Heart Failure - Definition and Diagnosis

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The concept of heart failure (HF) has evolved considerably with time. Terms such as forward or backward, left or right-sided, high or low output, systolic or diastolic HF and more recently, HF with or without systolic dysfunction have been used to characterize HF by clinicians. Every physician recognizes the signs and symptoms of HF, yet HF is frequently under- or over-diagnosed. The diagnostic difficulties are greater in the community settings, in the elderly, in the obese and in patients with other comorbidities. Diagnosing HF in advanced congested stage is not difficult. However, a combination of hepatomegaly, elevated jugular venous pressure and lower limb edema has a sensitivity of only 8% for the diagnosis of HF in the community. The clinical diagnosis of early HF in relatively asymptomatic stages remains a major challenge. Clinical history, symptoms and signs, when used in isolation, have only a limited value in diagnosing HF. Dyspnea on exertion is the most frequent symptom but is not specific. A history of acute pulmonary edema, paroxysmal nocturnal dyspnea, orthopnea and dyspnea when walking on the flat are relatively specific but not sensitive. Similarly, several signs are relatively specific but not very sensitive. On the other hand, only 54% of patients with clinically diagnosed HF have objective evidence of cardiac dysfunction. Thus, the clinical diagnosis of HF requires careful integration of all the available information. The clinicians often equate HF with congestive HF, but not all patients have volume overload at the time of initial or subsequent evaluation. Hence, the term "congestive heart failure" is preferred over the term "congestive heart failure".

The need for a uniform definition of HF cannot be overemphasized. The absence of uniform definition and diagnostic criteria results in considerable heterogeneity among patients classified as having HF in epidemiologic and clinical studies. A wide variation in the estimated prevalence of HF, ranging from 3 to 20 cases per 1000 population reported in the various studies, results from the varied definitions used for HF. Defining HF has been a surprisingly difficult task. In this article, we highlight the different definitions and the criteria used for the diagnosis of HF. Though HF may be viewed as a failure at myocardial, cellular, molecular, neurohumoral or bio-energetic levels, we limit ourselves to the clinician’s perspective.

Definition of Heart Failure

The process of definition of HF exposes the strengths and limitations of the concept of definition itself. 'Definition' entails description of a feature and its limits. Though HF can be redescribed, the proposed limits vary for the clinicians, epidemiologists, clinical scientists and individual patients. The lack of a diagnostic test or a specific finding with well-defined cut off precludes thinking of HF in the same way as perhaps for diabetes or hypertension. Numerous definitions of HF have been proposed over the years with none having a universal acceptance, some of which are summarized in Table 1. Many of the definitions are hypothetical and could not be tested. Unifying the various aspects of HF into an acceptable definition has remained an elusive task, as evident by the lack of consensus among the 130 definitions proposed by the reviewers for cardiovascular journals even in recent times.

A commonly used definition of HF is that ‘HF is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues’. Later, the textbooks refined the definition by adding ‘or does so only at elevated filling pressures’. The current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines define HF as a complex clinical syndrome that can result from any structural or functional cardiac disorder that, impairs the ability of the ventricle to fill with or eject blood. Both these definitions have appropriately placed the reduced cardiac output at the centerstage, but are not useful clinically as the cardiac output is not routinely measured. The European Society of Cardiology
(ESC) HF guidelines accept that a simple objective definition of chronic HF is currently impossible and instead, have suggested essential components of HF that include symptoms of exercise intolerance, signs of fluid retention and response to therapy, accompanied by objective evidence of cardiac dysfunction at rest.

**Diagnostic Criteria**

Notwithstanding the lack of uniform definition, the need for treatment of HF has led to more pragmatic approaches toward the diagnosis of HF based on certain criteria. Numerous complex scoring systems for the clinical recognition of HF have been devised. Framingham, Gothenburg, NHANES, Boston, Duke, Walma et al. and Gheorghiade et al. questionnaires and scores have been used as screening instruments for the diagnosis of HF in therapeutic trials and epidemiological studies. Many such scores are cumbersome and have been restricted to clinical or epidemiological research projects. All the scores retain the basic format of incorporating multiple signs and symptoms of HF and assigning them various weightage points (Table 2). The general approach is likely to be correct as none of the individual symptoms and signs of HF when used alone have significant value in diagnosing HF. Surprisingly, only the presence of rales is included as a criterion in all the different schemes.

Framingham criteria are the most known among clinicians and the Boston criteria are most commonly used in epidemiological studies and therapeutic trials. The Framingham questionnaire defines a series of major and minor criteria that include symptoms, signs and abnormalities on the chest X-ray. The diagnosis of HF is made in the presence of two major criteria or one major and two minor criteria. The Boston instrument explores the presence of symptoms and signs of HF in 3 categories of history, physical findings, and chest X-ray. Recently, the ESC has issued recommendations for the diagnosis of HF. The ESC criteria requires not only presence of symptoms and signs but also objective evidence of cardiac dysfunction and in doubtful cases, response to the treatment. These guidelines provide an operational definition of HF and have been generally accepted. However, one of the major limitations is the failure to define the minimum severity of symptoms, signs or cardiac dysfunction that is required for the diagnosis of HF.

The validation of the various proposed criteria have been less than distinguished. These criteria individually or in combination have been validated against a raised capillary wedge pressure (>12 or 15 mmHg), left ventricle (LV) ejection fraction (EF) <40% or diagnosis by a cardiologist as the gold standard. Recently, 2 large population-based studies have evaluated these criteria. In the EPICA study, a total of 5434 subjects, aged >25 years old, attending primary care centers in Portugal were evaluated using 7 clinical questionnaires with ESC criteria as the gold standard. Overall, the questionnaires showed good concordance, high specificity usually above 90% and low

**Table 1. Some selected definitions of heart failure (modified from Ref 7)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1933</td>
<td>Condition in which heart fails to discharge its contents adequately (Lewis)</td>
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<tr>
<td>1950</td>
<td>A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure (Wood)</td>
</tr>
<tr>
<td>1980</td>
<td>A pathological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues (Braunwald)</td>
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<tr>
<td>1985</td>
<td>A clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural and hormonal responses (Poole-Wilson)</td>
</tr>
<tr>
<td>1987</td>
<td>… syndrome … which arises when the heart is chronically unable to maintain an appropriately high blood pressure without support (Harris)</td>
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<tr>
<td>1988</td>
<td>A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias and shortened life expectancy (Cohn)</td>
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<tr>
<td>1993</td>
<td>Is the state of any heart disease in which, despite adequate ventricular filling, the heart’s output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits (Denolin et al.)</td>
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<tr>
<td>1996</td>
<td>A normal ventricular function, symptoms or signs of heart failure (past or current), and on treatment (with a favorable response to treatment) (Poole-Wilson)</td>
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<tr>
<td>2000</td>
<td>Congestive heart failure is defined as the inability of the left ventricle to generate an adequate cardiac output at rest or during exercise while operating at a normal or enhanced left ventricular filling pressure (Mandinov et al.)</td>
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<tr>
<td>2001</td>
<td>When the heart becomes the rate limiting factor for the circulation (DeTombe)</td>
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<tr>
<td>2001</td>
<td>Label for a cardiovascular syndrome that is lacking uniform criteria for definition (Eckardt)</td>
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</tbody>
</table>
sensitivity ranging from 35 to 84%. The application of these questionnaires increases the likelihood of diagnosis of HF from 4.3% pre-test to 25-35% post-test in most cases.33 The Gothenburg questionnaire was found to be the most balanced with high sensitivity (84%) and specificity (81%).33 The ICARe Dicomano study34 also compared ESC criteria with the other criteria. The incidence of HF found in 553 elderly (> 65 years old) population was 11.9%, 10.7%, 20.8%, and 9.0% using Framingham, Boston, Gothenburg and ESC criteria, respectively. Of these, the risk of cardiovascular death, incident disability, and HF-related hospital admissions were better predicted by the Boston criteria as compared to the other schemes.34

HF is now viewed as a ‘progressive’ disorder rather than only as a ‘symptomatic’ disorder. A reflection of the changing paradigm to the approach of HF is seen in the present ACC/AHA HF guidelines,6 which has devised a new classification of HF that focuses not only on patients with

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**Table 2. Comparison of diagnostic criteria for heart failure (modified from Ref 28, 29)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Framingham26</th>
<th>Gothenburg22,23</th>
<th>Walma24</th>
<th>Boston24</th>
<th>NHANES25</th>
<th>Gheorghiade15</th>
<th>Rotterdam28</th>
<th>EPICA sensitivity</th>
<th>EPICA specificity</th>
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<tr>
<td>Symptoms</td>
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<tr>
<td>PND</td>
<td>M</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>-</td>
<td>27</td>
<td>99</td>
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<tr>
<td>Orthopnea</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>-</td>
<td>25</td>
<td>99</td>
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<tr>
<td>Dyspnea at rest</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td></td>
<td>99</td>
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<tr>
<td>DOE</td>
<td>m</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>79</td>
<td>84</td>
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<td>Y</td>
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<td>Night cough</td>
<td>m</td>
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<td>MI or angina</td>
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<td>PTCA or CABG</td>
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<td>Neck vein distension</td>
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<td>-</td>
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<td>Y</td>
<td>33</td>
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<td>Increased JVP</td>
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<td>Y</td>
<td>Y</td>
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<td>Rales</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>97</td>
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<tr>
<td>S, gallop</td>
<td>M</td>
<td>-</td>
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<td>Y</td>
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<td>Hepatogastroesophageo reflux</td>
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<td>Edema</td>
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<td>Y</td>
<td>Y</td>
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<td>Y</td>
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<td>Circulation time ≥ 25 s</td>
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<td>Tachycardia</td>
<td>m</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
<td>23</td>
<td>94</td>
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<td>AF</td>
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<td>Y</td>
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<td>MI</td>
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<tr>
<td>Chest X-ray</td>
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<tr>
<td>Cardiomegaly</td>
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<td>-</td>
<td>-</td>
<td>Y</td>
<td>-</td>
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<td>Acute pulmonary edema</td>
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<td>Pleural effusion</td>
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<td>Y</td>
<td>Y</td>
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<td>PVH</td>
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<td>Alveolar changes</td>
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<td>Y</td>
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<td>Redistribution</td>
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<td>Y</td>
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<td>-</td>
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<tr>
<td>Pulmonary function</td>
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<tr>
<td>Vital capacity</td>
<td>m</td>
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PND: paroxysmal nocturnal dyspnea; DOE: dyspnea on exertion; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; JVP: jugular venous pressure; AF: atrial fibrillation; LVH: left ventricular hypertrophy; WHO: World Health Organization; PVH: pulmonary venous hypertension; M: major criteria; m: minor criteria; Y: positive diagnostic criteria.
established HF but also on patients at risk of HF. Accordingly, Stage A refers to the patient who is at high risk for developing HF but has no structural disorder of the heart (for example, hypertension, coronary artery disease, and diabetes); Stage B refers to an asymptomatic patient with a structural disorder of the heart (for example, left ventricular [LV] dysfunction, dilation, or hypertrophy); Stage C denotes the patient having underlying structural heart disease with past or current symptoms of HF; and Stage D designates the patient with end-stage disease who requires specialized treatment strategies. Only the latter 2 stages qualify for the traditional clinical diagnosis of HF for diagnostic or coding purposes.

**Diastolic Heart Failure**

The problems of definition and diagnostic criteria are even more apparent in our approach to diastolic HF. The estimated prevalence of diastolic HF among patients with HF has varied from 13-74% and the attitude to diastolic HF has also fluctuated from ignorance and over-acceptance, to skepticism and self-doubt. The term HF with preserved EF is often used interchangeably with diastolic HF. It is likely that HF with preserved systolic function includes a pathophysiologically heterogeneous group of conditions including ‘true’ diastolic dysfunction, subtle systolic dysfunction and some misdiagnosis. One study suggested that 3 principal diagnoses – ischemia, obesity, and lung disease may masquerade as diastolic HF. The mechanisms and pathophysiology of diastolic HF are evolving.

It is not often realized that diastolic HF is not always a backward failure, but may also result in low cardiac output. It is becoming increasingly apparent that diastolic HF in the community settings may be overdiagnosed. The multiple, variable, and non-standardized echocardiographic and Doppler findings suggestive of diastolic dysfunction have only added to the clinical uncertainty. Accordingly, definition and diagnostic criteria for diastolic HF are still less than optimally evolved.

The ACC/AHA suggests the diagnosis of diastolic HF is generally based on typical symptoms and signs of HF in a patient who is shown to have a normal left ventricular ejection fraction (LVEF) and no valvular abnormalities on echocardiography. Demonstration of diastolic dysfunction on echocardiography was not mandatory, but other possible explanations or disorders causing diastolic dysfunction need to be excluded. The validation for these criteria was offered later by Zile et al. who showed that in patients with LV hypertrophy, preserved LVEF (> 50%) and HF as diagnosed by Framingham criteria, diastolic abnormalities were almost invariably present on cardiac catheterization and Doppler. However, the different Doppler parameters evaluated in that study showed considerable variability.

Use of positive criteria for the diagnosis of diastolic dysfunction should be preferable in diagnosing diastolic HF than documenting the mere absence of systolic dysfunction. The ESC definition of diastolic HF requires the following 3 criteria to be simultaneously satisfied: symptoms or signs of HF, normal or only mildly abnormal LV systolic function, and abnormalities of LV relaxation, filling, diastolic distention or diastolic stiffness. The ESC defined echocardiographic parameters of diastolic dysfunction include a prolonged isovolumic relaxation time (IVRT) (>92 ms, 100 ms, and 105 ms in < 30 years, 30-50 years and >50 years old, respectively), the time constant of LV pressure decay (τ) > 48 ms, mitral Doppler flow velocity E/A < 1.0 and deceleration time (DT) >220 ms in <50 years old or E/A <0.5 and DT >280 ms in patients aged > 50 years, S/D ratio on the pulmonary vein Doppler >1.5 and >2.5 in < 50 years and > 50 years old, respectively, reverse pulmonary venous A wave flow velocity >35 cm/s, and pulmonary venous A wave duration exceeding the duration of the mitral A wave by >30 ms. However, these parameters are influenced by heart rate, filling pressure, machine settings and arrhythmias, and their proper measurement is technically challenging.

Vasan and Levy have proposed more complex criteria for the diagnosis of diastolic HF. Clinical symptoms and signs satisfying the Framingham criteria with LVEF > 50% within 72 hours of the HF event would qualify as probable diastolic HF. Addition of an objective evidence of diastolic dysfunction on cardiac catheterization would make it definite. Clinical HF with a LVEF > 50% documented after 72 hours of HF would qualify as possible diastolic HF. However, these criteria are empirical and a cardiac catheterization is unlikely to be performed in every patient with suspected diastolic HF. More recently, Thomas et al. have suggested diastolic HF to be defined in terms of symptoms, preserved LV systolic function, elevated neurohormones and impaired cardiac workload capacity, and have called for the exclusion of controversial echocardiographic parameters from the diagnostic criteria. The role of echocardiography as well as natriuretic peptides in the diagnosis of diastolic HF is described below.

**Role of echocardiography in the diagnosis of HF:** The role of echocardiography in the management of HF hardly requires any reemphasis, but HF cannot be satisfactorily defined solely on echocardiographic parameters. The definition of LV systolic function centers on ejection
fraction. The LVEF cut off taken to define systolic HF in various trials have ranged from 35%-45%.\(^\text{42,43}\) EF assessment is operator-dependent, and correlates poorly with exercise capacity and morbidity in HF.\(^\text{44}\) Since EF is normally distributed within the population, some people will lie outside the normal range (95% confidence interval) and have no cardiac disease.\(^\text{45}\) Furthermore, to equate EF with HF is erroneous, since EF does not directly reflect the cardiac output.\(^\text{46}\)

Echocardiography is the preferred method for documenting objective evidence of cardiac dysfunction at rest, a mandatory criterion for the diagnosis of HF in the ESC guidelines.\(^\text{47}\) However, echocardiography in a patient with HF may be falsely normal as in acute HF, where the changes in systolic, diastolic or valvular function may be transient and some patients may have abnormalities only on exertion. The proportion of HF patients with ‘falsely’ normal echocardiography would depend specially on the criteria for diastolic dysfunction used. However, as noted before, there are no universally accepted minimal criteria for the echocardiographic diagnosis of diastolic dysfunction.

Further, the availability of echocardiographic facilities remains a major concern. Access to echocardiography even in the developed countries is limited. A survey showed an access rate of 5% in Netherlands and 37% in United Kingdom.\(^\text{48}\) Recently, hand-held echocardiography has been shown to be useful in community screening of LV systolic dysfunction. The cost effectiveness of this approach is not yet determined. The availability of open access echocardiography will improve our ability to diagnose HF.\(^\text{49}\) Yet, HF remains a clinical diagnosis.

**Role of natriuretic peptides:** The idea of a biochemical marker that reliably diagnoses HF is appealing, especially if it can distinguish HF patients from other mimicking illnesses. Brain natriuretic peptide (BNP) and NT-pro BNP have emerged as markers of HF.\(^\text{50}\) In patients presenting with acute dyspnea, a BNP level < 100 pg/ml, suggests that HF is highly unlikely with a negative predictive value of 90% and a level > 500 pg/ml makes HF highly likely with a positive predictive value of 90%. The causes of a BNP level of 100-500 pg/ml include baseline BNP elevation due to stable underlying dysfunction, cor pulmonale, acute pulmonary embolism and renal failure. For ascertaining the cardiac cause of dyspnea in patients with glomerular filtration rate (GFR) < 60 ml/min, a BNP cut-point of > 200 pg/ml has been suggested. For the NT-proBNP assay, the recommended decision cutoff point is 125 pg/ml for both genders under 75 years of age and 450 pg/ml for 75 years and older. It is important to realize that BNP values may be falsely normal in flash pulmonary edema, HF upstream from the LV (i.e., acute mitral regurgitation) and obese patients [(body mass index (BMI) > 30 kg/m\(^2\)].\(^\text{51}\)

In contrast to acute HF, evidence for the use of BNP as a diagnostic test for chronic HF is limited. High BNP does not confirm the diagnosis and the BNP assay does not replace any test currently used to assess patients with chronic HF.\(^\text{52,53}\) Definition of a cut off value remains the Achilles’ heel for use of natriuretic peptides in chronic HF. The threshold level of 100 pg/ml is based on acute rather than chronic HF. Nearly 20% of patients with chronic HF have a BNP level < 100 pg/ml and a few patients with end-stage HF may have very low levels of BNP because of exhaustion of ventricular ability to generate the peptide. Moreover, many elderly hypertensive women with nephropathy but without HF have BNP levels > 200 pg/ml.\(^\text{54}\)

The role of BNP in screening asymptomatic patients at risk of HF is evolving. Due to conflicting evidence,\(^\text{54,55}\) the recent consensus statement on BNP\(^\text{56}\) states that BNP testing is not appropriate for screening asymptomatic, low-risk populations for LV systolic dysfunction. Though, plasma BNP may be useful in high-risk subgroups, it is not likely to reduce the need for echocardiography. For sequential BNP-echocardiography screening strategy, a lower cut off in the range of 20-75 pg/ml may be used that would have adequate negative predictive value\(^\text{56,57}\) and at times may reduce the need for echocardiography by as much as 50%.\(^\text{58}\)

The role of natriuretic peptides in diagnosing diastolic HF is emerging.\(^\text{59}\) The BNP levels in diastolic dysfunction are reported to be half of that found in systolic dysfunction, but patients with advanced diastolic dysfunction (restrictive filling pattern) have elevations similar to those with systolic dysfunction.\(^\text{55}\) In one study involving 294 patients referred for echocardiography,\(^\text{59}\) the BNP levels were higher in patients with symptoms and advanced diastolic dysfunction. However, other studies including patients with mild symptoms and with early diastolic dysfunction abnormalities have reported normal levels of natriuretic peptides.\(^\text{57,58}\) Thus, elevated levels of BNP along with advanced diastolic filling abnormalities might help to reinforce the diagnosis of diastolic HF, whereas normal or low BNP levels with early relaxation abnormalities are non-diagnostic.

Some studies\(^\text{59}\) have found that BNP levels, even less than those required to diagnose HF, predicted adverse cardiac outcomes and death over a mean period of 5 years. Hence, an elevated BNP level in a patient without HF may not really be false positive, but may identify patients at very early
stages of pathophysiologic processes of subclinical HF. However, serum BNP levels are influenced by many physiological variables including circadian rhythm, age, gender, obesity, exercise, heart rate, body posture, sodium intake and blood hemoglobin, and many diseases including coronary artery disease, cor pulmonale, acute pulmonary embolism and renal failure. It is suggested that elevated BNP levels in a community may be more predictive of the risk of overall vascular events than that of HF, but further studies are required.

Heart Failure in Specific Situations

Acute HF: The term 'acute HF' is thought to be misleading and inaccurate. Since many patients with HF develop symptoms gradually, hence the term decompensated HF is suggested. Instead, the recent ESC guidelines have approved the term 'acute HF' and included decompensated HF as one of the clinical scenarios. The ESC guidelines defined acute HF as the rapid onset of symptoms and signs secondary to abnormal cardiac function and described it as a clinical syndrome with reduced cardiac output, tissue hypoperfusion, increase in the pulmonary capillary wedge pressure, and tissue congestion. A detailed analysis of acute HF is beyond the scope of this review.

Elderly: The diagnosis of HF in the elderly is difficult as symptoms are insidious and non-specific with comorbidities often obscuring the signs of HF. Among 116 elderly patients (median age 86 years), the estimated specificities of clinical signs, chest X-rays and abnormal ECG for HF diagnosis according to ESC criteria were 50%, 20% and 9%, respectively. Further, more specific symptoms of HF like orthopnea and paroxysmal nocturnal dyspnea are infrequent. Thus, more reliance on objective evidence in the form of echocardiography seems justified. HF with preserved EF is more frequent. Confirmation of diastolic HF is problematic, as virtually all the diastolic Doppler parameters alter with age. A clear distinction between abnormal parameters due to 'ageing' or due to pathological process is lacking. The specificity of natriuretic peptides for diagnosing HF also decreases at older age.

Chronic renal failure: Clinical HF is found in about 25% of cases of chronic renal disease and the prevalence increases to 60-70% in end-stage renal disease (ESRD). But volume overload may be difficult to differentiate from real HF. Echocardiography is useful for this distinction. However, caution should be exercised in interpreting diastolic dysfunction as LV hypertrophy is universal in this population and the incidence of abnormal diastolic function is expected to be high. The role of BNP is promising. Even though the basal BNP levels are higher in patients with renal dysfunction, the levels are not shown to be elevated in patients without LV hypertrophy or dysfunction. Further, BNP neither correlates with volume status nor normalizes following hemodialysis in ESRD patients.

Miscellaneous: Certain situations like high output HF and HF with congenital heart disease pose different questions. In both these situations, the systolic and diastolic parameters on echocardiography may be normal. As congenital heart disease is defined as a structural abnormality of the heart that is actually or potentially of functional significance, any congenital heart disease may be taken to indicate cardiac dysfunction. Then it follows that any symptomatic patient with congenital heart disease has HF if ESC criteria are applied. Hence, different set of guidelines needs to be evolved for these specific situations. Further, in both these situations the role of natriuretic peptides may be limited. Elevated natriuretic peptides may not be indicative of HF in hyperthyroidism and in anemia. The natriuretic peptide levels are frequently elevated even in simple congenital heart disease like atrial septal defects, and may not normalize after correction.

Conclusions

The search of the Holy Grail for the definition of HF continues. The more pragmatic approach of relying on a set of criteria for the diagnosis of HF is currently practiced. A review of the available diagnostic criteria sensitizes the physician to the diagnosis of HF and improves the understanding of HF. The diagnosis of HF still seems to lie in the realms of integrative medicine.

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Insights into the Molecular Mechanisms of Plaque Rupture and Thrombosis

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Thrombosis superimposed on a ruptured atherosclerotic plaque initiates abrupt arterial occlusion and is the proximate event responsible for 60-80% of cases of acute coronary syndrome. When an atherosclerotic plaque ruptures, thrombogenic components of the plaque are exposed to circulating blood, leading to activation of the clotting cascade and thrombosis. Ruptured plaques and, by inference, plaques at risk for rupture (vulnerable or unstable plaques) generally contain a large acellular lipid-core with a reduced collagen content and fewer collagen synthesizing smooth muscle cells, a thinned out fibrous cap, intimal and adventitial inflammation with destruction of internal and external elastic membranes, enhanced plaque neovascularity and outward remodeling of the vessel wall. Coronary culprit lesions responsible for 60-70% of acute coronary syndrome evolve from only mildly or moderately stenotic lesions suggesting that such less obstructive lesions may be more prone to plaque rupture and thrombosis. Inflammation is implicated not only in the initiation and progression of atherosclerosis but also appears to play a critical role in promoting plaque vulnerability, plaque rupture and eventual thrombosis through its effect on matrix turnover and release of thrombogenic mediators. Understanding cellular and molecular mechanisms that contribute to plaque instability and plaque rupture will continue to provide novel insights into prevention of atherosclerosis, plaque rupture and thrombosis.

Cardiovascular disease is the leading cause of death for both men and women in the United States and much of the Western world and is predicted to be the leading global killer by 2020. Atherosclerosis is responsible for coronary heart disease, most strokes, and limb ischemia. Some of the clinical manifestations of atherosclerosis result from progressive luminal narrowing by an atherosclerotic plaque with inward or constrictive remodeling and exaggerated or paradoxical vasoconstriction; however, it is the development of a thrombus over an underlying plaque that causes the most acute and serious clinical manifestations of atherosclerotic vascular disease. Coronary thrombosis, therefore, is responsible for the vast majority of cases of unstable angina, acute myocardial infarction (AMI), and ischemic sudden death.

Rupture of Atherosclerotic Plaque Followed by Thrombosis

A large number of studies involving angiography, surgical exploration, angioscopy, biochemical markers, and autopsy evaluation have shown that coronary thrombosis is the proximate cause for abrupt coronary occlusion leading to AMI, unstable angina, and many cases of sudden cardiac death. Fissure or rupture of the fibrous cap is the underlying basis for 70-80% of coronary thrombi with extension of the thrombus into the plaque as well as into the lumen, and with propagation of the thrombus upstream from the site of cap rupture. Coronary stenoses produced by plaques with a ruptured fibrous cap and superimposed thrombus often produce a distinctive pattern on contrast angiography characterized as a "complex lesion." These lesions have eccentric stenoses bearing irregular or overhanging margins and luencies or filling defects.

