy and thrombectomy. A comparison between those in whom the clot disappeared, and those in whom the clot persisted revealed that the location of the LA clot (isolated LA appendage v. LA body) alone was a significant predictor of thrombus dissolution. There were no statistically significant differences in other parameters, such as valve orifice, LA size, mitral regurgitation, age, gender, and INR values between these groups.

Results

Incidence and location of thrombi: Of the 490 patients who underwent TEE, LA clots were present in 163 (33.2%). Isolated LA appendage clots were found in 88 patients (18%). Isolated LA body clots or LA appendage clots extending into the LA body were found in 75 patients (15.3%). LA spontaneous echocardiographic contrast (LASEC) was present in 365 patients (74.5%). None of the patients had right atrial thrombi.

Resolution of thrombi: TEE was repeated after 6 months of optimal oral anticoagulation in 50 out of 163 patients. These patients had maintained their INR in the range of 2.5–3.5, and were on regular follow-up. Nearly half the patients (48%) were above the age of 35 years (range 21–55 years). None of these patients had any other risk factors, such as diabetes mellitus, hypertension or smoking. A comparison of the baseline characteristics, echocardiographic parameters, and mean INR between the group of patients with isolated LA appendage clots (n=33) and the group with clots extending to the LA body (n=17) is given in Table 1. There were no statistically significant differences among these parameters between the two groups.

Table 1. Comparison of patients who underwent repeat TEE with isolated LA appendage clot versus those with clots extending to the LA cavity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=33)</th>
<th>Group B (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>33.9±7.82</td>
<td>33.8±9.01</td>
<td>ns</td>
</tr>
<tr>
<td>Males</td>
<td>10 (30.3%)</td>
<td>9 (52.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Females</td>
<td>23 (69.7%)</td>
<td>8 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>Mean MVO (cm²)</td>
<td>0.9±0.15</td>
<td>0.96±0.14</td>
<td>ns</td>
</tr>
<tr>
<td>Mean MPG (mmHg)</td>
<td>20.15±6.7</td>
<td>22.06±6.51</td>
<td>ns</td>
</tr>
<tr>
<td>Mean LA size (AP diameter, cm)</td>
<td>3.7±0.6</td>
<td>3.71±0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Mitral regurgitation (grade 1/4)</td>
<td>7 (21.2%)</td>
<td>4 (23.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean INR</td>
<td>2.87±0.3</td>
<td>2.89±0.23</td>
<td>ns</td>
</tr>
</tbody>
</table>

Group A: patients with isolated LA appendage clot; Group B: patients with clots extending to the body of the LA or isolated LA body clots; MVO: mitral valve orifice; MPG: mean pressure gradient; AP: anteroposterior; INR: international normalized ratio; ns: not significant; LA: left atrial; TEE: transesophageal echocardiography

Discussion

Conventional transthoracic echocardiography (TTE) has a poor yield in the detection of LA appendage thrombi.1 The posterior location of the LA in the chest as well as the poor
visualization of the LA appendage contribute to the lack of accuracy of TTE. On the other hand, TEE is an excellent method for detecting atrial thrombi, especially those located in the LA appendage.

There are few reports on the prevalence of LA body and LA appendage clots in patients with severe mitral stenosis and AF. In a small group of 50 patients with mitral stenosis and AF, Hwang et al.4 observed an LA thrombus in 28 patients (56%) by TEE. In another small study of 22 patients with mitral stenosis and AF, Karatasakis et al.5 observed an LA thrombus in 12 patients (54%). In our study of 490 patients, the prevalence was 33.5%. Considering the size of the study group, this can be considered a representative figure for the prevalence of LA thrombi in patients with severe mitral stenosis and AF. Thus, it can be stated that 1 out of every 3 patients with severe mitral stenosis and AF will have an LA thrombus.

Anticoagulation is conventionally used to reduce the risk of the thromboembolic events associated with AF. Oral anticoagulants act by inhibiting the synthesis of vitamin K-dependent coagulation factors. This prevents new thrombus formation, and promotes adherence and organization of old thrombi to the surrounding endocardium.6-8 However, recent studies have supported an alternative hypothesis of benefit that includes not only the prevention of new thrombus formation but also the resolution of existing thrombi.9

In situations in which a thrombus is already present, anticoagulation prevents further thrombus extension, thereby facilitating the action of endogenous fibrinolysis. A study conducted by Kandpal et al.10 showed that 41.7% of isolated LA appendage clots resolved in contrast to 12.5% of LA body clots in patients with mitral stenosis after 6 months of oral anticoagulation. Resolution of atrial thrombi after oral anticoagulation in patients with nonvalvar AF has also been examined in several studies.11,12

In the present study, it was seen that thrombi in the LA appendage disappeared on anticoagulation, whereas thrombi in the LA body did not. Success in resolving LA appendage thrombi vis-à-vis LA body thrombi is crucial, given that most clinically encountered thrombi are located in the LA appendage. This difference is possibly explained by the fact that patients with an LA body clot have a higher clot burden, which does not permit dissolution with endogenous fibrinolysis despite optimal anticoagulation. It is probable that clots localized to the LA appendage, with a much smaller clot burden, are dissolved by endogenous fibrinolysis, while effective oral anticoagulation prevents fresh thrombus formation.

A study conducted by Murillo et al.13 showed that PTMC can be performed in patients with an LA appendage clot with TEE guidance and fluoroscopic control. However, this can be fraught with the risk of embolism. Hence, the interventional cardiologist will always prefer the LA and LA appendage to be free of clots before embarking on balloon mitral valvotomy. Based on our study, it is possible to evolve a strategy of treatment in patients with severe mitral stenosis, AF, and LA thrombus. Patients with an LA thrombus extending well into the LA body can be directly referred for surgery, since they are unlikely candidates for closed procedures. However, patients with isolated LA appendage clot and mitral stenosis can afford to be on anticoagulation for a period of 6 months, and then undergo a repeat TEE, especially if they can be stabilized to NYHA class II or less. If the clot resolves, as in a good percentage of our subjects, these patients can undergo PTMC.

Some limitations of our study have to be emphasized. A repeat TEE was done in only about one-third of the patients with LA clots. The rest of the patients did not undergo a repeat TEE as part of the study because of one or more of the following reasons: valve morphology precluded PTMC, NYHA class III or class IV patients who were judged to need early surgical treatment, suboptimal anticoagulation, and irregular follow-up. Thus, the results of the study should be interpreted with some caution, and a further, large-scale study may be necessary to confirm the findings of our study.

The effect of anticoagulation on LASEC was not studied since the mere presence of LASEC was not considered to be a contraindication for PTMC. Also, it was not practically possible to determine the duration of AF in these patients, and correlate it with clot prevalence and resolution.

Conclusions: One-third of patients with severe mitral stenosis and AF have LA body or LA appendage clots. Isolated LA appendage clots in patients with rheumatic
mitral stenosis and AF can disappear with long-term anticoagulation. Such patients may become favorable candidates for PTMC. Clot dissolution with oral anticoagulation is unlikely in those with an LA body clot. These patients can be referred early for open mitral valvotomy and thrombectomy.

References
Membranous obstruction of the inferior vena cava (MOVC) is relatively common in Asia and Africa. Many cases have been reported from India. MOVC is one of the important causes of Budd–Chiari syndrome. Intervention is often necessary, as medical treatment is ineffective. The disease should be managed early, because long-standing MOVC can result in hepatocellular carcinoma. Till the introduction of balloon dilatation for treating MOVC cases, surgery was the only option available. Here, we report our experience with balloon angioplasty for managing these cases.

**Methods**

Between January 1999 and January 2002, 19 patients who were clinically diagnosed to have inferior vena cava (IVC) obstruction were taken up for the study. The disease was suspected when the patients presented with ankle edema, ascites, and prominent veins over the abdomen and back, with the direction of blood flow from below upwards. After taking a careful history, detailed physical examination was carried out in all the patients. Hematological tests, coagulation profile, liver function tests, and abdominal ultrasound with Doppler study of the IVC were undertaken.

After clinical diagnosis, the patients were taken up for inferior vena cavography, and subsequent angioplasty. Catheterization and angiography of the IVC was done through the femoral vein with a pigtail catheter. Simultaneous right atrial catheterization was done through the antecubital vein for simultaneous measurement of the pressure gradient between the IVC and right atrium (RA).

If the vena cavography demonstrated a complete obstruction, the IVC was first punctured by the stiff end of a guidewire inserted through a multipurpose catheter. Predilatation of the lesion was initially done with a peripheral angioplasty balloon (3×20 mm) if the Joseph balloon could not be negotiated across the site of the lesion. Angioplasty was attempted with the Joseph balloon, which is commonly used for balloon mitral valvotomy. The size of the balloon used varied from 22 to 24 mm, depending upon the size of the IVC. After the balloon was placed across the lesion, it was inflated and deflated 2–3 times. Repeat venography was done to show blood flow towards the RA. The success of the procedure was confirmed by demonstrating reduction or disappearance of the gradient between the IVC and RA.
Membrane is congenital or acquired. Yamamoto et al.4 have classified MOVC into 3 groups. In group A, there was incomplete obstruction of the IVC, in group B the obstructing membrane was complete and thin; in group C the membrane was complete and thick. Of the 17 patients who were taken up for angioplasty in our series, the membrane was complete in 13 (76.4%).

The mean age at presentation in our patients was 38±6.9 years. The majority of MOVC patients were also between 30–40 years of age in the series reported from South Africa by Simson.1 In our series, jaundice was evident in 5 cases (26.3%). It was present in 5.8% of patients in the series reported by Kohli et al.5 The high incidence of jaundice in our cases was probably due to late presentation of the patients. Ultrasound examination revealed the site of obstruction in 94.7% of our patients. Kohli et al.5 could identify obstruction of the IVC by plain ultrasonography in 91% of cases.

