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Review of Literature
C.

C.1 EPIDEMIOLOGY OF ACUTE MYOCARDIAL INFARCTION (AMI), REFRACTORY ANGINA and HEART FAILURE (HF)

The second half of the 20th century has witnessed a global spread of the cardiovascular disease epidemic. Even as CAD/CHD mortality rates are declining in industrialized countries, CAD epidemics are emerging or accelerating in most developing countries (Murray and Loper 1994). During the past 30 years, age-adjusted CAD mortality in the US dropped by more than 40% (Marmot et al 1992) and CAD rates have halved in the Australia, Canada, France, Japan and Finland. This has been attributed to population-based preventive measures coupled with high-risk treatment approach employing suitable primary prevention techniques, better treatment of these conditions, and secondary prevention strategies late in the recovery phase of these illnesses.

However, at the dawn of 21st century, South Asians are at a verge of cardiovascular epidemic and India is on the threshold of an epidemic for CAD. Epidemiological transition, with increasing life-expectancy and demographic shifts in population age-profile, combined with lifestyle related increases in the levels of cardiovascular risk factors, is accelerating CAD epidemic in India (Reddy et al 1993, Gupta et al 1997, Reddy et al 1998). CAD prevalence in urban populations increased from 3.5% in 1960’s to 9.5% in 1990’s. In rural areas it increased from 2% in 1970’s to 4% (Gupta et al 1996). Gillum et al (1996) has hypothesized that epidemiological evolution of cardiovascular diseases is classified into six stages derived from population levels of acculturation, urbanization, affluence, saturated-fat intake, salt intake and smoking. The prevalence of CHD initially
increases with a rise in these factors, then stabilizes, and finally decreases. In India these social and economic indices of epidemiological transition explain the increasing CHD prevalence (Gupta et al 1997, Reddy et al 1998).

Specific mortality data ideal for making comparisons with other countries are not available in India (Padmavati et al 2002). Population-based surveys, with all their attendant pitfalls in sampling design, sample size standardization and measurement errors, remain the most important source of information today (Reddy et al 1998). Old surveys pointed to a low incidence of Ischemic heart diseases (IHD), 1%-4%, whereas recent surveys show a figure of nearly 10% (96.7/1000). There are great regional variations (Bhatia et al 1995, Reddy et al 1998). These are obviously biased data and form the reason for the present impression of an “epidemic of IHD in India”. Data from Christian Medical College (CMC), Vellore and All India Institute of Medical Sciences, New Delhi (AIIMS) over a period of 30 years show a decline in admission for Rheumatic Heart Disease and an increase in admission for CAD (Bhatia et al 1995). In 1980, coronary artery bypass grafting (CABG) accounted for less then 10% of all cardiac surgeries. Today, it accounts for more than 60%. Every year 25,000 coronary bypass operations and 12 000 percutaneous transluminal coronary angioplasties (PTCAs) are carried out. Out of 42000 open heart operations done in 1999, only 11450 were performed in government hospitals (Girinath et al 2001). Urbanization is on the increase and is responsible for many of these changes in lifestyle.

According to the literature, acute myocardial infarction (AMI) is the first manifestation of IHD in approximately 50% to 70% of patients (Bechar et al 1992, Zucker et al 1997, Manfroi et al 2002). It has not yet been established whether any of the risk factors has an independent participation in the instability of the plaque for triggering MI as the first manifestation of IHD (Sullivan et al 1994). Despite
impressive advances in diagnosis and management over the last four decades, ST elevation MI (STEMI) continues to be a major public problem in the industrialized world and is becoming an increasingly important problem in the developing countries (Rogers et al 2000, Kesteloot et al 2002). In the US, nearly 1.1 million patients annually suffer from an AMI. More than 1 million patients with suspected AMI are admitted yearly to coronary care units in the US. Of particular concern from a global perspective are projections from the World Health Federation that the burden of disease in developing countries like India will become similar to those now afflicting developed countries (AHA update 2003). The overall mortality in STEMI is approximately 4-7% or even less in the published clinical trials (The GUSTO investigators 1993, GUSTO III investigators 1997, ASSENT-2 investigators 1999). However, this is not the case in the real world situations since patients in the trials are selected ones and the results of these trials are not applicable to about 50% of the clinical practice. A realistic view can be obtained from the registry data. The Registry data from Europe showed that mortality with AMI is around 3 times higher than what has been observed in clinical trials (Zeymer et al 2003). Data showing mortality and treatment trends in Indian patients after AMI are scarce in current era. A report from Jose et al (2004) has shown that the in-hospital mortality rate after AMI in a tertiary care hospital in India is 16.9 %, which is higher compared to the reports from the west.

As the survival of patients with primary coronary events continues to increase, the number of patients presenting with CAD unsuitable to further revascularization techniques and symptoms refractory to medical therapy also continues to rise. The prevalence of chronic refractory angina pectoris is unknown; however, in a given population it is likely to be related to the size of the main at-risk population, namely CABG patients. Data from key angioplasty versus coronary artery surgery studies reveal that more than 20% of
angioplasty patients and more than 10% of bypass surgery patients have angina a year after the procedure, often despite repeat revascularization [Whitlow et al 1999, CABRI Trial participants 1995]. Vein graft attrition (Bourassa et al 1984), native disease progression (Campeau et al 1984), and long-term survival [Varnauskas et al 1988, Chaitman et al 1990, RITA investigators 1993] combine to ensure a steady increase in recurrent angina over time until the death rate matches or exceeds the rate of recurrence. Data from post-CABG angiogram activity and disposal in our own center confirm that there is a strong correlation between the prevalence of post-CABG recurrent angina and the number of CABG survivors multiplied by time after surgery (Hammond et al 2000). Data from the national registry of cardiovascular diseases in Sweden show that both the incidence and rate of admission for myocardial infarction are declining. No data are available for the corresponding rates of angina pectoris, but for this diagnosis the admission rates are increasing (Mannheimer et al 2002). Whether this is a direct effect of more efficient treatment of patients with acute coronary syndromes, or reflects a change in the natural history of coronary heart disease is not clear. As 5–10% of patients with unstable angina develop MI or refractory angina in the hospital (Yusuf et al 1999), it seems likely that the number of patients presenting with refractory angina will increase. We have no accurate figures on the occurrence and frequency of refractory angina, nor is the prevalence of angina pectoris known in most communities. A recent report on a Spanish population aged 45 to 74 years and comprising 10,248 subjects gave overall angina prevalence figures of 7.3% and 7.7%, in men and women, respectively (Cossin et al 1999). The figures are likely to be higher in northern Europe. The proportion of these patients who will develop refractory angina is unknown, but a guessed estimate could be in the order of 5–10% of those with the diagnosis, or 3–7 per thousand in these age groups. There is a need for systematic registration recording to assess the burden of this disease, so as to obtain more accurate figures for the prevalence and
eventually incidence data. A Swedish survey of patients referred for coronary angiography because of stable angina pectoris performed by the Swedish Council of Technology Assessment in Health Care in 1994–1995 (Brorsson et al 1998, Mannheimer et al 2002), showed that 9.6% of the patients referred were rejected for revascularization despite severe symptoms. Another Swedish investigation made in 1998 in the form of an inventory of patients referred for coronary angiography to the national cardiothoracic centre showed that 5–15% of patients referred for coronary angiography probably have refractory angina (Mannheimer et al 1998). Data for prevalence of refractory angina pectoris in India is almost nil. As a global burden, it has been estimated that >1,00,000 patients each year may be diagnosed as having this condition (Mukherjee et al 1999).