Plaque Rupture: Relationship to Plaque Size and Stenosis Severity

Retrospective analysis of serial angiograms as well as prospective serial angiographic observations have suggested that in 60-70% of patients with acute coronary syndrome, a coronary angiogram performed weeks or months before the acute event had shown the culprit site to have <70% (often <50%) diameter narrowing. Thus, plaques producing non-flow-limiting and less than severe stenoses account for more cases of plaque rupture and thrombosis than plaques producing a more severe luminal diameter stenosis. Paralleling the angiographic data, stress testing in stable coronary disease patients has
shown that the site of ischemia on stress myocardial perfusion scintigraphy does not accurately predict the future site of AMI.28 This apparent clinical and angiographic paradox may be attributed to several factors29: less stenotic plaques outnumber the more severely stenotic plaques, more stenotic plaques are likely to promote collaterals which protect from clinically overt manifestations of coronary occlusion, angiography underestimates stenosis severity and finally less stenotic plaques may be more vulnerable to plaque rupture. Recent studies have shown that in addition to plaque size, positive remodeling (outward expansion) versus negative remodeling (vessel shrinkage or contraction) can play an important role in determining the net effect of a plaque on lumen size. Outward remodeling of unstable or vulnerable plaques may minimize luminal encroachment despite large plaque size. Human studies using intravascular ultrasound have, in fact, shown that outward arterial expansion due to positive remodeling is more common at culprit lesion sites in unstable angina, whereas inward or negative remodeling is more common in stable angina.30-32 Similarly, computer models show that larger lumens create greater circumferential stress on the fibrous caps, thereby probably increasing their likelihood of rupture.33 Finally, recent histomorphometric data suggest that plaques with prominent outward remodeling, on an average, contain a larger lipid-core and more inflammatory cells than plaques without outward remodeling.34 These histological attributes are known to be more prevalent in ruptured plaques and by inference in plaques at risk for rupture (vulnerable plaques).

**Relationship of Plaque Composition to Plaque Rupture**

Detailed histological assessment of ruptured plaques has shown several distinctive features which, when present before plaque ruptures, are also believed to indicate vulnerability to plaque rupture (Table 1). This hypothesis is the basis for the concept of “plaque vulnerability.” Plaques that rupture tend to be large, to demonstrate outward or positive remodeling, have a large lipid core often occupying ≥40% plaque volume, show inflammatory cell infiltration of the fibrous cap and adventitia, possess a thin fibrous cap depleted of collagen, glycosaminoglycans and smooth muscle cells and have increased adventitial and plaque neovascularity.2,4,30,35-44

**Lipid-core:** The acellular lipid core is composed of free cholesterol, cholesterol crystals, and cholesterol esters derived from lipids that have infiltrated the arterial wall and also lipids derived from the death, by apoptosis or necrosis, of foam cells, mostly macrophages. Accumulation of large quantities of free cholesterol has been shown to induce macrophage apoptosis through the activation of endoplasmic reticulum-mediated apoptotic gene program involving Caspases, which can be abrogated by partial deficiency of the Niemen-Pick disease type C gene; this enhanced apoptosis of macrophage-foam cells may thus contribute to expansion of the acellular lipid-core.35,45 Recently it has been suggested that red cell membranes may contribute to expansion of the lipid-core when intraplaque hemorrhage brings red cells into the plaque.46 Such hemorrhage may occur from rupture of increased number of neovessels that are abundant in atherosclerotic plaques. A large, eccentric lipid-core could contribute to plaque instability by conferring a mechanical disadvantage to the plaque through redistribution of circumferential stress to the shoulder regions of the plaque where nearly 60% of plaque ruptures tend to occur.33,36,47-49 Recent studies using genetic profiling have shown selective expression of a novel gene, perilipin, in ruptured human plaques. This is of considerable interest since perilipin inhibits lipid hydrolysis and could contribute to accumulation of lipids in the core, thereby contributing to plaque vulnerability.50 In addition, the lipid core contains prothrombotic, oxidized lipids and is impregnated with procoagulant tissue factor derived from apoptotic macrophages. These make the lipid core highly thrombogenic when exposed to circulating blood.51-55

**Plaque inflammation:** A number of studies have shown that ruptured plaques contain more inflammatory cells compared to intact plaques. These cells are mostly monocyte-macrophages, but also include activated T-cells, dendritic cells and activated degranulating mast cells expressing proteolytic enzymes tryptase and chymase. Inflammatory cells are often found adjacent to the sites of fibrous cap rupture and around the lipid-core as well as in the adventitia around areas of neovascularization.38,56-60 Inflammatory cells are probably recruited into the atherosclerotic plaques by cell adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1, and chemokines, such as monocyte chemoattractant protein

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<th>Table 1. Phenotype of a plaque at risk for rupture</th>
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<td><strong>Large acellular lipid-core (≥40% plaque volume)</strong></td>
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<td><strong>Thin fibrous cap depleted of collagen and smooth muscle cells</strong></td>
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<td><strong>Adventitial expansion with outward (positive) remodeling</strong></td>
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<td><strong>Inflammatory cell infiltration</strong></td>
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<td>(Monocyte-macrophages, activated T cells, dendritic cells and degranulating mast cells of fibrous cap and around lipid-core, and adventitia)</td>
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<td><strong>Increased plaque neovascularity and hemorrhage</strong></td>
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(MCP)-1, interleukin-8 and eotaxin. They are then retained and activated in the vessel wall through the activity of other cytokines such as the macrophage colony stimulating factor. Another potential avenue for the entry and recruitment of inflammatory cells inside the atherosclerotic lesion may be through the adventitial neovascularure, which is enhanced in atherosclerosis.

It has also been suggested that inflammatory cells may be derived from either resident arterial and/or bone marrow-derived progenitor cells. Factors that contribute to recruitment and activation of inflammatory cells and the inflammatory response in atherosclerosis include oxidized lipids, cytokines such as macrophage colony-stimulating factor (M-CSF), increased angiotensin II activity, elevated arterial pressure, diabetes, obesity, insulin resistance, smoking, chronic infections remote from the arterial wall, possible infectious organisms in the vessel wall (Chlamydia pneumoniae, cytomegalovirus, etc.) and activation of the immune system with release of pro-inflammatory mediators such as interferon gamma, CD40-ligand etc. in response to antigens such as oxidized low-density lipoprotein (LDL), heat-shock proteins, beta glycoprotein and possibly others. In addition, a deficiency of natural anti-inflammatory molecules such as IL-10 and transforming growth factor beta may also promote plaque inflammation and an unstable plaque phenotype. Our laboratory has also identified a role for TLR-4 toll like receptor 4 and myeloid differentiation factor (MyD88)-mediated innate immune signaling in the pathogenesis of experimental atherosclerosis.

### Pathophysiologic Link between Plaque Inflammation and Plaque Rupture

The structural components of the fibrous cap include matrix molecules such as collagen, elastin and proteoglycans, derived from smooth muscle cells. The cap protects the deeper components of the plaque from contact with circulating blood, but thins out in the vicinity of rupture. Thinning of the fibrous cap is generally considered to be a prelude to rupture and is a sign of vulnerability. Fibrous caps from ruptured plaques contain less extracellular matrix (collagen and proteoglycans) and fewer smooth muscle cells than caps from intact plaques.

We and others have hypothesized that depletion of matrix components, specifically fibrillar collagens, from the fibrous cap due to an imbalance between synthesis and breakdown, leads to cap thinning. This predisposes the fibrous cap to rupture, either spontaneously or in response to hemodynamic or other triggers (Fig. 1). Enhanced matrix breakdown has been primarily attributed to a host of matrix-degrading metalloproteinases (MMPs) and other proteases such as cathepsins and tryptase/chymase that are expressed in atherosclerotic plaques by inflammatory cells (macrophages, foam cells, mast cells), and to a lesser extent, by smooth muscle cells and endothelial cells. These enzymes can degrade all components of the extracellular matrix and have been shown to be catalytically active both in vitro as well as in vivo. The activity of MMPs is tightly regulated at the level of gene transcription, and also by their secretion in an inactive zymogen form that requires extracellular activation and co-secretion of the tissue inhibitors of metalloproteinases (TIMPs). Thus, increased gene transcription, enhanced activation, and reduced activity of TIMPs can individually or together create an environment for increased matrix degradation.

All the components necessary for the activation of the MMP pathway exist in atherosclerotic plaques. Latent forms of MMPs can be activated by plasmin [produced by the plasminogen activator (uPA) from plasminogen by macrophages], trypsin, and chymase (derived from degranulating mast cells). Increased MMP production can be induced by oxidized lipids, reactive oxygen species, chlamydial heat shock protein (HSP), CD-40 ligation, inflammatory cytokines, tenasin-C derived from macrophages, and hemodynamic stress. In addition to MMPs, increased expression of cysteine and aspartate proteases of the cathepsin family, as well as reduced expression of their inhibitor, cystatin-C, in human atherosclerotic lesions, may also contribute to increased matrix breakdown in atherosclerosis.

In addition to matrix degradation, matrix depletion may also result from reduced synthesis due to a decrease in the number of smooth muscle cells or a reduction in their synthetic function. The activated T-cell-derived cytokine, interferon gamma, inhibits collagen gene expression in smooth muscle cells in vitro. This suggests that activated T-cells in the plaque may inhibit matrix synthesis by producing interferon-gamma. Several investigators have demonstrated increased smooth muscle cell death by apoptosis in human plaques, and several key players of the death-signaling pathway have been identified in atherosclerotic lesions. Other stimuli that may induce smooth muscle cell death in atherosclerosis include oxidized lipids and the epidermal growth factor (EGF)-like domain of macrophage-derived tenasin-C (normally cryptic, but exposed when MMPs cleave the intact tenasin-C molecule) and apo C1-enriched high-density lipoprotein (HDL).
Role of Plaque Inflammation in Thrombosis

Following plaque rupture, thrombosis is triggered when thrombogenic components of the plaque are exposed to circulating blood. Thrombogenic components include collagen and the lipid-core. The lipid-core tends to be the most thrombogenic part of the plaque in part due to direct platelet activating effects of oxidized lipids but in large measure due to lipid-core being impregnated with catalytically active tissue factor that activates the extrinsic clotting cascade leading to thrombin generation and thrombus formation at sites of plaque rupture.52,54,55 The major source of tissue factor in the lipid-core appears to be the apoptotic macrophage.106 Thus inflammatory cells mainly contribute to plaque thrombogenicity by providing a source of tissue factor. Lipid ingestion, exposure to oxidized lipids, cytokines such as CD 40 ligand and other proinflammatory stimuli activate macrophages to produce tissue factor.2 Apoptosis of endothelial cells, which has been shown to occur in response to hypochlorous acid produced through inflammatory cell-derived myeloperoxidase enzyme may also contribute to the thrombogenicity of atherosclerotic lesions.109,110

Insights from Experimental Models of Plaque Rupture

Despite numerous attempts, no convincing and consistently reproducible animal model of spontaneous atherosclerotic plaque rupture and thrombosis is currently available. In the past, investigators have injected catecholamines, lipopolysaccharide (LPS), and Russel’s viper venom to trigger thrombosis in rabbits with atherosclerosis, but such models bear little resemblance to human plaque rupture or thrombosis.111 In another rabbit model, Rekhter and colleagues112 used a balloon incorporated in the arterial wall to study the role of lipid accumulation and macrophage infiltration on vulnerability to rupture. However, this model also bears little resemblance to human disease.112 Similarly, endothelin injections in apo E null mice have been shown to trigger acute myocardial necrosis, but coronary plaque rupture and thrombosis were not the underlying mechanism.113 Recent research with apo E null mice revealed that there were frequent atherosclerotic lesions resembling vulnerable plaques in the innominate artery. Although intraplaque hemorrhage was observed, frank rupture and thrombosis were not demonstrated.114 Other investigators have described findings suggestive of plaque rupture and thrombosis in the innominate artery of genetic variations of apo E null mice that were fed a lard-based high-fat diet.115

Overexpression of MMP-1 has failed to produce plaque rupture in mice; paradoxical reduction in atherosclerosis was actually observed with MMP-1 overexpression, raising some questions about the role of MMPs as the critical mediator of plaque rupture.116 Recently, Calara et al.117 reported findings suggestive of plaque rupture and
thrombosis in apo E and LDL-receptor null mice, but the overall frequency was quite low. Von der Thusen and colleagues\textsuperscript{118} reported evidence of plaque rupture in murine models of atherosclerosis in response to vasopressor infusion when the pro-apoptotic gene p53 was overexpressed locally in carotid plaques. However, this model again suffers from the drawback that both p53 overexpression and pressor stimuli were required making it less of a model of spontaneous plaque rupture and thrombosis. Despite these limitations, search for a model of spontaneous plaque rupture and thrombosis continues.

Potential Role of Extrinsic Triggers in Plaque Rupture

Rupture of a vulnerable plaque may occur spontaneously without obvious triggers. However, in some cases plaque rupture may follow events, such as extreme physical activity (especially in someone unaccustomed to regular exercise), severe emotional trauma, sexual activity, exposure to illicit drugs (cocaine, marijuana, amphetamines), exposure to cold, or acute infection.\textsuperscript{119-127}

While plaque rupture often leads to thrombosis with the clinical manifestations of an acute coronary syndrome, it may also occur without clinical manifestations (silent plaque rupture). In approximately 40-80\% of cases of acute coronary syndrome, multiple plaque ruptures have been demonstrated in arterial segments remote from the acute culprit site.\textsuperscript{128} The thrombotic response to a plaque rupture is probably regulated by the thrombogenicity of the exposed plaque constituents, the local hemorrheology (determined by the severity of underlying stenosis), shear-induced platelet activation, and also by systemic thrombogenicity and fibrinolytic activity.\textsuperscript{2,4} Lipid-rich plaques may be more thrombogenic than fibrous plaques, probably because of the high content of tissue factor in the lipid core.\textsuperscript{5,5} The major source of tissue factor appears to be the macrophage. Apoptosis of macrophages may impregnate the lipid core with tissue factor-laden micro particles, making the lipid-core highly thrombogenic.\textsuperscript{53} Inflammatory cells, therefore, may be critical in influencing plaque thrombogenicity.

Recent studies in our laboratory have shown that plaques of smokers contain more tissue factor and inflammatory cells (macrophages) compared to non-smokers, perhaps contributing to the high thrombotic risk in smokers.\textsuperscript{129} Furthermore, coronary collaterals may also influence the clinical outcomes of acute coronary occlusion. Several investigators have suggested that organization and healing at the site of plaque rupture and thrombosis may eventually lead to rapid progression of plaque and worsening of stenosis, thereby providing a mechanism for atherosclerosis progression.\textsuperscript{130}

Plaque Erosion and Calcified Nodules

Coronary thrombi have been observed overlying atherosclerotic plaques in 20-40\% of cases, without rupture of the fibrous cap.\textsuperscript{2,4,13,132} Such thrombi occur over plaques with superficial endothelial erosion. These erosions are particularly common in young victims of sudden death, in smokers, and in women. Plaques under such thrombi do not have a large lipid-core, but rather a proteoglycan-rich matrix. The prevalence of inflammation is also lower than that in plaque rupture. The precise mechanisms of thrombosis in this scenario are unknown. It is conceivable that thrombosis in such cases is triggered by an enhanced systemic thrombogenic state (enhanced platelet aggregability, increased circulating tissue factor levels, depressed fibrinolytic state).\textsuperscript{2,4} Activated circulating leucocytes may transfer active tissue factor by shedding micro particles and transferring them onto adherent platelets.\textsuperscript{133,134} It is possible that these circulating sources of tissue factor (rather than plaque-derived tissue factor) contribute to thrombosis at sites of superficial endothelial denudation such as in plaque erosion. In addition, endothelial cell apoptosis may also increase local thrombogenicity accounting for both endothelial denudation and thrombosis in plaque erosion.\textsuperscript{109,110} Furthermore, severe deficiencies of antithrombotic molecules, thrombomodulin, and protein-c receptor, on advanced atherosclerotic lesions may also contribute to thrombosis.\textsuperscript{135} Erosion of a calcified nodule within an atherosclerotic plaque has also been reported as an uncommon cause of coronary thrombosis.

Implications for Plaque Stabilization Through Change in Plaque Phenotype

Many angiographic studies have shown that risk factor modification leads to reduced new lesion formation, less lesion progression, and in some cases, actual regression. However, these studies have also shown that the magnitude of vaso-occlusive clinical event reduction is far greater than that accounted for by the relatively small changes in stenosis severity. This apparent discrepancy has led to the hypothesis that risk factor modification (a) may induce plaque regression and reverse remodeling with little net change in stenosis severity, or (b) may not change plaque mass or stenosis severity, but might reduce the propensity for plaque rupture and thrombosis by changing the
composition of the plaque. The latter possibility is referred to as "plaque stabilization". Studies in animals have in fact shown that lowering lipids through diet, statin therapy, or direct administration of apo A-I and HDL-like particles can deplete lipids, reduce inflammation, sometimes reduce MMP and tissue factor levels, and increase the collagen content of atherosclerotic lesions. Thus, plaque composition change can be achieved in animal models.

Similarly, 3 months of therapy with pravastatin also favorably modifies human carotid plaque composition to a more stable phenotype, providing the first human data paralleling the results from animal models. It can be postulated, therefore, that reducing lipids and inflammation in atherosclerotic plaques may help lower the risk of plaque rupture and subsequent thrombosis. Also, such a plaque-stabilizing effect may account for the clinical benefits of risk factor modification by lifestyle changes and drug therapy [lipid-modifying drugs, angiotensin-converting (ACE) enzyme and angiotensin-II receptor blockers]. Future additional approaches may include direct administration of HDL and its apolipoproteins, and novel HDL-boosting compounds such as inhibitors of cholesterol ester transfer protein (CETP), orally effective apo A-I mimetic peptides, PPAR agonists and inhibitors of the endocannabinoid system such as rimonabant.

Conclusions
Atherosclerosis is a chronic immuno-inflammatory disease characterized by lipid and matrix deposition, neoangiogenesis, inflammation and immune activation, vessel wall remodeling and abnormal vasomotor regulation. Inflammatory/immune gene activation appears to be a common pathophysiological underpinning in the evolution and progression of atherosclerosis. The natural history of atherosclerotic vascular disease is characterized by episodes of plaque rupture and superficial endothelial erosion leading to thrombus formation, which is the proximate event responsible for acute ischemic syndromes. Considerable evidence implicates inflammation in the process of plaque rupture and subsequent thrombosis with multiple risk factors serving as potential pro-inflammatory triggers. Risk factor modification appears to reduce acute vaso-occlusive events primarily by changing the plaque phenotype from one that is vulnerable to rupture into the one that is less prone to rupture. This process of plaque stabilization represents a novel paradigm in atherosclerosis management.

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Third Heart Sound Revisited: A Correlation with N-Terminal Pro Brain Natriuretic Peptide and Echocardiography to Detect Left Ventricular Dysfunction

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Background: Auscultation of the third heart sound is an age-old sign for predicting ventricular dysfunction. New technology and biomarkers like two-dimensional echocardiography and N-terminal pro brain natriuretic peptide, respectively, have sidelined the utility of this sign, which does not involve any cost and is readily accessible. We sought to find the predictive accuracy of third heart sound and its correlation with N-terminal pro brain natriuretic peptide and ejection fraction using two-dimensional echocardiography to detect left ventricular dysfunction in patients of acute coronary syndrome.

Methods and Results: One hundred and ten patients presenting with acute coronary syndrome [acute ST elevation myocardial infarction (n=74) and non-ST elevation myocardial infarction (n=36)] were prospectively studied. A senior cardiologist, blinded to N-terminal pro brain natriuretic peptide and ejection fraction results auscultated for a left ventricular third heart sound in each patient. Ejection fraction was measured using modified Simpson’s technique on two-dimensional echocardiography and N-terminal pro brain natriuretic peptide was measured using electrochemiluminescence assay. Median levels of N-terminal pro brain natriuretic peptide were used to provide a dichotomous approach for analysis of the data. Third heart sound was present in 40 patients (acute ST elevation myocardial infarction: n=27, non-ST elevation myocardial infarction: n=13) and absent in 70 patients (acute ST elevation myocardial infarction: n=47, non-ST elevation myocardial infarction: n=23).

The sensitivity and specificity of third heart sound for predicting N-terminal pro brain natriuretic peptide above median was 65.5% and 92.7%, respectively. The positive and negative predictive value was 90% and 73%, respectively. The N-terminal pro brain natriuretic peptide of those having third heart sound was 4081±2705 pg/ml compared to 1239.3±1169 pg/ml in those without third heart sound (p<0.001). The sensitivity of third heart sound to detect ejection fraction < 45% was 67.9% while the specificity was 74.4%. The positive and the negative predictive values were 47.5% and 87.1%, respectively. The ejection fraction of patients having third heart sound was 47.5±11.3% compared to 56±10.4% without third heart sound (p<0.001).

Conclusions: Auscultation of third heart sound has a good specificity and predictive value for predicting elevated N-terminal pro brain natriuretic peptide and left ventricular dysfunction. Thus age-old clinical cardiology still holds its forte in this new era of technology-driven cardiology. (Indian Heart J 2005; 57: 31-34)

Key Words: Third heart sound, N-terminal pro brain natriuretic peptide, Left ventricular dysfunction

Auscultation of the third heart sound (S₃) is an age-old sign for predicting left ventricular (LV) dysfunction. For most of this century, the stethoscope has served as a critical diagnostic tool in cardiovascular evaluation. Most importantly there is no cost involved and it is readily accessible. The new technology and biomarkers like two-dimensional (2D) echocardiography and N-terminal pro brain natriuretic peptide (NT- ProBNP) respectively, have sidelined the utility of this physical sign as an indicator of LV dysfunction. S₃ is produced by the ‘sudden cessation of distention of the ventricle in early diastole’, as was first described by Potain in 1876. Abnormal S₃ is seen due to the limitation of the longitudinal expansion of LV from altered physical properties. It is heard 120-200 ms after A₂ and is a low frequency sound best heard in the left lateral position.
The S₃, when encountered in the older individual without primary valvular disease or disease states marked by high cardiac output, usually signifies reduced systolic function of one or both ventricles together with increased filling pressure within the affected chamber.² When encountered in this setting, this sound virtually ensures that the left ventricular ejection fraction (LVEF) is below 50%; moreover, it is regularly present when the ejection fraction (EF) drops below 30%.³ The presence of S₃ even when found in the setting of primary valvular disease, usually signals the presence of systolic dysfunction together with elevation of LV filling pressure.⁴ Imaging techniques that demonstrate ventricular enlargement and reduced systolic wall motion provide similar information, but the S₃ additionally signifies the presence of an abnormally high filling pressure, and thus decompensation of the involved ventricle.

Barriers to the widespread use of this clinical tool involve unfamiliarity with physical diagnosis and clinical skills. As more sophisticated laboratory tests become available, they have the potential to replace our clinical skills and there is a risk that those skills will subsequently deteriorate as was seen in some recent studies.⁷⁻⁸ NT-ProBNP and 2D echocardiography are standards to identify LV dysfunction but the simple auscultation of S₃ can reliably predict LV dysfunction and obviate the need for these expensive tests. Levels of NT-ProBNP also correlate with LV dilation, remodeling, dysfunction, and death among patients presenting with acute ST elevation myocardial infarction (STEMI).⁹ NT-ProBNP is a marker of LV dysfunction and has been established as a sensitive tool to diagnose heart failure.¹⁴⁻¹⁵ Therefore, we sought to find out the accuracy of S₃ to suitably predict LV dysfunction and see its correlation with NT-ProBNP and EF in a patient population of acute coronary syndrome (ACS).

Methods
We studied 110 patients admitted to our department presenting with a diagnosis of ACS which included acute STEMI (n=74) and non-ST elevation MI (NSTEMI) (n=36). These patients were prospectively studied and a senior cardiologist, blinded to NT-ProBNP and EF results auscultated for an LV S₃ in each patient. Blood was drawn in a fasting state within 8 hours of auscultation and assayed using the Elecsys ProBNP Electrochemi-luminiscence sandwich assay kit provided by Roche Diagnostics. The test is a 2 polyclonal antibody directed against NT-ProBNP, and has a measuring range of 5-35000 pg/ml. All patients were subjected to a detailed echocardiography and Doppler evaluation. Qualitative and quantitative assessment of segmental and global LV dysfunction was done in all patients with a Hewlett Packard Sonos 5500 machine and its calculation software. Patients were evaluated using modified Simpson's technique to calculate the EF. The study was cleared by the ethics committee of the university and conformed to the guidelines of good clinical practice which included getting an informed consent from the patients. SPSS 11.5 software was used for analysis of the data obtained. The student’s t test, Fisher’s exact test and Chi-square test were used to test the significance between the study groups. Risk analysis was carried out by calculating odds ratio (OR) and 95% confidence interval (CI).

Results
S₃ was present in 40 (36%) patients with more positives in STEMI group as compared to NSTEMI group [STEMI: n=27 (67%) v. NSTEMI: n=13 (33%)] and S₃ was absent in 70 patients (STEMI: n=47, NSTEMI: n=23). The median levels of NT-ProBNP (1525 pg/ml) were taken to provide a dichotomous analysis of the data; the levels were above median in 90% (36/40) of the patients having S₃ versus 27% (19/70) of those without S₃. The maximal sensitivity of S₃ to detect LV dysfunction, as defined with NT-ProBNP above median was 65.5% and the specificity was 92.7%. The positive predictive value was 90% while the negative predictive value was 73%. The mean NT-ProBNP of those having S₃ in the full cohort was 4081±2705 pg/ml versus 1239±1169 pg/ml in those without S₃ (p<0.001), with a Chi-square value of 40.23 (p<0.00001) and OR of 24.16 (95% CI 7.06-102.1). The presence of S₃ was also correlated with a low EF (<45%) and the maximal sensitivity of S₃ to detect EF below 45% was 67.9% while the specificity was 74.4%. The positive predictive value was 47.5% and the negative predictive value was 87.1%. The EF of patients in the cohort having S₃ was 47.5±11.3% versus 56.0 ± 10.4% in those without S₃ (p<0.001) with Chi-square value of 16.10 (p<0.001) and OR of 6.13 (CI 2.2-17.48) for the presence of S₃ to indicate LV dysfunction as correlated with low EF (Table 1).