In our series, 2 patients (10.5%) had additional obstruction of the hepatic vein. Combined obstruction has been reported in 7 out of 75 cases studied by Kohli et al.5

Medical treatment is ineffective.6 Previously, surgical options included membranotomy, done by a finger7 or metal bougie,8 or cavoatrial shunts done to bypass the obstruction.

Angioplasty has become the treatment of choice for MOVC. Successful dilatation has been reported in 93.3%–100% of cases from India.5,9 In our series, procedural success was 88.2%. In all our successful cases, the site of complete obstruction could be punctured by the stiff end of the guidewire. The obstruction can also be pierced by Brockenbrough’s septal puncture needle, which was used by Kar et al.9 and Patel et al.10 with excellent results.

In earlier studies, either a pulmonary balloon 8 or Inoue balloon11,12 has been used to dilate an obstruction of the IVC. We attempted dilatation using a Joseph balloon with gratifying results. It is safe with a high success rate. The balloon could be reused several times, which is important, as the majority of our patients are poor.

Restenosis was detected in 20% of our patients during follow-up. 14.3% of cases developed restenosis in the series by Kohli et al.5 Tyagi et al.,13 however, reported a very high incidence (36.4%) of restenosis.

Conclusions: Membranous obstruction of the IVC can give rise to substantial morbidity because of massive ascites and ankle edema. A high index of suspicion is necessary, as the disease is often confused with cirrhosis of the liver. Ultrasonography with Doppler study of the IVC can be diagnostic, though vena cavography is required for confirmation. In the majority of patients, obstruction can be successfully tackled by balloon angioplasty without...
fear of rupture of the IVC. Long-term follow-up of post-angioplasty patients is necessary to further validate the success of the procedure.

References

Sonographically Guided Thrombin Injection for the Treatment of Femoral Artery Pseudoaneurysm

Pravin K Goel, Nitin Modi, Sanjay Saran Baijal, Manoj Kathuria, Surendra K Agrawal
Departments of Cardiology, Radiology, and Cardiovascular and Thoracic Surgery,
Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow

The formation of pseudoaneurysm in the femoral artery after cardiac catheterization is a well-recognized complication occurring in 1%–4% of cases. It is traditionally managed surgically and has a high morbidity. Prolonged ultrasound-guided compression of the neck of the pseudoaneurysm, and ultrasound-guided injection of thrombin into the aneurysm are newer modalities of treatment especially for small aneurysms. We describe the case of a giant pseudoaneurysm of the right femoral artery, post-arteriography, which was successfully managed with ultrasonographically guided percutaneous thrombin injection. (Indian Heart J 2003; 55: 365–367)

Key Words: Pseudoaneurysm, Femoral artery, Thrombin

Femoral artery pseudoaneurysm is an uncommon but well-recognized complication after percutaneous arterial catheterization. The incidence of pseudoaneurysm formation is reported to be up to 1% after diagnostic studies, and 3.2% after interventional procedures. Traditionally, these pseudoaneurysms require reparative surgery. In 1986, Cope et al. described the technique of percutaneous thrombin injection for small pseudoaneurysm in the iliac, femoral, and popliteal arteries. There is, however, limited experience with this technique on large aneurysms. We describe a case of a large pseudoaneurysm successfully managed with percutaneous intra-aneurysmal injection of bovine thrombin.

Case Report
A 66-year-old hypertensive, nondiabetic, nonsmoker male underwent diagnostic cardiac catheterization through the right femoral artery using 6 F arterial sheath. Five thousand units of heparin was given during the procedure, and post procedure, the right lower limb was immobilized for 6 hours. After 6 hours, the patient was allowed to carry out his routine activities and was to be discharged the following day. However, about 18 hours post procedure, the patient complained of severe pain in the right groin with obvious swelling of the thigh. There was no external bleeding from the puncture site. Doppler study of the femoral artery showed a large pseudoaneurysm (10×4×4 cm) with a narrow neck of 0.5 cm. The aneurysm was largely located anterior to the femoral artery all along its length, for up to about 10 cm below the puncture site. Ultrasound-guided compression of the neck was tried but was not successful. Considering the large size of the aneurysm, ultrasonographically guided thrombin injection into the pseudoaneurysm was planned.

Technique: After taking informed consent, a complete Doppler assessment of the aneurysm and the patency of distal run-off was obtained. The right groin was prepared, draped and an echo-probe placed directly over the pseudoaneurysm. Obliteration of flow into the aneurysm was confirmed by compression of the neck of the pseudoaneurysm with the color mode on. Under local anesthesia, a 22-gauge spinal needle was then passed percutaneously directly into the pseudoaneurysm cavity under ultrasonographic guidance. The tip of the needle was positioned within the center of the cavity, to keep it away from the neck. A small 2 ml syringe containing bovine thrombin (Parke Davis) 1000 U/ml concentration was attached to the needle and 1 ml injected into the cavity with continuing compression of the neck. The echogenicity within the aneurysm was seen to increase immediately, but on color Doppler study repeated after 3–4 min, some flow into the cavity was still seen. Thrombin injection was repeated using the same technique and, this time, dense

Correspondence: Dr PK Goel, Department of Cardiology, SGPGIMS, Rae Bareli Road, Lucknow 226014. e-mail: pkgoel@sgpgi.ac.in
occurs in 1%–3% of cases following percutaneous arterial catheterization. The treatment options are surgical repair, covered stents, coil embolization or, ultrasound-guided compression and direct percutaneous thrombin injection. Operative repair is usually associated with high morbidity secondary to delayed ambulation and/or wound infection. Fellmeth in 1991 described ultrasound-guided compression repair. With this treatment, flow into the pseudoaneurysm is halted by applying pressure with the ultrasound probe to the neck of the pseudoaneurysm and maintaining such pressure until spontaneous thrombosis of the aneurysm cavity occurs. This procedure, however, is often very painful, and has an overall success rate as low as 45% to up to 100%, but a recurrence rate of up to 30%. 

The technique of ‘clotting aneurysm’ by direct injection of diluted thrombin was first described in 1986 by Cope et al. For the next decade, however, not much attention was given to this technique, and it is only in the past 1–2 years that there has been a resurgence of interest, with multiple studies showing success rates of 96%–100% (Table 1). The overall complication rate of this technique is less than 2% and the most dreaded complication is downstream embolization. Samal et al. described the technique of balloon occlusion of the neck of the aneurysm by using a contralateral approach to prevent spillover of thrombin into the distal circulation in 4 cases. We in our limited

Table 1. Results from different studies for ultrasound-guided thrombin injection for the obliteration of femoral artery pseudoaneurysm

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Success (%)</th>
<th>Number of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman et al.8</td>
<td>40</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>Edgerton et al.7</td>
<td>47</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>Samal et al.10</td>
<td>4</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Sheiman et al.11</td>
<td>(Simple) 45</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(Complex) 5</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>Paulson et al.12</td>
<td>26</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>Kang et al.13</td>
<td>74</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>La Perna et al.14</td>
<td>70</td>
<td>94</td>
<td>0</td>
</tr>
<tr>
<td>Hughes et al.15</td>
<td>9</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Sievert et al.16</td>
<td>29</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Morrison et al.17</td>
<td>39</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Brophy et al.18</td>
<td>15</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Lennox et al.19</td>
<td>30</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Pezzullo et al.20</td>
<td>23</td>
<td>96</td>
<td>1</td>
</tr>
<tr>
<td>Tamim et al.21</td>
<td>10</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Vermeulen et al.22</td>
<td>8</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Taylor et al.23</td>
<td>29</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td>Wixon et al.24</td>
<td>11</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Liau et al.25</td>
<td>5</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
experience, however, found that a transient compression given to the proximal femoral artery during injection of thrombin, and confirmation of no flow into the aneurysm with color/angi mode, may be as good a method to avoid spillover, which also avoids the need for further invasive handling of the already damaged site. We do feel, however, that caution must be exercised with AV fistula and aneurysm involving bifurcation of the femoral artery as in such cases a spillover could occur using ultrasound-guided compression alone. Most failures/recurrences were observed in patients with complex aneurysms, i.e., multilobed aneurysms. Other possible complications could include allergy to bovine thrombin and the formation of a multilobed aneurysms. Other possible complications could include allergy to bovine thrombin and the formation of a multilobed aneurysms. Other possible complications could include allergy to bovine thrombin and the formation of a multilobed aneurysms.

Among the other nonsurgical approaches, it may be worth mentioning the technique of temporary coil placement in the pseudoaneurysm sac, described recently by Trehan et al. This technique, however, is more invasive with a 5 F sheath being placed directly into the aneurysm sac, and a PDA coil (8 mm) kept in place for over 2 hours before its final removal. Experience with this technique is limited to a small aneurysm only.

We conclude that sonographically guided direct thrombin injection into the aneurysm sac is a safe, quick, and effective technique for managing a giant pseudoaneurysm at the the puncture site. It is well tolerated by the patient, with low morbidity, and avoids the need for surgery, and could thus be considered as a first-line therapy in these patients.

References

Stenting of a Septal Perforator for Post-Myocardial Infarction Angina

Vijay Trehan, Saibal Mukhopadhyay, Umamahesh C Rangasetty, Jamal Yusuf, Mohit D Gupta, UA Kaul
Department of Cardiology, GB Pant Hospital, New Delhi

Occlusion of a septal perforator branch alone, without the involvement of the left anterior descending coronary artery, leading to acute myocardial infarction is unusual. We report a case in which an isolated severely stenotic thrombus-containing first septal artery causing intractable post-myocardial infarction angina was successfully dilated and stented. (Indian Heart J 2003; 55: 368–369)

Key Words: Septal artery, Stents, Myocardial infarction

Acute myocardial infarction (AMI) is usually caused by the thrombotic occlusion of a major epicardial vessel. Branch occlusion alone, causing AMI in the absence of involvement of a major epicardial artery, is unusual. We report a case in which a patient with anteroseptal myocardial infarction (MI) and intractable post-MI angina was found to have isolated 90% obstruction of the first septal perforator artery, which was successfully dilated and stented.