Chronic Heart failure (CHF) is the end stage of all diseases of the heart and is a major cause of morbidity and mortality. The most common causes of HF are CAD and hypertension. HF is an epidemic affecting approximately 2–4 million Americans and nearly 15 million people worldwide (Ho et al 1993). Studies of the epidemiology of HF have been complicated by the lack of universal agreement on a definition of HF, which is primarily a clinical diagnosis. National and international comparisons have therefore been difficult, and mortality data, post-mortem studies, and hospital admission rates are not easily translated into incidence and prevalence. HF is estimated to account for about 5% of admissions to hospital medical wards, with over 100,000 annual admissions in the UK. The overall prevalence of HF is 3–20 per 1000 population, although this exceeds 100 per 1000 in those aged 65 years and over. The overall incidence is likely to increase in the future, because of both an ageing population and therapeutic advances in the management of AMI leading to improved survival in patients with impaired cardiac function (Davis et al 2000). In the US alone, approximately 550,000 new cases of HF are diagnosed each year (AHA update 2005). Moreover, HF is a disease of aging, and with
the advancing median age of the US population, the prevalence of HF is projected to increase by 2- to 3- fold by the year 2010 (Adams et al 2001).

From a worldwide perspective, the number of patients meeting the WHO definition for HF has grown to > 10 million. The overall prevalence of clinically identified CHF has been estimated from population studies, such as the Framingham study (Ho et al 1993), the U.S. National Health and Nutrition Examination Survey (NHANES)-1 (Schocken et al 1992) and the Study of Men Born in 1913 (Eriksson et al 1989). The overall incidence of CHF has been estimated at 0.1-0.2% (McMurray et al 1998, Murdoch et al 1999, Petrie et al 2001), based on data from the Framingham (Ho et al 1993) and Rochester studies in the U.S.A. (Cowie et al 1999), and studies from Finland (Remes et al 1992) and most recently the U.K. (Cowie et al 1999). However, with each additional decade of life the incidence of CHF doubles, and the incidence of HF in those older than 85 years is 2-3%. Data regarding prevalence of CHF in India is lacking. Diabetes is an important risk factor for HF in Asian Indian patients (Desai et al 2005). Small studies have attempted to emphasize the importance of patient non-compliance with prescribed therapy as a leading precipitating factor for CHF in an Indian setting, which can be prevented by appropriate cost-effective strategies aimed to improve patient compliance (Joshi et al 1999). HF is a worldwide problem of nearly epidemic proportions. The management of HF has progressed rapidly over the past 10 years. New Drugs and Device therapy in HF are being investigated; however, the most appropriate treatment strategy remains prevention.

Primary prevention is based on control of atherosclerosis risk factors. The Framingham Heart Study in USA played vital role in defining the risk factors for CHD incidence in general population (Grundy et al 1998). The traditional risk factors such as smoking, high blood pressure, high serum cholesterol level and diabetes are
applicable to the majority of cases in India. Factors other than these also increase the likelihood of developing CHD which include obesity, physical inactivity, family history of premature CHD, insulin resistance syndrome, hypertriglyceridemia, small dense low-density lipoprotein (LDL) particles, increased lipoprotein(a) levels, increased serum homocysteine, and abnormalities in several coagulation factors. The syndrome X characterized by atherogenic dyslipidemia (borderline high LDL cholesterol; raised triglycerides, dense LDL particles, low HDL cholesterol), hypertension, insulin resistance and non-insulin dependent diabetes, and a procoagulant state is also emerging as an important factor. However, the emerging risk factors—abdominal obesity, high triglycerides, insulin resistance, the so-called metabolic syndrome, elevated homocysteine levels, fibrinogen factors, etc.—need not be invoked to explain the present high incidence of heart attacks as they are yet to be proven as being causative in this era of evidence-based medicine. Control of the traditional risk factors may suffice in any preventive program (Padmavati et al 2002).

Besides the traditional and newer risk factors, the reason for the present high prevalence has been attributed to the Barker hypothesis which suggests poor maternal nutrition with impaired fetal growth results in low birth-weight, short birth length and small head circumference. These adverse influences program the development of adaptive metabolic and physiologic responses with an increased risk of glucose intolerance, hypertension, dyslipidemia and adult CVD (Barker et al 1995). This scenario is not difficult to envisage in India, especially with increased survival of these infants due to better childcare.
C.2 PATHOPHYSIOLOGY AND CLINICAL ASPECTS OF AMI, REFRACTORY ANGINA and HF

C.2.1 PATHOPHYSIOLOGY OF ANGINA AND AMI

The coronary circulation supplies the heart with oxygen and nutrients to maintain cardiac function and thus supply the remainder of the body with blood. The systemic metabolic needs may change rapidly and widely, thus requiring rapid adaptation of cardiac function and coronary blood flow. Imbalance in myocardial oxygen demand and supply can produce myocardial ischemia with contractile cardiac dysfunction, angina, arrhythmias, infarction, and possibly death. Coronary artery disease (CAD) is most commonly due to obstruction of the coronary arteries by atheromatous plaque. The interaction between the vulnerable atherosclerotic plaque and thrombus formation, a process referred to as atherothrombosis, is the cornerstone of ACS (Corti et al, 2002).