When the two subgroups (i.e. STEMI and NSTEMI) were analyzed separately, in the STEMI cohort NT-ProBNP levels in patients with S₃ were 4436±2919 pg/ml versus 1554±1275 pg/ml in those without S₃ (p<0.001), while in the NSTEMI cohort NT-ProBNP with S₃ it was 3342±2110 pg/ml and 595±491 pg/ml in those without S₃ (p<0.001). No significant difference was seen in the NT-ProBNP levels if S₃ was present, depending on the type of MI i.e. STEMI or NSTEMI. In patients having S₃ along with STEMI, NT-ProBNP levels were 4436±2919 pg/ml while in NSTEMI with S₃ it was 3342±2110 pg/ml (p=0.25).
The correlation of S3, NT-ProBNP and low EF showed a positive correlation in the full cohort and in the STEMI subgroup but significant correlation was not seen in the NSTEMI subgroup. The presence of S3 was significantly more in patients having NT-ProBNP above median (1525 pg/ml) and EF <45%. Presence of S3 was significantly more in patients having NT-ProBNP above median (1525 pg/ml) and EF <45%.

However, a significant difference was seen between the groups with regards to the NT-ProBNP levels if S3 was absent (1554±1275 pg/ml in STEMI v. 595±491 pg/ml in NSTEMI (p=0.005). Similarly, when the EF was analyzed separately in the two subgroups, in the STEMI cohort EF in patients with S3, it was 47±11% versus 54±10% in those without S3 (p<0.001), while in the NSTEMI cohort EF with S3 was 49±11% versus 61±9.7% without S3 (p<0.01). Again, no significant difference was seen in EF depending on the type of MI, if S3 was present (p=0.60) while difference was significant when S3 was not present (p=0.02) (Table 2). The correlation of S3, NT-ProBNP and low EF showed a positive correlation in the full cohort and in the STEMI subgroup but significant correlation was not seen in the NSTEMI cohort presumably due to the small size of myocardial damage and lesser LV dysfunction (Table 3).

Table 1. Baseline characteristics with and without S3

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>S3 present</th>
<th>S3 absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-ProBNP above median (n)</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>ProBNP below median (n)</td>
<td>4</td>
<td>51</td>
</tr>
<tr>
<td>ProBNP (pg/ml) (mean±SD)</td>
<td>408±12705</td>
<td>1239±169</td>
</tr>
<tr>
<td>Ejection fraction &lt;45% (n)</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Ejection fraction ≥45% (n)</td>
<td>21</td>
<td>61</td>
</tr>
</tbody>
</table>

Ejection fraction (%), mean±SD: STEMI: 47±11 vs NSTEMI: 56±10.44 p<0.001*

*Statistically significant; S3: third heart sound

Table 2. Comparison of NT-ProBNP and EF in the presence and absence of S3 in STEMI and NSTEMI subgroups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>STEMI S3+ (n=27)</th>
<th>NSTEMI S3+ (n=23)</th>
<th>p-value</th>
<th>STEMI S3- (n=47)</th>
<th>NSTEMI S3- (n=23)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-ProBNP (pg/ml) (mean±SD)</td>
<td>4436±2391</td>
<td>3342±2110</td>
<td>0.25</td>
<td>1554±1275</td>
<td>595±491</td>
<td>0.005</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>47±11</td>
<td>49±11</td>
<td>0.60</td>
<td>54±10</td>
<td>61±9.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Statistically significant

A significant difference was seen in the NT-ProBNP levels and EF in the type of MI, if S3 was absent.

Table 3. Correlation of S3 with NT-ProBNP depending on the type of MI

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>R</th>
<th>T</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cohort S3+ (n=40)</td>
<td>-0.42</td>
<td>2.85</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Full cohort S3- (n=70)</td>
<td>-0.46</td>
<td>4.30</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>STEMI S3+ (n=27)</td>
<td>-0.46</td>
<td>2.85</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>STEMI S3- (n=47)</td>
<td>-0.46</td>
<td>2.85</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NSTEMI S3+ (n=13)</td>
<td>-0.30</td>
<td>1.04</td>
<td>0.30</td>
</tr>
<tr>
<td>NSTEMI S3- (n=23)</td>
<td>-0.32</td>
<td>1.55</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Statistically significant

Correlation seen between NT-ProBNP and ejection fraction in larger infarcts and in the full ACS cohort.

Discussion

The presence of LV dysfunction is the most important prognostic factor in assessing risk in patients with ACS. In the present practice LV functions, as measured by 2D echocardiography and more recently NT-ProBNP, have assumed importance as gold standards both for detecting LV dysfunction and for prognosticating in ACS. Not long ago, S3 was a clinical sign that was considered a reliable indicator of LV dysfunction and an adverse prognostic index in ACS. Of late, interest in this clinical sign seems to have diminished and the skills needed to identify it also seem to be declining. The common belief associated with S3 is that it is abnormal beyond 40 years of age and is recognized by the ‘company it keeps’. As a matter of fact it is produced by the decreased rate of filling into ventricle along with the ventricle having a large end-systolic volume; it may also be produced by the dynamic impact of LV to chest wall in these patients. More importantly the presence of S3 in AMI reflects severe LV dysfunction and also predicts a higher mortality. In recent time the data regarding BNP/NT-ProBNP is accumulating rapidly and its usefulness is being reiterated. BNP is a marker of high LV end-diastolic pressure in symptomatic patients of LV dysfunction and its usefulness in the diagnosis of heart failure in an urgent care setting has been established.

Recenty data is emerging on the role of NT-ProBNP in risk stratification of patients of ACS. Its value in predicting both short- and long-term poor outcome, including LV dysfunction and mortality has been shown by a recent meta analysis by Galvani et al. Packer has raised doubts regarding the usefulness of BNP and the decisonal cut off levels required to diagnose heart failure, but data continues to pour in with a number of studies favoring the role of BNP/NT-ProBNP in diagnosing and guiding therapy. Cleland and Goode stated that natriuretic peptides have evolved from being fashionable to useful, to being necessary now. Although clinical judgment, along with the utility of S3, is supreme but in this era of evidence-based medicine it would be prudent to quantify the same if possible, specially to root out the alarming decline in clinical skills as was reported by Magione and Nieman. Study by Marcus et al. also brought out the usefulness of the S3 in predicting an elevated level of BNP. They studied a heterogeneous group of 100 consecutive adult outpatients presenting to a general cardiology clinic prospectively and measured BNP levels within 8 hours. They concluded that mean BNP levels were significantly higher in patients with an S3. The presence of S3 was 41% sensitive and 97% specific for elevated BNP levels.

In our study this clinical sign was associated with
significantly higher mean levels of NT-proBNP in the presence of an auscultable $S_3$ (4081±2705 pg/ml v. 1239±1169 pg/ml, p<0.001) irrespective of whether the patient had STEMI or NSTEMI. Using a cutoff median value 1532 pg/ml, the correlation of $S_3$ to predict NT-ProBNP above median in patients of ACS had a sensitivity of 65.5% and specificity of 92.7%. The positive and negative predictive values were 90% and 73% respectively for $S_3$ to indicate high NT-ProBNP. This in turn suggests LV dysfunction along with poorer adverse outcomes and need for more attention while using 2D echocardiography.

This strengthens our view that the presence of $S_3$ in STEMI, as the presence of this cost-free test does away with the need for expensive investigations which may not be universally available. If $S_3$ is absent and the patient has NSTEMI, one can safely rule out LV dysfunction, and expect a good prognosis. In case of an STEMI however, if $S_3$ is absent, NT-ProBNP may need to be measured and is specifically looked whether the patient has NSTEMI or STEMI, as the presence of this cost-free test does away with the need for expensive investigations which may not be universally available. If $S_3$ is absent and the patient has NSTEMI, one can safely rule out LV dysfunction, and expect a good prognosis. In case of an STEMI however, if $S_3$ is absent, NT-ProBNP may need to be measured and is specifically looked whether the patient has NSTEMI or STEMI.

ACS ranges from unstable angina to a small non-transmural MI to a large transmural MI with NT-ProBNP levels rising in a continuum depending on the size of the infarct and degree of LV dysfunction. $S_3$ appears at a point somewhere along the curve where LV dysfunction is hemodynamically significant. By this time NT-ProBNP levels are also significantly high. Our findings suggest that $S_3$ must be meticulously looked whether the patient has NSTEMI or STEMI, as the presence of this cost-free test does away with the need for expensive investigations which may not be universally available. If $S_3$ is absent and the patient has NSTEMI, one can safely rule out LV dysfunction, and expect a good prognosis. In case of an STEMI however, if $S_3$ is absent, NT-ProBNP may need to be measured and is specifically looked whether the patient has NSTEMI or STEMI.

**Conclusions:** Auscultation of the third heart sound has good specificity and predictive values for predicting LV dysfunction, and correlates suitably with expensive tests such as NT-ProBNP levels and 2D echocardiography. Thus, the age-old clinical cardiology still holds its forte in this new era of technology-driven cardiology.

**References**

Natural History of Secundum Atrial Septal Defect Revisited in the Era of Transcatheter Closure

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Background: Several reports in the past have described the natural history of atrial septal defects, most dealing with a decrease in size or spontaneous closure of the defect. Some recent articles have also described an increase in size of the defect in a sizable number of cases which may be important in the current era of transcatheter closure. We analyzed the data of 52 consecutive cases diagnosed to have secundum atrial septal defect in the first year of life, seen over the last six years at our center.

Methods and Results: All infants with a defect size of ≥4 mm on echocardiography were included. The first and the last echocardiographic images with a minimum interval of 6 months were used for analysis. Cases were divided into three groups depending upon the defect diameter (small: 4-5 mm, moderate: 6-8 mm and large: ≥ 9 mm). The age ranged from one day to 12 months (mean 2.9±3.2 months). On a follow-up of 0.7 to 7.0 years (mean 2.9±1.4 years), the septal defect reduced in size in 24 (46%) cases with complete closure in 14 of these. The size remained same in 13 (25%) and enlarged in 15 (29%) cases. The likelihood of closure was highest in small defect group as compared to the large defect group (p<0.05). Similarly, enlargement was more often seen in large defects.

Conclusions: Small atrial septal defects of 4 mm to 5 mm are very likely to decrease in size or completely close on follow-up. Larger defects, on the other hand may remain large or enlarge further in a significant proportion of cases. A close observation is required for these cases if being considered for transcatheter closure. (Indian Heart J 2005; 57: 35–38)

Key Words: Atrial septal defect, Echocardiography, Natural history

Atrial septal defect (ASD) is a relatively benign congenital cardiac defect, rarely producing symptoms or congestive heart failure in infancy and childhood. Spontaneous closure of ASD has been well described in literature. The rates of spontaneous closure have varied from 3% to 67% in literature.1-5 This wide range is perhaps related to (i) the age at presentation, as closure is more likely when an ASD is diagnosed in the first year of life2,3 and (ii) the size of the ASD at diagnosis, as spontaneous closure is more likely when the defect is small.6,7 Spontaneous closure of ASD is less likely after the age of two years, but in small sized defects (<6 mm) it is seen in up to 40% of cases after the age of five years.7 In view of spontaneous reduction in the size of ASD, it is generally recommended to wait till 2 or 3 years of age, before undertaking surgical or device closure in an asymptomatic child.8

The issue of natural history is being revisited due to the widespread use of non-surgical, transcatheter techniques for closure of ASD. Most natural history studies in the past have described the spontaneous decrease in size or complete closure of ASD while increase in size being seen in only a small proportion of cases.6,7,9 However, there are few recent articles where enlargement of the defect has been demonstrated in a significant percentage of cases, in some making them unsuitable for device closure.10,11 The purpose of our study was to analyze the retrospective data of cases with isolated secundum ASD seen over the last six years at our centre.

Methods

Records of all children diagnosed to have an isolated secundum ASD in the first year of life between 1997 and 2003 were taken for analysis. The diagnosis was based on echocardiography and only those cases with a defect diameter of ≥ 4 mm, showing left-to-right shunt and

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associated with volume overload of the right ventricle were included. Although several serial echocardiograms were performed in many patients, only the first and the last echocardiograms were used for analysis. Cases with an interval of <6 months between first and last echocardiograms were not included in the study. In cases where ASD was closed by surgery or device, the last pre-operative echocardiographic image was used for analysis.

There were a total of 62 cases identified as having an isolated secundum ASD in our database. Ten cases were excluded for the following reasons: first seen beyond one year of age, <6 months interval between first and last echocardiogram or echocardiographic images were suboptimal for analysis. Those with multiple defects in atrial septum or having aneurysm of the fossa ovalis region interfering with correct sizing of the defect were also excluded.

The remaining 52 cases were included in the study. ASD size was measured in subcostal long and short axis views on the cross sectional image and the largest diameter was noted. Presence of a T sign (thickening of edges of defect) helped in correct measurement in most cases. Color flow imaging was used to document left-to-right flow across the ASD, but no measurements were made based on color flow due to risk of overestimation of size. Right ventricular volume overload of varying degree was present in all cases on initial echocardiography.

The patients were classified according to the size of the defect as seen on first echocardiogram: (i) patients with small defect (ASD diameter 4-5 mm), (ii) patients with moderate defect (ASD diameter 6-8 mm) and, (iii) patients with large defect (ASD diameter ≥9 mm).

**Follow-up echocardiography:** Depending on the size of the defect on last echocardiogram, the final defects were classified into: (i) Closed: no defect seen either on cross sectional imaging or on color Doppler along with normal right heart size, (ii) Reduced: a reduction in size by >2 mm from the initial size, (iii) Same: an increase or decrease in size by ≤2 mm from the initial size, (iv) Enlarged: An increase in size by >2 mm.

A note was also made of surgical or device closure during the follow-up period. An ASD size of ≥20 mm was considered as possibly unsuitable for device closure in a child with the currently available devices.

**Results**

**General characteristics:** A total of 52 cases were eligible for inclusion in the study. Thirty-three were females and 19 were males giving a female to male ratio of 1.7. Their age ranged from one day to 12 months with a mean of 2.9 ±3.2 months. The interval between first and last echocardiography ranged from 0.7 years to 7 years, with a mean of 2.9±1.4 years.

In 21 (40%) patients, the ASD was considered as small (size 4-5 mm), in 15 (29%) it was moderate (6-8 mm) and in 16 (31%) cases it was a large defect (>9 mm).

Fig. 1 shows the follow-up results for the whole cohort. Of the total 52 cases, the size of ASD decreased in 24 (46%) cases, completely closing in 14 (27%). In 13 (25%) children, the size did not change significantly (initial size 7.0±2.16 mm, final size 6.46±2.50 mm). The size of ASD increased significantly in 15 (29%) cases from 9.13±4.50 mm to 15.53±4.76 mm (p<0.005).

**Relation to initial ASD size** (Fig. 2): Analysis in the various subgroups according to the initial ASD size revealed a high chance of spontaneous closure in the small defect group. Ten of 21 (48%) closed in the small defect group as compared to 3 of 15 (20%) in moderate and only one of 16 (6%) patients in large ASD group (p<0.01 for small v. large ASD group). Larger defects had a higher potential to enlarge with time (7 of 16), although some small defects also enlarged (4 of 21).

**Age at diagnosis:** All the cases included in the study were
<1 year of age. Age at diagnosis also influenced the chances of spontaneous closure of ASD. Complete closure was seen in 8 of 24 cases (33.3%), when diagnosis was made in first month of life. There were only three complete closures when the ASD was diagnosed beyond three months of life (3 of 17, 17.6%). However, this difference was not statistically significant. Chances of enlargement of ASD were not related to the age at diagnosis (8 of 24 diagnosed in first month vs. 6 of 17 diagnosed beyond 3 months).

**Enlargement of ASD:** ASD enlarged in 15 cases, it was small to begin with in 4 of these, moderate in 4 and large-sized in the rest of 7 patients. In 5 of these 15 cases, the ASD size increased to ≥20 mm. None of these 5 cases had a small or moderate defect to begin with; the initial ASD size was large, being ≥13 mm in all. One of these five cases also developed mitral regurgitation secondary to mitral valve prolapse.

A total of 13 patients underwent closure of ASD, only two of these had a small defect initially. The closure was done by device in 4 cases and by surgery in 9.

**Discussion**

Although ASD is the second most common congenital heart disease in children, there are still few unanswered questions related to the appropriate timing and the preferable technique for closure. Since patients with even large ASDs are mostly asymptomatic, closure is recommended around 3 to 5 years of age, before the child goes to school. Postponing surgery to this age also allows for spontaneous closure of ASD in some children. Delaying surgery to the teenage years or beyond may be harmful as shown in the study by Murphy et al.

With the availability of transcatheter device closure, the ideal method of ASD closure has also become an issue of discussion in several studies. Since the first transcatheter ASD closure by Mills and King in 1976, device closure is becoming more popular and several modifications of these devices have taken place. Device closure has the advantage of being non-surgical thereby obviating the need for sternotomy. The results are comparable to surgery as regards success rate, morbidity and complications. The reduced duration of hospitalization is an added benefit of device closure. However, with the currently available devices, large defects and those with inadequate rims surrounding the defect cannot be closed. Hence the recent data showing an enlargement of ASD over a period of time in a significant number of cases, rendering them unsuitable for device closure is a matter of concern.

Such data may prompt interventional cardiologists to close ASD in smaller children so as not to miss the window of opportunity. The complication rate of device closure in very small children is likely to be higher.

We analyzed the change in defect size in 52 children over a follow-up of 0.7 to 7 years. The ASD size decreased in 24 with complete closure in 14. It remained the same in 13 and in 15 (29%) cases, the ASD size increased. In the study by McMahon et al., an increment in diameter was seen in a much higher number of cases (68 of 104 cases, 68%). According to these authors, the growth of ASD over time may be related to the increased blood flow through the defect along with an intrinsically compliant nature of the atrial septum. In their series, ASD enlarged to ≥20 mm in 13 (12%) cases. In our data, ASD enlarged to that size in 5 of 52 (9.6%) cases. These cases may be considered unsuitable for device closure at young age with the currently available devices.

**Effect of initial size of ASD on natural history:** In the study by McMahon et al., ASD increased from an initial size of 3-6 mm in 17 of 34 (50%) cases, becoming ≥12 mm in 3 cases. In one case it increased from 3 mm to 20 mm on follow-up. The spontaneous closure was seen in only 3 (9%) cases in the small ASD group. This is in contrast to our findings where ASD decreased from an initial size of 4-6 mm in 13 of 26 (50%) cases, completely closing in 12. The size increased in only 6 (23%) and remained the same in 7 (27%). An increase to ≥12 mm was seen in only 3 cases.

In our study, spontaneous closure also occurred in a significant percentage of cases (14 of 52, 27%). The smaller ASDs were more likely to close over a period of time. Of ASDs with initial diameter of ≤5 mm, 10 of 21 (48%) closed, whereas only one of 16 ASDs with initial diameter of ≥9 mm closed completely. In the study by McMahon et al., only 4% of ASDs closed spontaneously. Of these 4 cases had initial diameter of ≤5 mm.

In the study by Helgason and Jonsdottir, 89% of ASDs with diameter of 4 mm either closed or decreased in size. In only 2 (6%), the ASD size increased. The reduction in size and spontaneous closure was also more common in ASD measuring 5 to 6 mm (93% of cases). In only one case did the ASD enlarge. However, in their group of ASD measuring ≥8 mm in diameter, none closed spontaneously; although 2 (8%) decreased in size; 24 of their 26 cases with large ASD (92%) had either an increase in size or and it was closed surgically. So in their study, the probability of ASD closure was very high in small and moderate defects (≤6 mm), but very low for large defects (≥8 mm). According to Radzik et al., also, defects of ≥8 mm have little chance of spontaneous closure even when first diagnosed within 3 months of life. Similar observations were made.
from our data. In our study only 2 of 21 (95%) cases needed surgical closure in the small ASD group where defect diameter was 4 to 5 mm, whereas 8 of 16 (50%) cases underwent device or surgical closure in the large ASD group with diameter of ≥9 mm. The bigger defects either remained the same or further increased in size in 12 of 16 cases. Hence the initial size of the ASD may be predictive of the natural history to some extent.

The causes of spontaneous closure as described in literature are: growth of the heart stretching the edges of an ellipsoid defect, thus bringing the edges together, continuous growth of the septum secundum after birth or sepal aneurysm formation.

Limitations: As our study was retrospective, it had all its associated disadvantages. Secondly, the ASD size as measured on echocardiogram might not be quite accurate as often the defect is ellipsoid. We chose the largest diameter in two subcostal views, although even this may change during the different phases of cardiac cycle.

Conclusions: The secundum ASDs with defect size of 5 mm or less are very likely to further decrease in size or close completely over a period of time and may be followed every mm or less are very likely to further decrease in size or close completely over a period of time and may be followed every

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Serum Leptin Levels in Acute Myocardial Infarction

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Background: Several studies have shown an association of serum leptin levels with cardiovascular diseases. The present study was undertaken to assess levels of serum leptin in patients presenting with acute ST segment elevation myocardial infarction.

Methods and Results: Ninety-four consecutive patients presenting with acute ST segment elevation myocardial infarction were studied and 46 controls were taken from patients who presented with chest pain but had no history of myocardial infarction in the past. There were 59 patients with anterior wall infarction and 31 had inferior wall infarction and in 4 it was a combination of anterior and inferior wall infarction. The serum leptin levels in patients with myocardial infarction was 6.51±6.76 ng/ml versus 2.86±2.22 ng/ml in controls. In the multivariate analysis the odds ratio for serum leptin with myocardial infarction was 1.45 with a 95% confidence interval of 1.2 to 1.8.

Conclusions: Our results suggest that serum leptin level is elevated in patients with acute ST segment elevation myocardial infarction.

Key Words: Serum leptin, Acute myocardial infarction, Risk factors

Leptin is a 167 amino acid peptide secreted from the adipocytes into the circulation and communicates the peripheral nutritional status to specific hypothalamic centers. Related to the amount of body fat, leptin is also associated with increased heart rate, blood pressure and sympathetic nervous activity and contributes to platelet aggregation. Several recent studies have suggested that serum leptin can be an independent risk factor for cardiovascular diseases. Wallace et al. demonstrated that higher plasma leptin concentration in hypercholesterolemic men was associated with increased risk of a future coronary event. They have shown in a large prospective study that plasma leptin is a novel, independent risk factor for coronary events. Soderberg et al. documented that the elevated plasma leptin levels strongly predict first acute myocardial infarction (AMI) in men. Barouch et al. identified a novel direct link between serum leptin level and cardiovascular structural remodeling.

The aim of the present study was to examine the role of serum leptin in patients with AMI and in a group of patients presenting with chest pain.

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the solution in the wells was aspirated and washed four times with the wash solution provided. The final color development step was addition of 100 µl of chromogenic solution followed by incubation for 30 min at room temperature in dark in a rack shaker set at 700 rpm. The reaction was stopped by addition of 200 µl of stop reagent to each well and the absorbance was measured at 450 nm using Bio-Rad microplate reader.

**Statistical methods:** The results were expressed in terms of mean ± standard deviation. The statistical significance of difference between the means was evaluated by the student’s t test for normal data and Mann-Whitney U test for non-normal continuous data. The multivariate analysis was done using logistic regression; SPSS 11.0 software was used for the analysis purpose.

**Results**

A total of 140 subjects were studied. Group I consisted of 94 patients with STEMI. In Group II, 46 control subjects were included. The baseline characteristics of the patients and controls are shown in Table 1. Hypertension was slightly higher in the controls with a borderline statistical significance. Incidence of diabetes and BMI was not found to be statistically significantly different between cases and controls.

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) (years)</td>
<td>52.7±10.2</td>
<td>52.5±9.2</td>
<td>0.92</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76</td>
<td>41</td>
<td>0.21</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (33.0)</td>
<td>23 (50.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30 (31.9)</td>
<td>15 (32.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>2 (2.1)</td>
<td>2 (4.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3±4.1</td>
<td>24.3±3.2</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Values in parenthesis are percentages
IHD: ischemic heart disease; BMI: body mass index

Of the 94 patients with STEMI, 59 had anterior wall infarction, 31 had inferior wall infarction and in 4 it was a combination of anterior and inferior infarction. Seventeen (36.95%) patients in the control arm were subsequently found to have CAD. Six had single vessel disease, 9 had double vessel disease and 2 had triple vessel disease. The bio-chemical values are summarized in Table 2. Leptin levels were significantly higher in patients than in controls (6.51±6.76 v. 2.86±2.22 ng/ml).

In the multivariate analysis smoking was found to be a significant risk factor in patients with AMI. Incidence of diabetes, serum lipids and BMI was not found to be statistically different between cases and controls in both univariate and multivariate analysis. In addition, serum leptin level had an odds ratio (OR) of 1.45 for myocardial infarction, with a 95% confidence interval (CI) of 1.2 to 1.8 which was statistically significant (Table 3). We used several cut off values to find out a level at which it may be important. As shown in Table 4, none of the controls had values of serum leptin ≥ 8 ng/ml.