Case Report

A 52-year-old male, a known hypertensive on irregular treatment, presented to us with refractory post-MI angina. He had had an anteroseptal MI 48 hours earlier for which he was thrombolized with streptokinase (1.5 million U over 1 hour) within 3 hours of the onset of chest pain. The patient was taken up for coronary angiography and possible revascularization. Coronary angiogram revealed a thrombus-containing 90% discrete stenosis of the first septal perforator artery just after its origin (Figs 1a and 1b). The left anterior descending coronary artery (LAD) along with the other epicardial vessels were normal. The patient was taken up for angioplasty. He was given a bolus of abciximab (0.25 mg/kg body weight) followed by an infusion of 10 µg/min for 12 hours. The lesion in the septal perforator artery was crossed with a Luge Wire (Boston Scientific Scimed, Inc., USA), and serially dilated with a 2.5×12 mm and 3×13 mm balloon. Following balloon dilatation, a check angiogram revealed TIMI 2 flow with 50% residual stenosis. A mounted stent of 3×13 mm (Bx Velocity, Cordis, USA) was deployed at 14 bars, and persistent TIMI 3 flow was achieved (Fig. 2). There were no complications during or after the procedure. The patient became asymptomatic and was discharged after 72 hours. On follow-up of nearly a year, the patient is asymptomatic.

Discussion

The interventricular septum (IVS) forms the vital wall for both the ventricles, and constitutes about one-third of the total left ventricular (LV) mass. The septal perforator

Correspondence: Dr Umamahesh C Rangasetty, Department of Cardiology, GB Pant Hospital, New Delhi 110002.
e-mail: maheshpgi@yahoo.com

Fig. 1a. Anteroposterior cranial view showing significant eccentric stenosis in the first septal perforator artery just after its origin.
Trehan et al. Stenting of a Septal Perforator Post-MI

369

There have also been reports of angioplasry of the septal perforators, usually done in patients with critical stenosis or total occlusion of the LAD. Recently, there have been a couple of reports of stenting of a septal perforator artery. One was in a post-coronary bypass surgery patient with an occluded LAD, while the other was in a patient with multivessel disease. However, to the best of our knowledge, there have been no reports of angioplasty or stenting of an isolated culprit septal artery. The first septal perforator, apart from supplying the IVS, also supplies the bundle of His, and in 50% hearts, the atrioventricular node. Our patient, with refractory post-MI angina due to occlusion of the first septal perforator, was at increased risk of reinfarction that could have disrupted either the conduction system or the IVS, causing its rupture. Unlike the epicardial arteries, septal arteries are subjected to a higher extraneous pressure. Although long-term results of angioplasty of the septal perforator have not shown increased rates of restenosis, the behavior of stents in response to a high extrinsic pressure needs to be observed. This situation is similar to the stenting of myocardial bridges.

References


branches of the LAD \(^2\) contribute blood supply to the anterior two-thirds of the IVS. Obstruction of the septal perforators in patients with diffuse coronary artery disease is common. However, isolated obstruction of a septal perforator artery is very rare. Till date, there have been 2 case reports of isolated septal artery obstruction.\(^3,4\) There have also been reports of angioplasty of the septal perforators, usually done in patients with critical stenosis or total occlusion of the LAD.\(^5,6\) Recently, there have been a couple of reports of stenting of a septal perforator artery. One was in a post-coronary bypass surgery patient with an occluded LAD,\(^7\) while the other was in a patient with multivessel disease.\(^6\) However, to the best of our knowledge, there have been no reports of angioplasty or stenting of an isolated culprit septal artery. The first septal perforator, apart from supplying the IVS, also supplies the bundle of His, and in 50% hearts, the atrioventricular node.\(^9\) Our patient, with refractory post-MI angina due to occlusion of the first septal perforator, was at increased risk of reinfarction that could have disrupted either the conduction system or the IVS, causing its rupture. Unlike the epicardial arteries, septal arteries are subjected to a higher extraneous pressure. Although long-term results of angioplasty of the septal perforator have not shown increased rates of restenosis,\(^1\) the behavior of stents in response to a high extrinsic pressure needs to be observed. This situation is similar to the stenting of myocardial bridges.

References

Mitral Valve Replacement on a Beating Heart

Harinder S Bedi, Raman P Singh, Vipin Goel, Purshottam Lal
Metro Heart Institute, Noida

We report the case of a patient who needed mitral valve replacement but was at a high risk of myocardial injury with the conventional technique (cardioplegic arrest on cardiopulmonary bypass). Valve replacement was carried out on a beating heart on cardiopulmonary bypass by perfusing the heart continuously with oxygenated noncardioplegic normothermic blood via the coronary sinus. (Indian Heart J 2003; 55: 370–372)

Key Words: Mitral valve replacement, Cardiopulmonary bypass, Beating heart

Cardioplegic techniques carry with them the almost obligatory sequel of some degree of reperfusion injury. Any technique that avoids the ischemic component of cardioplegia and an arrested heart by keeping the heart beating will go a long way in reducing iatrogenic damage to the heart. While the heart–lung machine can be avoided in most cases of coronary artery bypass grafting (CABG), it is still mandatory in open heart valvular surgery. We present a case of a high-risk mitral valve operation performed on a beating heart.

Case Report

A 15-year-old girl presented with orthopnea and congestive heart failure. She was a known case of rheumatic heart disease with severe mitral regurgitation, moderate mitral stenosis, severe pulmonary artery hypertension, and severe functional tricuspid regurgitation. The diagnosis was confirmed by echocardiography. She did not show much improvement with aggressive medical therapy, and was taken up for emergency surgery. Since she would have been at a high risk of reperfusion injury if standard techniques of cardioplegic arrest were used, a technique of on-pump beating heart surgery was planned.

The operation was performed through a median sternotomy. After heparinization, total cardiopulmonary bypass (CPB) was established by aortic and bicaval cannulation. The patient was actively warmed to 36.5°C, and pulsatile flow maintained at the highest pressure that was safely kept, keeping the mean systemic pressure above 60 mmHg. The pump flow was kept at 2.5 L/min/m², and the FiO₂ was kept at 100%.

A retrograde self-inflating coronary sinus cannula (Medtronic DLP, Grand Rapids, MI) was inserted by a standard closed technique. The position was confirmed by palpation, and the balloon positioned as close to the coronary sinus ostium as possible to avoid right ventricular malperfusion. The central perfusion port was connected to the standard cardioplegic line circuit, and oxygenated unmodified (noncardioplegic) blood primed into the cannula. With an aortic root vent and maximal venous drainage, retrograde perfusion was started, and simultaneously the aorta was cross-clamped. Retrograde perfusion flow was maintained at 250–300 ml/min with constant monitoring of the intracoronary sinus pressure via its integral pressure line, keeping a mean coronary sinus pressure of 40 mmHg. A phosphodiesterase inhibitor—milrinone 0.5 µg/kg/min—was infused in the retrograde line by a syringe pump to increase the retrograde perfusion flow by inducing vasodilatation. Samples of the blood entering the coronary sinus and of the blood in the aortic root vent were taken for analysis and calculation of the oxygen extraction ratio across the myocardium. The left atrium was now opened and mitral valve replacement with preservation of the posterior mitral apparatus carried out on the beating heart (Figs 1 and 2). At the end of the procedure, the cardiac cavities were filled with blood (by inflating the lungs) and with warm saline, and the left atrium was closed. The aortic root vent was kept on suction, the aortic cross-clamp released, and the retrograde coronary sinus cannula removed. The right atrium was opened, and a standard repair (DeVega annuloplasty) of the tricuspid valve carried out.
Good visualization of the mitral valve apparatus was possible, and the procedure was completed without any technical difficulty. Despite the motion of the heart, the on-pump and totally decompressed state of the heart caused by cardiac venting resulted in a good quality of the visual field, equaling that of the conventional technique, and technical accuracy was not affected.

An oxygen extraction ratio of 52% across the myocardium was noted:

\[
\text{Oxygen extraction ratio across the myocardium} = \left( \frac{O_{2CS} - O_{2AR}}{O_{2A}} \right) \times 100
\]

where, \(O_{2CS}\): arterial \(O_2\) content (i.e. going into the coronary sinus);

\(O_{2AR}\): \(O_2\) content of blood from the aortic root;

\(O_{2A}\): \(O_2\) content (arterial).

\[
[O_2\text{content} = 1.36 \text{ ml} O_2/g \times Hb \times O_2\text{saturation} + (0.003 \times pO_2)]
\]

The high extraction is suggestive of the fact that the myocardium uses up the oxygen being delivered by the retrograde route.

The CPB time was 98 min while the aortic cross-clamp time was 52 min. The heart continued to be in sinus rhythm during and after the procedure. There was no evidence of ischemia—no ST segment changes and no rhythm disturbance occurred during the retrograde perfusion. The patient was weaned away from CPB without any inotropic support, and was extubated within 5 hours of reaching the ICU. She made an uneventful recovery, and was discharged on postoperative day 6.

**Discussion**

In spite of improvements in myocardial protection techniques, some perioperative adverse effects of myocardial ischemia caused by aortic cross-clamping, cardioplegia, and reperfusion remain. Even with continuous warm blood cardioplegia (considered by some as the best form of myocardial protection as it keeps the heart in an aerobic state), some degree of perioperative myocardial stunning still occurs. \(^1\) Cardiac dysfunction may be caused by myocardial edema intrinsic to the diastolic state of the arrested heart, \(^4\) and the inevitable reperfusion injury that follows the unclamping of the arrested heart. Ischemia followed by reperfusion is invariably followed by the generation of oxygen-free radicals, which produce myocardial injury. To counter this, various scavengers of oxygen-free radicals have been added to cardioplegic solutions in an attempt to inhibit the injury. \(^5\), \(^6\) Keeping the heart beating results in less myocardial edema, and better cardiac function. \(^4\)

Retrograde coronary sinus perfusion as a method of myocardial perfusion is not new. In 1956, Lillehei et al. \(^7\) reported an aortic valve replacement using coronary sinus perfusion at 125 ml/min. Oxygenated blood is perfused from the coronary sinus and reaches the myocardium via the coronary venous system and the capillaries, and goes out via the arterial end as in retrograde cardioplegia. We have previously used retrograde perfusion on the beating heart to perform CABG without CPB. \(^2\), \(^3\) The technique of beating heart valve surgery involves the constant retrograde perfusion of pure normothermic oxygenated blood into the coronary sinus.