C.2.1.1 The Atherosclerotic Process

Atherosclerosis begins when the innermost layer of the artery, called intima/endothelium, gets damaged (Figure C.1). Possible causes of damage to arterial wall are free radical generation, elevated levels of oxidized serum cholesterol, TG, fibrinogen, Hcy and also high blood pressure, obesity, lifestyle, cigarette smoking and environmental pollutants are responsible for the same. LDL, often referred to as bad cholesterol, is a crucial factor for the initiation and progression of atherosclerosis. Oxidation of LDL renders it sticky and facilitates its deposition on the internal lining of blood vessel walls. Oxidized LDL (oLDL) is not recognized by the liver and can be recognized by the scavenger receptors of the macrophages. This induces sub-endothelial lipid accumulation and leads to foam cell formation, which is the earliest hallmark of atherosclerosis (Steinberg et al 1989). Another hallmark of atherogenesis, leukocyte recruitment and accumulation, also occurs early in lesion generation. Very early after initiation of
hypercholesterolemia, leukocytes adhere to the endothelium and diapedese between endothelial cell junctions to enter the intima, where they begin to accumulate lipids and become foam cells. In addition to the monocyte, T lymphocytes also tend to accumulate in early human and animal atherosclerotic lesions. The expression of certain leukocyte adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and selectins (E selectin, P-selectin) on the surface of the endothelial cell regulates the adherence of monocytes and T cells to the endothelium (Nakashima et al 1998, Iiyama et al 1999, Plutzky et al 2001). Once adherent to the endothelium, migration of leucocytes into the arterial wall involves the action of protein molecules which includes chemoattractant cytokines such as interferon-γ, tumor necrosis factor-α and interleukin-2, or chemokines such as monocyte chemoattractant protein-1 (MCP-1) (Luster et al 1998). Once recruited to the arterial intima, stimuli like Macrophage colony stimulating factor (M-CSF) augment the expression of LDL receptors called scavenger receptors on the monocytes, following which they imbibe lipid and become a foam cell, or lipid-laden macrophage. Up to this point in the development of the nascent atheroma, the lesion consists primarily of lipid-engorged macrophages. This ultimately results in the formation of a fatty streak. Complex features such as fibrosis, thrombosis, and calcification do not characterize the fatty streak, the precursor lesion of the complex atheroma. Further, to the macrophage foam cells recruitment to the artery wall, various proinflammatory mediators, both proteins such as cytokines and chemokines and various eicosanoids and lipids such as platelet-activating factor are secreted. These phagocytic cells also elaborate large quantities of oxidant species such as superoxide anion in the milieu of the atherosclerotic plaque (Griendling et al 2001). This assembly of inflammatory mediators can promote inflammation in the plaque and thus contribute to the progression of lesions. These activated macrophages further secrete potent smooth muscle cell

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chemoattractant molecules such as platelet-derived growth factor (PDGF), which eventually leads to smooth muscle cell migration from the media to the intima, activation and proliferation promoting extracellular matrix accumulation within the evolving atherosclerotic plaque. Eventually the large atherosclerotic plaque juts out into the lumen of the artery (McCance and Heuther 1998).
Figure C1: Schematic diagram of the evolution of the atherosclerotic plaque

1: Accumulation of lipoprotein particles in the intima. The modification of these lipoproteins is depicted by the darker color. Modifications include oxidation and glycation; 2: Oxidative stress, including products found in modified lipoproteins, can induce local cytokine elaboration.; 3: The cytokines thus induced increase expression of adhesion molecules for leukocytes that cause their attachment and chemoattractant molecules that direct their migration into the intima.; 4: Blood monocytes, upon entering the artery wall in response to chemoattractant cytokines such as monocyte chemoattractant protein 1 (MCP-1), encounter stimuli such as macrophage colony stimulating factor (M-CSF) that can augment their expression of scavenger receptors.; 5: Scavenger receptors mediate the uptake of modified lipoprotein particles and promote the development of foam cells. Macrophage foam cells are a source of mediators such as further cytokines and effector molecules such as hypochlorous acid, superoxide anion (O₂⁻), and matrix metalloproteinases.; 6: Smooth muscle cells in the intima divide other smooth muscle cells that migrate into the intima from the media.; 7: Smooth muscle cells can then divide and elaborate extracellular matrix, promoting extracellular matrix accumulation in the growing atherosclerotic plaque. In this manner, the fatty streak can evolve into a fibrofatty lesion.; 8: In later stages, calcification can occur (not depicted) and fibrosis continues, sometimes accompanied by smooth muscle cell death (including programmed cell death, or apoptosis) yielding a relatively acellular fibrous capsule surrounding a lipid-rich core that may also contain dying or dead cells and their detritus.

IL-1 = interleukin-1; LDL = low-density lipoprotein.
C. 2.1.2 Clinical Syndromes of Atherosclerosis: Angina & Infarction

Serial angiographic and pathoanatomical observations indicate that progression of CAD involves two distinct processes: a fixed and hardly reversible process: Atherosclerosis, and a dynamic and potentially reversible process that punctuates the slow progression in a sudden and unpredictable way, are causing rapid coronary occlusion: Thrombosis. The initiation and evolution of the atherosclerotic plaque generally last many years over which it remains clinically silent. During the initial phases of atheroma development, the plaque usually grows outward, in an abluminal direction. Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as compensatory enlargement, a type of vascular remodelling. Eventually, the growing atheroma encroaches upon the arterial lumen to a degree that that impedes blood flow through the artery. This causes an imbalance between myocardial O₂ requirements and myocardial O₂ supply and precipitates myocardial ischemia. The two primary characteristics of the clinically symptomatic atherosclerotic plaque are a fibromuscular cap and an underlying lipid-rich core. An advanced, complex, relatively lipid-poor atheromatous lesion with a fibrous cap that compromises the lumen of the coronary artery is the most common cause of fixed coronary artery stenosis responsible for stable syndromes like chronic stable angina (Fuster et al 1992). Conventional approaches to restoring this balance between oxygen supply and demand focus on disruption of the underlying disease process through medications, life-style modifications or revascularization techniques, such as CABG or PCI. However, symptoms of stable angina that are thought to be caused by ischemia due to advanced CAD and which are not controllable by a combination of maximal anti-anginal medications, PCI or CABG persist in an increasing number of patients. This constitutes the Chronic refractory angina pectoris.
Most acute coronary events are caused by disruption of atherosclerotic plaque in an epicardial coronary vessel, followed by complete occlusion of vessel by thrombosis (Fuster et al 1985, Falk et al 1991). Pivotal Studies by DeWood and Collegues (1986) showed that coronary thrombosis is the critical event resulting in acute coronary syndromes including MI. Most MIs are precipitated by plaque disruption with superimposed thrombosis, with or without concomitant vasoconstriction, causing a sudden and critical reduction in coronary blood flow (Falk et al 2001). Any atherosclerotic plaque may rupture due to natural causes, such as shear forces in the artery of gradual decay. A subset of advanced, but not necessarily stenotic, atherosclerotic plaques are particularly dangerous—the vulnerable plaques—because of high risk of rupture that may precipitate luminal thrombosis. The risk of plaque rupture depends more on the plaque type than on plaque size or degree of narrowing caused by the plaque. Lipid accumulation, cap thinning, macrophage infiltration, and local loss of smooth muscle cell destabilize plaques, making them vulnerable to rupture. In contrast, smooth muscle cell-mediated healing and repair processes stabilize plaques, protecting them from rupture (Falk et al 1995). Plaque erosion may occur due to the actions of metalloproteases and the release of other collagenases and proteases in the plaque, which result in thinning of the overlying fibromuscular cap. The action of proteases, in addition to hemodynamic forces applied to the arterial segment, leads to a disruption of the endothelium and fissuring or rupture of the fibromuscular cap. The degree of disruption of the overlying endothelium can range from minor erosion to extensive fissuring that result in an ulceration of the plaque. The loss of structural stability of a plaque often occurs at the juncture of the fibromuscular cap and the vessel wall—a site otherwise known as the plaque's "shoulder region". When plaque rupture occurs, platelets enter into the lesion and platelet adhesion, activation and aggregation follows (Porth and Carol, 1998) (Figure C.2). After an initial platelet monolayer forms at the site
of the ruptured plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, there is production and release of thromboxane A₂ (a potent local vasoconstrictor), further platelet activation, and potential resistance to thrombolysis. In addition to the generation of thromboxane A₂, activation of platelets by agonists promotes a conformational change in the glycoprotein (GP) IIb/IIIa receptor. Once converted to its functional state, this receptor develops a high affinity for amino acid sequences on soluble adhesive proteins (i.e., integrins) such as von Willebrand factor (vWF) and fibrinogen. Since vWF and fibrinogen are multivalent molecules, they can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation. The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the ruptured plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin. Fluid-phase and clot-bound thrombin participate in an auto amplification reaction that leads to further activation of the coagulation cascade. During the whole process, the mural thrombus initially impedes the blood flow in the artery, but does not reach the occlusive state or will only be transiently occlusive, causing acute coronary syndromes like unstable angina and Non ST segment elevation MI (NSTEMI). Eventually, the thrombus, containing platelet aggregates and fibrin strands completely occludes the artery results in acute myocardial infarction (AMI) with ST segment elevation in the electrocardiogram, commonly referred as STEMI. In rare cases, AMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic, particularly inflammatory diseases.
AT III = Antithrombin III
Xa = Factor Xa
PAF = Platelet Activating Factor
TxA2 = Thromboxane A2
ADP = Adenosine Diphosphate
LMWH = Low molecular weight Heparin