**Table 2. Comparison of biochemical values between patients and controls**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg%)</td>
<td>183.23 ± 46.02</td>
<td>178.09 ± 45.70</td>
<td>0.53</td>
</tr>
<tr>
<td>LDL (mg%)</td>
<td>105.38 ± 35.90</td>
<td>107.87 ± 41.32</td>
<td>0.71</td>
</tr>
<tr>
<td>Triglycerides (mg%)</td>
<td>167.04 ± 100.85</td>
<td>163.93 ± 110.23</td>
<td>0.87</td>
</tr>
<tr>
<td>HDL (mg%)</td>
<td>43.34 ± 14.94</td>
<td>41.65 ± 16.39</td>
<td>0.54</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>6.51 ± 6.76</td>
<td>2.86 ± 2.22</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Values in parenthesis are percentages
LDL: low-density lipoprotein; HDL: high-density lipoprotein

**Table 3. Results of multivariate analysis**

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>Confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.948</td>
<td>0.836 - 1.076</td>
<td>0.410</td>
</tr>
<tr>
<td>HR</td>
<td>1.065</td>
<td>1.024 - 1.108</td>
<td>0.002*</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.041</td>
<td>0.967 - 1.120</td>
<td>0.284</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.990</td>
<td>0.981 - 1.000</td>
<td>0.489</td>
</tr>
<tr>
<td>LDL</td>
<td>0.959</td>
<td>0.890 - 1.033</td>
<td>0.273</td>
</tr>
<tr>
<td>HDL</td>
<td>0.958</td>
<td>0.888 - 1.035</td>
<td>0.277</td>
</tr>
<tr>
<td>Serum leptin</td>
<td>1.484</td>
<td>1.390 - 1.650</td>
<td>-</td>
</tr>
<tr>
<td>Smoking</td>
<td>3.051</td>
<td>1.179 - 7.896</td>
<td>0.021*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.328</td>
<td>0.134 - 0.807</td>
<td>0.015*</td>
</tr>
</tbody>
</table>

* Statistically significant; insignificant variables were excluded stepwise.
BMI: body mass index; HR: heart rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein

**Table 4. Serum leptin levels**

<table>
<thead>
<tr>
<th>ng/ml</th>
<th>Patients (n=94)</th>
<th>Controls (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>41 (43.61)</td>
<td>36 (78.26)</td>
</tr>
<tr>
<td>4-7</td>
<td>36 (38.29)</td>
<td>10 (21.73)</td>
</tr>
<tr>
<td>8-12</td>
<td>5 (5.31)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>12 (12.76)</td>
<td>-</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

**Discussion**

In our study, serum leptin levels were significantly elevated in patients with STEMI. This is the first report from India to show that serum leptin levels are higher in patients with acute STEMI. Meisel et al. demonstrated that there was an increase in serum leptin level within 48 hours of myocardial infarction. According to their results, leptin level declined from day 3 onward and reached almost the
baseline by day 5 following myocardial infarction. Fujimaki et al. studied leptin levels in 21 patients with AMI and in 15 age-matched controls. They found a significant negative correlation between serum leptin and interleukin-6 levels. Tamer et al. from Turkey reported that in a group of 30 patients with myocardial infarction, leptin levels were significantly higher in patients than in 15 healthy controls. Despite small sample size, serum leptin level appeared to convey higher OR for myocardial infarction in our study. In a nested case reference study from Sweden, Soderberg et al. found that 62 men with first myocardial infarction had higher BMI, plasma insulin, serum leptin and diastolic blood pressure (BP) than the reference. High leptin levels had higher BMI, plasma insulin, serum leptin and diastolic blood pressure (BP) than the reference. High leptin levels (OR 8.97; 95% CI: 1.73-46.5) remained a significant risk factor for AMI in a multivariate model.

Stejskal et al. examined 48 probands who were hospitalized for acute coronary syndrome. The persons with AMI had leptinemia and a higher concentration of interleukin-6. No correlation was found between leptinemia and body weight in this study. Fujimaki et al. measured serum leptin level in 21 patients with AMI and 15 age-matched controls and found a significant negative correlation between the peak concentration of serum leptin and interleukin-6.

The lack of significant difference in lipid values between cases and controls in our study may be a type 2 error due to small sample size.

Interrelationship of inflammation and leptin:
Adipose tissue is the source of circulating leptin, C-reactive protein (CRP) is synthesized by the liver, largely under the regulation of the proinflammatory cytokines, primarily interleukin-6. Other proinflammatory cytokines such as interleukin-1 and tumor necrosis factor-α (TNF-α) may contribute to hepatic synthesis of CRP. Adipocytes are important sources of circulating interleukin-6 and express TNF-α. Hence, adipocytes, by serving as a common source for both leptin and inflammatory cytokines contribute to CRP synthesis, which may explain in part the interaction between CRP levels and leptin. Moreover, interleukin-1, interleukin-6 and TNF-α, which contribute to increase in CRP, may act directly on fat cells to increase leptin secretion in settings of acute inflammation, further supporting adipose tissue as a potential common pathway contributing to the leptin-CRP interaction.

There are several reasons for serum leptin to increase the cardiovascular risk. The leptin (i) stimulates vascular smooth muscle cell proliferation (ii) accelerates vascular calcification (iii) induces oxidative stress in endothelial cells that may contribute to atherogenesis (iv) promotes coagulation by increasing platelet adhesiveness.

CRP promotes secretion of inflammatory mediators by vascular endothelium, increases cell adhesion molecule expression, opsonizes low-density lipoprotein (LDL) for uptake by macrophages in atherosclerotic plaque, decreases endothelial nitric oxide synthase expression and activity, and activates vascular smooth muscle cells. The association between serum leptin and CRP provide evidence that they are the metabolic and inflammatory mediators of cardiovascular disease processes.

Link between leptin, obesity, diabetes and cardiovascular risk: Under physiological condition the amount of leptin produced by fat tissues is directly related to the mass of adipose tissues. Both leptin deficiency (ob/ob mice) and leptin resistance (db/db mice having a defective leptin receptor) lead to hyperphagia and decreased energy expenditure in the host. Predictably, this leads to obesity, the insulin resistance type of diabetes, and a decrease in lean body mass. Correction of leptin deficiency in the ob/ob mouse causes a marked reduction in food intake and a normalization of its weight.

The biological actions of leptin are mediated largely through interactions with its cognate receptor expressed in the hypothalamus. Subsequent studies demonstrated that leptin receptors (OB-R) have a widespread tissue distribution including liver, kidney, lungs, pancreas, and heart. This predicts that leptin will have a wide-ranging influence on metabolism and possibly also cardiac structure and function.

In contrast to primary leptin deficiency observed in the ob/ob mouse, in the clinical setting, the most common leptin abnormality in patients is "receptor insensitivity," leading to secondary circulating leptin excess and peripheral leptin resistance. In the commonest clinical settings of leptin resistance or leptin receptor insensitivity, there is also concurrent insulin resistance or insulin receptor insensitivity. This insulin-resistant state is well recognized in obesity, hypertension, heart failure and after myocardial infarction. In these settings, circulating leptin levels are elevated, and in fact the serum leptin level is an independent predictor for cardiovascular morbidity and mortality in these conditions. Furthermore, fasting plasma leptin levels are associated with increased myocardial wall thickness, independent of body weight composition and blood pressure levels.

Barouch et al. have found that leptin deficiency in the ob/ob mice in fact led to ventricular hypertrophy. The degree of hypertrophy is independent of body mass. Most
interestingly, exogenous administration of leptin in this primary leptin deficiency model reduces the ventricular hypertrophy very quickly. This suggests that the leptin receptors, which are present in the myocardium, may also have a primary remodeling effect. In current era, excessive caloric intake, what was designed originally to prevent us from starvation now comes back to haunt us as the body secondarily tries to protect us from caloric excess. Therefore, the solution for the left ventricular hypertrophy and remodeling in obesity is not necessarily through leptin infusion, rather the more appropriate strategy will be to correct the original abnormalities that led to the receptor downregulation and insensitivity. This involves weight reduction, caloric restriction, restoration of metabolic receptor sensitivity, and reversal of many of the abnormalities that triggered the body to develop these secondary defensive maladaptations.

Limitations of the study: In our study we did not include subjects without chest pain. Therefore, our results are likely to underestimate the level of serum leptin in the given population. If controls were selected from normal subjects it is likely that the leptin levels in them may have been lower and there could have been a wide difference. Secondly, we did not assess the role of inflammatory markers such as high sensitivity C-reactive protein and its possible role along with leptin in this subgroup of patients. Hence a larger study inclusive of an inflammatory marker will provide further insight in this subject.

Conclusions: Our observations strongly suggest that serum leptin levels are elevated in acute STEMI. Thus serum leptin may be an important metabolic factor during acute myocardial infarction and it could possibly be a risk factor.

Acknowledgements

We would like to specially thank Ms. Nithya, department of Biostatistics for her statistical help in this study.

References

Post-Operative Outcome of Ventricular Reshaping by Septal Exclusion in Patients with Severe Left Ventricular Dysfunction

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Original Article

The goal of surgical treatment in patients of coronary artery disease (CAD) should not only be prevention of ongoing ischemia, but also to alleviate the deleterious effects of previous infarctions on the ventricular structure and function.

Although different techniques have been employed by various surgeons, their goal has been to achieve total myocardial revascularization and at the same time resect all the non-functional scarred area in order to restore the original ventricular geometry as far as possible. Since February 2003, we started performing the technique of septal exclusion in patients with anteroseptal myocardial infarction (MI) to restore the ventricular geometry and thereafter follow up its clinical and morphological outcome in the patients.

Methods

Between February 2003 and December 2003, 30 consecutive patients underwent septal reshaping with a septoapical dacron patch using a septal anterior wall linear suture. Of the 30 patients, 22 had an associated large left ventricular (LV) aneurysm which was managed using the Dor technique. Nine patients had associated LV apical clot which was removed intraoperatively. In 3 patients, preoperatively diagnosed grade III/IV ischemic, functional mitral regurgitation (MR) was repaired by posterior felt annuloplasty. These patients had isolated annular dilation with normal valve leaflets and subvalvular apparatus. Twenty-six patients were males with mean age of 63.3±0.8 years. The mean LV ejection fraction (LVEF) was 32.6±4.2% (15-35%). The pre-operative characteristics are shown in Table 1. Twenty-one patients had chronic stable angina while 9 patients had ongoing unstable angina not responding to medical treatment. Five patients had recent MI of less than one month duration. Six patients were in congestive heart failure. Seven patients had grade II/III MR of which only 3 patients required mitral valve repair by posterior felt annuloplasty. An echocardiographically demonstrable akinetic scar was present in all patients (Fig. 1). All patients were on beta-blockers, angiotensin-
converting enzyme (ACE) inhibitors and diuretics prior to surgery. In all, 6 patients required intraaortic balloon pump (IABP). In 2 patients, IABP was inserted pre-operatively for unstable angina and hypotension and in 4 patients it was put intra-operatively, post-anesthesia induction in view of high pulmonary artery (PA) pressure and low ejection fraction (<30%). Dobutamine stress echocardiography or a stress thallium was done only in the stable patients pre-operatively to assess the degree of viability. It was not done in the 9 patients who were unstable with ongoing angina. Holter monitoring was performed for all patients to rule out any form of arrhythmias pre-operatively and if present, they were put on appropriate antiarrhythmic treatment prior to surgery.

**Surgical technique:** With the patient on normothermic cardiopulmonary bypass (CPB), with both antegrade cardioplegic arrest and retrograde cardioplegia maintenance, the heart is first inspected carefully for the akinetic or dyskinetic area. This is further confirmed by palpation which reveals a thinned out ventricular wall and associated dimpling with it. This mainly corresponds to the region supplied by the left anterior descending artery (LAD).

Once arrested, the left ventricle is opened at the apex and cavity inspected for any thrombus which is first removed. From there the incision is extended toward the base of the heart by 4-6 cm, running parallel to the LAD and septum depending on the size of the heart. The wall is once again palpated for extent of thinning and all the non-functional wall is considered for resection. We preserve and revascularize the LAD wherever possible provided it is not included in the area involving the scar, which may help in revascularizing some uninvolved collateral vessels of septum and viable anterior wall. Thereafter the extent of septal scarring and thinning is evaluated and from the area where the healthy septum and anterior wall start, an oblique linear suture with interrupted U stitch (2-0 Ticron) is taken which joins the anterior wall to the septum. Care is taken to start as high up as possible in the healthy area of septum. The suture line is stopped at the level of base of posterior papillary muscles. Two separate sutures are taken if the scar is big. Four stitches (3-0 prolene) are then positioned, the first one in the septum at the end of the last interrupted suture, the second one at the level of new apex, the third one deep in the septum, at the border between the scar and the healthy posterior septum, and the fourth one in the anterior wall, again at the edge of the scar in the healthy area. An oval dacron patch is then tailored and fixed with the four prolene stitches previously placed. It is then sutured along the septum and the anterior wall forming the new apex. This now represents the new distal akinetic septum. A patch is preferred over pericardium as it is more safe in terms of possibility of cut through or tear and appropriate circular reorganization of the LV cavity. The complete septum now constitutes the patch upto the apex and the healthy remaining superior septum (Fig. 2). The incision is then closed in double layer. Once the ventricular region has been completed, bypass grafting is carried out including a graft to the proximal LAD whenever necessary.

**Table 1. Pre-operative demographic profile**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.3 ± 0.8 (43-72)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (86.7)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>NIDDM</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>HTN</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32.6 ± 4.2 (15 - 35)</td>
</tr>
<tr>
<td>Pre-operative IABP</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>II</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>III</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (13.3)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages
NIDDM: non-insulin dependent diabetes mellitus; HTN: hypertension; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; IABP: intra-aortic balloon pump; NYHA: New York Heart Association
possible. Both retrograde, antegrade or combined blood cardioplegia and graft cardioplegia are used for myocardial protection.

Mitral valve repair: The mitral valve was repaired by means of an overreductive posterior felt annuloplasty using a teflon felt. Intraoperatively all patients had both radial and femoral arterial pressure, thermodilution pulmonary artery catheter and transesophageal echocardiography (TEE) for monitoring. On CPB, milrinone (0.05 mg/kg) and magnesium 2 gm was routinely added and once the aorta was unclamped (after closure of ventriculotomy), low dose dobutamine (5 µg/kg/min) and nitroglycerin (depending on systolic pressure and systolic vascular resistance) were electively added. Epinephrine or norepinephrine were added depending on the systemic pressure and cardiac output and later titrated to adjustable doses once the patient was weaned off CPB. All the drugs were continued in the intensive care room and gradually weaned once the cardiac index was normal and overall condition of patient was stable. Generally all patients were on mechanical ventilation overnight and were weaned off next morning if they were stable. Once patients were off inotropes, they were put on oral β blockers, ACE inhibitors and diuretics.

Follow-up: All patients had mandatory pre-operative transthoracic echocardiography (TTE) and TEE. The TEE was repeated intraoperatively prior to sternotomy and immediately after, the patient was put off CPB. Echocardiography was repeated in recovery room only if indicated but was routinely done once patient was off inotropes and prior to discharge. All cardiac volumes were obtained using Simpson’s method. All patients were on 100% follow-up in outpatient department where TTE was repeated at 3 monthly interval.

Statistical analysis: Pre-operative and post-operative echocardiographic results were expressed as mean value± standard deviation. Statistical analysis was done using student’s paired t test. A p value of <0.05 was considered significant.

Results

Table 2 and Table 3 show intra-operative and post-operative variables, respectively. Four patients required IABP after induction of anesthesia for high pulmonary artery pressures and low cardiac output. There were two mortalities in the group. The first was a 56-year-old male with LVEF of 25% and was on pre-operative IABP for unstable angina. Patient did well till post-operative day 2 when he developed intractable ventricular arrhythmia not responding to amiodarone infusion and DC shock. He died...

Fig. 2. Post-operative TEE showing linear septal patch (P) with formation of neo apex.

TEE: transesophageal echocardiography

Table 2. Intra-operative variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of grafts</td>
<td>2.4±0.8</td>
</tr>
<tr>
<td>LAD graft</td>
<td>12 (40.0%)</td>
</tr>
<tr>
<td>IABP (post-induction)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>87±11</td>
</tr>
<tr>
<td>Aox time (min)</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>Total operative time (hrs)</td>
<td>5.26 ± 0.86</td>
</tr>
<tr>
<td>Grade II/III MR</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Mitral repair</td>
<td>3 (10.0%)</td>
</tr>
</tbody>
</table>

LAO: left anterior descending artery; IABP: intra-aortic balloon pump; CPB: cardiopulmonary bypass; Aox: aortic cross clamp; MR: mitral regurgitation

Table 3. Post-operative results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation time (hrs)</td>
<td>18.6 ± 4.3</td>
</tr>
<tr>
<td>Reexploration for bleeding</td>
<td>Nil</td>
</tr>
<tr>
<td>Perioperative MI*</td>
<td>Nil</td>
</tr>
<tr>
<td>Stroke</td>
<td>Nil</td>
</tr>
<tr>
<td>Low cardiac output (&lt;48 hrs)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Prolonged ventilation (24 hrs)</td>
<td>8 (26.7%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Residual significant MR</td>
<td>Nil</td>
</tr>
<tr>
<td>Cardiac intensive care unit (hrs)</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>9.0 ± 1.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (6.7%)</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; MR: mitral regurgitation

*CPK (MB) > 10% of CPK levels in 6 hours post-operative blood sample with or without associated electrocardiographic changes and echocardiogram suggestive of new wall motion abnormalities
on post-operative day 4. The second patient with LVEF of 20% had a history of ventricular arrhythmia and was already on amiodarone. He developed intractable ventricular arrhythmias on the post-operative day 3 and died on post-operative day 5. In both the patients the post-operative echocardiography showed good septoapical patch with neo apex and no MR. The mean post-operative follow-up was 4.2 ± 1.6 months (1-7 months). In the post-operative TTE, the excluded chamber could be seen full of blood with thrombus over few weeks.

The NYHA class improved from 2.9 ± 1.1 to 1.7 ± 0.3 (p < 0.001). Echocardiographic results are shown in Table 4. There was a significant reduction in left ventricular volumes with an improvement in the LVEF. The sphericity index reduced while no significant change was seen in the longitudinal length. All three patients in whom MR was repaired had 0/1+ MR while no new MR developed in the other patients.

**Table 4. Echocardiographic results**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal value</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV (ml)</td>
<td>102 ± 18</td>
<td>171.0 ± 31</td>
<td>113.3 ± 22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>41 ± 14</td>
<td>123.2 ± 35</td>
<td>64.55 ± 16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>54 ± 14</td>
<td>42.36 ± 7</td>
<td>47.64 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>59 ± 7</td>
<td>26.4 ± 5</td>
<td>40.34 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Std</td>
<td>0.60 ± 0.06</td>
<td>0.84 ± 0.05</td>
<td>0.71 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LL (cm)</td>
<td>7.8 ± 0.3</td>
<td>7.51 ± 0.3</td>
<td>7.76 ± 0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean follow-up 4.2 ± 1.6 months (1 month – 7 months)

Discussion

It is evident from the present experience that surgical treatment for patients with CAD and severe LV dysfunction secondary to anteroseptal infarction needs an aggressive approach. The pathophysiology of a failing heart shows that the ventricular chamber dilates to compensate for loss of contractile function of the infarcted segment. This results in increased wall tension and decreased systolic shortening, resulting in increased myocardial oxygen consumption in an already compromised heart. All this leads to an aneurysmal dilation of the heart, and subsequent congestive heart failure. If the associated papillary muscles are involved in the infarcted area, MR sets in, thus compounding the load on the failing heart. Further, the paradoxical motion of the dyskinetic septum contributes to the reduction in stroke volume and cardiac output. This progressive ventricular dilation along with its scar tissue may become the nidus for subsequent ventricular arrhythmias. We lost two patients as a result of intractable ventricular arrhythmias. In fact, poor ventricle function is one of the strongest risk factors for new onset intra-operative or post-operative sustained ventricular arrhythmias.6 However, the treatment is debatable. We routinely use intravenous (IV) amiodarone, administered in doses of 2.5 to 5 mg/kg initially given as single bolus and thereafter started as a continuous infusion for all patients who show any evidence of ventricular arrhythmias. This is generally started intra-operatively and continued till the post-operative period when we feel that patient is fully loaded, is arrhythmia-free for a minimum of 24 hours and clinically stable. This is converted to oral amiodarone and continued for 3 months post-operatively. However, if no ventricular arrhythmias are seen intra-operatively or immediate post-operatively, all our patients are still put on regular β-blockers.

The degree of septal or free anterior wall necrosis is variable depending on the level of LAD occlusion. Therefore the treatment of such patients is incomplete with only myocardial revascularization and some form of treatment has to be undertaken for the akinetic dysfunctional segments. As recently recommended by Mickleborough et al,7 an aggressive approach to revascularization and ventricular reconstruction in patients with CAD and poor LV function is required. We too feel that adverse remodeling needs to be prevented and near normal ventricular shapes and size should be aimed for without delay. This will save the deterioration of the residual viable muscles, which will directly effect the wall stress, chamber dilation and finally the ejection fraction and the ultimate surgical outcome.

Although a conservative management for such high risk patients is also a possibility, but ongoing angina is difficult to ignore. Athanasules et al.8 advocated myocardial revascularization without resection of the akinetic areas as did others.5 As recommended by Buckberg,10,11 we also feel that this technique not only addresses volume reduction but also restores a conical fiber orientation to aid the improvement in stroke volume and LVEF. At the same time it also prevents the onset of MR secondary to annular dilation.12 Although the question of how much cavity to reduce is always debatable, it is difficult to predict the adequacy of residual ventricular volume for proper diastolic filling. In this technique the new septum is formed by the superior septum and the patch that replaces either the dyskinetic or akinetic septum. The improvement in the NYHA class shows the adequacy of the residual pump. Another point to consider would be, why not do the reconstruction on beating heart. This approach, we feel is still questionable, as also pointed by others.13 The advantage
of assessing the ventricular wall to conduct a complete endocardiectomy and to be sure of suture placement is possible only on a quiet, arrested heart.

Few studies have also suggested that blocking the activated neuroendocrine system in CHF by surgical reduction of LV size may prolong survival, however further confirmation is required. Thus all means are now sought for tackling this subset of patients surgically before a stage is reached when transplantation is the only option left.

Conclusions: We are exploring this technique of septo-ventricular exclusion which preserves an adequate diastolic volume and provides better hemodynamic stability with good clinical and morphological results.

References
Conscious Off-Pump Coronary Artery Bypass Surgery

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Wockhardt Heart Institute, Bangalore

Background: Cardiothoracic surgery has been previously performed successfully under thoracic epidural anesthesia alone. Between October 2001 and December 2003, we performed 123 conscious off-pump coronary artery bypass surgeries using epidural anesthesia as the sole anesthetic. This technique is an alternative to cardiothoracic surgery performed under general anesthesia. Certain modifications in the technique facilitate the process.

Methods and Results: There were 24 female patients and 99 male patients with mean age of 58.6±6.2 years; 12 patients underwent repeat coronary artery bypass surgery. All the patients underwent epidural catheterization on the evening before surgery. Out of the 123 patients scheduled for coronary artery bypass surgery, 120 underwent off-pump coronary artery bypass surgery successfully; 4 patients underwent off-pump surgery via left thoracotomy and the rest through mid sternotomy. These patients received 295 grafts in all (single graft in 26 patients, double in 42 patients, triple in 35 patients, and quadruple in 20 patients). Three patients required conversion to general anesthesia and one to cardiopulmonary bypass. There was no mortality in the group.

Conclusions: Our experience suggests that by modifying the surgical techniques, we can accomplish conscious coronary artery bypass surgery.

Key Words: Epidural anesthesia, Off-pump surgery, Coronary artery bypass grafting

Over the past years conscious cardiac and thoracic surgeries have been reported infrequently. There are reports including our own, about an alternative anesthetic technique for performing the conscious off-pump coronary artery bypass (COPCAB) operations—under thoracic epidural anesthesia (TEA) as the sole anesthetic without general anesthesia (GA).1-3 In order to perform this surgery, certain modifications in the surgical techniques are required; we herewith discuss our modifications. The advantages of the above said techniques are avoidance of (i) ischemic events during intubation of the trachea, (ii) cardiac depression due to general anesthesia and premedication drugs, (iii) injury during tracheal intubation, and (iv) ventilator-related problems. The other benefits such as cost reduction and reduced intensive care unit (ICU) and hospital stay are also the reasons behind advocating this technique

Methods
Between October 2001 and December 2003, 123 patients underwent coronary artery bypass grafting (CABG) without endotracheal GA, using TEA alone, with the approval of the hospital ethical committee. The primary criterion for selection was a cooperative, understanding patient with a normal airway and significant coronary artery disease (CAD). We avoid the technique in patients with cardiomegaly, ejection fraction (EF) <30% and in presence of aortic regurgitation. Patients with contraindications for performing an epidural block such as lack of consent, infection at the local site of injection, continued use of antiplatelet medicines, bleeding disorders, past surgery of the cervical and upper thoracic spine were not subjected to epidural anesthesia. The pre-operative characteristics of the patients are shown in Table 1. The patients continued to take their usual medications except antiplatelets. If the patients were being treated with low-molecular-weight heparin, we switched over to infusion of unfractionated heparin, which was stopped 6 hours prior to insertion of the epidural catheter and recommenced after epidural catheterization.

Epidural anesthesia: The epidural catheter was inserted on the evening before surgery. Pre-operative investigations included complete hemogram and liver and renal function tests. Epidural catheter (16 gauge) was inserted under...
Table 1. Patient characteristics

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<table>
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<tr>
<td>Male/female</td>
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<td>Midline incision</td>
<td>119</td>
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<td>Thoraco</td>
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<tr>
<td>Redo CABG</td>
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<td>Unstable angina</td>
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<tr>
<td>AWTI</td>
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</table>

Midline: median sternotomy; Thoraco: left anterior thoracotomy; Redo CABG: repeat coronary artery bypass grafting; CVA: past cerebrovascular accident; COPD: chronic obstructive pulmonary disease; AWTI: anterior wall myocardial infarction of less than 2 months duration.

Management of pneumothorax: If the pleura is opened inadvertently during sternotomy or during dissection of LIMA, one of the following steps are undertaken. Pleural breach is repaired with appropriate suture or continuous positive airway pressure (CPAP) of 5-10 cm of water is applied using Siemens 900C ventilator. Small holes in the pleura do not interfere with respiratory mechanism and can be managed with CPAP alone. If the pleural membrane is breached at several places and cannot be repaired by suturing, an intercostal pleural drainage tube is inserted and connected to intercostal drainage system to which a negative pressure of 20 cm of water is applied. Bilateral pneumothorax can also be handled in a similar fashion.

Surgical technique

Sternotomy and harvesting of conduits: Before making the incision, complete analgesia from suprasternal notch to upper abdomen was confirmed. Sternotomy was performed in the inspiratory phase of the respiration. In thin individuals oscillating saw was used. Before spreading the sternum by sternal spreader, the connective tissue between the pleural reflection and the left table of the sternum was dissected away carefully by blunt dissection to facilitate harvesting of left internal mammary artery (LIMA). If the pleura is reflected away adequately 2-3 cm away from the lateral margin of the LIMA it is possible to open the sternum to the operator’s requirement without causing a breach in the pleura. The LIMA is dissected avoiding diathermy during the expiratory phase of the respiratory cycle (because the chest and therefore the LIMA move toward the operator during expiration). Radial artery is also dissected without any additional infiltration of local anesthetics. Saphenous vein is harvested and local anesthetic is infiltrated, if necessary.