Matsumoto et al. \(^8\) recently performed a beating heart
valve procedure on 25 patients with good results. They showed, by intraoperative monitoring, that myocardial tissue oxygen saturation (SO₂) levels were maintained at the preoperative physiologic values throughout the procedure. A good myocardial oxygen consumption, as noted by us, indicates that the myocardium is in a state of aerobic metabolism that is maintained by the retrograde coronary sinus perfusion.

The advantages of the technique are: a perfused beating heart that does not have to "work" (pump blood); no reperfusion injury (as there is no ischemia); an uninterrupted performance of the operation; a long period of continuous oxygenated blood delivery that maintains the beating of the heart; appropriate pH, effective delivery of substrates, and removal of acid metabolites; more uniform oxygenated blood distribution in the presence of any associated coronary artery stenosis; testing of the mitral valve repair, when performed, can be done under the actual physiologic conditions of a normal left ventricular tone with preserved three-dimensional architecture of the beating heart (with conventional techniques, the mitral valve is in a motionless flaccid state that may not accurately reflect its function in the beating heart); avoidance of injury to the ostia of the coronary arteries; and the possibility of performing ablation for atrial fibrillation on the beating heart. The normothermic state of the blood ensures maximal vasodilatation of the cardiac veins, and steady, uniform flow and distribution. Should the flow be inadequate or if there is malperfusion, it will be reflected by ECG changes (ST segment changes, bradycardia, arrhythmias, etc.), and the flow can be suitably adjusted.

The option of converting to the conventional technique—cardiac arrest with hyperkalemic blood cardioplegia—is always immediately available, if the surgeon is not satisfied with the beating heart technique.

The beating heart technique is thus a useful addition to the armamentarium of the cardiac surgeon in dealing with patients undergoing high-risk valve surgery. A comparison of this procedure versus the arrested heart technique in a large group of patients is required to judge the superiority of the beating heart technique.

References

Transcatheter Closure of Native Pulmonary Artery for the Elimination of Accessory Pulmonary Blood Flow After Bidirectional Glenn Shunt

Anil Sivadasan Radha, Bhava RJ Kannan, Raman Krishna Kumar
Division of Pediatric Cardiology, Amrita Institute of Medical Sciences and Research Centre, Kochi

We report a case where excessive accessory pulmonary blood flow via the native pulmonary valve after cavopulmonary anastomosis resulted in pulmonary hypertension and heart failure. This flow was successfully eliminated in the cardiac catheterization laboratory using an Amplatzer duct occluder that was placed across the native pulmonary valve. (Indian Heart J 2003; 55: 373–375)

Key Words: Catheter intervention, Amplatzer duct occluder, Cavopulmonary shunt

Bidirectional Glenn shunt (BDGS) is frequently performed as part of a multistaged palliation of congenital heart disease in patients with a single ventricle physiology to decrease the volume overload in patients who are candidates for future Fontan type repair.1,2 It is often advocated as an intermediary step for high-risk patients.3 Traditionally, accessory sources of pulmonary blood flow, such as from the native pulmonary valve, are eliminated to minimize pulmonary artery (PA) pressure after cavopulmonary anastomosis (Glenn shunt). Recently, however, there is a growing trend towards preservation of blood flow through the native pulmonary valve to improve saturation. However, occasionally patients can develop heart failure when blood flow through the native pulmonary valve is excessive. We report a child who presented with elevated PA pressures due to excessive antegrade pulmonary blood flow after a Glenn shunt and the successful interruption of this additional flow using an Amplatzer duct occluder (ADO).

Case Report

The patient was an 11-year-old boy with severe cyanosis (basal saturation of 65%) and marked limitation of physical activity. The anatomic diagnosis was situs solitus, D-loop, levocardia, bilateral superior vena cava (SVC), double outlet right ventricle, multiple muscular ventricular septal defects (VSDs), and severe infundibular and valvar pulmonic stenosis. At the age of 3 years, the child underwent atrial septectomy with Brock procedure (enlargement of right ventricular outflow in relation to the pulmonary valve). Cardiac catheterization at admission showed elevated right atrial (mean: 18 mmHg) and PA pressures (29/17 mmHg, mean: 23 mmHg) with a pulmonary-to-systemic blood flow ratio of 3:1, and the calculated indexed pulmonary vascular resistance was 0.14 Wood units/m². He underwent rightsided cavopulmonary anastomosis with ligation of the left SVC and enlargement of the atrial septal defect. Ligation of the PA could not be done as planned due to dense adhesions in the region of the main pulmonary artery (MPA). His immediate postoperative course was uneventful. On postoperative day 11, it was noticed that he had prominent neck vein pulsations, and prominent chest wall veins, which were seen to drain from above downwards. Besides, he had an overt right heart failure with ascites and hepatomegaly. Echocardiography showed systolic retrograde pulsatile flow in the right SVC due to excessive antegrade flow from the right ventricle into the PA.

Informed consent was taken and cardiac catheterization was performed under conscious sedation. The femoral vessels and the right subclavian vein were cannulated percutaneously. The SVC pressure tracing showed a biphasic wave pattern and was markedly elevated (38/18 mmHg, mean 26 mmHg). The PA angiogram showed normal branch pulmonary arteries with rapid wash-off of the contrast, and the PA annulus measured 12.5 mm. The pulmonary valve was crossed in a retrograde fashion with a 0.035” exchange length (300 cm) Roadrunner wire...
The wire was snared with a 10 mm Amplatz gooseneck snare (Microvena Corp., MN, USA), and was brought out of the left femoral venous sheath to form a veno-venous wire loop. A 7 F Swan–Ganz catheter was passed over the wire from the groin and the balloon at the tip of the catheter was inflated (Fig. 1) to occlude the MPA. The PA pressures on balloon occlusion decreased to 25/14 mmHg (mean: 17 mmHg) without any fall in aortic saturation. A 9 F long sheath (Cook Inc., Bloomington, IN, USA) was introduced from the subclavian vein and across the pulmonary valve into the right ventricular outflow tract. A 16/14 ADO (AGA Medical, MN, USA) device was advanced through the sheath, and a small part of the retention disc was extruded from the sheath into the ventricle just below the valve and then pulled against the pulmonary valve. The device was deployed such that the waist straddled the pulmonary valve (Fig. 2). Gentle pulling and pushing of the device under echocardiographic and fluoroscopic guidance was done to ensure stability of the device. The device was released after confirming that the flow across the cavopulmonary anastomosis was unobstructed. The patient recovered uneventfully. Three months later, he had gained weight (2.5 kg) and restarted attending his school after a gap of 2 years. He had a resting saturation of 88% and was symptom-free.

Discussion

Cavopulmonary anastomosis is used as an intermediary stage prior to completion of a Fontan type of repair in those with a single ventricle physiology. It is controversial whether an additional source of systemic-to-pulmonary artery flow is beneficial. In some instances, it is thought to improve oxygenation, decrease the incidence of pulmonary arteriovenous fistula formation, and promote the growth of the pulmonary arteries. However, it may result in elevation of the SVC pressure, with interference of the blood flow to the pulmonary arteries. Additionally, depending on its magnitude, it may add an additional volume load on the left ventricle. In our patient, the SVC pressure was markedly elevated. The pressure tracing prior to closure was suggestive of pulsatile flows. Temporary balloon occlusion of the MPA resulted in a substantial decrease in the SVC pressures and eliminated venous pulsatility. This conclusively showed that excessive pulmonary blood flow through the native pulmonary valve was responsible for the adverse hemodynamics.

Even though the ADO is conventionally used for closure of a patent ductus arteriosus, it was well suited for this purpose, as its flat retention disc allows positioning of the device without interfering with the flow through the Glenn anastomosis. It allows easy testing of the stability of the...
device before release. We chose an oversized duct occluder instead of a muscular VSD occluder because it is less expensive. The precise positioning of the device such that it straddles the pulmonary valve is critical. If the device is too far into the ventricle, it could slip down and get embolized through the systemic circuit. If the device is placed entirely distal to the pulmonary valve, it can migrate distally and can occlude the branch pulmonary arteries. Because of the absence of a retention disc on the pulmonary arterial aspect, we chose to oversize the device substantially.

Conclusions: This report demonstrates the unconventional use of an ADO for occlusion of the native pulmonary valve. This offers an easy and nonsurgical solution in this subset of patients who would otherwise need repeat surgical procedures. Temporary balloon occlusion is a useful maneuver to ascertain the contribution of accessory pulmonary blood flow so that the benefits of eliminating this flow can be predicted.

References
Coronary sinus electrograms generally represent the sequence of left atrial activation, and are very helpful in localizing and differentiating left lateral accessory pathway-mediated tachycardia from other supraventricular tachycardias. The activation of the coronary sinus from the left atrium occurs through muscle bridges, which may be discrete or form an intermingled continuum. These muscle bridges, if disconnected, may dissociate the coronary sinus from the left atrium, in which case the coronary sinus electrograms do not represent left atrial activation, and do not help to understand, or may cause misinterpretation of, the mechanism of supraventricular tachycardia. We report one such case of orthodromic supraventricular tachycardia mediated through the left lateral accessory pathway in which the coronary sinus got dissociated from the left atrium during radiofrequency ablation. (*Indian Heart J* 2003; 55: 376–378)

**Key Words:** Left lateral accessory pathway, Coronary sinus, Radiofrequency ablation

Radiofrequency (RF) ablation for accessory pathways (APs) is safe and effective.\(^1\,^2\) The mapping of APs involves the use of multipolar electrodes placed at different sites. Coronary sinus (CS) electrograms assume an important role (particularly for left-sided pathways), and generally represent the sequence of left atrial (LA) activation.\(^3\) We report a case of an orthodromic tachycardia using a concealed left lateral AP in which the activation sequence in CS electrograms reversed following an attempt at RF ablation without altering the AP conduction.