Figure C.2: Process of Thrombus formation

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C.2.2 CLINICAL ASPECTS OF ANGINA AND AMI

Angina pectoris is a discomfort in the chest or adjacent area caused by myocardial ischemia. The chest discomfort, heaviness or pain is usually retrosternal and brought by exertion. Anginal “equivalents” such as dyspnoea, fatigue and eructations are also common manifestations. No elevation of cardiac biomarkers is associated with angina, which differentiates it from infarction. Refractory angina manifests as continuing anginal symptoms at rest or on exertion inspite of maximal pharmacological treatments and underlying disease not amenable to revascularization (PCI or CABG).

AMI may have unique presentations in individual patients. The degree of symptoms ranges from none at all to sudden cardiac death. Unlike stable angina, AMI is usually associated with prolonged (>30 minutes), sever pain occurring at rest, which is at instances intolerable. The discomfort is usually described as choking, visc-like or heavy pain, but it can also be characterized as a stabbing, knife-like, boring, or burning discomfort. The paint is usually retrosternal in location, but often radiates down the ulnar aspect of the left arm, producing tingling sensation in the left wrist, hand and fingers. In some patients, it may be epigastric or may radiate to shoulders, upper extremities, neck, jaw and interscapular region, usually favouring the left side. Other symptoms include nauseas, vomiting, and feelings of profound weakness, dizziness, palpitations, cold perspirations and a sense of impending doom. The heart rate may vary from a marked bradycardia to rapid regular or irregular tachycardia. Majority of patients with uncomplicated STEMI are normotensive, or occasionally hypertensive. However, in cardiogenic shock following AMI, hypotension prevails. Fever may develop as a non-specific response to tissue necrosis. AMI may occur at any time of the day, but mostly appear to be clustered around the early morning hours and/or are associated with demanding physical activity. Approximately 50% of patients have some warning symptoms (angina pectoris or an anginal equivalent) prior to the infarct (Ryan et al 1999).
C. 2.3 PATHOPHYSIOLOGY OF HF

Heart failure, a complex clinical syndrome, arises from a process of ventricular dysfunction (acute or chronic), where the venous return to the heart is normal but the heart is unable to pump sufficient blood to meet the body’s metabolic needs at normal filling pressures. The ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure (CHF) in the Adult defined heart failure 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 (Hunt et al 2001). HF commonly refers to the chronic syndrome, or CHF. Various etiologies responsible for CHF are tabulated in Table C.1.

Table C.1. General Etiologies of Cardiac Failure

<table>
<thead>
<tr>
<th>General Cause</th>
<th>Specific Examples</th>
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</thead>
<tbody>
<tr>
<td>Coronary vascular</td>
<td>Acute ischemic episodes, post myocardial infarction</td>
</tr>
<tr>
<td>Myocardial</td>
<td>Cardiomyopathies-dilated, hypertrophic, restrictive</td>
</tr>
<tr>
<td>Valvular</td>
<td>Aortic or mitral regurgitation</td>
</tr>
<tr>
<td>Rhythm disturbances</td>
<td>Tachycardia-induced heart failure</td>
</tr>
<tr>
<td>Pericardial</td>
<td>Tamponade, pericardial constriction</td>
</tr>
</tbody>
</table>

Abnormalities during systole and/or diastole may be present in HF. In so-called systolic HF, an impairment of myocardial contractility causes weakened systolic contraction, which leads, ultimately, to a reduction in stroke volume and cardiac output, inadequate ventricular emptying, cardiac dilatation, and often elevation of ventricular diastolic pressure. Idiopathic dilated cardiomyopathy is the prototype of systolic HF. In diastolic HF, the principal abnormality is impaired relaxation and filling of the ventricle, which leads to an elevation of ventricular diastolic pressure at any given diastolic volume. Failure of relaxation can be functional and transient, as during ischemia, which
reduced the ATP required for the sarcoplasmic reticulum (SR) pump to lower cytoplasmic Ca$^{2+}$. A stiffened, thickened ventricle can cause chronically impaired ventricular filling. Typical conditions in which diastolic failure occurs are restrictive cardiomyopathy secondary to infiltrative conditions, such as amyloidosis or hemochromatosis, as well as hypertrophic cardiomyopathy. The concentric hypertrophy associated with chronic hypertension can also impair ventricular filling but rarely causes overt HF. In many patients with cardiac hypertrophy and dilatation, systolic and diastolic failure coexists; the left ventricle both empties and fills abnormally. There may be cardiac dilatation, but the ventricle's pressure-volume relation is shifted, raising the ventricular diastolic pressure at any given volume.

Although a defect in myocardial contraction is characteristic of systolic heart failure (Hasenfuss et al 2002, Houser et al 2003), many conditions may cause such a defect. These include a primary abnormality in the heart muscle, as occurs in cardiomyopathy, or an abnormality secondary to a chronic excessive workload as in hypertension or valvular heart disease. In ischemic heart disease, systolic heart failure results from a loss in the quantity of normally contracting cells (secondary to myocardial necrosis and apoptosis) and/or from transient loss of function in reversibly ischemic (hibernating) myocardium (Braunwald et al 2001).