Table 1. Patient characteristics

| Male/female          | 99/24   |
| Midline incision     | 119     |
| Thoraco              | 04      |
| Redo CABG            | 12      |
| Obesity              | 21      |
| Peripheral vascular disease | 16 |
| Diabetes mellitus    | 64      |
| Hypertension         | 49      |
| CVA                  | 17      |
| Renal failure        | 6       |
| COPD                 | 39      |
| Unstable angina      | 9       |
| AWTI                 | 4       |

Midline: median sternotomy; Thoraco: left anterior thoracotomy; Redo CABG: repeat coronary artery bypass grafting; CVA: past cerebrovascular accident; COPD: chronic obstructive pulmonary disease; AWTI: anterior wall myocardial infarction of less than 2 months duration.

Electrocardiographic (ECG) monitoring at the widest intervertebral space between C7 to T2 with the patient in sitting position. 3-4 cm of the epidural catheter was kept indwelling in the epidural space.

On the day of surgery, the patients were pre-medicated with fentanyl 3 µg/kg body weight, and midazolam 50 µg/kg intramuscularly half an hour before surgery. After administering the test dose (3 ml of 2% xylocaine with 1:200,000 epinephrine), epidural anesthesia was accomplished with 10 to 14 ml of 0.5% bupivacaine and the level of analgesia was noted; a further 3-5 ml of 0.25% bupivacaine was administered depending on the level of analgesia. After this, we set up an infusion of a mixture of 0.125% bupivacaine and fentanyl 5 µg/ml at the rate of 5 ml/hour via a syringe pump. The same surgeon operated on all the patients. The patients were kept warm by a warming blanket. In repeat CABG cases, the pleura is reflected away adequately 2-3 cm away from the lateral margin of the LIMA it is possible to open the sternum to the operator’s requirement without causing a breach in the pleura. The LIMA is dissected avoiding diathermy during the expiratory phase of the respiratory cycle (because the chest and therefore the LIMA move toward the operator during expiration). Radial artery is also dissected without any additional infiltration of local anesthetics. Saphenous vein is harvested and local anesthetic is infiltrated, if necessary.

Pneumothorax can also be handled in a similar fashion.

Management of instability of the heart due to spontaneous downward movement of the diaphragm: Conventional stabilization by placing pads to support the heart posteriorly before applying Octopus®3 (Medtronic Inc, Minneapolis, USA) may not work as effectively due to the downward movement of the diaphragm. The heart has to be supported of its own through a stabilizer which is independent of the diaphragm, that is, by supporting it with pericardial sling sutures, or Starfish® (Medtronic Inc, Minneapolis, USA). Sometimes, despite these measures, the heart may slip away from Octopus® so that continuation of grafting may not be possible. In such an event, the surgical assistant may have to support the heart using a suitable retractor or with his fingers. In spontaneously breathing patient it is important to be sure of the stability of the heart before proceeding with grafting.

Off-pump coronary artery bypass grafting: All the patients were heparinized with 2 mg/kg of heparin and activated clotting time (ACT) was kept over 300 s by additional 1 mg/kg of heparin if ACT was found to be less. The epicardial stability for performing the distal anastomosis of the graft was attained by using Octopus®3 in all the cases and additional stability was achieved by Starfish® tissue stabilizer. Coronary artery anastomosis was performed after epicardial stability was achieved with one or a combination of the above mentioned tissue stabilizers. At the end of the grafting and hemostasis, protamine sulfate was ad-
ministered in the dose of 2 mg/kg and return of ACT to normal values was considered as an end point to reversal of heparin. After the completion of surgery, patients were transferred to the intensive care unit while monitoring the same parameters as in the operating room. Post-operative analgesia was maintained in the intensive care unit with intermittent boluses of fentanyl 25 µg and tramadol 50 mg twice a day in the epidural catheter. Estimation of cardiac enzymes like creatine phosphokinase (CPK) M and B fractions and troponin-T was undertaken 12 hours after the completion of the surgery. Epidural catheter was left in situ for about 2-3 days for the purpose of post-operative analgesia and was removed when the patient was pain-free. Post-operative analgesia was achieved by administration of buprenorphine in the dose of 1 to 2 µg/kg at 12 hourly intervals. At the time of removal of the epidural catheter, normalcy of ACT was confirmed. All the results were expressed as mean ± standard deviation.

Hemodynamic management: If the reduction in the mean arterial pressure was required during proximal anastomosis, it was achieved by adopting anti-trendelenberg position and running an infusion of nitroglycerine in doses of 50 to 100 µg/min. Hemodynamic stability was achieved with combination of trendelenberg position, intravenous crystalloid administration and infusion of dopamine at the rate of 5-10 µg/kg/min. Reduction of mean arterial pressure to values <20% of the basal was considered as hypotension. If the hemodynamic stability was not achieved despite these measures, heart was returned to the pericardial cradle and surgery recommenced after stabilizing hemodynamic parameters.

Indication for conversion to general anesthesia and/or cardiopulmonary bypass: GA was indicated whenever there was inadequate analgesia, hemodynamic instability, coughing (which did not improve with restoration of the heart into the pericardial cavity and CPAP) and uncontrollable movement of the patient. After administration of GA, cardiopulmonary bypass (CPB) was indicated if the hemodynamic parameters progressively deteriorated in spite of inotropic support (up to 10 µg/kg/min of dopamine), restoration of the heart into the pericardial cavity and if new life threatening arrhythmias developed.

Results

Out of a total of 123 patients who were scheduled to undergo COPCAB, 120 underwent the planned procedure, while the other three required either general anesthesia or CPB in addition to GA. The first patient had arrhythmias causing hemodynamic disturbances and required conversion to GA and CPB. Other two patients who required conversion to GA had mediastinal movements caused by coughing, causing difficulty in carrying out the coronary artery anastomoses. Nine patients were receiving either infusion of heparin or injection of low-molecular-weight heparin, who consented to COPCAB. We stopped heparin 6 hours prior to (low-molecular-weight heparin 12 hours before) epidural catheterization. Heparin was restarted after epidural catheterization. Peri-operative course of all the patients was uneventful. All the patients were either asleep or lightly sedated during the surgery. Diaphragmatic respiration was adequate in most of the patients, but one patient required assisted respiration for about 20 min to combat inadequate diaphragmatic excursions.

A well-sedated spontaneously breathing patient offers no extra difficulties during the harvesting of LIMA, as the lungs and the pleura move lesser toward the surgeon harvesting the LIMA, as against controlled ventilation. LIMA was used in 117 out of 123 patients. The reasons for not using LIMA in the other 6 patients were injury to the proximal portion of LIMA in one and functioning LIMA in 5 patients who were scheduled to undergo repeat surgery. One of the minimally invasive direct coronary artery bypass (MIDCAB) patients received an "H" graft from LIMA to left anterior descending (LAD) by an interposition of a piece of saphenous vein graft. Radial artery was used as a LIMA - radial "Y" graft in 61 patients and as a free graft in 9 patients and saphenous vein was used in 32 patients. Fig. 1 shows the hemodynamic details of the intra- and post-operative period. Sixty-four patients had systemic hypotension during the grafting of obtuse marginal (OM) artery which was treated by institution of an infusion of 5 µg/kg/min of dopamine and/or restoring the heart to the pericardial cradle.

The patients received 295 grafts in all (single graft in 26
The duration of surgery was 174±18.4 min, time taken for anastomosis was 9.8±2.6 min, grafts/patient was 2.4, blood loss per patient in 48 hours was 267±106.5 ml. Twenty-seven patients developed pneumothorax during the course of surgery. Pneumothorax poses technical difficulty to the operating surgeon during grafting because of the pendulluft movement of the mediastinum especially so in the MIDCAB. Thirty-seven patients became restless whenever the mean arterial pressure decreased during the grafting of high diagonals, posteriorly present OMs and sometimes during posterior descending artery. Increasing the dose of dopamine to 10 µg/kg/min and restoring the cardia in the pericardial cradle, and assisting their respiration for about 5 min reversed this. One patient developed elevation of ST segment and subsequently had ventricular fibrillation while performing the OM grafting. Although the rhythm could be restored to normal sinus after internal defibrillation, we converted the anesthesia to GA so that the rest of the procedure could be carried out without apprehension. Two patients developed coughing during OM grafting. Assisting their respiration, increasing the dosage of dopamine and returning the heart to the pericardial sac did not help them. In both these patients anesthesia was converted to endotracheal GA. One patient developed inferior wall myocardial infarction on the day after the surgery and 2 developed anterolateral ischemia on day 4; two of them did not require any further interventions. The patient with anterolateral ischemia was readmitted to the ICU and dobutamine 5 µg/kg/min therapy was instituted to improve the left ventricular function. All the patients were questioned about their experience of anesthesia and surgery. Fifty-four patients were unable to recall any events from the time of transfer to the operating room, and the rest were pleased with the anesthesia. There were no life threatening arrhythmias in the post-operative period in any of these patients. Atrial fibrillation was noted in 2 patients who required cardioversion and supplemental therapy with amiodarone infusion. The mean stay in ICU was 10.9±4.2 hours and in the hospital, 3.9±3.2 days. There was no operative/early mortality. The compliance of these patients to physiotherapy was good and there were no pulmonary complications necessitating interventions such as mechanical ventilation or airway instrumentation to clear tracheobronchial secretions.

**Follow-up results:** We have about 18 months follow-up of our series. There were 2 deaths in our series, both due to non-cardiac causes. One patient died 8 months after the surgery, because of hepatic failure due to worsening of pre-existing liver dysfunction and the other of cerebrovascular accident 14 months after the surgery. Out of the 64 patients who underwent stress test, 2 were positive and 1 patient out of this group had occlusion of the vein graft to the OM. We did 16 coronary angiograms and 1 out of 54 grafts studied was obstructed (we do not perform angiograms routinely in all our patients).

**Discussion**

MIDCAB, OPCAB and thoracic surgery have been performed in conscious patients with acceptable results. Although GA is considered safe, it is not without complications, therefore it becomes necessary to look at other options available to us and TEA is one such option.

Avoidance of GA may be potentially beneficial to the patient. Although GA has been used for a large number of patients without significant complications, data show that hemodynamic response to tracheal intubation, suction of the endotracheal tube and extubation may occasionally lead to myocardial ischemia and pose a potential risk in patients with CAD.

Thoracic epidural anesthesia provides satisfactory conditions for off-pump CABG by dilating the coronary arteries, and the internal thoracic artery. The advantages of TEA include potential beneficial effects on the systemic and pulmonary hemodynamics. Several other benefits of epidural anesthesia like reduced stress response, cost and blood loss make it an attractive option to be employed during cardiac surgery. While performing COPCA, we have ready access to assessment of cerebral function in most of the patients. The occurrence of restlessness, when the mean arterial pressure reduced during surgery in 37 patients in our series, may have been due to inadequate cerebral perfusion. Reduction of irritability following increase in mean arterial pressure may suggest the possible scope of ready availability of monitoring of brain function.

The disadvantages of TEA include: risk of hematoma, inability to use the transeosophageal echocardiography (TEE) and infection. Admitting the patient a day before the surgery for the sake of performing epidural catheterization, thus increasing the total hospitalization days is another limitation. In our center we admit all the patients a day before the surgery (not as a prerequisite for epidural catheterization), therefore we do not consider this a major disadvantage. Even in centers where patients are admitted on the day of cardiac surgery, epidural catheters can be inserted 4 to 5 hours before the time of probable heparinization and the technique of TEA as the sole anesthetic can be practiced. Some workers introduce
epidural catheter on the operating table itself and allow about an hour from the time of epidural catheterization to heparinization.7

A spontaneously breathing patient may cough, usually during the grafting on the lateral and the inferior walls. The reason may be venous congestion due to left ventricular dysfunction causing pulmonary venous congestion or mitral regurgitation causing increased left atrial pressure. This problem is unique to COPCAB and not appreciated during endotracheal GA. It can be treated by increasing the inotropic support, instituting vasodilator therapy, assisting the spontaneous respiration and restoration of the heart to the pericardial cavity. If the problem cannot be solved by the above measures, endotracheal GA may have to be instituted. Conversion to GA has been reported by various authors citing coughing, inadequate diaphragmatic excursions, mediastinal movements as reasons.1,2 Maintaining the pleural integrity is shown to benefit the patients in the post-operative period.8

The occurrence of epidural hematoma remains a fear, which has not been documented in the literature.6,9 However, it is unlikely that clinicians will widely adopt the epidural anesthetic in cardiac surgery until they are convinced that the risk of paraplegia from an epidural hematoma is infinitesimal and the clinical benefits well validated.

Other modifications such as maintaining quiet ambience, silence among the surgical team members, avoiding leaning on the patient's body parts and noisy handling of surgical instruments should be strictly followed to prevent physical and psychological injury to a conscious patient.

The cost incurred per patient was not studied as a part of this work. However, the cost of conscious surgery is reasonably less because various items such as endotracheal tube, ventilator tubings, anesthetic drugs and ventilator-related disposables are dispensed with. The cost is further reduced because of absence of ventilation, reduced length of stay in the ICU, reduced hospital stay and overall reduction in the manpower required in managing these patients. Resumption of oral feeding as early as one hour after surgery not only improves the morale of the patients but also reduces the cost of intravenously administered fluids and drugs.

Conclusions: COPCAB can be performed in a select group of patients incorporating a few changes in the surgical technique as suggested. Patient's consent as well as a willing surgeon are the important factors that govern this mode of anesthesia. Conversion to GA and CPB may be required in some of these patients.

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Plasma CRP Level Predicts Left Ventricular Function and Exercise Capacity in Patients with Acute Myocardial Infarction

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Background: C-reactive protein estimation can help in predicting short- and long-term prognosis after acute myocardial infarction. High plasma C-reactive protein level in the acute phase strongly indicates a poor clinical outcome of the patients with myocardial infarction.

Methods and Results: One hundred consecutive patients admitted with ST elevation myocardial infarction in the intensive coronary care unit in our hospital who were able to do symptom-limited treadmill test during early recovery phase were studied. Plasma C-reactive protein was measured at the time of admission by immunoturbidity method. The normal value of the C-reactive protein was taken as 0.8 mg/dl. Echocardiographic study was done on day three of admission and ejection fraction was estimated by modified Simpson’s method. Symptom-limited treadmill exercise test was done in all the patients. Patients were classified into two groups based on level of C-reactive protein: those with low C-reactive protein level (1.26±0.91 mg/dl, n=40) and those with high C-reactive protein level (6.52±3.97 mg/dl, n=60). Ejection fraction was lower in high C-reactive protein group (46.7±11.9%) compared to low C-reactive protein group (56.9±7.7%) (p=0.011). Exercise capacity was lower in high C-reactive protein group (2.8±1.4 METs) compared to low C-reactive protein group (5.5±2.5 METs) (p=0.027).

Conclusions: C-reactive protein levels are an index of the severity of myocardial necrosis which translate to worse left ventricular function. Higher the C-reactive protein level, lower the ejection fraction and worse may be the prognosis. (Indian Heart J 2005; 57: 54-57)

Key Words: Left ventricular function, Acute myocardial infarction, C-reactive protein

C-reactive protein (CRP) directly participates in myocardial injury of acute myocardial infarction (AMI). High CRP levels in the acute phase strongly indicate poor early clinical outcome of the patients with AMI. In AMI, the peak plasma value of CRP can also be used to predict the risk of cardiac rupture as well as short- and long-term prognosis. Estimation of CRP levels in acute phase may provide valuable information on left ventricular (LV) function and exercise capacity and can help in long-term risk stratification after AMI.

This study investigated the relationship between plasma CRP levels in AMI and LV ejection fraction (LVEF) and exercise capacity.

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Methods

One hundred consecutive patients (90 males and 10 females) with AMI admitted to our hospital were studied. These patients fulfilled the following criteria for AMI: (i) typical chest pain for > 30 min, (ii) >1 mm ST elevation in limb leads or two consecutive chest leads, (iii) new onset left bundle branch block (LBBB), (iv) elevated CK-MB. In this study, only patients who were able to do symptom-limited treadmill test (TMT) were included. Patients with hypotension, complete atrioventricular (AV) block, non-sustained ventricular tachycardia and ongoing ischemic changes were excluded. Only patients who survived for more than 3 days following infarction were included in this study. The patients evaluated for atypical chest pain constituted the control group.

The mean age of patients was 50 years (50.1±8 years).
Electrocardiogram (ECG) was taken at the time of admission. The isoelectric line was defined as the level of the preceding TP segment and ST segment elevation was measured at the 'J' point. Two ml of blood was taken before thrombolysis and plasma CRP level was estimated by immunoturbidity method by auto analyzer. Normal value of CRP was < 0.8 mg/dl. None of the patients had other conditions known to modify the plasma CRP level i.e. collagen vascular disease, advanced liver disease, malignancy and septicemia. Patients with other inflammatory infectious diseases, i.e. chronic obstructive pulmonary disease/bronchitis, pulmonary tuberculosis or arthritis were also excluded. Blood for CK-MB was taken and estimated by auto analyzer CK-MB level <14 U/L was considered as normal. All patients with AMI were thrombolyzed with 1.5 million units of streptokinase. Aspirin, isosorbide dinitrate, beta blocker etc. were used in routine manner. Echocardiography was done in all patients on day three; the LV volume and EF were evaluated by modified Simpson's method. Doppler diastolic indices were also calculated.

Symptom-limited exercise electrocardiography was done by modified Bruce protocol after 8-10 days of admission. Functional exercise capacity in terms of METs, ST segment changes, symptoms and arrhythmias were noted.

**Statistical analysis:** Variables were expressed as mean±SD, and compared with the use of a commercially available statistical package. Statistical significance of differences between the two groups was determined and values were calculated. A p value <0.05 was considered as significant.

Computer analysis of the collected data was done using Epidemiological Information Package 2002 (EPI-2002) developed by Center for Diseases Control and Prevention (CDC), USA for World Health Organization.

**Results**

We classified the patients into two groups based on the level of CRP. Group 1 consisted of patients with CRP level ≤ 3 mg/dl. Group 2 consisted of patients with CRP level >3 mg/dl. In Group 1 the mean CRP level was 1.26±0.91 mg/dl (n=40) and in Group 2 the mean CRP level was 6.52±3.97 mg/dl (n=60). The clinical characteristics of the two groups are shown in Table 1. There was no significant difference between age, sex ratio, risk factors, systolic and diastolic blood pressure (BP) on admission, heart rate, thrombolysis, ST elevation on admission and time of onset to sampling of blood for CRP. Mean CK-MB level was higher in Group 2 (36.3±2.7 IU/L) than in Group 1 (mean CK-MB: 24.1±2.1 IU/L). EF was lower in Group 2 (46.7±11.9%) compared to Group 1 (56.9±7.7%) (p=0.011); severity of diastolic dysfunction was greater in Group 2 (IVRT: 88 ms; DT:166 ms) than in Group 1 (IVRT: 123 ms; DT:246 ms) (p=0.068) (Table 2).

Exercise capacity was lower in Group 2 (2.8±1.4 METs) than in Group 1 (5.5±2.5 METs, p=0.027) (Table 3); ST depression in V₅ at peak exercise was higher in Group 2 (2.10±0.7 mm) than in Group 1 (2.10±0.7) (p=0.03) (Table 3). In our study positive ST response was 66% in Group 1 and 70% in Group 2 (p=0.03) (Table 3).

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<tr>
<th>Characteristics</th>
<th>Low CRP group (Group 1, n=40)</th>
<th>High CRP group (Group 2, n=60)</th>
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<td></td>
<td>Mean CRP level, mg/dl</td>
<td>1.26±0.91</td>
<td>6.52±3.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onset of chest pain and blood</td>
<td>8.01±1</td>
<td>9.01±1</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>sampling time, hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total ST elevation at time of</td>
<td></td>
<td>0.060</td>
<td>0.64</td>
</tr>
</tbody>
</table>

BP: blood pressure; bpm: beats per minute; CRP: C-reactive protein
C-reactive protein is a hepatically derived marker of low grade systemic inflammation that largely reflects circulating cytokine formation. It is produced from liver in response to cytokine stimulation (interleukine 1 and 6). According to AHA/CDC recommendations, CRP levels are classified as: low CRP < 1 mg/dl; average 1-3 mg/dl; and high CRP >3 mg/dl. Higher CRP levels in patients with AMI indicate an increased risk of subsequent coronary events because CRP is associated with inflammation of coronary vessels. It is reasonable to suggest that high CRP levels are associated with adverse outcome as a result of coronary instability. CRP, at least, partially reflects the extent of myocardial necrosis and can be used to predict in-hospital and long-term outcome in patients with AMI. Several large-scale prospective studies have shown the inflammatory marker - high sensitivity CRP (hs-CRP) to be a potent predictor of future MI, stroke and peripheral vascular occlusion among apparently healthy men and women, as well as among high-risk smokers and the elderly. Levels of hs-CRP are also elevated among those with acute coronary syndromes at high risk for recurrent events and among post-MI patients at high risk for recurrent instability. These effects are independent of other risk factors and appear to add to the predictive value of lipid screening in terms of risk prediction. However, there remains much confusion as to when it may be appropriate to measure CRP levels, and what to do about them when they are found to be elevated.

CRP is a non-specific, highly sensitive marker of inflammation. One postulate regarding the unstable character of acute coronary syndrome is inflammation of the atherosclerotic lesion. Hence elevated plasma CRP levels in patients with acute coronary syndrome on admission and its persistence after discharge may indicate a state of persistent inflammation and instability with poor short- and long-term prognosis. This was observed in various studies. The association of elevated CRP and poor prognosis in patients with acute coronary syndrome is independent of other serum markers of myocardial cell injury and necrosis like cardiac troponin and CK-MB.

Suleiman et al. showed that plasma CRP level obtained within 12 to 24 hours of symptom onset is an independent marker of 30-day mortality and the development of heart failure in patients with AMI. CRP levels may be related to inflammatory processes associated with infarct expansion and post-infarction ventricular remodeling. Anzai et al. showed that cardiac rupture, LV aneurysm formation, and one-year cardiac mortality were associated with an elevation of serum CRP early after AMI. Berton et al. showed that first-day hs-CRP is a strong independent predictor of both heart failure progression and depressed LV ejection fraction in AMI. In contrast to above studies, Kimura et al. showed that elevated CRP immediately after onset of AMI is associated with less myocardial damage and better LV function in reperfused anterior AMI. They have suggested that two mechanisms may account for the myocardial protective effect associated with the elevation of CRP. First, silent myocardial ischemia, which is frequently associated with unstable angina, and in which CRP levels may increase greatly, and may exert an ischemic preconditioning effect on the myocardium. Second, inflammation induces expression of angiogenic growth factors associated with reduced infarct size, and endogenous production of nitrous oxide protects the myocardium from ischemic reperfusion injury.

Conclusions: In our study we found that EF and exercise capacity were lower in high CRP group compared to low CRP group. As echocardiogram was done only on day three after AMI, a lot of stunned myocardium may be present, which is the limitation of this study.

Table 3. Results of symptom-limited stress electrocardiography

<table>
<thead>
<tr>
<th></th>
<th>Low CRP group</th>
<th>High CRP Group</th>
<th>P value</th>
<th>r value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Group 1, n=40)</td>
<td>(Group 2, n=60)</td>
<td></td>
<td></td>
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<tr>
<td>Exercise capacity, METs</td>
<td>5.5±2.5</td>
<td>2.80±1.4</td>
<td>0.027</td>
<td>+0.62</td>
</tr>
<tr>
<td>ST depression in V₅, mm</td>
<td>1.62±0.4</td>
<td>2.10±0.7</td>
<td>0.03</td>
<td>+0.58</td>
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<tr>
<td>Double product</td>
<td>28700</td>
<td>29300</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References
1. Tomoda H, Aoki N. Prognostic value of C-reactive protein levels within six hours after the onset of acute myocardial infarction. Am Heart J 2000; 140: 324-328
Impact of high-sensitivity C-reactive protein on predicting long-term mortality of acute myocardial infarction. Am J Cardiol 2003; 91: 931–935
Non-Surgical Transpericardial Catheter Ablation of Post-Infarction Ventricular Tachycardia

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Care Hospital, The Institute of Medical Sciences, Hyderabad

Non-surgical transpericardial approach for catheter-based epicardial radiofrequency ablation of post-infarction left ventricular tachycardia has been described as an alternative and additive procedure to standard endocardial technique for delivery of radiofrequency energy in difficult situations. We report our initial experience with this approach in three patients of post-infarction recurrent ventricular tachycardia, refractory to multiple antiarrhythmic drugs. Ablation was successful in terminating the tachycardia in two and in modifying the circuit to be amenable for control with single antiarrhythmic drug in one patient. There were no serious acute or long-term complications related to the procedure. Epicardial approach is an effective and safe adjunct to standard endocardial ablative technique for patients of post-infarction ventricular tachycardia. (Indian Heart J 2005; 57: 58–61)

Key Words: Ventricular tachycardia, Radiofrequency ablation, Myocardial infarction

Successful percutaneous epicardial radiofrequency (RF) ablation by transpericardial route has been reported to be successful for treatment of ventricular tachycardia (VT) in Chagasic cardiomyopathy and for ischemic VT occurring late after inferior myocardial infarction (MI).1-4 Epicardial VT circuits are common in Chagasic cardiomyopathy and in a substantial proportion of post-infarction scar VT which lead to difficulty in delivering adequate RF energy for a successful ablation of the VT circuit by the standard endocardial approach.5,6

Case Reports

We report our initial experience with this technique for treatment of scar VT refractory to medical therapy in three patients. All patients continued to be on amiodarone for the study and were in fasting state, when taken up for the procedure. Two multipolar catheters were inserted through the femoral venous approach and placed in the coronary sinus and right ventricle. Programmed ventricular stimulation was carried out at twice the diastolic threshold with 1 ms pulse. Up to three timed extra stimuli at two-drive cycle lengths were delivered from right ventricular (RV) apex and RV outflow tract. Conventional mapping was performed in all three patients; in addition, Case 2 underwent electroanatomical three-dimensional (3D) mapping (CARTO). If hemodynamically stable VT was induced, endocardial mapping was done and if electrograms were found suboptimal, mapping catheter was introduced into the pericardial space through the subxiphoid route. In one patient, elective epicardial approach was undertaken in view of a large posterobasal left ventricular (LV) aneurysm with thrombus.