**Case Report**

A 23-year-old man was referred to our institute for recurrent episodes of supraventricular tachycardia (SVT) lasting for several hours. He was taken up for an electrophysiologic study and possible ablation. The AH interval was 110 ms while the HV interval was 45 ms. Retrograde conduction on ventricular pacing was eccentric, with earliest activation at the distal CS (Fig. 1a). An SVT with a cycle length (CL) of 330 ms could easily be induced with a single atrial extrastimulus, with a retrograde atrial activation sequence similar to that during ventricular pacing (Fig. 1b).

After a trans-septal puncture, a 7 F ablation catheter (Cordis Webster) was introduced to map the left free wall AP along the lateral mitral annulus. During ventricular pacing, a site with the shortest VA interval preceding all other atrial activations was chosen for the application of RF energy (Fig. 2). During the RF application, it was realized that the retrograde activation sequence had changed to one resembling concentric activation (Fig. 3a).

The RF lesion was completed after 60 s, and the stimulation protocols repeated. An SVT could be induced again but with a different activation sequence (proximal to the distal CS sequence, and earliest activation at the His bundle site) (Fig. 3b). On observing this change in the atrial activation sequence, this tachycardia was thought to be either an atypical atrioventricular nodal re-entrant tachycardia or a slow conducting anteroseptal AP. A diagnosis of ectopic atrial tachycardia was excluded by overdrive pacing from the right ventricle. This resulted in entrainment of the tachycardia with the same atrial sequence and, on abrupt termination of pacing, the return sequence was an A–V electrogram favoring re-entry rather than atrial tachycardia.\(^4\) However, on mapping with the ablation catheter around the mitral annulus, it was soon
realized that the shortest VA interval was still around the lateral mitral annulus with the CS electrograms not truly reflecting the activation sequence in the LA (Fig. 4). Delivering another RF pulse at this site, which was slightly more anterior to the previous site, resulted in termination of the tachycardia with a retrograde conduction block. Subsequent ventricular pacing demonstrated a complete VA block (Fig. 5), and no tachycardia could be induced despite isoprenaline infusion, and multiple atrial and ventricular extrastimuli.

**Discussion**

The diagnosis of an orthodromic tachycardia using a lateral concealed AP was confirmed by the earliest retrograde activation sequence recorded at the distal CS during the tachycardia. This was similar to the atrial activation pattern during ventricular pacing. During the RF pulse, the change in the atrial activation sequence from an eccentric to a
concentric sequence during ventricular pacing made us believe that the AP had been eliminated. However, when SVT could easily be induced thereafter, careful mapping was performed to understand the mechanism of this “new” tachycardia. The mapping at the lateral mitral annulus clearly demonstrated that this was the same orthodromic tachycardia but with an altered sequence of activation in the CS electrograms. The atrial signal on the ablation catheter preceded the atrial recording on the His bundle and proximal CS recordings (Fig. 4). Therefore, atrial activation was not concentric (as suggested by CS and His bundle recordings). This was confirmed by the fact that an RF pulse at this site resulted in the termination of SVT with a retrograde block, after which a VA block was demonstrated, and the SVT could not be reinitiated. This change in epicardial (CS) sequence without a change in endocardial activation probably resulted from the initial RF pulse, which could have caused a dissociation between the LA and CS. Recent histologic studies have demonstrated that the lumen of the CS contains myocardium that is continuous with CS ostial–right atrial myocardium. It is possible that there was a discrete bridge connecting the LA to the distal CS in this patient, which got disconnected following the initial RF pulse, and resulted in a change of sequence without a change in the mechanism of the tachycardia.

CS recordings generally represent LA activation. It is, however, important to understand the complex histology and interconnections between the LA and CS. The example in this report represents the disconnection between the LA and CS following the initial RF pulse. Chauvin et al. recently demonstrated an electrical dissociation between the CS and LA in a group of patients with atrial flutter and atrial fibrillation. In a series of 159 patients, Luria et al. discussed an intra-atrial conduction block along the mitral annulus during AP ablation. Alberte et al. and Vasconcecos et al. have described a case each in which dissociation quite similar to the present report occurred following an attempt at ablation of the lateral AP. It is important to understand these mechanisms since an inability to recognize the dissociation could have resulted in the erroneous diagnosis of a second tachycardia leading to inappropriate treatment.

References

9. Vasconcecos JTM, Costa ERB, Galvaofilho SDS. Block of the mitral–pulmonary isthmus during ablation of a single left-sided accessory pathway causing different patterns of retrograde atrial activation. Arq Bras Cardiol 2002; 78: 504–509
Left atrial appendage aneurysm (LAA) is a rarely encountered congenital defect. Most LAA aneurysms are diagnosed incidentally. They can result in arrhythmias or systemic embolization. We report the case of a 12-year-old male with a massive left atrial appendage aneurysm who presented with effort intolerance and supraventricular arrhythmia. The diagnosis was made by transthoracic echocardiography. Magnetic resonance imaging and left atrio-gram were also done before surgical resection. (Indian Heart J 2003; 55: 379–381)

Key Words: Left atrial appendage, Supraventricular tachycardia, Echocardiography

Case Report

A previously healthy 12-year-old boy presented with a 6-month history of effort intolerance, retrosternal pricking type of chest discomfort, and palpitations. His NYHA functional status had progressed to class III. The pulse, blood pressure, and jugular venous pressure were normal. His cardiac examination revealed normal apical impulse in the left 5th intercostal space. Heart sounds were normal without murmurs or gallops. The initial electrocardiogram (ECG) was normal, and when repeated during palpitations, showed narrow QRS nodal re-entrant tachycardia at a rate of 235/min.

Chest X-ray PA view showed cardiomegaly with a CT ratio of 64% with straightening of the left heart border. It showed filling out of the cardiac bay (Fig. 1). The lateral view X-ray confirmed that the enlarged chamber was the left atrium (LA). Lung markings were unremarkable.

Transthoracic echocardiography revealed a very large (15×10 cm) echo-free space compressing the left ventricle (Figs 2, 3). The chamber connected to the LA in the region of the LAA. Autocontrast was present within the LAA aneurysm due to sluggish flow (Fig. 2). To-and-fro blood flow was demonstrated using Doppler echo (Fig. 3). The relative size and location of the aneurysm was delineated by magnetic resonance imaging (MRI) (Fig. 4). Cardiac catheterization confirmed normal chamber pressures and saturations. The LA injection by trans-septal puncture opacified a large chamber adjacent to the left heart (Fig. 5).

The patient was operated on cardiopulmonary bypass. The aneurysm was resected and the histopathology report confirmed benign cardiac and fibrous tissue. His symptoms improved rapidly and he is now doing well 10 months after the resection without recurrence of palpitation.
life on routine chest X-ray. It is likely that an aneurysm of the LAA is initially small and asymptomatic, and becomes obvious only after years of enlargement. Stasis in the aneurysmal cavity accounts for thrombosis and systemic embolization. LAA aneurysms can present with chest pain, palpitations or systemic embolization. Nevertheless, most cases are asymptomatic. Although our case had a massive LAA aneurysm and autocontrast, he did not have any embolic episodes.

Discussion

Aneurysm of the LAA can be secondary to left ventricular dysfunction, mitral valve pathology, or herniation of the LAA through a pericardial defect. Primary congenital aneurysm of the LAA with an intact pericardium is a rare anomaly. Intrapericardial LAA aneurysm is due to congenital weakness involving the LAA or LA free wall. Aneurysm may mimic a mediastinal or cardiac tumor.

Although congenital in origin, most cases are asymptomatic in childhood. In most of the patients, the condition is diagnosed in the second to fourth decades of life on routine chest X-ray. It is likely that an aneurysm of the LAA is initially small and asymptomatic, and becomes obvious only after years of enlargement. Stasis in the aneurysmal cavity accounts for thrombosis and systemic embolization.

LAA aneurysms can present with chest pain, palpitations or systemic embolization. Nevertheless, most cases are asymptomatic. Although our case had a massive LAA aneurysm and autocontrast, he did not have any embolic episodes.
Physical examination is often unrevealing. ECG may reveal tachyarrhythmia, as in our case. A radiographic differential for filling out of the cardiac bay region (Fig. 1) includes partial absence of the pericardium along with atrial herniation through the defect, paracardiac tumors or cysts, enlarged coronary sinus, aneurysmal dilatation of the LA due to mitral valvular disease, and pulmonary artery aneurysm.

Echocardiography, radionuclide angiography, CT scan, MRI, and cardiac catheterization have been used to establish the diagnosis. Angiography requires trans-septal puncture, and may not detect an LAA aneurysm filled with a thrombus. In our case, the diagnosis was made during screening echocardiography. Due to adequate demonstration of the aneurysm and its origin by transthoracic windows, transesophageal echocardiography (TEE) was not required.

Foale et al. proposed the following criteria to diagnose congenital LAA aneurysm: (i) origin from an otherwise normal LA; (ii) well-defined communication with the LA; (iii) position within the pericardium; and (iv) distortion of the LV free wall by the aneurysm.

Our patient fulfilled all the 4 criteria for the diagnosis of an LAA aneurysm.

Associated anomalies such as atrial septal defect (ASD), persistent left superior vena cava, anomalous pulmonary venous drainage, and renal artery anomalies have been reported. Aneurysmectomy abolishes recurrent arrhythmias and thromboembolism. Thus, surgical resection, with or without cardiopulmonary bypass, is recommended even in asymptomatic patients.