C. 2.3.1 Adaptive Mechanisms

Inadequate adaptation of the cardiac myocytes to increased wall stress in order to maintain adequate cardiac output following myocardial injury (acute or chronic) is the inciting event in HF. A number of adaptive mechanisms aid the heart faced with an increased hemodynamic burden (such as pressure or volume overload) or that has sustained loss of myocardium or contractility (Katz et al 2000), which include:
1. The *Frank-Starling mechanism* operating through an increase in preload to sustain cardiac performance.

2. *Increased afterload*, as occurs in aortic stenosis and hypertension, also augments wall tension, leading to concentric hypertrophy, which in turn restores elevated ventricular wall stress to normal. However, ventricular hypertrophy impairs ventricular filling, and if the hypertrophy is insufficient to restore wall stress to normal, the ventricle dilates and this increases wall stress further, leading to a vicious circle.

3. *Redistribution of a subnormal cardiac output* away from the skin, skeletal muscle, and kidneys with maintenance of blood flow to the brain and the heart.

4. *Neurohumoral adjustments*, which augments myocardial contractility by activation of adrenergic systems leading to nor-epinephrine (NE) release and tend to maintain arterial pressure and perfusion of vital organs by activation of rennin-angiotensin-aldosterone system (RAAS) (Floras et al 2004). Like the other adaptive mechanisms, when neurohumoral adjustments are severe and chronic they impair cardiac function.

C. 2.3.2 Biochemical Abnormalities In HF

There is no unifying theory providing a biochemical basis for heart failure. However, a number of abnormalities have been described.

*Reduction in Cardiac Efficiency:* The common forms of low-output systolic heart failure, secondary to coronary atherosclerosis, hypertension, cardiomyopathy, and certain valvular and congenital lesions, are characterized by an absolute or a relative reduction in the external work delivered by the heart, while myocardial oxygen consumption remains normal or nearly so. Therefore, the external efficiency, i.e., the ratio of external work performed to energy consumed, is often depressed (Ingwall et al 2004).
Alterations in Energy Metabolism: When heart failure occurs in the presence of acute or chronic ischemia, it can be attributed to reduced myocardial energy supplies. Severe ventricular hypertrophy and/or dilatation of any etiology can also cause relative ischemia, especially in the subendocardium, and this can impair both ventricular contraction and filling (Hardy et al 1991, Ingwall et al 2004).

Alterations in Regulatory Proteins: Changes in the cardiac regulatory proteins frequently occur in chronic heart failure. These include a reduction of myosin ATPase activity, which may be caused by an alteration in the expression of troponin T and/or of myosin light chain kinase 2, alterations that could be responsible for lowering the rate of interaction between myosin and actin myofilaments, leading to systolic HF (Solaro et al 1998, Izumo et al 2004).

Abnormalities of Excitation-Contraction Coupling: Substantial evidence supports the view that in many forms of heart failure the delivery of Ca$^{2+}$ to the contractile sites is reduced, thereby impairing cardiac performance. Impaired expression of the genes encoding the proteins regulating Ca$^{2+}$ movements can impair both myocardial contraction and relaxation and thereby contribute to the development of HF (Flesch et al 1996, Winslow et al 1999, Hobai et al 2001).

C. 2.3.3 Neurohumoral and Cytokine Adjustments

A reduction in cardiac output following myocardial injury evokes a series of neurohumoral adjustments, which, at different times, may be adaptive and maladaptive. Although they maintain arterial perfusion pressure in the face of a sudden reduction of cardiac output, these neurohumoral adjustments increase the hemodynamic burden and oxygen requirements of the failing ventricle (Colucci et al 2005).

The Adrenergic Nervous System activation: It causes the release of epinephrine (E) and NE (Leier et al 1990), along with the vasoactive substances endothelin-1 (ET-1) and vasopressin, causes
vasoconstriction, which increases afterload, and, via an increase in cAMP, causes an increase in cytosolic Ca\textsuperscript{2+} entry. The increased Ca\textsuperscript{2+} entry into the myocytes augments myocardial contractility and impairs myocardial relaxation (Katz et al. 2000, Piacentino et al. 2003), thus leading to increase in myocardial energy expenditure and further decrease in cardiac output (Houser et al. 2003, Monte et al. 2003). Ultimately, increased energy expenditure causes myocardial cell death, resulting in HF and further reduction in cardiac output, starting an accelerating cycle of further increased neurohumoral stimulation and further adverse hemodynamic and myocardial responses as described above. The elevation in plasma NE while being directly toxic to cardiac myocytes, is also responsible for a variety of signal-transduction abnormalities, such as down-regulation of beta1-adrenergic receptors, uncoupling of beta2-adrenergic receptors, and increased activity of inhibitory G-protein. Changes in beta1-adrenergic receptors result in overexpression and promote myocardial hypertrophy (Bisognano et al. 2000, Colucci et al. 2005).

The Renin-Angiotensin-Aldosterone System (RAAS): When cardiac output declines, the RAAS is also activated leading to salt and water retention, resulting in increased preload and further increase in myocardial energy expenditure. Increases in renin and increased beta1-adrenergic activity as a response to decreased cardiac output results in an increase in angiotensin II (Ang II) levels and, in turn, aldosterone levels. There is also an increase in circulating arginine vasopressin (antidiuretic hormone) that contributes to renal retention of water. Ang II, along with ET-1, is crucial in maintaining effective intravascular homeostasis mediated by vasoconstriction and aldosterone-induced salt and water retention (Newby et al. 1998, Muders et al. 1999). Ang II causes further increase in energy expenditure and also mediates myocardial cellular hypertrophy, promoting progressive loss of myocardial function. The neurohumoral factors above lead to myocyte hypertrophy and interstitial fibrosis,
resulting in increased myocardial volume and increased myocardial mass, as well as myocyte loss. This remodelling process leads to early adaptive mechanisms, such as augmentation of stroke volume (Starling mechanism) and decreased wall stress (Laplace mechanism), and later, maladaptive mechanisms such as increased myocardial oxygen demand, myocardial ischemia, impaired contractility, and arrhythmogenesis.

Endothelin: The concentration of ET-1 is increased in HF (Serneri et al 2000) and has exaggerated vasoconstrictor effects in the renal vasculature, reducing renal plasma blood flow, glomerular filtration rate, and sodium excretion.

Tumor Necrosis Factor (TNF)-alpha: The overexpression of a number of cytokines also appears to play a prominent role in the pathogenesis of HF. Apart from ET-1, other vasoactive systems playing role in pathogenesis of CHF include adenosine receptor system, TNF-alpha. Elevations in TNF-alpha levels have been consistently observed in CHF and seem to correlate with the degree of myocardial dysfunction (Mann et al 2004).