Subxiphoid approach to pericardial space: After proper asepsis of subxiphoid area, a regular epidural needle (Tuohy 17 guage, effective length 7.9 cm and total length 10 cm, outer diameter 1.5 mm) was introduced at 45° toward left scapula and advanced toward cardiac silhouette under fluoroscopic guidance, till negative pressure was felt. While approaching the heart, few ml of contrast media was injected and after confirming position of the needle in the pericardial space, a soft floppy tip wire was introduced through the needle. An 8 F sheath was advanced over the wire and a quadripolar deflectable 4 mm tip catheter was introduced for mapping and ablation (Fig. 1). Coronary angiogram (CAG) and left ventriculogram were done to delineate the coronary artery and LV anatomy.

Case 1: A 65-year-old male with coronary artery disease
(CAD), old inferior wall MI, mild LV dysfunction presented with recurrent VT despite amiodarone, mexelitine and beta-blocker therapy, requiring repeated DC cardioversions. Echocardiogram revealed inferoposterior akinesia with LV ejection fraction (EF) of 45%. Baseline electrocardiogram (ECG) showed qR in III and aVF leads; clinical VT rate was 200 beats per min (bpm) and showed right bundle branch block (RBBB) morphology with north-west axis. He had single vessel [right coronary artery (RCA)] disease with evidence of recanalization on CAG. Hemodynamically stable VT (cycle length 312 ms) similar in morphology to that of clinical VT was induced in the lab with double extra stimuli from right ventricular apex. Activation mapping revealed suboptimal electrograms endocardially and early electrograms epicardially at the diaphragmatic surface with the electrograms 60 ms earlier than surface QRS during VT. RF energy was delivered through the epicardial catheter at the site of optimal electrograms during VT and could terminate the VT in 3.8 s. Post-RF ablation, the patient remained in sinus rhythm and VT was non-inducible with programmed ventricular stimulation.

Case 2: A 53-year-old male with previous inferior and right ventricular infarction presented with recurrent VT while on combination of amiodarone, mexelitine and metoprolol, and required repeated cardioversions. Echocardiogram revealed inferoposterior hypokinesia, mild LV dysfunction and mild mitral regurgitation. Baseline ECG showed qR complexes in inferior leads with deep T inversions in inferolateral leads. His clinical VT had a rate of 200 bpm with a very broad QRS of left bundle branch block (LBBB) morphology with left axis deviation. His CAG revealed 30% bifurcation disease of mid left anterior descending (LAD) artery and total occlusion of mid segment of dominant RCA. Hemodynamically stable VT resembling clinical VT (cyclelength 315 ms) was induced in the lab with two extra stimuli from right ventricular outflow tract. Both epicardial and endocardial mapping was done guided by CARTO system and continuous fragmented electrical activity during VT was obtained on the epicardial surface of the inferior wall (Fig. 2). RF delivery through the epicardial catheter during VT abolished the tachycardia in 4.2 s (Fig. 3). Subsequently, another VT of different morphology (cycle length 400 ms) could be induced which was ablated from the right ventricular endocardial approach. No further VT was inducible and patient remained in sinus rhythm.
Case 3: An elderly man, 70-year-old, presented with recurrent VT, not converting pharmacologically with multiple parenteral antiarrhythmic drugs including xylocaine and amiodarone requiring repeated electrical cardioversion for termination. Echocardiogram revealed a large posterobasal aneurysm with suspicion of a clot and preserved LV function (EF: 50%). Despite anticoagulation, thrombus persisted. The baseline ECG showed large q waves in inferior leads. Tachycardia ECG showed broad QRS rhythm of RBBB morphology with extreme right axis deviation at a rate of 150 bpm. CAG revealed long segment proximal RCA lesion. Patient was unwilling to undergo revascularization procedure. In view of the LV thrombus, he was taken up for epicardial RF ablation of the VT. Clinical VT was induced in the lab and RF energy was delivered epicardially on the posterobasal segment. The tachycardia circuit could be modified so as to be inducible with difficulty and had a longer cycle length. Subsequently, on small dose of oral amiodarone, he is free from VT recurrences.

Follow-up: Over a mean follow-up period of 24 months, all three patients are doing well without symptomatic recurrences on single antiarrhythmic drug (amiodarone).

Discussion

VT in Chagas disease is known to be predominantly due to epicardial circuits. Also, about 20% of scar-related VTs are of epicardial origin. Occurrence of the VT circuits in epicardial or subepicardial location may be the reason for some of the unsuccessful outcomes in standard endocardial RF catheter ablative procedures.

Mapping of arrhythmia foci or circuits that are deep within the myocardium or in the epicardium has been attempted in open-chest heart surgery and with RF ablation in two ways. Small, 2 F electrode catheters have been introduced into the coronary sinus and advanced into the cardiac veins. With this technique, epicardial circuits can sometimes be identified, but only when veins cross the region of the circuit.

The other technique of epicardial mapping for ablating VT was initially introduced in 1996 by Sosa et al. for ablating VT due to Chagas disease. Briefly, this procedure consists of introducing a standard ablation catheter into the pericardial space using a subxiphoid puncture technique. Having attained success in this subset of patients, they later extended use of this novel technique to ablating post-infarction VT and VT after cardiac surgery. Studies with intraoperative mapping have shown epicardial circuits to be common in post-infarction VT related to LV inferior wall. In their study of 14 patients with recurrent and drug-refractory post-infarction VT, Sosa et al. found this technique to be feasible and safe, without any serious complications. Eighteen of the 30 patients induced VT were considered mappable. Of these, 7 were terminated by epicardial RF application and 3 by standard endocardial procedure. These 7 patients who underwent epicardial RF ablation remained asymptomatic for 14 ± 2 months. In patients with incessant VT, Brugada et al. reported 80% success rate (8 of 10 patients) with epicardial approach for performing RF ablation and no procedural complications. This approach has been reported to be feasible and effective by others in small number of patients.

Of particular concern in this technique is the proximity of RF energy application to an epicardial coronary artery and the potential danger of its damage. Studies in mongrel dogs have shown that when RF energy was delivered adjacent to major coronary artery such as LAD, the effects were limited to the media but when delivered above the artery, severe intimal hyperplasia and intravascular thrombosis can occur. Sosa et al. described three approaches to minimize this complication: (i) coronary angiogram is done in the beginning of procedure and subsequently distance between the ablation catheter tip and the coronary artery were observed prior to RF pulse delivery, taking this angiography as reference, (ii) by analyzing the position of ablation catheter in relation to apex of heart where large coronary arteries are unlikely to be present and the distance from coronary sinus catheter, (iii) by observing the distance between ablating catheter and epicardial veins of the heart during retrograde injection of contrast into the coronary sinus, assuming that coronary artery runs near the vein.

Experimental studies have shown that the shortest acceptable distance between catheter tip and a major coronary artery should be three times the length of the catheter tip. Thus, for a standard ablation catheter tip of 4 mm, the closest permissible distance would be 12 mm from a major coronary artery.

Limitations of this technique include the possibilities of ventricular perforation, hemopericardium and occurrence of mediastinitis by accumulation of extravascular contrast injected to check needle position during entry. All the manipulation maneuvers inside the pericardium may also cause an inflammatory response in the days after the procedure. Sosa et al. reported accidental right ventricular perforation in 4 patients of a total of 53 epicardial procedures, even though hemopericardium drainage was necessary only in three patients in whom a small quantity (50 ml) was drained. Brugada et al. did not detect any pericardial effusion either immediately after the procedure...
or on the day of hospital discharge. The other concern with epicardial procedure is possible resistance and hindrance to catheter movement by adhesions produced by prior MI or previous heart surgery but in practice, it was not found to pose any serious limitation to catheter manipulation. Evaluation is also required to know if the RF lesions delivered epicardially are proarrhythmogenic as the catheter is not bathed in blood unlike with the standard endocardial delivery.  

Epicardial approach has several potential advantages. Endovascular complications such as pseudoaneurysms, arterial emboli from aorta, stroke from coagulum formed by the ablation itself and complications from heparin are reduced.

Conclusions: Epicardial radiofrequency ablation by transpericardial approach is feasible, safe and effective in selected patients of post-infarction ventricular tachycardia arising from left ventricular inferior wall. In such a group of patients, it is an alternative approach in those with left ventricular thrombus and serves as useful adjunctive procedure when standard endocardial approach is not successful.

References

Use of PercuSurge in Primary Angioplasty

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Thrombus load and its subsequent distal embolization causing slow flow makes primary angioplasty a challenging task. Although data is scanty, these complications may be potentially mitigated by use of distal protection devices. We report 6 cases of PercuSurge distal protection device-assisted primary angioplasty. All lesions were stented with patients achieving brisk TIMI 3 flow; none of the patients had in-hospital major adverse cardiac events. The strategy of PercuSurge Guardwire-assisted primary angioplasty seems encouraging in improving successful outcome in this subset of patients. (Indian Heart J 2005; 57: 62-64)

Key Words: Coronary angioplasty, Coronary artery disease, Distal protection device

The no-reflow phenomenon is defined angiographically as acute reduction in coronary flow—Thrombolysis In Myocardial infarction (TIMI) grade 0-1 in the absence of dissection, thrombus, spasm or high grade residual stenosis at the original target lesion.

The potential mechanisms for microvascular dysfunction include vasospasm, distal embolization of thrombus or other debris, oxygen-free radical-mediated endothelial injury, capillary plugging by erythrocytes and neutrophils and intracellular/interstitial edema with intramural hemorrhage.

Various techniques are available for the prevention or reduction of slow or no-flow phenomenon but none have yet been validated for prevention of the phenomenon. We report the use of PercuSurge distal protection device (Medtronic, GA, USA) in 6 cases of primary angioplasty.

Brief Report

Patients were taken up for primary angioplasty as per standard indication. After coronary angioplasty and identification of culprit vessel, the lesion was crossed using PercuSurge Guardwire.

The Guardwire balloon was placed just distal to the site of thrombus (lesion) prior to major branch, where thrombus could embolize. Using the aspiration catheter without inflating the balloon of the Guardwire, two aspirations were done across the lesion. Following aspiration with the catheter, thrombus load was noted to be much reduced. This was followed by inflation of the Guardwire balloon and stenting. After stenting, the aspiration catheter was reinserted to aspirate any remaining debris or thrombus. The Guardwire balloon was then deflated and in all six patients, the post-procedure flow was seen to be TIMI 3. Aspiration was performed prior to Guardwire balloon inflation to maintain flow in the culprit vessel and allow the operator to correctly select the site for Guardwire balloon inflation. The PercuSurge system in this condition was made to act as both thrombectomy device (aspiration without Guardwire balloon inflation) and a distal protection device (Guardwire balloon inflation and aspiration). The balloon occlusion time was around 5 min.

The characteristics of patients are shown in Table 1. It is seen that left anterior descending artery (LAD) was the commonest artery involved. The smallest vessel diameter was 2.75 mm and the lesion length varied from minimum of 12 mm to a maximum of 20 mm. Abciximab was used in only 2 out of 6 patients and at the end of the procedure, all patients had TIMI 3 flow.

Procedural success rate was 100% with all six patients having brisk (TIMI 3) flow after balloon dilation and stent implantation. In-hospital, the patients had no further chest pain or any fresh ischemic electrocardiographic changes. Patients were discharged on day 8 on aspirin, clopidogrel, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor and a lipid lowering drug.

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Discussion

In the catheterization laboratory, no-reflow usually manifests as electrocardiographic changes and chest pain depending on the myocardial territory, and may induce a spectrum of ischemic manifestations including conduction disturbances, hypotension, myocardial infarction (MI), cardiogenic shock or even death. No-reflow has been associated with 10-fold higher incidence of death and MI compared to patients without no-reflow.4

A major obstacle for interventional cardiologist during primary angioplasty is the distal embolization of particulate matter leading to slow or no-flow phenomenon and many at times resulting in a no-flow vessel where the vessel completely fills but there is no distal run off. This not only results in diminished blood flow to the distal vascular bed but also causes peri-procedural, end-organ ischemia and infarction as demonstrated by perfusion defects and elevation of cardiac enzymes.5,6 A variety of distal protection devices are under development. The PercuSurge Guardwire is a balloon occlusion thrombectomy device which has been approved by the United States Food and Drug Administration (FDA) for use in saphenous vein graft intervention.

The PersuSurge Guardwire consists of a wire containing a central lumen which communicates with a low-pressure distal occlusion balloon incorporated on the tip. The wire serves as both angioplasty guidewire and provides protection from distal embolization. An inflation device allows controlled expansion, and sizing of the occlusion balloon in the target vessel. The export aspiration catheter is used to remove the debris from the treated vessel before the balloon is deflated and antegrade flow in the vessel is established.

In the Saphenous vein graft Angioplasty Free of Embolic Randomized (SAFER) multicenter study,7 in which 801 patients undergoing saphenous vein graft intervention were randomized to either stenting with a conventional guidewire or with Guardwire plus distal protection device, major adverse coronary event rate at 30 days reduced by nearly 50%.

Although there is yet no multicenter data on the use of PercuSurge in primary angioplasty, there have been single-center reports where PercuSurge device or only its export aspiration catheter has been used to reduce distal atheroembolization or for thrombosuction during angioplasty. Kalaria et al.8 showed that in two patients with recent MI, significant thromboembolic debris was aspirated with use of PercuSurge with technical success and without any complication.

In a study of 12 patients undergoing primary percutaneous intervention, using only the export aspiration catheter for primary thrombosuction, gross thrombi were obtained from 9 (75%) patients and no peri-procedural complications were noticed.9 We selected six patients for the use of PercuSurge Guardwire protection device. The patients with calcified or small vessel ≤2.5 or those who had more of obstructive element as compared to thrombotic lesion (as guided by prominent collaterals) were not selected for PercuSurge use.

Conclusions: Our experience with the use of the PercuSurge Guardwire in primary angioplasty has been very encouraging; however, more data will be required to substantiate its usefulness.

References


Congestive Heart Failure in Unoperated Tetralogy of Fallot: Can Hypoxia be a Cause?

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All India Institute of Medical Sciences, New Delhi

Congestive heart failure (CHF) as a presentation in unoperated children of tetralogy of Fallot (TOF) is rare. The presence of such a complication demands further investigation. Myocardial hypoxia is a less well-known reason of ventricular dysfunction in TOF. We report the case of a 10-year-old boy of TOF with severe global ventricular dysfunction and hypercyanotic spells, in whom a right-sided modified Blalock-Taussig shunt resulted in marked improvement of systemic arterial oxygen saturation and CHF.

Case Report
A 10-year-old boy weighing 22 kg was referred to our cardiac clinic for progressively increasing cyanosis and dyspnea. He had been cyanosed since 3 months of age that had progressively worsened and he was in New York Heart Association (NYHA) class IV at the time of surgery. On examination, he was well-nourished, but had tachypnea and tachycardia. Blood pressure was 110/80 mmHg. He had cyanosis, clubbing, facial edema, elevated jugular venous pressure, ascites, and marked hepatomegaly. Cardiac apex was palpable in 6th intercostal space, 1 inch lateral to mid-clavicular line. A short ejection systolic murmur was audible at mid-left sternal border. Chest X-ray revealed cardiomegaly with a cardiothoracic ratio of 0.75, decreased pulmonary vascular markings, and bilateral pleural effusion (Fig.1). The electrocardiogram showed a QRS axis of +180°, right atrial enlargement and right ventricular hypertrophy. Important laboratory investigations were as follows: hemoglobin 22.0 gm/dl, hematocrit 66.0%, total leucocyte count 7500/mm³ with normal differential count, platelet count 100,000/mm³, total bilirubin 1.1 mg/dl with direct bilirubin 0.4 mg/dl, prothrombin time 15.0 s, blood urea 74 mg/dl, serum creatinine 1.2 mg/dl; serum calcium 7 mg/dl, arterial PH 7.26, PaO₂ 30.0 mmHg, PaCO₂ 34.0 mmHg, and systemic arterial oxygen saturation 54%. Thyroid function tests were normal. The urine analysis showed no proteinuria.

Echocardiogram revealed typical anatomy of TOF. Pulmonary arteries were of normal size and confluent. There was minimal mitral and tricuspid regurgitation and marked biventricular dysfunction. The left ventricular (LV) ejection fraction (LVEF) was 22% and the right ventricular ejection fraction was reduced but was not computed (Table 1). There was no aortic regurgitation.

Cardiac catheterization was performed for diagnostic confirmation of this unusual presentation, to define coronary artery anatomy and to identify the presence of major aortopulmonary collaterals, if any. It revealed elevated end-diastolic pressure of the right ventricle (systolic/end-diastolic: 92/5-17 mmHg) and marked right ventricular dilation with severe global hypokinesia. The aortic saturation was 54%. The pulmonary arteries were confluent. There was single perimembranous ventricular septal defect (VSD) with aortic override. The coronary arteries were normal and there were no large aortopulmonary collaterals.

Key Words: Congenital heart disease, Tetralogy of Fallot, Congestive heart failure
An emergency right-sided modified Blalock-Taussig anastomosis (6 mm polytetrafluoroethylene graft) was performed. The patient was discharged on digoxin, diuretics, and aspirin. A chest X-ray 6 months after shunt placement confirmed a decrease in cardiomegaly and significant increase in exercise tolerance. The echocardiogram showed a functional shunt with improved biventricular function (Table 1). The shunt was taken down and total repair of TOF was performed 18 months later. Presently at 13 years of age, he is doing well. Echocardiogram revealed normal LV function and no residual lesions.

**Table 1. Fractional shortening and ejection fraction before and after Blalock-Taussig shunt and total correction**

<table>
<thead>
<tr>
<th>Months after systemic-pulmonary shunt</th>
<th>Months after intracardiac repair</th>
<th>Fractional shortening (%)</th>
<th>Ejection fraction (%)</th>
<th>Oxygen saturation (%)</th>
<th>Hematocrit (%)</th>
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<tr>
<td>0</td>
<td>-</td>
<td>9</td>
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<td>60</td>
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**Discussion**

Although ventricular dysfunction and CHF is a well-known consequence of long-standing hypoxia, this phenomenon is uncommon in TOF. Rowe noted that since the right ventricle is effectively decompressed by the VSD, CHF never occurs in TOF unless there are co-existing unusual anatomic and physiologic features i.e. anemia, infective endocarditis, systemic hypertension, viral myocarditis, aortic and pulmonic regurgitation, and other structural defects, like abnormal attachments of tricuspid or mitral leaflets causing partial or complete closure of the VSD.

Both the duration of cyanosis and degree of volume overload have been incriminated as the contributing factors to abnormal systemic ventricular function. A proper balance between myocardial oxygen supply and demand is essential for adequate cardiac functioning. Low systemic oxygen saturation, increased coronary vascular resistance secondary to polycythemia and long-standing volume overloaded ventricle with increased ventricular wall tension have been incriminated as the contributing factors to abnormal LV function. Polycythemia and increased blood viscosity resulting from cyanosis also interfere with oxygen delivery. During times of stress, tachycardia, elevated blood pressure and decreased systemic oxygen saturation result in repeated episodes of myocardial hypoxia and subsequent fibrosis. Though hypoxia increases glycolysis in myocardial cells, oxidative metabolism decreases proportionately, leading to inefficient utilization of glucose and myocardial dysfunction.

Ultrastructural studies of the operatively resected right ventricular muscle of patients of TOF have revealed several degenerative changes including cellular and myofibrillar disorganization, abnormalities of the Z-band material, myofibrillar lysis, proliferation of the sarcoplasmic reticulum, increased thickness of the basal laminae, cellular atrophy, loss of intercellular connections, and interstitial fibrosis. The degenerative changes observed are more common in adults and are of varying grades of severity among individuals with cyanotic heart diseases. They are quite different from changes such as mitochondrial disruption, glycogen depletion, sarcolemmal damage and clumping of nuclear chromatin that are associated with acute myocardial ischemic necrosis. Jarmakani et al. quantitated right ventricular end-diastolic volume, ejection fraction and systolic output in patients with TOF, and speculated that the decreased ejection fraction was not due to decreased preload or increased afterload but due to impaired ventricular function secondary to chronic hypoxia. Adjunctive support of this
hypothesis is the decreased right ventricular ejection fraction in patients with transposition of the great vessels. These authors reported improved ventricular performance in a selected group (hemoglobin <16 gm/dl) of patients of TOF after an elective shunt procedure. As there is a direct relation between the severity and duration of cyanosis and hemoglobin concentration, it is possible that in a group of patients, prolonged and severe hypoxia leads to irreversible myocardial damage whereas in other groups, the hypoxic damage may be of lesser magnitude, phasic, and may be reversed by alleviating the hypoxia by shunt or corrective surgery. Our patient had signs of biventricular failure and there was no other discernible cause for the same. There was nothing to suggest viral myocarditis and there was rapid subjective and objective improvement after placement of the aortopulmonary shunt. The relatively large diameter of polytetrafluoroethylene graft (6 mm) increased the left-sided return and would likely have worsened CHF due to viral myocarditis. His dramatic improvement after shunting, the operative findings of classic TOF without associated defects and his good functional capacity 18 months after shunt placement and later total repair led us to believe that he developed cardiac failure due to hypoxia.

Histopathological analysis of the operatively resected crista at the time of total correction revealed marked interstitial fibrosis, myofibrillar lysis, varying degrees of cellular atrophy and proliferation of smooth endoplasmic reticulum. These findings suggest that depressed ventricular muscle function in patients of TOF is variable and may be related to histologic alterations.

Conclusions: Our patient illustrates an uncommon mechanism of CHF in TOF. Such children may benefit from a staging procedure prior to intracardiac repair. Further studies on the effect of duration and degree of hypoxia on myocardial structure and function are warranted.

References
Brief Report

Seroma Following Modified Blalock-Taussig Shunt Resulting in Subsequent Occlusion of the Shunt Which was Opened by Balloon Angioplasty

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We report the case of a 9-year-old boy with tetralogy of Fallot who had undergone left modified Blalock-Taussig shunt. The patient developed seroma around the shunt which was excised surgically. The patient developed total occlusion of the shunt post-operatively with clinical deterioration. We used emergency percutaneous angioplasty to successfully treat the patient. (Indian Heart J 2005; 57: 68-70)

Key Words: Blalock-Taussig shunt, Seroma, Congenital heart disease

Although modified Blalock-Taussig (BT) shunt is a common procedure carried out in patients with tetralogy of Fallot, seroma is a rare complication seen in these patients post-operatively. Our patient developed a seroma 3 months after surgery which was later excised by open thoracotomy. Post-operatively, the patient had clinical deterioration with total occlusion of BT shunt. The patient underwent an emergency percutaneous balloon dilation of the graft as a life-saving procedure.

Case Report

The patient, a 9-year-old boy was diagnosed to have tetralogy of Fallot associated with repeated cyanotic spells since the age of 6 months. However, he was not treated for the past 8 years. He was admitted to a public hospital in January 2004 and underwent a left modified BT shunt (size 6 mm). He was asymptomatic over the next 3 months. He started having intermittent fever since May 2004 and was initially treated by oral antibiotics (amoxicillin, cefuroxine) on outpatient basis. However, due to persistence of fever and dyspnea he was referred to us in the first week of June 2004. On examination he appeared toxic, cyanosed and dyspnic. There was a continuous murmur heard over the BT shunt site; however there was reduced air entry on the left side of the chest with dull percussion note.

His blood count revealed leukocytosis of 12,000/mm² with 80% neutrophils. Chest X-ray revealed a large homogeneous opacity suggestive of a mass lesion in the upper and middle lobe (Fig. 1). Echocardiogram revealed patent left BT shunt with other features of tetralogy of Fallot. On echocardiography no vegetation was seen, however there was gradient of 40 mmHg in the shunt with a large echogenic mass surrounding the shunt and encroaching on the left pulmonary artery. It was initially suspected to be a hematoma/pseudoaneurysm with thrombus. Blood cultures were negative. The computerized tomographic (CT) scan revealed a large homogenous mass in the left upper and middle zones of the lung around the BT shunt. An ultrasound-guided fine needle aspiration cytology yielded amber-colored turbid fluid which was difficult to aspirate, and on microscopy showed pus cells

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Fig. 1. Chest X-ray in posteroanterior view showing seroma (large homogeneous mass in the left upper zone of the lung) prominently.
and few red blood cells without any organisms. Detailed chemical analysis could not be undertaken due to inadequate quantity. On aspirate, pus cells was an unexpected finding as most of the seromas are sterile in nature. Bacterial cultures of the fluid were negative.

The patient was initially treated with intravenous antibiotics (vancomycin, amikacin and ceftazidime). However, since there was no improvement in the clinical condition, he was subjected to open thoracotomy on 15th June 2004. Histopathology revealed the mass excised from around the graft to be a seroma and measured 6 x 5 x 4 cm. The cut surface was grey white with few cystic areas measuring 4 mm each. Microscopy revealed the seroma cavity to be made up of fibrocollagenous tissue with moderate lymphocytic infiltrate.

His intraoperative course was relatively stable. Post-surgically, there was deterioration in the clinical condition with deepening cyanosis. He had severe hypoxia with an oxygen saturation of 28-30%. The echocardiography revealed a blocked BT shunt with no flow across it. After an attempt to correct the metabolic milieu, it was decided to take the patient to the catheterization laboratory for balloon dilation of the blocked BT shunt.

**Procedure:** The patient was transferred to the catheterization laboratory on the ventilator. His saturations at that point in time were around 22% to 28% with the systolic blood pressure of 75 mmHg. The patient had a right aortic arch. The left BT shunt was crossed with a 0.014" Galeo wire and was first dilated with a small 1.5 mm diameter balloon at its nominal pressure. Subsequent dilation was done with a 6 mm diameter balloon as the size of the BT shunt graft was 6 mm diameter. The flow improved remarkably, yet the oxygen saturation persisted to a maximum of 37%. Urokinase 80,000 units was infused locally over 20 min, this was followed by 2 mg of nicorandil (Figs 2 and 3).