References
Noncompacted Left Ventricle in Association With Dysplastic Tricuspid Valve

Saibal Mukhopadhyay, Jamal Yusuf, Umamahesh C Rangasetty, Vijay Trehan
Department of Cardiology, GB Pant Hospital, New Delhi

A 20-year-old normotensive female admitted with right-sided hemiparesis of acute onset due to a cerebral infarct was referred from the neurology ward for echocardiography to rule out a cardiac source of embolism. Two-dimensional (2-D) echocardiography revealed a normal-shaped, nondilated left ventricle with prominent trabeculations and deep intertrabecular recesses (Fig. 1, double arrow). The trabeculations were localized predominantly in the mid and apical segments of the left ventricular lateral, anterior and inferior walls. The ratio of the noncompacted to the compacted layer measured at end-systole was greater than 2:1 (Fig. 2). The affected segments revealed hypokinesia, and the overall left ventricular ejection fraction was 38%. On color Doppler echocardiography, the deep intertrabecular recesses were seen filling with blood from the left ventricular cavity during diastole.

**Fig. 1.** Transthoracic four-chamber view showing prominent trabeculations with deep recesses in the lateral wall (↑↑) of the left ventricle. The single arrow (↑) shows the thick, incompletely coapting septal and anterior tricuspid leaflets, and the enlarged right atrium.

**Fig. 2.** Short-axis view of the left ventricle at papillary muscle level showing thick, spongy endocardium and thin, compact epicardium.

**Fig. 3.** Color Doppler showing a laminar jet of severe tricuspid regurgitation across the tricuspid valve.

**Fig. 4.** Continuous-wave Doppler revealing a peak velocity of the tricuspid regurgitant jet of 1 m/s.
with reversed flow in systole. No thrombus could be detected in the intertrabecular recesses. The mitral and aortic valves were normal. The right atrium was enlarged (Fig. 1) and the septal and anterior leaflets of the tricuspid valve appeared thickened with incomplete coaptation in systole (Fig. 1, single arrow). There was no excessive apical displacement of the septal leaflet as seen in Ebstein’s anomaly. Color Doppler echocardiography across the tricuspid valve revealed a laminar jet of severe tricuspid regurgitation (TR) (Fig. 3) with continuous-wave Doppler revealing a peak velocity of the regurgitant jet of 1 m/s (Fig. 4). Thus, a diagnosis of dysplastic tricuspid valve was made. The right ventricle and pulmonary valve were normal.

Noncompacted myocardium has been frequently reported in patients with congenital left or right ventricular outflow tract obstruction. In these patients with a “spongy myocardium”, the recesses represent “persisting sinusoids” that fail to regress during ontogenesis due to persistent pressure overload, and communicate with the coronary arteries.1–3 In contrast, isolated ventricular noncompaction (IVNC) is considered a congenital anomaly due to the arrest of compaction of the loose myocardial meshwork during fetal ontogenesis,4 when the intertrabecular recesses covered with endothelial cells are filled with blood from the ventricular cavity without evidence of communication to the epicardial coronary artery system.2,5 These recesses predispose to local thrombus formation but are often missed on echocardiography when associated with prominent trabeculations.6

Noncompacted myocardium and tricuspid valve dysplasia as individual conditions are well described. Our patient had all the characteristic echocardiographic features of left ventricular noncompaction as described by Jenni et al.4 along with a coexistent congenital anomaly—tricuspid valve dysplasia—a combination not yet reported in the literature, to the best of our knowledge. Early diagnosis of ventricular noncompaction and the correct management of such patients is crucial, as the clinical morbidity includes heart failure, caused by progressive ventricular dysfunction, arrhythmias and systemic embolic events.7

Our patient presented with asymptomatic left ventricular dysfunction detected incidentally on echocardiography, but there was no clinical evidence of right ventricular systolic dysfunction. The patient was put on medical therapy with a combination of beta-blockers and ACE inhibitors (to arrest negative remodeling and the progression of heart failure), and oral anticoagulants to prevent the formation of thrombi in the left ventricle.

References

Seropositivity of *Chlamydia pneumoniae* and *Helicobacter pylori* Among Coronary Heart Disease Patients and Normal Individuals in a South Indian Population

The search for new risk factors that can satisfactorily explain the prevalence and severity of coronary heart disease (CHD) has brought into focus the role of infections, particularly the association of *Helicobacter pylori* (*H. pylori*) *Chlamydia pneumoniae* (*C. pneumoniae*), and cytomegalovirus with CHD. Although many such studies are available from western countries, studies in the Indian context are lacking. Identification of a causal linkage of any kind of infection with CHD can lead to timely intervention with antibiotics, which may decrease the disease burden.

One hundred and seventeen angiographically proven patients (35–79 years of age) with unstable angina (UA), and 16 patients with chronic stable angina (CSA) were matched with 90 healthy blood donors (20–60 years of age) free from clinical CHD confirmed by 12-lead resting ECG. Fasting serum samples were drawn from these healthy controls and patients. *C. pneumoniae* and *H. pylori*-specific IgG was detected by the ELISA technique.

A total of 59 (58%), 9 (56%), and 48 subjects (53%) were seropositive for *H. pylori* in the UA, CSA, and control groups, respectively. The number of subjects seropositive for *C. pneumoniae* in the UA, CSA, and control groups were 67 (66%), 15 (94%), and 73 (81%), respectively. No significant statistical difference in seropositivity was found between the study group and the controls, either for *H. pylori* or for *C. pneumoniae*. The prevalence of *H. pylori* reported in our study is within the range reported in studies from India (40%–74%). There has been no report on the seropositivity of *C. pneumoniae* from India till date. Our study showed a high prevalence of *C. pneumoniae* (70.1% in patients, and 81% in controls), which is in agreement with the normal Chinese population (61.5%).

It has been postulated that in countries with poor socioeconomic conditions, there may be a link between CHD and some undefined environmental exposures, including infections. It is possible that cardiovascular risk increases with cumulative or earlier exposure to more pathogens or specific potentially atherogenic microbes.

**References**


Abhijit Chaudhury, D Rajasekhar, SAA Latheef, G Subramanyam

Departments of Microbiology and Cardiology
Sri Venkateswara Institute of Medical Sciences, Tirupati
Delayed Tamponade Following the Sudden Braking of a Speeding Vehicle

Motor vehicle accidents often cause blunt cardiac trauma with pericardial hemorrhage and rapid tamponade. We describe a patient who presented with bleeding, not to the emergency services, but to the cardiologist.

A 63-year-old hypertensive male on beta-blockers presented with a 3-day history of dyspnea on exertion and profound weakness. His symptoms started 1 day after the sudden braking of his car while he was travelling in the back seat without a seat belt. He reported having protected himself by holding onto the seat in front of him, and denied impact to the chest. He was well for a few hours but developed pain in the back of the neck the same night. Over the next 3 days, he developed progressive weakness and dyspnea. On examination, his pulse rate was 80 bpm (on atenolol) and the blood pressure 140/90 mmHg with a pulsus paradoxus of 10 mmHg. The jugular venous pressure was elevated to 15 mmHg and heart sounds were faint. The ECG showed a relative decrease in the QRS voltages compared to the previous recording. A chest X-ray showed an enlarged cardiac silhouette with a cardiothoracic ratio of 70%.

The patient’s hemoglobin level was 12 g%; it had been 14.5 g% during a routine health checkup 3 months earlier. Serum transaminases and alkaline phosphatase were elevated three-fold, as is common in subacute tamponade. The troponin T concentration was normal (<0.01 ng/ml). Echocardiography revealed a moderate-size pericardial effusion with collapse of the right atrium, and exaggerated respiratory variation in the tricuspid and mitral Doppler flow velocities. The patient underwent a therapeutic tapping of the pericardial fluid. Seven hundred and twenty ml of bloody fluid was aspirated via the subxiphoid approach and a pigtail catheter left inside for 24 hours. There was no recurrence of effusion, and the patient made an uneventful recovery. The fluid had a hemoglobin content of 10 g%, was sterile on culture and had no malignant cells. The patient was doing well on follow-up at 6 months.

We believe that the bleeding resulted from an injury caused by the sudden deceleration of the car. Subacute traumatic pericardial bleeds should be managed and followed up like other cases of pericardial hemorrhage, including long-term follow-up for the development of constrictive pericarditis.

References


Rajiv Bajaj, Harbans Singh Wasir
Department of Cardiology
Batra Hospital
New Delhi
Comparison of Carvedilol and Metoprolol on Clinical Outcomes in Patients With Heart Failure in the Carvedilol or Metoprolol European Trial (COMET): Randomized Controlled Trial


Summary

COMET was a multicenter, randomized, double-blind, parallel-group trial comparing the effects of carvedilol and metoprolol on the clinical outcome of patients with chronic heart failure (CHF). The study involved 3029 patients from 341 centers in 15 European countries. Symptomatic NYHA classes II–IV (<5% were class IV) CHF patients receiving both angiotensin-converting enzyme inhibitors (ACE-I) and diuretics for at least 2 weeks were included in the study. All of them had left ventricular (LV) systolic dysfunction as evidenced by ejection fraction (EF) ≤35% or left ventricular end-diastolic dimension (LV-EDD) >6 cm, and fractional shortening (FS) <20%. Patients with an unstable medical condition, uncontrolled hypertension or recent change in treatment were excluded from the study. Carvedilol (1511 patients) was started at 3.125 mg twice daily, and doubled every 2 weeks to achieve a target dose of 25 mg twice daily. Metoprolol was started at 5 mg twice daily, and stepped up to 50 mg twice daily. The patients were followed up for a mean duration of 58±6 months. The baseline characteristics were similar in both the groups. The mean age was 62±11 years, one-fifth were female, mean duration of CHF was >40 months, and more than 50% had an ischemic etiology. The mean EF was 26%±7%. About 60% of patients were receiving diuretics but very few patients were receiving angiotensin receptor blockers (ARBs). The primary end-point of the study was all-cause mortality. Later, a composite end-point of all-cause mortality or all-cause admission was admitted as a second primary end-point in recognition of its importance, after publication of the findings of the MERIT-HF study. The all-cause mortality was 17% lower with carvedilol (34% vs. 40%; 95% Cl: 0.74–0.93, p=0.0017). The survival advantage was apparent within 6 months, and was consistent among all the subgroups. The composite end-point was also 6% lower in the carvedilol group, though this was statistically nonsignificant (74% vs. 76%; 95% Cl: 0.86–1.02, p=0.122).