Vasodilator Peptides: Among various vasodilator peptides released by the dilated heart, best known are the natriuretic peptides; atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). When stretch receptors in the atria (ANP and BNP) and ventricles (BNP) are activated, these hormones (or their prohormones) are released and act on specific natriuretic peptide receptors, which increase the concentrations of cGMP in the kidney, adrenal glomerulose, vascular smooth muscle, and platelets. Urine volume and sodium excretion are augmented, vascular resistance is reduced, and the release of renin and the secretion of aldosterone are reduced. These effects, while beneficial, are not sufficiently powerful to oppose the sodium-retaining and vasoconstrictor influences of the other neurohumoral systems activated in HF. Elevated circulating concentrations of ANP and particularly BNP correlate with a poor prognosis in HF (Sugimoto et al 1997, Talwar et al 2000).
The activation of the adrenergic nervous system and the renin-angiotensin-aldosterone system and the enhanced elaboration of endothelin and arginine vasopressin appear to be adaptive in acute, severe heart failure. However, they all appear to exert a maladaptive response in chronic heart failure. Inflammatory cytokines and oxidative stress are emerging as potent noxious stimuli as well. Together they result in a vicious circle, causing myocyte hypertrophy, remodeling, and cell death, the latter often due to myocardial apoptosis, all resulting in further impairment of cardiac function and myocardial injury (Figure C.3).

Figure C.3:
Interplay between cardiac function and neurohumoral and cytokine systems. Myocardial injury, of many etiologies, can depress cardiac function, which in turn causes activation of the sympathoadrenal system (SAS) and the renin-angiotensin-aldosterone system (RAAS) and the elaboration of endothelin, arginine vasopressin (AVP), and cytokines such as tumor necrosis factor (TNF-alpha). In acute heart failure (left), these are adaptative and tend to maintain arterial pressure and cardiac function. In chronic heart failure (right), they cause maladaptive hypertrophic remodeling and apoptosis, which cause further myocardial injury and impairment of cardiac function. The horizontal line on the right (*) shows that chronic maladaptive influences can be inhibited by angiotensin converting enzyme inhibitors, β-adrenergic blockers, angiotensin type I receptor blockers, aldosterone antagonists, and endothelin type A blockers.
C.2.3.4 Heart Failure - A disturbance of the myocardial pump

In the final analysis, in systolic HF the basic problem is depression of the myocardial force-velocity relationship and of the length-active tension curve, reflecting reductions in the contractile state of the myocardium (Figure C.4, curves 1 to 3 & Figure C.5 right). In diastolic failure there is upward displacement of the diastolic pressure-volume relation. In many instances, cardiac output and external ventricular performance at rest are within normal limits but are maintained at these levels only by an increased end-diastolic fiber length and an elevated left ventricular end-diastolic volume (LVEDV), i.e., through the operation of the Frank-Starling mechanism (Figure 4, points A to D). The elevation of left ventricular preload is associated with increases in the left ventricular end diastolic pressures (LVEDP), pulmonary capillary wedge pressure (PCWP) and thus pulmonary artery pressure (PAP), contributing to the dyspnea experienced by patients with HF, while elevation of right ventricular preload raises systemic venous pressure and contributes to the development of edema. The improvement of contractility that normally accompanies augmented adrenergic activity during exercise is attenuated or even prevented by norepinephrine depletion and downregulation of myocardial β receptors, which occur in severe HF (Figure 4, curves 3 and 3'). The factors that augment ventricular filling during exercise in the normal individual push the failing myocardium along its flattened length-active tension curve, and although the LV may perform somewhat better at this higher diastolic volume, this occurs only as a consequence of an inordinate elevation of LVEDV and LVEDP and, therefore, of the PCWP and PAP. The latter intensifies dyspnea and limits the exercise capacity. LV failure becomes fatal when the myocardial length-active tension curve is depressed (Figure 4, curve 4) to the point at which cardiac performance fails to satisfy the requirements of the peripheral tissues even at rest, and/or the LVEDP and PCWP are elevated to levels that result in pulmonary edema (Figure 4, point E) (Braunwald et al 1976).
Figure C.4:
Diagram showing the interrelationship of influences on ventricular end-diastolic volume (EDV) through stretching of the myocardium and the contractile state of the myocardium. Levels of ventricular EDV associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required during rest, walking, and maximal activity are designated on the ordinate. The dashed lines are the descending limbs of the ventricular performance curves, which are rarely seen during life but that show what the level of ventricular performance would be if EDV could be elevated to very high levels.

Figure C.5:
The responses of the left ventricle to increased afterload, increased preload, and increased and reduced contractility are shown in the pressure-volume plane. ESPVR, end-systolic pressure-volume relation; E_E, the slope of the end-systolic pressure-volume relation.
Left. Effects of increases in preload and afterload on the pressure-volume loop. Since there has been no change in contractility, ESPVR is unchanged. With an increase in afterload, stroke volume falls (1 → 2); with an increase in preload, stroke volume rises (1 → 3).
Right. With increased myocardial contractility, the normal ESPVR moves to the left of the normal line (lower end-systolic volume at any end-systolic pressure) and stroke volume rises (1 → 3). With reduced myocardial contractility, the ESPVR moves to the right; end-systolic volume is increased and stroke volume falls (1 → 2).
C.2.4 CLINICAL ASPECTS OF HF

From a clinical viewpoint, the causes of heart failure are classified into two broad categories: (1) *underlying causes*, comprising the structural abnormalities—congenital or acquired—that affect the peripheral and coronary vessels, pericardium, myocardium, or cardiac valves and lead to the increased hemodynamic burden, increased myocardial stress, or coronary insufficiency responsible for heart failure, and (2) *precipitating causes*, including the specific causes or incidents that precipitate worsening HF (Chin et al 1997, Tsuyuki et al 2001). These include infection, anaemia, thyrotoxicosis & pregnancy, arrhythmias, rheumatic, viral or other forms of myocarditis, infective endocarditis, Physical, dietary, fluid, environmental, and emotional excesses, Systemic hypertension, Myocardial infarction, Pulmonary embolism etc.

Apart from systolic and diastolic HF, HF may be described as high-output or low-output, acute or chronic, right-sided or left-sided, and forward or backward (Givertz et al 2005). These descriptors are often useful in a clinical setting, particularly early in the patient's course, but late in the course of chronic HF the differences between them often become blurred.

The concept of backward HF contends that in HF, one or the other ventricle fails to discharge its contents or fails to fill normally. As a consequence, the pressures in the atrium and venous system behind the failing ventricle rise, and retention of sodium and water occurs as a consequence of the elevation of systemic venous and capillary pressures and the resultant transudation of fluid into the interstitial space. In contrast, the proponents of the forward HF hypothesis maintain that the clinical manifestations of HF result directly from an inadequate discharge of blood into the arterial system. According to this concept, salt and water retention is a consequence of diminished renal perfusion and excessive proximal tubular sodium reabsorption and of excessive distal tubular reabsorption through activation of the RAAS (Schrier et al 1999).
It is useful to classify patients with HF into those with a low cardiac output, i.e., low-output HF, and those with an elevated cardiac output, i.e., high-output HF. The former occurs secondary to ischemic heart disease, hypertension, dilated cardiomyopathy, and valvular and pericardial disease, while the latter is seen in patients with HF and hyperthyroidism, anaemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease. In clinical practice, however, low-output and high-output HF cannot always be readily distinguished.