Post-procedure, the oxygen saturation was around 37% and the blood pressure around 80 mmHg systolic. Two hours after the balloon dilation with the systolic blood pressure of 100 mmHg, his saturation improved to 92%, without any inotropic support. The patient had a remarkable recovery; he was subsequently discharged on propranolol and advised to undergo total correction.

**Discussion**

Aortopulmonary shunts are commonly performed in the patients of tetralogy of Fallot with hypoplastic pulmonary arteries. The surgical complications seen after shunt procedures are hematoma, pseudoaneurysm formation and shunt leakage. Seroma is a rare complication seen in these patients after BT shunt.1, 2 There are few case reports of seroma formation following shunt surgery in the medical literature.1, 3 Seroma formation in the mediastinum and/or thorax is seen following surgery involving the esophagus and the stomach.4 Seroma formation normally takes place within 2-3 months following surgery as was seen in our patient,1 however it may be seen even after 8 years.3 Seromas are collections of serum and lymph that become symptomatic or clinically apparent after operations in which subcutaneous lymphatic channels are disrupted.2 Seroma may contain multiple cystic areas some of which contain hemorrhagic fluid. Microscopically, seroma cavity is made up of fibrocollagenous tissue with lymphocytic infiltrate.3

![Fig. 2. The totally occluded Blalock-Taussig shunt.](image2)

![Fig. 3. Good flow is seen across the shunt after emergency balloon angioplasty.](image3)
Patients with seroma present with intermittent stridor, respiratory distress and/or episodic desaturation within weeks of surgery. Most of the seromas reported in medical literature are seen encompassing the graft. Aspiration, using sterile technique, with a large bore (14 to 16 guage) needle or angiocatheter followed by application of pressure dressing, may promote obliteration of the seroma and eventual healing. Chronic seromas may be difficult to obliterate with periodic aspiration and placement of closed suction drain may be necessary to prevent recurrence. Total occlusion of the BT shunt following excision of the seroma, as was seen in our case has not been reported. The cause of blockage of the shunt could be thrombosis within the graft (due to inadequate hydration) or trauma to the graft due to handling during the surgery. A total blockage of BT shunt causes clinical decompensation of the patient. Percutaneous balloon angioplasty of a stenosed BT shunt is a known modality of treatment in occluded shunts. Its safety and efficacy has been proved in experienced hands. This mode of intervention has proved to be life-saving in patients with acute closure/stenosis of the BT shunt.

References
Coarctation of Aorta Presenting as Acute Abdominal Pain

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Coarctation of aorta is the most common cardiovascular cause of secondary hypertension. The condition is correctable although early diagnosis is often not made. We report the case of a 9-year-old child who was admitted with severe intractable abdominal pain as the presenting symptom of post-subclavian coarctation of aorta with hypertension. His pain resolved after control of hypertension with parenteral antihypertensives and the narcotic analgesics. He subsequently underwent transcatheter balloon dilation of the coarctation of aorta and remains well with normal blood pressure on follow-up. (Indian Heart J 2005; 57: 71–72)

Key Words: Coarctation of aorta, Abdominal pain, Hypertension

A cute abdominal pain can be a distressing experience for a child as well as the treating doctor. Symptoms associated with surgically correctable causes include bile-stained vomitus, asymmetric pain, local tenderness and peritonism. We report the case of a 9-year-old child who was admitted to our hospital with severe intractable abdominal pain as the presenting symptom of post-subclavian coarctation of aorta with hypertension, the reasons for delay in its diagnosis and the definitive treatment given.

Case Report

A 9-year-old, previously healthy boy was admitted to the pediatric surgical ward of our hospital with acute abdominal pain. He was having severe colicky pain in the upper abdomen associated with vomiting of 5 days duration, with no relief of symptoms with parenteral antispasmodics. There was no history of fever, cough, skin rashes, diarrhea or dysuria. He looked sick, mildly dehydrated with a pulse rate of 86/min, respiratory rate of 28/min and blood pressure (BP) of 143/87 mmHg in the right upper limb. Local examination revealed a soft, flat abdomen with tenderness in the epigastrium and both iliac fossae. He was kept nil orally but needed frequent parenteral antispasmodics and narcotic analgesics for control of his severe abdominal pain. All baseline investigations including full blood count, sickle cell screen, blood sugar, urea, electrolytes, liver function tests and serum amylase were normal. His urine was negative for porphobilinogen and culture was negative. A day later he developed greenish vomitus but passed normal stools. Abdominal X-ray and ultrasound examination were normal. A barium meal and follow through examination was done to rule out malrotation, which was also normal.

In view of persistence of severe pain two days after admission, a pediatric medical consultation was requested. Abdominal examination was not contributory. However a detailed cardiovascular examination revealed feeble femoral pulses with systolic hypertension in the upper extremities (BP in left arm 173/105 mmHg, left leg 128/98 mmHg). Precordial examination showed normal heart sounds, systolic ejection click and grade 3/6 ejection systolic murmur in the upper left sternal border. The ocular fundi were normal. Electrocardiogram (ECG) revealed evidence of left ventricular hypertrophy. Chest X-ray showed cardiomegaly with the aortic indentation producing the reverse ‘E’ or ‘S’ sign. Echocardiogram showed severe post-subclavian coarctation of aorta with pressure gradient of 50 mmHg by Doppler and bicuspid aortic valve. The abdominal pain was considered secondary to the severe hypertension with reduction in renal and enteric blood flow, as no other cause of pain could be identified. The child was shifted to the pediatric intensive care unit and started on labetalol and morphine infusion for the control of severe hypertension and abdominal pain. Color Doppler study of the celiac axis and superior mesenteric artery were normal. After 24 hours, his hypertension and abdominal pain resolved. He was started on oral propranolol and cardiac
catheterization done later revealed classical post-subclavian coarctation (Fig. 1). He subsequently underwent elective transcatheter balloon dilation of coarctation of aorta in our hospital and remains well with normal blood pressure on follow-up.

Acute abdominal pain can be a distressing experience for a child and elucidation of its cause sometimes remains difficult for the treating doctor. Symptoms associated with surgically correctable causes include bile-stained vomiting, asymmetric pain, local tenderness and peritonism. Common causes of acute abdominal pain in children include appendicitis, mesenteric adenitis and non-specific abdominal pain. Uncommon causes include infective diarrhea, food poisoning, sickle cell crisis, gall stones, pancreatitis, peptic ulcer, acute intermittent porphyria, malrotation, intussusception, ureteric calculi, urinary tract infection, pneumonia, diabetic ketoacidosis and Henoch-Schönlein purpura. Coarctation of aorta is the most common correctable cardiovascular cause of hypertension. It occurs in 6% to 8% of all cases of congenital heart defects and twice as common in males. The diagnosis is often missed unless the patient develops congestive heart failure usually in early infancy or presents with a cardiac murmur and hypertension usually in older children. Symptoms of late presentation may also include headache, fatigue, chest pain, pain in the legs after exercise or rarely intracranial hemorrhage. The diagnosis of coarctation of aorta was obviously delayed in the surgical ward for the above child, due to lack of attention to the admission BP of 143/87 mmHg while in pain, an incomplete clinical examination and absence of a chest X-ray in the initial work up. Acute abdominal pain which responded only to parenteral anti-hypertensives and narcotic analgesics is a rather unusual presenting symptom of coarctation of aorta with hypertension and poorly documented in the medical literature. It has been reported after balloon dilation or surgical repair (post-coarctectomy syndrome) due to mesenteric arteritis. Aortic dissection is extremely rare in childhood. Complications of coarctation of aorta include hypertension, left ventricular failure, aortic dissection, premature coronary artery disease, infective endocarditis, and cerebrovascular accidents. Surgical repair or balloon angioplasty is indicated in patients with a transcoarctation pressure gradient of >30 mmHg. Post-procedure complications include residual or recurrent hypertension, recurrent coarctation, development of aortic aneurysm and the possible sequelae of associated bicuspid aortic valve. In a pediatric review regarding early diagnosis of coarctation of aorta, the mean and median ages at referral were 8.4 and 5.8 years, respectively. Since early detection and treatment are essential to prevent the complications, routine measurement of upper and lower limb blood pressures during at least one physical examination after the neonatal period is advisable.

In conclusion, this report describes the atypical presentation of post-subclavian coarctation of aorta in a 9-year-old child with severe intractable abdominal pain, the delay in its diagnosis and the relief of symptoms with appropriate therapy. It also underscores the importance of the traditional method of a complete physical examination, including measurement of the blood pressure in both upper and lower limbs.

References

Ruptured Left Sinus of Valsalva Aneurysm to Right Atrium

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A 6-year-old child presented with left sinus of Valsalva aneurysm opening in right atrium. Origin of sinus of Valsalva from left aortic sinus and its opening into right atrium is extremely rare. The anomaly was corrected surgically by patch closure at the aortic end. Follow-up echocardiography did not reveal any residual shunt in right atrium. *(Indian Heart J 2005; 57: 73–75)*

**Key Words:** Congenital heart disease, Sinus of Valsalva aneurysm, Aortic-cardiac fistula

The ruptured sinus of Valsalva aneurysm in children is infrequently reported. It may be congenital or acquired, and is often associated with ventricular septal defect (VSD) or aortic valve abnormality. A rare case of a six-year-old child presenting with left sinus of Valsalva aneurysm opening in right atrium is reported.

**Case Report**

A 6-year-old male child was evaluated for a systolic murmur at 6 months of age and was diagnosed having a small restrictive perimembranous VSD with left-to-right shunt with a peak velocity of 4.2 m/s across the defect on Doppler echocardiography. He was admitted with history of gradually progressive breathlessness of 1-year duration. Clinically, he was not anemic, blood pressure (BP) was 100/50 mmHg, heart rate was 96 beats per min (bpm) and jugular venous pressure (JVP) was elevated. Cardiac evaluation revealed volume-loaded left ventricular (LV) type of cardiomegaly with a loud continuous murmur in left parasternal area. Chest X-ray revealed pulmonary plethora with cardiomegaly. A 12-lead electrocardiogram (ECG) showed left ventricular hypertrophy (LVH) with right atrial (RA) enlargement. Two-dimensional (2D) echocardiography and Doppler evaluation showed dilated cardiac chambers without any evidence of VSD or patent ductus arteriosus. There was a high velocity continuous jet in RA at coronary sinus origin and left aortic sinus of Valsalva was dilated.

Patient was subjected to cardiac catheterization with a diagnosis of ruptured left sinus of Valsalva to RA, which revealed a significant step-up in oxygen saturation at RA level (Table 1). Catheter could not be negotiated from RA to left atrium (LA). An aortic root angiogram in postero-

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SaO2: oxygen saturation of blood; SVC: superior vena cava; RA: right atrium; RV: right ventricle; PA: pulmonary artery; LV: left ventricle

anterior (PA) view opacified dilated left coronary sinus with a fistulous track originating from the sinus opening into RA (Fig. 1). Selective left and right coronary angiography showed normal-sized coronary ostia with normal coronary arterial distribution. LV angiogram in 60° left anterior oblique (LAO) with 20° cranial angulation did not show VSD.

Patient was subjected to surgery with a diagnosis of ruptured left sinus of Valsalva to RA. Per-operatively, the aortic root was dilated and a thrill was palpable over RA. Aortic valve was tri-leaflet and competent. There was a patulous vertical opening of the track, which was located 1 cm posterior and superior to the ostium of left coronary artery. A probe put into fistula could be negotiated into RA through an oval opening in the posterior wall of RA situated just above the opening of coronary sinus. The aortic opening of the aneurysm was closed by horizontal mattress sutures and reinforced with Teflon buttresses carefully avoiding any injury to left coronary ostium. After the repair,
aortic valve and ostium appeared normal. At the time of discharge, Doppler echocardiography did not show any turbulent flow in RA. One year post-operatively, child was asymptomatic and his clinical and echocardiographic evaluation showed normal-sized cardiac chambers without any residual shunt detected at RA level.

Discussion

Ruptured sinus of Valsalva aneurysm is infrequently encountered in pediatric population. An aneurysm of sinus of Valsalva may be congenital or acquired, arising due to dehiscence in attachment of media of the aorta to the annulus fibrosus of the aortic valve ring leading to progressive dilation of the intervening wall and/or formation of fistulous track. They frequently occur with VSD or aortic valve abnormality underlining their congenital origin. Acquired ones are caused either by endocarditis, syphilis or atherosclerosis. Right sinus is involved in nearly 70% of all the patients and non-coronary sinus is involved in approximately 29%. They commonly protrude and rupture into right ventricle and RA.

The left sinus of Valsalva aneurysm, a rare anomaly, typically protrudes into anatomically adjacent cardiac structures i.e. LV, LA, pericardium, pulmonary artery or even the epicardium. Unruptured aneurysms of left sinus are typically symptom-free and are diagnosed during angiography or post-mortem. When symptomatic, they most often lead to coronary ischemia by involving the origin of left coronary artery, either by direct compression or by spontaneous dissection, presenting as an acute coronary syndrome and even cardiogenic shock. An intra-cardiac rupture occurs typically into LV or LA. A small rupture may be asymptomatic due to small shunt but classically it produces an aortocardiac fistula with a picture similar to acuteaortic regurgitation. Intracardiac rupture of left sinus of Valsalva into RA is extremely rare. It is probably because right-sided cardiac chambers are not in close proximity with the left sinus. A literature search revealed only 4 earlier antemortem case reports of rupture of left sinus of Valsalva to RA involving 7 patients. It can also rupture into pulmonary artery giving rise to aortic run off. Extra-cardiac rupture into pericardium may produce cardiac tamponade.

Etiopathogenesis of such anomalies also deserves mention. While the congenital nature of structural defect in the aortic root is considered to be the cause of aneurysm formation in almost all cases, presentation beyond fourth decade in the adulthood lends some credence to another mechanism – atherosclerosis, as a contributory factor to aneurysm formation. There are a few case reports suggesting Takayasu’s arteritis as the cause of aneurysm formation. Its association with VSD in more than half the patients and coexistence of aortic valve abnormality, aortic coarctation and Marfan’s syndrome favor a congenital origin. Bacterial endocarditis, chest trauma or syphilis may also be responsible for some cases. Rupture is generally believed to be spontaneous, partly depending on the size of aneurysm. Bacterial endocarditis occurring in an aneurysm may also lead to its rupture.

Echocardiography, both transthoracic and trans-esophageal, cardiac catheterization and angiography, helical computerized tomographic (CT) angiography and magnetic resonance imaging (MRI) are useful for confirmation of diagnosis and planning a surgical approach. It is generally believed that any aneurysm, ruptured or unruptured should be operated because of potential morbidity and mortality associated with it. Surgical correction involves removal of aneurysm and direct or patch closure of aortic defect, while protecting the aortic valve and origin of coronary arteries.

Present patient is unique in various ways. Firstly, origin of aneurysm from left sinus is rare. Its rupture into RA is even rarer. Rupture of aneurysm in a low-pressure chamber is generally an acute event but rupture in present patient was spontaneous as there was no history of acute event.
Presence of VSD during infancy in this patient is also unusual since VSD is almost always an association of right sinus aneurysm. Absence of involvement of coronaries despite aneurysm originating from the left sinus in our case is again unusual. Asymptomatic status of patient and normal echocardiogram after the surgical correction indicate the benefit of the surgical procedure in our case. However, there are no randomized trial data to support the surgical approach.

References

Thrombolytic Therapy for Acute ST Segment Elevation Myocardial Infarction: Should it be Given to All Patients?

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Anyone who has treated an ST segment elevation myocardial infarction (STEMI) with thrombolytic therapy knows that not all patients respond the way we would like them to respond. Ideally, the ST segment elevation should return to baseline, and the patient should become pain-free. When this happens, we congratulate ourselves because we have limited the infarction size and preserved viable myocardium. Unfortunately this does not happen in every case. The question is why does it not happen in every case?

Explanation for Failure of ST Segment Elevation to Return to Isoelectric Baseline

There can be several reasons. One of the explanations might be that the drug did not reach the clot that occluded the artery. Another explanation is that the clot burden was so great that the dose of the drug was not enough to penetrate the entire clot. A third possibility relates to pharmacogenetics, since all patients will not respond the same way to every drug given. This lack of uniform ST segment elevation reduction is quite evident when results of large clinical trials are analyzed.

Results of Clinical Trials

Clinical trials generally give average results. In every clinical trial there are hyper-responders and non-responders to any given drug including thrombolytic therapy. Thus, if the patient fails to respond (decrease of ST segment elevation) within 30 or 40 min to a thrombolytic drug, it might be worth considering adding another dose, recognizing the fact that the risk of bleeding may increase. However, since the goal is to get the artery open as soon as possible and reperfuse ischemic myocardium, one must make that judgment call based on the overall condition of the patient, i.e. a patient in cardiogenic shock due to an anterior myocardial infarction versus a patient with a stable inferior infarction.

Culprit Lesions versus Multivessel Thrombosis

Most cardiologists have not given much thought to multivessel coronary artery thrombosis in patients with STEMI. Recently, Garbo and colleagues reported few patients with acute thrombosis of several coronary arteries presenting with acute STEMI. The authors reported four cases of simultaneous multi-vessel thrombotic obstruction of the coronary arteries documented at coronary angiography and subsequently treated with coronary angioplasty.

Mechanism of Multivessel Coronary Artery Thrombosis

The mechanism of multiple vessel coronary thrombosis in patients with evolving “large” myocardial infarctions may be due to decreased cardiac output and poor perfusion of other vessels at risk. Another hypothesis is that the inflammatory process associated with acute coronary syndrome and coronary artery thrombosis is not limited to one blood vessel; there may be a generalized systemic arterial inflammation,thus setting up some sort of systemic prothrombotic condition with resultant multiple thromboses. However, the exact cause of simultaneous multivessel acute coronary occlusion of coronary arteries remains elusive and speculative and the number of patients who have this problem is unknown and perhaps infrequent.

Should We be Focusing on the “Culprit Lesion”?

Since coronary artery disease is really a systemic problem, focusing only on the culprit vessel that may be producing symptoms and causing electrocardiographic changes may be incorrect. Instead we should consider the possibility that multiple vessels are at risk and thrombolytic therapy may be the therapy of choice as first line treatment. In my opinion, one can attack this problem safely and effectively with thrombolytic therapy initially, followed by percutaneous coronary intervention (PCI) (angioplasty/stent).

Burke and Virmani indicate that the prevalence of multiple acute coronary artery thrombosis at autopsy varies from 25% to 50% of lethal acute thrombosis. However,
others have reported considerably fewer multiple coronary thrombi in sudden cardiac death patients, i.e. less than 10%. In an editorial on the reason for multiple site thrombosis, Falk\textsuperscript{3} speculates that several possibilities exist: (i) activation of smoldering inflammation and plaques with synchronized increase in thrombogenicity; (ii) simultaneous triggering of rupture-prone plaques; and (iii) simultaneous thrombosis on thrombosis-prone plaques, precipitated by a systemic thrombophilic state. Falk\textsuperscript{3} further suggests that since “atherosclerosis is a systemic disease it needs systemic treatment” and concludes that “a target lesion-based approach alone will not eliminate the threat posed by all other existing coronary plaques and their overall risk determines prognosis in the long-term.”

What does all of this mean for those of us who see patients with acute myocardial infarction? The information made one think about how important it is to use thrombolytic therapy in these patients even though one might opt for acute emergent angioplasty. It has always been my bias that unless there is no delay in getting a patient to the catheterization laboratory, the patient should receive thrombolytic therapy prior to going to the catheterization laboratory if the laboratory is not immediately available. If the ST segments return to baseline and the patient becomes pain-free and the vessels demonstrate grade 3 TIMI flow and TIMI myocardial perfusion, perhaps one can relax (although some believe that PCI/stent is good therapy even in this circumstance). But, if these conditions do not result, angioplasty of the culprit lesion is certainly warranted.

**Conclusions**

Cardiologists must be aware of the possibility of multiple site coronary thromboses in patients who are slow responders to thrombolytic therapy. Although it may be a rare clinical finding, the single culprit vessel concept in unstable coronary artery disease patients needs to be challenged, since, as many have pointed out, this is a systemic disease that needs systemic treatment. A target lesion-based approach will not limit the threat posed by all other existing coronary plaques. Thus, to answer the question posed in the title of this article, I believe that thrombolytic therapy should be given in all patients with acute STEMI unless there is a contraindication. Randomized clinical trials are underway to test this hypothesis.

**References**

Cobra Head Deformity of Amplatzer Septal Occluder

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A 32-year-old female with symptoms of increasing dyspnea and a large ostium secundum atrial septal defect (ASD) was referred to us for possible transcatheter closure of the same. On echocardiography, a 32 mm ostium secundum ASD with left to right shunt was noted with no other associated anomalies. The defect had adequate tissue margins along the mitral valve, coronary sinus and right upper pulmonary vein. She was taken up for balloon sizing of the defect and possible percutaneous closure with an Amplatzer septal occluder (ASO) device. Using a 37 mm sizing balloon (Meditech, Boston Scientific, USA) the stretched diameter of the defect was assessed to be 38 mm. So, a 40 mm ASO (AGA Medical, Minnesota) was selected to close the defect under fluoroscopic and transesophageal echocardiographic (TEE) guidance. The device attached to its delivery cable was introduced into the left atrium through a 14 F Mullins sheath (Cooks, USA). There was no problem in negotiating the device through the delivery sheath to the left atrium. Following release of the left atrial disc into the left side of the ASD with the waist aligned properly across the septum (as seen on TEE), the delivery sheath was withdrawn further to release the right atrial disc. But on release, the right atrial disc failed to achieve its proper configuration. On TEE, no structures could be seen in the right atrium that could prevent the device from opening fully. Further, in bicaval view the right atrial disc was seen lying within the right atrial cavity without protrusion into the superior or inferior vena cava that could have also prevented the right atrial disc from expanding fully. The unexpanded right atrial disc along with the waist with a normally opened left atrial disc gave the appearance of the head of a cobra snake best seen in the 40º left anterior oblique with 30º cranial view (Fig. 1). As there were no structures restricting the opening of the right atrial disc, we felt that the large right atrial disc along with the waist may have rotated preventing it from regaining its normal
shape. So the device attached to its delivery cable was rotated in a clockwise direction that resulted in the disc and waist assume their normal shape (Fig. 2). Keeping the possibility of spontaneous rotation (maybe in anti-clockwise direction), we rotated the delivery cable in clockwise direction to see if the device could be untwisted. By this simple manipulation the device untwisted and regained its normal memory and shape. However, if clockwise rotation failed to undo the twist, we were prepared to withdraw the device within the delivery sheath, take it outside, untwist it manually and then reload it for implantation because anti-clockwise rotation of the delivery cable carried the risk of unlocking the device during rotation within the sheath. After the device regained its normal shape, there was no problem in unscrewing the device from the delivery cable. Realization of this simple fact and the manipulation led to successful deployment of the 40 mm ASO device without any residual shunt.

The ASO made from nitinol wires exhibit excellent shape memory. This allows the device to be introduced through a relatively small sheath and return to its original configuration when released into an unrestrained position from the delivery sheath. However, certain abnormal stress on the device can alter its shape memory and cause it to assume abnormal shapes. Cobra head deformity of the left atrial disc along with the waist has been well described by Cooke et al.\(^1\) The mechanisms proposed by Cooke et al.\(^1\) are: (i) opening of the device against the wall of atrium, atrial appendage or pulmonary vein orifice, (ii) difficulty during loading of the device resulting in abnormal stress on the device affecting its shape memory, or (iii) twisting of the device during advancement against resistance through a smaller sheath. However, none of these factors were present in our case. Till now only one case of cobra head deformity secondary to incomplete opening of the atrial disc has been described and the mechanism proposed is spontaneous rotation of the disc in ASO devices >18 mm (because of greater length of wire between the disc margin and the center of the device) that compromises the device memory.\(^2\) This same phenomenon occurred in our case and simple clockwise rotation of the delivery cable attached to the device led to the cobra hide its unpleasant head quickly. It is important for every interventionist to be familiar with this complication, as it can be easily corrected if recognized before delivery of the device.

**References**

Electrocardiographic Changes in Submassive Pulmonary Embolism

Surface electrocardiograms (ECG) of 37 documented cases of submassive pulmonary embolism were evaluated after excluding various confounding factors like pulmonary disease, intraventricular conduction defects, old myocardial infarction, left ventricular systolic dysfunction and electrolyte imbalance. Twenty-seven patients had evidence of pulmonary embolism on computed tomography (CT) of thorax and 10 patients had ventilation-perfusion scan suggestive of pulmonary embolism. A 19-lead ECG (including leads I to V9 and V3R to V6R) was recorded in all cases at the time of admission and subsequently daily for next 4 to 6 days of hospitalization. Sinus tachycardia was the commonest finding (67.6%). Other findings with decreasing frequency were S wave of any magnitude in lead I (56.7%), S wave of > 1.5 mm in leads I and aVL (54%). ECG findings, conventionally considered suggestive of right ventricular overload, had very low sensitivity [S, Q, T > 20 mm in lead I; Q, T > 20 mm in leads V1-V6].

T wave inversion (8.1%) and ST segment elevation (5.4%) in leads V1 to V6 was the commonest new change observed in sequential ECG recorded during 48 hours following admission. Twenty-one (56.7%) patients had ST segment depression in leads V1, V4; 18.9% of patients had ST segment depression in leads V1-V4. Small subendocardial right ventricular infarct can also produce similar ECG finding. ST segment elevation with Q wave in any one of the right precordial leads (V3R to V6R) was observed in 37.8% cases at admission. Other workers8,9 have observed that there is always some time delay between onset of symptoms and appearance of this electrocardiographic finding. Mechanism of this ECG change and reason for delay after onset of symptoms is not clear. Progressive right ventricular dilatation with secondary right ventricular ischemia could be held responsible for it. Ciurzynski et al.2 also described a direct correlation between end-diastolic right ventricular diameter and sum of negative T waves in V1-V6. Small subendocardial right ventricular infarct can also producesimilar ECG finding. ST segment elevation with negative deflection of P wave in lead V1 was observed less frequently (54%) and S>R in lead I (RAD) was still less frequent (18.9%). Therefore, even small S wave in lead I is important, more so if it is a new transient change. Clear RAD (R/S < 1 in lead I) was seen in only 20.6% of our cases on day 1 and one more patient developed it on subsequent ECG. Petrov1 observed RAD without right bundle branch block (RBBB) in only 20% cases of massive pulmonary embolism. Ciurzynski et al.2 also reported it in less than one-third cases of hemodynamically significant pulmonary embolism. This ECG finding, therefore, has very low sensitivity. S, Q, T was observed in 40% of our cases on day 1. Another 3 (5.4%) cases developed it on subsequent days. Prevalence of this finding has ranged from 3% to 60% in previous studies of massive pulmonary embolism. Its incidence is still lower in non-severe pulmonary embolism.3 Thus, this electrocardiographic finding has low sensitivity in diagnosing both massive and submassive pulmonary embolism. In our study, S, Q, T alone were present only in 40% of our cases in our study. Previous studies have reported an incidence of 0-1% in small emboli4,5 and 7-26% in patients of massive pulmonary embolism. P-pulmonale, therefore, has low sensitivity even in patients with massive pulmonary embolism. Ciurzynski et al.2 observed p-pulmonale only in patients with symptom duration of > 14 days. In the study of Cutforth and Oram,1 5 out of 6 patients with p-pulmonale showed this finding only after 1 to 9 days. Any increase in P-wave height over an ECG recorded before embolism or in subsequent ECG recorded during hospitalization can be a useful diagnostic clue for pulmonary embolism.