Sudden cardiac death was the most common mode of death, accounting for 43% of deaths in the carvedilol group, and 44% in the metoprolol group. Circulatory heart failure contributed to one-third of deaths in both the groups. Three-fourth of the patients in the carvedilol arm reached the target dose (mean dose 41.8±14.6 mg), whereas 78% achieved the target dose in the metoprolol group (mean dose achieved 85±28.9 mg). However, the reduction in heart rate was greater in the carvedilol group (13.3 beats/min vs. 11.7 beats/min; 95% Cl: 2.7 to –0.6). The incidence of side-effects and drug withdrawals (32%) were similar in both the groups. The authors concluded that carvedilol extends a survival advantage vis-a-vis metoprolol in patients with symptomatic CHF.

Comments

In patients with symptomatic CHF, the aims of treatment are two-fold. The first and foremost is to relieve symptoms and second, even more important than the first, is to improve survival. While diuretics and digoxin are well known for the symptom relief they provide in CHF, they confer very little, if any, survival advantage. In this context, the only drugs that improve survival are ACE-I, beta-blockers, aldosterone antagonists, and ARBs. However, the benefit achieved by a combination of these renin–angiotensin–aldosterone system (RAAS) modifying drugs is still controversial. For instance, the VAL-HEFT study showed that while a combination of ACE-I with ARB, or beta-blocker (BB) with ARB was beneficial, the combination of all three agents (ACE-I + BB + ARB) is actually detrimental. The second issue has been the actual drug used. Among the beta-blockers, carvedilol (COPERNICUS, CHRISTMAS, CAPRICORN), metoprolol (MDC, MERIT-HF), and bisoprolol (CIBIS I and II) have all been shown to be useful. However, which of these beta-blockers, if any, is more beneficial is still uncertain. Theoretically, metoprolol and bisoprolol are both β₁-selective, and should therefore be more effective. Carvedilol is not only β₁-selective and β₂-active, but also blocks the α₁-adrenergic receptors. However, carvedilol has several other mechanisms by which it can be useful in patients with CHF. It increases insulin sensitivity, and has potent antioxidant action, thereby improving endothelial dysfunction and reducing apoptosis. Indeed, a recent meta-analysis has suggested that the use of carvedilol led to a greater improvement in EF (one of the prime mechanisms for improvement of survival) as compared to metoprolol. The COMET trial is the first large study to compare these two drugs head-on. This study suggests that carvedilol is superior to metoprolol not only in reducing the combined rate of mortality and hospital admission but, more importantly, in improving survival (as much as 17% over a 5-year period). However, this study is not without limitations. The mean dose of metoprolol, i.e. 85 mg, is much lower than that achieved in the MERIT-HF study (>162 mg). Secondly, the salt of metoprolol, i.e. metoprolol succinate (metoprolol CR/XL) used in the MERIT-HF study. Some studies have shown that the succinate salt may have at least 30%–35% reduced bioavailability as compared to the succinate salt. Indeed, the reduction in heart rate and blood pressure was higher in the carvedilol arm, perhaps reflecting inadequate dosage in the metoprolol arm. Another important limitation of the study was that follow-up EF values were not obtained.
Efficacy of Perindopril in Reduction of Cardiovascular Events Among Patients With Stable Coronary Artery Disease: Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial (the EUROPA Study)


Summary
EUROPA was a randomized, double-blind, placebo-controlled, largest-ever trial of the angiotensin-converting enzyme inhibitor (ACE-I) perindopril, evaluating the reduction of cardiac events in low-risk patients with proven coronary artery disease (CAD) but with no evidence of CHF. It enrolled 13,655 patients ≥18 years of age, and documented CAD as evidenced by previous MI, coronary revascularization, angiographically proven CAD (>70% stenosis) or positive stress test in men. Patients with evidence of CHF, hypotension/uncontrolled hypertension or due for PCI, recent use of ACE-I or angiotensin receptor blockers (ARBs), renal insufficiency or elevated serum potassium (>5.5 mmol/L) were excluded from the study. The primary end-point was combined CVS mortality + nonfatal AMI + survival of sudden cardiac death (SCD). Patients initially received 4 mg perindopril for 4 weeks, increased to 8 mg for another 4 weeks. Patients were then randomized to receive either 8 mg perindopril or a placebo for at least 3 years, the dose being reduced to 4 mg if it was not tolerated. The mean follow-up was 4.2 years. Overall, baseline characteristics were similar in both the groups. The mean age was 60±9 years, and 85% were male. They were generally low-risk CAD patients, 9.2% on platelet inhibitors, 62% on beta-blockers, and 48% on statins. Perindopril significantly reduced the combined end-point from 9.9% in the placebo group to 8% (RR 20%, p=0.0003). The beneficial effect became apparent at 1 year of treatment, and was seen in all the sub-groups. Perindopril use was associated with a reduction in all the secondary end-points as well. Total mortality reduced by 11% (ns). MI decreased by 23.9% (p=0.001), and CHF decreased by 39.2% (p=0.002). About 50 patients needed to be treated with perindopril over 4 years to prevent one major CVS event, and this benefit was over and above the medications already being used.

Comments
The HOPE study has already established the role of ACE-I, especially ramipril, in patients with high-risk CAD. In the EUROPA study, perindopril was chosen because of its antischismic and antiatherogenic effects, its Effects on cardiovascular remodeling, and its blood pressure-lowering effect. The baseline characteristics of the EUROPA study were different from those of the HOPE study. In the HOPE study, all the patients were ≥55 years, whereas in the EUROPA study, at least one-third of patients were <55 years. In addition, more HOPE patients had diabetes mellitus, hypertension, stroke, and obstructive peripheral vascular disease. This difference is well reflected in the placebo event rates, where the total mortality in the HOPE study versus the EUROPA study was 12.2% vs. 7.4%; CVS mortality 8.1% vs. 4.4%, and Q wave MI 3.2% vs. 2.1%. With this background, the results of the EUROPA study were even more remarkable and, indeed, may appear to extend the indication of ACE-I to even low-risk CAD patients. However, if we look carefully, even the CAD patients enrolled in the two studies were different. In the HOPE trial, only about one-third of the patients were post-MI, whereas in the EUROPA trial, nearly two-thirds were post-MI. The role of ACE-I in post-MI is already well established. If we consider subgroup analysis, the benefit in the non-MI patients was not statistically significant in the EUROPA study. In other words, perindopril is effective in only those patients who have suffered a prior MI. Thus, these results cannot be directly extrapolated to the garden variety of CAD patients; rather, they are more applicable to the post-MI population. Furthermore, another important limitation of the EUROPA study is that the ejection fraction was not considered. Since most patients in the EUROPA study were post-MI, it is likely that the mean ejection fraction in this study would be low. The role of ACE-I in patients with a low ejection fraction is again well established. It can be argued that the effect of perindopril could be due to its antihypertensive effect. However, the BP reduction was small, 5/2 mmHg, which could not account for the large reduction in CVS events. To better understand the mechanism of CVS event reduction, 5 substudies of EUROPA are under way. The PERTINENT study is evaluating the predictive value of several plasma and serum markers associated with atherosclerosis, and the effect of perindopril on these levels. The PERFECT study will measure blood flow in the brachial artery using B-mode imaging. The PERSPECTIVE study aims to investigate the effects of perindopril on progression and regression in diabetics, and the PERGENE study will genetically characterize the EUROPA population. The results of these studies are expected within a year. Another interesting point that has emerged from the EUROPA study is that mortality reduction was superior in the subgroup of patients on beta-blockers. The reduction of events in patients not on beta-blockers was statistically insignificant. Further studies will be required to clarify this concept.
Beneficial Effect of Immediate Stenting After Thrombolysis 
in Acute Myocardial Infarction


Summary

The Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III) study is a multicenter, randomized, prospective, controlled trial in which immediate stenting after full thrombolysis was compared with the conservative approach of delayed stenting after 2 weeks in patients presenting with acute STEMI. The study included patients presenting within 12 hours of the onset of symptoms with diagnostic electrocardiograms who had no contraindication to thrombolysis. Angiographic inclusion criteria were an infarct-related coronary artery >2.5 mm, diameter stenosis of at least 70% or TIMI flow <grade 3. Patients were recruited from community hospitals located within 34 km of an interventional center. Reteplase was administered in 2 boluses of 10 IU 30 min apart. Patients also received 250 mg aspirin IV, and a bolus of 5000 IU heparin, followed by an infusion adjusted to maintain an activated partial thromboplastin time of 50 to 70 ms. During thrombolysis, the patients were randomized to either immediate or elective stenting. Patients randomized to immediate stenting were shifted to interventional centers within 6 hours where the infarct-related artery was stented; 2 weeks later, a repeat angiography was performed. The second group underwent elective angiography and stenting performed at 2 weeks. Patients in both the groups were clinically followed up at regular intervals, and repeat angiography was scheduled at 6 months. A total of 163 patients were included in the study. Group I (immediate stenting group) had a significant reduction in the combined end-point of ischemic events, death, reinfarction, and target lesion revascularization at 6 months (25.6% v. 50.6%, p=0.001). This beneficial effect was largely driven by a reduction in recurrent ischemic events (4.9% v. 28.4%, p=0.01). On an intention-to-treat basis, immediate stenting was also associated with a reduction in the 6-month combined end-point of death, reinfarction, and target vessel revascularization (27.7% v. 39.8%, p=0.049). Patients with stenting showed an improvement in LV function at 2 weeks with further improvement at 6 months, whereas the delayed stenting group (group II) showed no statistically significant improvement in LV function. Major bleeding complications occurred in 9.8% of patients who underwent immediate stenting versus 7.4% in the delayed stenting group (p=0.374). There were 5 deaths in group II within 48 hours of thrombolysis, whereas all the patients in group I survived the acute phase. Immediate stenting after thrombolysis is significantly more beneficial compared to delayed stenting.