Many of the clinical manifestations of HF result from the accumulation of excess fluid behind either one or both ventricles. This fluid usually localizes upstream to (behind) the ventricle that is initially affected. Patients in whom the left ventricle is hemodynamically overloaded (e.g., aortic stenosis) or weakened (e.g., postmyocardial infarction) develop dyspnea and orthopnea as a result of pulmonary congestion, a condition referred to as left-sided HF. In contrast, when the underlying abnormality affects the right ventricle primarily (e.g., congenital valvular pulmonic stenosis or pulmonary hypertension secondary to pulmonary thromboembolism), symptoms resulting from pulmonary congestion is uncommon, and edema, congestive hepatomegaly, and systemic venous distention, i.e., clinical manifestations of right-sided HF, are more prominent.

The clinical manifestations of HF depend importantly on the rate at which the syndrome develops and time elapsed for the compensatory mechanisms to be operative. Acute HF is usually predominantly systolic, and the sudden reduction in cardiac output often results in systemic hypotension without peripheral edema. In contrast, in CHF, arterial pressure is ordinarily well maintained until very late in the course, but there is often accumulation of edema. There is a wide spectrum of potential clinical presentations with heart failure (Remme et al 2001). For most of the patients, Breathlessness, a cardinal manifestation of left ventricular failure, may arise with progressively increasing severity as (1) exertional dyspnea, (2) orthopnea, (3) paroxysmal nocturnal dyspnea, (4) dyspnea at rest, and...
Acute pulmonary edema. Attacks of paroxysmal dyspnea in resting patients usually occur at night. Paroxysmal nocturnal dyspnea is a common clinical feature associated with Cheyne-Stokes respiration in patients with heart failure (Quaranta et al 1997). Elevation in pulmonary pressures is one of the main stimuli for dyspnea (Mancini et al 1995). Diurnal variation in PAP has been investigated as a major cause for nocturnal rise and worsening of CHF patients (Gibbs et al 1989). Exercise capacity is limited for a variety of reasons in patients with HF, including abnormalities in central and peripheral cardiovascular function (Pina et al 2003). The primary central limitations to exercise in patients with HF include the development of dyspnea related to pulmonary vascular congestion and the failure of the cardiovascular system to provide sufficient blood flow to exercising muscles. A rapid improvement in the peripheral vascular response to exercise after intensive, hemodynamically guided therapy has been demonstrated (Johnson et al 1999). Other signs and symptoms of low cardiac output include fatigue, effort intolerance, cachexia, and renal hypoperfusion. Patients with right ventricular failure have jugular venous distention, peripheral edema, hepatosplenomegaly, and ascites.
C.3 CURRENT TRENDS IN THE MANAGEMENT OF AMI, REFRACTORY ANGINA and HF

The ACC/AHA has released clinical practice guidelines for the management of acute ST elevation MI (AMI) (Antman et al 2004), chronic angina (Gibbons et al 2003) and chronic heart failure (Hunt et al 2005). These guidelines have been incorporated in the overall management of these patients. The following is an abridged summary of some of the recommendations from these clinical practice guidelines. The customary ACC/AHA classifications I, II, and III are used that summarize both the evidence & expert opinion and provide final recommendations for patient evaluation and therapy: Class I refers to conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class I refers to conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa, weight of evidence/opinion is in favour of usefulness/efficacy while for Class IIb, usefulness/efficacy is less well established by evidence/opinion. Class III refers to conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

C.3.1 DIAGNOSTIC MODALITIES IN AMI

Epidemiological reports from the WHO and AHA beginning in the late 1950s required the presence of at least two of the following: characteristic symptoms, electrocardiographic changes, and a typical rise and fall in biochemical markers for the diagnosis of myocardial infarction (Table C.2) (Luepker et al 2003). The aspects of diagnosis of MI by various techniques have been provided in Table C.3 (Alpert et al 2000).
Table C.2. Revised Definition of MI (Alpert et al 2000)

**Criteria for acute, evolving, or recent MI**

Either one of the following criteria satisfies the diagnosis for an acute, evolving, or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a. Ischemic symptoms
   b. Development of pathologic Q waves on the ECG reading
   c. ECG changes indicative of ischemia (ST-segment elevation or depression)
   d. Coronary artery intervention (e.g., coronary angioplasty)

2. Pathological findings of an acute MI

**Criteria for established MI**

Either of the following criteria satisfies the diagnosis for established MI:

1. Development of new pathological Q waves on serial ECG readings. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.

2. Pathological findings of a healed or healing MI

*CK = creatine kinase; ECG = electrocardiographic.*

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Table C.3. Aspects of Diagnosis of Myocardial Infarction by Different Techniques

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Myocardial cell death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry</td>
<td>Markers of myocardial cell death recovered from blood samples</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Evidence of myocardial ischemia (ST and T wave abnormalities)</td>
</tr>
<tr>
<td></td>
<td>Evidence of loss of electrically functioning cardiac tissue (Q waves)</td>
</tr>
<tr>
<td>Imaging</td>
<td>Reduction or loss of tissue perfusion</td>
</tr>
<tr>
<td></td>
<td>Cardiac wall motion abnormalities</td>
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</tbody>
</table>

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C.3.1.1 Non-invasive testings

(A) Electrocardiogram:

A 12 lead ECG is recommended as the first step of evaluation of AMI patients (class I). Ischemic ST segment elevation and hyperacute T wave changes occur as the earliest sign of acute infarction. Majority of AMI patients show ST elevation with raised serum markers, however minority had predominance of electrocardiographic features such as bundle branch block (BBB), ST depression, T-wave inversion or even a normal ECG (Rude et al 1983, Califf et al 1992).

(B) Laboratory Findings

Living heart cells contain certain enzymes and proteins including Troponin I, Troponin T, Creatinine Phosphokinase (CK), CK myocardial band (CK-MB), myoglobin etc which slowly leak into the bloodstream when myocyte necrosis occurs following MI. Elevated levels of these markers is identification of MI (Zabel et al 1993). Estimation of cardiac specific troponins in recommended for the evaluation of patient with STEMI (Class 1).

(C) Imaging Modalities:

a) Two dimensional echocardiography is also a useful tool in evaluation of patients with chronic CAD, by assessing global and regional left ventricular function in the absence and presence of ischemia, as well as in establishing left ventricular hypertrophy and associated valve disease. In the setting of acute coronary ischemia, inadequate perfusion of the myocardium leads to a reduction in wall motion and systolic thickening of the myocardium which can be detected by echocardiography (Cheitlin et al 2003). Doppler echocardiography that allows assessment of blood flow in the cardiac chambers and across cardiac valves is used in conjunction with two-dimensional echocardiography. It is helpful in detecting and assessing the severity of mitral or tricuspid regurgitation after STEMI (Reimold et al 1998, Spodick et al 2003). Echocardiographic evaluation is recommended for the initial evaluation of the patients in selected
cases (Class IIa indication) as well as for the estimation of infarct size post AMI (Class I)

\textit{b) Other Imaging Modalities:}

Various imaging techniques like Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Nuclear Imaging using Technetium (Tc) sestamibi SPECT approach can be useful for initial evaluation of AMI (Class III), assessing infarct size (Class I), collateral flow and jeopardized myocardium; determining the effects of the infarct on ventricular function; and establishing prognosis of AMI patients (Klocke et al 2003). The practical applications of these techniques is however limited because of the need to transport the patients in the emergency condition.