ST segment elevation and T wave inversion in leads V1-V6 was the commonest sequential ECG change. Cutforth and Oram1 also observed that depth of T wave inversion in leads V1-V4 may increase sequentially over next 2-3 days without any fresh embolism. Ferrari et al.2 also observed that there is always some time delay between onset of symptoms and appearance of this electrocardiographic finding. Mechanism of this ECG change and reason for delay after onset of symptoms is not clear. Progressive right ventricular dilatation with secondary right ventricular ischemia could be held responsible for it. Ciurzynski et al.2 described a direct correlation between end-diastolic right ventricular diameter and sum of negative T waves in V1-V6. Small subendocardial right ventricular infarct can also producesimilar ECG finding. ST segment elevation with Q wave in any one of the right precordial leads (V3R to V6R) was observed in 37.8% cases at admission. Other workers8,9 have observed that this is a very early but transient sign of moderate to severe pulmonary embolism. Prominent R wave and ST segment elevation in lead aVR are considered signs of pulmonary embolism10,11 but detailed information regarding changes in this lead are not available. We found R wave of > 2 mm and ST elevation of > 1 mm in 18.9% and 32.4% cases, respectively on day 1. Thus, changes in lead aVR alone have low sensitivity in diagnosing pulmonary embolism.

ECG evidence of left atrial (LA) overload i.e. p-mitrale or prominent negative terminal deflection of P wave in lead V1 was seen in 8% cases in our study. Significant right atrial (RA) enlargement is also known to produce prominent negative deflection of P wave in lead V1.12 A cute RV dilation
shifts interventricular septum (IVS) to left resulting in increased left ventricular end-diastolic pressure (LVEDP). This could also strain LA. We are, however, not sure if pulmonary embolism resulted in this finding or this ECG abnormality was present in these patients prior to embolism. We observed LAD in 13.5% cases. Presence of LAD prior to embolism could not be excluded in these patients. Other have also reported this finding. However, Lynch et al. observed that leftward shift of frontal plane QRS axis was common in pulmonary embolism and an axis <30 at the time of onset of symptom was twice as frequent as RAD. No satisfactory explanation for such occurrence is available.

We observed deep S wave (>20 mm) in leads V1-V3 in 16.2% of our cases. Dilated right ventricle occupying whole of anterior aspect of heart and displacing left ventricle posteriorly could explain this finding in some of our cases. ST segment depression in leads V1-V6 or in leads I, II, V5-V6 was seen in 18.9% and 56.7% cases, respectively in our study. Watanabe et al. described ST segment depression in leads V5-V6 with T wave inversion in III, aVF, V1 to V3 in patients of pulmonary embolism during episodes of pulmonary embolism. Ahonen noted ST segment depression in leads I, V5 and V6 in 74% cases of fatal massive pulmonary embolism. ST segment depression in precordial leads could be due to RV dilation, clockwise rotation and shift of transition zone to left. Hypoxia or concomitant coronary artery disease could also contribute to this ECG finding.

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Optimizing Intra-Aortic Balloon Timing by Pulse Oximeter Tracing

Intra-aortic balloon pump (IABP) is the most widely used cardiac assist device, and is the mainstay of therapy in patients with acute coronary syndrome, post-cardiotomy cardiac failure and elective pre-operative use in high risk patients for myocardial revascularization. It is important to get the ideal point for inflation and deflation of the balloon to get the maximum benefit from balloon pumping and avoid the deleterious effects of improper timing. Initial manual timing is mandatory and is done by a visual adjustment against the direct arterial trace. We describe a simple technique of optimizing timing when a reliable and crisp direct invasive arterial trace is not available.

We used the probe of the pulse oximeter attached to one of the fingers of the hand. The trace of the pulse oximeter is sharp (Fig. 1) as compared to the damped direct arterial waveform. The exact timing of inflation is adjusted at the dicrotic notch as seen on the pulse oximeter trace. Similarly, the exact point of deflation is adjusted using the visual display on the screen.

Proper intra-aortic balloon timing interfaces balloon actuation with the mechanical events of the cardiac cycle. The resultant counterpulsation augments aortic pressure during diastole and reduces peak pressure during systole. One of the most important factors upon which optimal augmentation depends is timing of inflation. The latest generation of intra-aortic balloon pump has become quite sophisticated with advanced computer microprocessor units which allow accurate timing. However, initial manual determination of inflation and deflation points are required before automatic timings can be effectively used. In the manual mode, the operator examines the point of inflation superimposed over the arterial waveform while finetuning the delay interval to synchronize inflation with diastole. The control for deflation essentially determines the duration of inflation. Failure to adjust timing parameters can result in ineffective diastolic augmentation or allow prolonged balloon inflation with its attendant deleterious effects. With late inflation of the balloon, the period of diastolic augmentation is shortened with sub-optimal coronary perfusion and reduced therapeutic effects. Early inflation before the closure of the aortic valve is more deleterious with increased myocardial wall stress, increased left ventricular end-diastolic volume and pressure (LVEDV and LVEDP), aortic regurgitation, decreased cardiac output and possible intra-cardiac shunting if mechanical defects are present. Early deflation before isovolumetric contraction will reduce the therapeutic effects of counterpulsation. There will be suboptimal coronary perfusion, potential for retrograde coronary and carotid blood flow and suboptimal afterload reduction and increased myocardial oxygen consumption (MVO₂). With late deflation left ventricular ejection is impeded, afterload and MVO₂ are increased and there may be adverse hemodynamic consequences in patients who have true ventricular aneurysm, mitral regurgitation or ventricular septal defect.

The only accurate method of adjusting the timing manually is to finetune the point of inflation and deflation according to the arterial waveform. Quite often the arterial waveform from the balloon lumen may get damped as the pressure line in the lumen of the balloon is very narrow and long. Similarly the waveform in the contralateral femoral line may be damped as it is below the balloon. The radial artery line in a post-operative patient may also be damped. In cases requiring prolonged IABP support reliable arterial line may not be available. Therefore, the operator may have no accurate means of determining whether the balloon timing is optimal.

We have noted that the trace of the pulse oximeter with the probe placed on any finger of the hand can give a good idea of the timing of inflation and deflation. The trace corresponds very accurately with the direct invasive arterial trace. The pulse oximeter has dual wavelength spectrophotometers with plethysmographic capabilities that function by placing a pulsating arterial vascular bed between a 2-wavelength light source and a light detector. We have used this method in 50 cases to optimize IABP timing. In all these cases the direct arterial waveforms were damped. We crosschecked the accuracy of this method by
comparing the waveforms in 25 cases where the intra-aortic balloon was inserted electively and the arterial waveform was crisp. The arterial waveform and the pulse oximetry trace matched very well and there is a good temporal relationship between the two. We have previously successfully used the pulse oximeter trace to confirm the presence or absence of distal leg perfusion where Doppler examination was inconclusive.

Our simple technique provides a good visualization of the optimal timing of IABP and is recommended in cases where the direct arterial trace is damped. It may be useful for the designers of IABPs to integrate a pulse oximeter module also in the console so that the point of inflation and deflation can be superimposed on the pulse oximeter trace for optimizing balloon timing.

References

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Randomized, Placebo-Controlled Trial of Adding Clopidogrel to Aspirin in 46,000 Acute Myocardial Infarction Patients (COMMIT/CCS-2 - Clopidogrel)

Presented at ACC, 2005

The aim of the present trial was to evaluate the role of clopidogrel compared with placebo among patients with ST elevation myocardial infarction (MI) presenting within 24 hours of symptom onset. Patients were randomized to up to 4 weeks of treatment with clopidogrel (75 mg/day; n=22,958) or placebo (n=22,891). All patients were also given aspirin 162 mg/day. Those undergoing primary angioplasty or with a high risk of bleeding were excluded. Patients were also randomized in a factorial design to treatment with metoprolol or placebo. Baseline characteristics were comparable between the treatment arms. Fibrinolytic therapy was used in 50% of patients and anticoagulants in 74%. Other concomitant medications included angiotensin-converting enzyme (ACE) inhibitors (68%), nitrates (94%), anti-arrhythmics (22%), diuretics (23%), and calcium antagonists (12%). The primary endpoint of all-cause mortality by hospital discharge (mean 16 days) was significantly lower in the clopidogrel group (7.7%, n=1728 v. 8.1%, n=1846, p=0.03). Additionally, the co-primary composite endpoint of death, reinfarction, or stroke was lower in the clopidogrel group (9.3%, n=2125 v. 10.1%, n=2311, p=0.002). Reinfarction was lower in the clopidogrel group (2.1% v. 2.4%, p=0.02) but stroke did not differ by treatment group (0.9% v. 1.1%, p=NS). Despite the lack of a loading dose in this trial, the endpoint curves began to diverge as early as day one. Any major bleed occurred in 0.58% of the clopidogrel group and in 0.54% of the placebo group (p=NS). However, the incidence of minor bleeding was not reported, and it is unknown if the risk of bleeding would be higher had patients undergone revascularization. Benefit of clopidogrel in primary composite endpoint was observed in all of the pre-specified subgroups, including gender, age, time from symptom onset, and fibrinolytic use. In conclusion, among patients with ST elevation MI, treatment with clopidogrel was associated with a reduction in mortality and in the composite of death, MI or stroke compared with placebo as was also shown in CLARITY-TIMI 28 trial. Clopidogrel prevented 10 major vascular events per 1000 patients treated without any increase in major bleeding.

Paclitaxel-Eluting Stent v. Sirolimus-Eluting Stent for the Prevention of Restenosis in Diabetic Patients with Coronary Artery Disease (ISAR DIABETES)

Presented at ACC, 2005

The aim of the present randomized, single center trial was to evaluate the role of paclitaxel-eluting stent, Taxus compared with sirolimus-eluting stent, Cypher among diabetic patients with symptomatic coronary artery disease with de novo lesions. Patients were randomized to stent implantation with either the Taxus stent (n=125) or Cypher stent (n=125). Patients underwent angiographic follow-up at 6-8 months. Baseline clinical and angiographic characteristics were comparable between the treatment groups, with a lesion length of 12.4 mm in the Taxus group and 13.8 mm in the Cypher group. The primary endpoint of late in-stent lumen loss at angiographic follow-up at 6 to 8 months was 0.67 mm in the Taxus group and 0.43 mm in the Cypher (p=0.86 for non-inferiority; p=0.002 for superiority of the Cypher v. the Taxus group). Angiographic restenosis occurred more frequently in the Taxus group (16.5% v. 6.9%, p=0.03). Target lesion revascularization at 9 months was performed in 12.0% of the Taxus group and 6.4% of the Cypher group (p=0.13). There was no difference in 9-month mortality (4.8% for Taxus v. 3.2% for Cypher, p=0.52) or myocardial infarction (2.4% v. 4.0%, p=NS). Among diabetic patients with coronary artery disease, treatment with the sirolimus-eluting stent was associated with a lesser late lumen loss at 6-8 months angiographic follow-up compared to treatment with the paclitaxel-eluting stent. Whether the angiographic benefits will also lead to clinical improvement needs to be further evaluated. The results of the present trial should be restricted to high-risk population of diabetic patients, and should not be extrapolated to other patient subgroups.
Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent (Cypher) and the Paclitaxel-Eluting Stent (Taxus) (REALITY)

Presented at ACC, 2005

The present trial was conducted to evaluate efficacy and safety of sirolimus-eluting stent (SES), Cypher compared with paclitaxel-eluting stent (PES), Taxus among patients with de novo coronary lesions. Patients were randomized to stent implantation with either Taxus (669 patients with 941 lesions) or Cypher (684 patients with 970 lesions). Direct stenting was allowed. Use of aspirin and clopidogrel and glycoprotein IIb/IIIa inhibitor was at the physician’s discretion. There were 1911 lesions in the 1353 patients with an average of 1.94 stents used per patient. Baseline clinical and angiographic characteristics were well-matched between the treatment groups, with 28% diabetics. Lesions were relatively complex, with 86.4% classified as BII or C, 27.6% >20 mm in length, and 5.2% bifurcation lesions. Procedural success was 95% in each group. At 8 months angiographic follow-up, Cypher group had larger in-stent minimum lumen diameter (2.00 mm v. 1.85 mm), less late in-stent lumen loss (0.09 mm v. 0.31 mm), and reduced percent diameter stenosis (23.1% v. 26.7%), (p<0.0001 for all comparisons). However, the primary endpoint of binary in-lesion restenosis did not differ between the treatment groups (9.6% for Cypher group v. 11.1% for Taxus stent group, p=0.32). At 8 months clinical follow-up, there was no difference in secondary endpoint of major adverse cardiac event (MACE) (9.2% for Cypher group v. 10.6% for Taxus group, p=0.41) or any component of MACE (death 1.8% v. 1.2%, p=0.50; myocardial infarction (MI) 4.8% v. 5.5%, p=0.62; target lesion revascularization 5.0% v. 5.4%, p=0.81, respectively). Stent thrombosis by 30 days was higher in the Taxus stent group (1.8% v. 0.4%, p=0.0196 for as-treated analysis; 1.6% v. 0.6%, p=0.0723 for intent-to-treat analysis). In conclusion, among patients with de novo coronary lesions, despite better angiographic parameters at 8 months i.e. minimum lumen diameter, late lumen loss, and percent diameter stenosis in the Cypher group, there was no difference in the primary endpoint of binary restenosis or in the clinical MACE rate at 8 months, suggesting both drug-eluting stents are effective in reducing restenosis. Although the absolute number of stent thrombosis was small, the increase in-stent thrombosis through 30 days in Taxus group needs close observation.

Arterial Revascularization Therapies Study Part II: Sirolimus-Eluting Stents for the Treatment of Patients with Multivessel de novo Coronary Artery Lesions (ARTS-II)

Presented at ACC, 2005

The present trial was conducted to evaluate efficacy and safety of sirolimus-eluting stents (SES) in patients with multivessel disease. Six hundred and seven patients were enrolled in the registry in a non-randomized, open-label manner and treated with SES. Patients with left ventricular ejection fraction (LVEF) of < 30%, overt congestive heart failure, history of cerebrovascular accident, transmural myocardial infarction (MI) in previous week, severe hepatic or renal disease, diseased saphenous veins, neutropenia or thrombocytopenia, intolerance or contraindication to aspirin or clopidogrel, or need for major surgery were excluded from the study. Patients were compared to historical controls from the Arterial Revascularization Therapies (ARTS)-1 trial, both coronary artery bypass graft (CABG) surgery (n=602) as well as bare metal stents (BMS) arms (n=600). Few baseline differences were found when comparing patients from present trial with ARTS-1 patients. In ARTS-2, patients were more frequently diabetic (26.2% v. 18.2%) and they more often had 3-vessel disease (54% v. 28%). Lesions were more frequently complex (13.9% v. 7.5% Type C lesions). More stents were implanted per patient than in ARTS-1 BMS (3.7 v. 2.8) group and longer lengths of stent were implanted (73 mm v. 48 mm). Looking at the primary endpoint at 1 year, there was no difference in the incidence of major adverse cardiac and cerebrovascular events (MACCE) comparing the ARTS-2
Randomized, Placebo-Controlled Trial of Early Metoprolol in 46,000 Acute Myocardial Infarction Patients (COMMIT/CCS-2-Metoprolol)

Presented at ACC, 2005

The aim of the present trial from China was to evaluate the role of beta-blocker, metoprolol compared with placebo among patients with ST elevation myocardial infarction (MI) presenting within 24 hours of symptom onset. Patients undergoing primary angioplasty and with systolic blood pressure <100 mmHg, heart rate <50 beats per minute (bpm), or II/III degree atrioventricular (AV) block were excluded. Patients were randomized to treatment with metoprolol (3 intravenous injections of 5 mg each followed by oral 200 mg/day for up to 4 weeks; n=22928) or placebo (n=22923). All patients were also given aspirin 162 mg/day. Patients were also randomized in a factorial design to treatment with clopidogrel or placebo. Fibrinolytic therapy was used in 50% of patients and anticoagulants in 74% patients. Baseline characteristics were comparable between the two treatment groups. Anterior infarction was in 50% of patients. First intravenous injection of study drug treatment was given in 98.5% of patients in the metoprolol group and 98.6% in the placebo group and all three injections were given in 90.2% and 96.0%, respectively. Oral treatment was completed in 86.2% and 91.6%, respectively. There was no difference in the primary endpoint of death, reinfarction or cardiac arrest by treatment group at hospital discharge (7.7% vs. 7.8%, p=NS). Reinfarction was lower in the metoprolol group (2.0% vs. 2.5%, p=0.002). Ventricular fibrillation occurred less frequently in the metoprolol group (2.5% vs. 3.0%, p<0.001) but there was no difference in other cardiac arrests (3.8% vs. 3.9%, p=NS). Death due to shock occurred more frequently in the metoprolol group (2.2%, n=496 vs. 1.7%, n=384), while death due to arrhythmia occurred less frequently in the metoprolol group (1.7%, n=388 vs. 2.2%, n=498). Cardiogenic shock was overall higher in the metoprolol group (5.0%, n=1141 vs. 3.9%, n=888, p<0.0001). Particularly early in the treatment period (2.1% vs. 1.4% on day 0) and among patients with Killip class II (7.9%) vs. 6.5%) or class III (16.2% vs. 10.4%). Among patients with ST elevation MI, treatment with metoprolol was not associated with a reduction in the primary endpoints of death, reinfarction or cardiac arrest compared with placebo. There was a reduction in reinfarction in the metoprolol group. However, cardiogenic shock and death from shock occurred more often in patients treated with metoprolol, especially in those with reduced left ventricular function, as demonstrated by the Killip class. Additionally, the risk was largest early in the treatment period on days 0 and 1, suggesting that intravenous therapy during the acute phase of the infarction should be avoided.
Prospective Evaluation of Enhanced External Counter Pulsation in Congestive Heart Failure (PEECH)

Presented at ACC, 2005

Enhanced external counter pulsation (EECP) therapy has previously been shown to be beneficial for patients with chronic stable angina. However, data in patients with heart failure are scarce. The aim of the present trial was to evaluate the role of EECP in patients with stable heart failure with NYHA Class II or III symptoms, ischemic or non-ischemic etiology, left ventricular (LV) ejection fraction <35%, optimal pharmacologic therapy, ability to exercise >3 min, limited by shortness of breath or fatigue (not by angina). Patients were randomized to EECP with optimal pharmacologic therapy (n=93) or optimal pharmacologic therapy alone (n=94). EECP therapy consists of a series of inflatable cuffs that are rapidly inflated at the onset of diastole and rapidly deflated at the onset of systole in order to replicate the hemodynamic properties of intra-aortic balloon counter pulsation. EECP was administered for 35 sessions of 1-hour each and continued for 7 weeks. Patients underwent exercise stress test at baseline and 3 months. Optimal pharmacologic therapy included angiotensin-converting enzyme (ACE) inhibitors (76%) or angiotensin receptor blockers (ARB)(19%) and beta-blockers (85%). Baseline characteristics were well balanced between treatment groups. Ischemic etiology was present in 69% of patients and 65% were in NYHA class II. Baseline ejection fraction was 26%. Increase in exercise duration by at least 60 s at 6 months occurred more frequently in the EECP group compared with controls (35.4% v. 25.3%, p=0.016). There was no difference in the co-primary endpoint of increase in peak VO₂ of at least 1.25 ml/min/kg between groups (22.8% for EECP v. 24.1% for control, p=NS). Change in exercise duration was longer in the EECP group compared with control as early as one week (26.4 s increase v. 10.0 s decrease, p=0.01) and maintained through 6 months (24.7 s increase v. 9.9 s decrease, p=0.01). Improvement in NYHA class was more common in the EECP group compared with controls at 1 week (33.3% v. 11.4%, p<0.001) and maintained through 6 months (31.3% v. 14.3%, p<0.001). Change from baseline in Minnesota Living with Heart Failure score was greater in the EECP group at 1 week (-8.9 v. -3.4, p=0.01) and 3 months (-7.1 v. -2.9, p=0.01) but did not differ at 6 months (-3.7 v. -2.9, p=NS). Serious adverse events were reported in 30.3% of the EECP group and 29.5% of the control group (p=NS). In conclusion, among patients with systolic dysfunction, stable heart failure symptoms and treated with optimal pharmacologic therapy, use of EECP was associated with improvement in exercise duration, NYHA class and quality of life but no difference in change in peak VO₂ compared with optimal pharmacologic therapy alone.

Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTAX)

Presented at ACC, 2005

The aim of the present trial was to compare efficacy of sirolimus-eluting stent, Cypher with paclitaxel-eluting stent, Taxus among patients with coronary artery disease (CAD). Patients were randomized to stent implantation with either the Cypher stent (n=503) or the Taxus stent (n=509). There were no restrictions on lesion site, number of lesions, lesion complexity, or length of lesions. In a pre-specified manner, a subset of 600 patients underwent angiographic follow-up at 8 months. The study was conducted at a single institution and was funded wholly by the hospital. All patients received aspirin (100 mg/day), clopidogrel (300 mg loading dose and 75 mg/day subsequently) and unfractionated heparin. There were 1401 treated lesions in the 1012 patients, with an average of 1.2 stents used
Intracoronary Autologous Bone-Marrow Cell Transfer after Myocardial Infarction: A Double-Blind, Randomized, and Placebo-Controlled Clinical Trial

Presented at ACC, 2005

The aim of the present trial was to evaluate the role of intracoronary autologous bone-marrow cell transfer compared with placebo after myocardial infarction (MI) on functional recovery. Within 24 hours of acute MI following successful percutaneous coronary intervention (PCI), patients were randomized in a double-blind fashion to intracoronary autologous bone-marrow cell transfer (n=32) or placebo (n=34). Bone marrow aspiration was performed and transferred to an open infarct-related artery. Bone-marrow cell harvest volume averaged 130 ml, with 304 million total nucleated cells and 172 mononuclear cells. The transfer was performed intracoronary using over-the-wire balloon catheter during 3 coronary occlusions, each lasting 2-3 min. The infarct artery was the left coronary in 62% of patients and the right coronary in 37%. Patients were monitored in-hospital for 7 days and underwent follow-up through 4 months. Positron emission tomography (PET) and magnetic resonance imaging (MRI) were performed at the initial hospitalization and at 4 months follow-up. Post-PCI, TIMI flow grade 3 was present in 91% of patients. All but 1 patient received aspirin, and glycoprotein IIb/IIIa inhibitors were used in 78% of the patients. Baseline clinical and angiographic characteristics were comparable in the two treatment groups. Presenting syndrome was stable angina in 49%, acute coronary syndrome in 51%, and ST elevation myocardial infarction in 22% of the patients. Device success occurred in 99% of patients. The primary endpoint of major adverse coronary event (MACE) at 9 months was lower in the Cypher group compared to the Taxus group [6.2% v. 10.8%, hazard ratio (HR) 1.80, 95% CI 1.16-2.80, p=0.009]. Individual components of 9 months MACE were death (1% v. 2.2%, p=NS), MI (2.8% v. 3.5%, p=0.148), and target lesion revascularization (4.8% v. 8.3%, HR 1.77, p=0.025) for the Cypher stent and the Taxus stent groups, respectively. The endpoint of target vessel failure was also lower in the Cypher stent group (7.0% v. 11.6%, p=0.012). Stent thrombosis did not differ by treatment group (2.0% for the Cypher stent group and 1.6% for the Taxus stent group). On subgroup analysis, the treatment benefit in the primary endpoint for the Cypher stent group was notably better in diabetics (HR 3.27, p=0.013) than the non-diabetics (HR 1.51, p=0.110). Among the angiographic cohort, late lumen loss was lower in the Cypher stent group compared with the Taxus stent group both—in-stent (0.13 mm v. 0.25 mm, p<0.001) and in-lesion (0.19 mm v. 0.32 mm, p=0.001). Likewise, binary restenosis was also lower in the Cypher stent group compared to the Taxus stent group—in-stent (3.2% v. 7.6%, p=0.013 and in-lesion (6.7% v. 11.9%, p=0.02). In conclusion, among patients with CAD, treatment with the sirolimus-eluting stent, was associated with a reduction in MACE at 9 months compared to treatment with the paclitaxel-eluting stent driven primarily by a reduction in the need for target lesion revascularization.
recent reperfusion therapy following MI, treatment with intracoronary autologous bone-marrow cell transfer was associated with reductions in infarct size compared with placebo but was not associated with changes in LV systolic functional recovery. Additionally, bone-marrow transfer was not associated with an increase in myocardial blood flow or oxidative metabolism on PET scan.
Calendar of Conferences/CSI Executive Committee

December 1-4, 2005, 57th Annual Conference of Cardiological Society of India and 15th Asian Pacific Congress of Cardiology, Mumbai, India

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Santanu Guha, Kolkata
S B Gupta, Mumbai
Balram Bhargava, New Delhi
Satyendra Tewari, Lucknow
Dhiman Kahali, Kolkata
Rakesh Gupta, New Delhi
C Lakshmikantan, Chennai
A K Maity, Kolkata
Bikash Kumar Chatterjee, Kolkata
B N Shahi, New Delhi

Immediate Past President
R J Manjuran, Tiruvalla