Comments

Thrombolysis results in TIMI-3 flow in only 60% of patients with acute MI. Moreover, around a third of those thrombolysed have recurrent ischemia. Numerous studies have shown that primary PCI is superior to pharmacologic thrombolysis with higher reperfusion rates, and improved event-free survival. The main drawback remains the immediate availability of centers with the facility for PCI. Hence, in a real-world situation, a considerable time delay is usually encountered in transportation of the patient, and mobilization of appropriate resources. As we are aware, time is all-important in salvage of the myocardium. The ACC/AHA recommends a door-to-balloon time of 90±30 min, but in a day-to-day situation, this is usually not possible. In the National Registry of Myocardial Infarction (NRMI), there was a median treatment time delay of >2 hours in almost 90% of patients. In the recently published results of the DANAMI-2 study, there was a lower composite end-point of death, MI or stroke at 30 days in patients who were transferred from community hospitals to tertiary care centers with intervention facilities, compared with patients receiving on-site thrombolysis (8.5% v. 14.2%, p=0.002). A similar benefit has been seen in the PRAGUE study, as well as the AIR-PAMI study. Though these trials have shown that the time delay in PCI is offset by the superiority of the results of angioplasty over thrombolysis, the door-to-balloon time remains important. In the NRMI registry, a door-to-balloon time >2 hours was associated with an increase in mortality. Numerous thrombolysis trials have shown that the time from the onset of symptoms to vessel recanalization is a predictor of myocardial salvage and survival. Given the lack of widespread availability of PCI centers, alternative approaches with a combination of pharmacologic and mechanical revascularization methods are being tried. The rationale behind facilitated PCI was to improve outcomes by attempting to achieve earlier reperfusion while awaiting definitive intervention at a center with PCI facility. This combination approach is an attempt to buy time, and widen the therapeutic window for revascularization. Moreover, patients have a better TIMI flow grade and lesser thrombus burden, thus reducing the chances of microvascular embolization, improving lesion focus, and improving the overall results. However, earlier attempts with this complementary therapy were not encouraging. Data from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-I) study, and the European Cooperative study group showed no benefit in survival or ventricular function, and were in fact associated with a higher complication rate. However, the development of bolus thrombolytics with enhanced fibrin sensitivity, and excellent safety and efficacy profiles, along with improvement in PCI hardware, including thrombectomy and distal protection devices, have led to a resurgence in the use of facilitated PCI.

In this trial, the time to angiography was 6.7 hours, exceeding the currently recommended time. But the setting was a real-world situation that would be commonly encountered in practice. In the SIAM III study, over 60% of patients in the immediate stenting group had TIMI-3 flow; this figure increased to 98%. This translated into an improved LV function at 2 weeks and 6 months. Despite the long time taken till intervention, there was a clear benefit, and no increase in the complication rates. In conclusion, this trial has proved the relative superiority of thrombolysis followed by immediate stenting, despite the time involved in transfer to the tertiary care center. The use of Gp IIb/IIIa antagonists would further improve the outcome of immediate stenting. In conclusion, immediate stenting after thrombolysis is safe, and improves event-free survival as well as ventricular function compared with elective stenting at 2 weeks following MI.
Sirolimus-Eluting Stents Versus Standard Stents in Patients With Stenosis in a Native Coronary Artery


Summary

The SIRIUS investigators conducted a randomized double-blind trial in 1058 patients with a newly diagnosed single lesion in a native coronary artery, comparing a sirolimus-eluting stent with a standard stent. Although previous trials have shown a reduction in restenosis rates with sirolimus stents, the patients enrolled were at a lower risk for restenosis with discrete lesions. This study enrolled patients with more challenging coronary lesions with the majority (56%) having class B2 or C lesions (ACC/AHA classification). The average vessel diameter was 2.8 mm, and the mean lesion length was 14.4 mm. There were 533 patients in the sirolimus stent group, and 525 in the standard stent group. The groups were well matched with respect to demographical characteristics, cardiac risk profile, symptomatology, lesion anatomy, and procedural factor. Follow-up angiography (performed in around 85% of patients in both groups) showed that the minimal luminal diameter stenosis, and the late lumen loss in the in-stent zone as well as the in-segment zone were significantly (p=0.001) better in the sirolimus stent group.

There was a higher rate of in-stent restenosis and in-segment stenosis (35.4% and 36.3%, respectively) in the standard stent group compared with the medicated stent group (3.2% and 8.9%, respectively). Intravascular ultrasound revealed a reduced neointimal volume in the in-stent zone (4.4 mm³ vs. 57.6 mm³, p<0.001). The primary end-point of target vessel failure rate (composite of death from cardiac causes, myocardial infarction, and repeat revascularization) within 270 days was reduced by 58% with sirolimus stents (110 patients vs. 56 patients, p<0.001). This reduction was driven largely by a decrease in the frequency of the need for revascularization of the target vessel (16.6% vs. 4.1%, p<0.001)). Diabetes was significantly associated with an increased risk of restenosis along with reference vessel diameter and lesion length. However, sirolimus stents showed a consistent benefit even in these high-risk subgroups as compared with standard stents.

Comments

Sirolimus (rapamycin) is a macrolide antifungal with powerful immunosuppressant properties; it inhibits several regulators of cell-cycle progression, and the migration of vascular smooth muscle cells. This unique property led to its use in coronary artery stents to prevent neointimal proliferation. The Randomized Study with the Sirolimus Eluting Bx Velocity Balloon Expandable Stent (RAVEL) showed a significant reduction in the frequency of in-stent restenosis (from 26.6% to 0%). The present study enrolled patients with a higher frequency of cardiac risk factors, such as diabetes and hypercholesterolemia, more complex morphology, and longer lesions. In the RA VEL study, there were no type C lesions, and the mean lesion length was 9.58±3.25 mm compared with 14.4±5.8 mm in the present study. Similarly, only 19% of the patients had diabetes and 40% dyslipidemia compared with 26% and 74% in this study, respectively. Intravascular ultrasound revealed a 92% reduction in neointimal volume, a 77% reduction in the rate of target lesion revascularization, and an 85% reduction in the rate of non-QMI. The high frequency of in-segment restenosis compared to in-stent restenosis (8.9% vs. 3.2%) in the sirolimus stent group was due to a higher rate of restenosis at the proximal margin of the stent, and is attributed to balloon injury to the vessel prior to stent deployment. The authors recommend the use of shorter balloons and longer stents that would have no exposed balloon-injured area. The restenotic lesions were focal compared with diffuse disease with standard stents, and hence more amenable to complex balloon angioplasty. The encouraging results from the trial suggest that special stents may maintain their superiority over standard stents in a diverse patient population. As sirolimus-coated stents move into general use, and with a longer follow-up, it is likely that the rate of restenosis will be higher. This trial has shown the beneficial effect of sirolimus-coated stents in a population at a higher risk, and with more complex disease than previous studies.
Calendar of Conferences

November 14–15, 2003, 4th Annual Conference of Nuclear Cardiological Society of India, Vellore, India
Contact: Organizing Secretary
Department of Nuclear Medicine
Christian Medical College
Vellore, Tamil Nadu, India
Fax: 0416 2232103
e-mail: nuclear@cmcvellore.ac.in

November 7–10, 2004, 77th Scientific Session, American Heart Association (AHA), New Orleans, Louisiana, USA
Contact: American Heart Association
7320 Greenville Avenue
Dallas TX 75231, USA
Tel: 1 214 373 6300
Fax: 1 214 373 3406

December 4–7, 2003, 55th Annual Conference of Cardiological Society of India, Kolkata, India
Contact: Dr Asok Kumar Kar, Organizing Secretary
Indian Heart House
P-60, CIT Road, Scheme VIIM,
Kankurgachi, Kolkata 700054, India
Fax: 033 355 6308
e-mail: csi@cal2.vsnl.net.in

November 26–28, 2004, 3rd International Congress on Cardiovascular Disease, Taipei, Taiwan
Contact: Dr CE Chiang
Taiwan Society of Cardiology
7F, No. 27, Min-Chuan, West Road
Taipei 104, Taiwan
Fax: 886 2 25076180
e-mail: tsoc@tsoc.org.tw; cjchen@doh.gov.tw

January 9–11, 2004, Joint Meeting of International Society for Heart Research and International Academy of Cardiovascular Sciences, Lucknow, India
Contact: Professor VK Puri, Organizing Secretary
Department of Cardiology
CSM Medical University
Lucknow, India
Fax: 0522 225 5830
e-mail: vijaykumarpuri@hotmail.com

November 28–30, 2004, 10th World Congress on Clinical Nutrition, Thailand
Contact: Dr Buncha Ooraikul
or Dr Tapan Basu, Department of Food Science and Nutrition, University of Alberta, Edmonton
Canada T6G 2M
Fax: 403 4924821
e-mail: buncha.ooraikul@ualberta.ca

May 6–9, 2004, 4th Congress of the Asian Pacific Society of Atherosclerosis and Vascular Disease, Bali, Indonesia
Contact: Dr Slamet Suyono, MD
Pacto Convex Ltd, Lagoon Tower Level B-1
Jagarta Hilton International
Jl Gatot Subroto, Jakarta 10270, Indonesia
Fax: 62 21 5705798
e-mail: pactoltd@idola.net.id

May 21–25 2005, 4th International Conference on Preventive Cardiology, Foz do Iguassu, Brazil
Contact: Dr Mario Maranhao, Chairman, Congress
Internationales SA/Lady Groot Congress Events
P.O. Box 83005 1080. AA Amsterdam
The Netherlands
Fax: 31 20 6758236
e-mail: prcardio2005@congresOsint.com.ar