C.3.1.2 Catheter Based Invasive Diagnostic Procedures

\textbf{(A) Coronary Angiography}

Angiography is an invasive test that may be performed on patients who have very incapacitating angina that does not respond to medical therapy and for planning surgical procedures. A narrow tube is inserted into an artery, usually in the leg or arm, and then threaded up through the body to the coronary arteries. A dye is injected into the tube and an X-ray records the flow of dye through the arteries. This process provides a map of the coronary circulation, revealing any blocked areas. Major complications include stroke, heart attacks and kidney damage, but these risks are very low (about 0.1%) if the procedure is done in a center that performs at least 300 of these operations every year. Allergic reactions can also occur. Many experts believe this procedure is overused. The procedure is expensive, and 10% to 30% of patients who have this procedure have normal results. Coronary arteriography/angiography remains the “gold standard” for identifying the presence of absence of arterial narrowing in CAD and provides the most reliable anatomical information for determining the appropriateness of medical therapy, percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG) surgery in

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patients with Ischemic CAD (Popma et al 2005). Diagnostic angiography is recommended in all AMI patients who are candidates for revascularization (Class I)

(B) Intravascular Ultrasound Imaging

Intravascular ultrasound technique is an advanced adjunctive invasive imaging modality that can be performed at the time of coronary angiography and provides precise characterization of the vessel wall and extent of atherosclerosis.

C.3.2 TREATMENT STRATEGIES IN AMI

The goals of management & therapy in AMI are the expedient restoration of normal coronary blood flow and the maximum salvage of functional myocardium. These goals can be met by a number of medical interventions and adjunctive therapies.

C.3.2.1 Oxygen:
Supplemental oxygen should be administered to patients with arterial oxygen desaturation (SaO2 less than 90%) (Class I). It may be administered to all patients with uncomplicated AMI during the first 6 hours (Class IIa)

C.3.2.2 Nitroglycerin:
Nitroglycerin may be administered to relieve ischemic pain and is clearly indicated as a vasodilator in patients with STEMI associated with LV failure (Class I). Nitrates in all forms should be avoided in patients with initial systolic blood pressures less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, in patients with marked bradycardia or tachycardia (Come et al 1976), and in patients with known or suspected RV infarction. In view of their marginal treatment benefits, nitrates should not be used if hypotension limits the administration of beta-blockers, which have more powerful salutary effects.
C.3.2.3 Analgesia:
Morphine sulphate is the analgesic of choice for management of pain associated with ST elevation AMI (Class I)

C.3.2.4 Aspirin:
In a dose of 162 mg or more, aspirin produces a rapid clinical antithrombotic effect caused by immediate and near-total inhibition of thromboxane A\(^2\) production. Aspirin should be given promptly and certainly within the first 24 hours of AMI, at a dose between 162 and 325 mg and continued indefinitely at daily dose of 75-62 mg (Class I).

C.3.2.5 Beta blockers
Oral beta-blockers are recommended in all AMI patients irrespective of the reperfusion strategy employed (Class I). Intravenous beta blockers are recommended in patients with tachyarrhythmia and hypertension (Class IIa). Immediate beta-blocker therapy appears to reduce the magnitude of infarction and incidence of associated complications in subjects not receiving concomitant fibrinolytic therapy, the rate of reinfarction in patients receiving fibrinolytic therapy, and the frequency of life-threatening ventricular tachyarrhythmia.

C.2.3.6 Reperfusion Therapy
Evidence exists that expeditious restoration of flow in the obstructed infarct artery after the onset of symptoms in AMI patients is a key determinant of short- and long-term outcomes regardless of whether reperfusion is accomplished by fibrinolysis or Percutaneous Coronary Interventions (PCI) (Boersma et al 2003, De Luca et al 2003, De Luca et al 2004) (Class I). PHARMACOLOGICAL REPERFUSION is multipronged approach consisting of fibrinolytic agents that digest fibrin, antithrombins that prevent the formation of thrombin and inhibit the activity of thrombin that is formed and antiplatelet therapy. MECHANICAL REPERFUSION, on other hand comprises of PCI and CABG. Several issues like time from onset of symptoms, risk of mortality, risk of bleeding, and time required to transport to skilled PCI laboratory needs to be considered in the selecting the type of reperfusion therapy.
(A) Thrombolytic therapy:

Restoration of coronary blood flow in MI can be accomplished pharmacologically with the use of a thrombolytic/fibrinolytic agent (GISSI investigators 1986, The TIMI Study Group 1989, Franzosi et al 1998). Thrombolytic therapy is indicated for patients with a presentation compatible with MI and ST segment elevation, or new onset of a bundle branch block, who present less than 12 hours of symptom onset (class I). The available thrombolytic agents share the common property of plasminogen activation, which accelerates the natural process of fibrinolysis. Streptokinase, prototype of nonfibrin selective agent is a bacterially derived product, whereas fibrin specific agents include alteplase (t-PA), which is genetically produced, reteplase, tenecteplase and lanoteplase are its deletion and substitution mutants increasing their fibrin specificity other agents include urokinase, anistreplase and staphylokinase. The GUSTO trial established that an accelerated alteplase/heparin regimen was superior to two streptokinase/heparin regimens (GUSTO Investigators 1993). Reteplase has been shown to produce slightly higher 60- and 90-minute angiographic patency rates than accelerated alteplase, while adverse-event rates were equal (GUSTO III investigators 1997). Presently available and commonly used agent in Indian population is Streptokinase due to the unavailability/cost factor of other agents. The most critical variable in achieving successful fibrinolysis is time from symptom onset to drug administration. Bleeding is the most common and potentially serious complication associated with these agents (Dubois et al 2003). Fibrinolytic therapy is contraindicated (Class I) in patients with neurological contraindications, intracranial hemorrhage, uncontrolled hypertension or ischemic stroke. Combination of half dose of fibrinolytic therapy with platelet GP IIb/IIIa inhibitors is also recommended in selected patients (Class IIa), however not in patient with >75 yrs of age (Class III).
(B) Percutaneous Coronary Interventions (PCI):

Reperfusion of the infarct artery can also be achieved by a catheter-based strategy. This approach has evolved from passage of a balloon catheter over a guidewire followed by introduction of coronary stents (Van De Werf et al 2002). When PCI is used in lieu of fibrinolytic therapy, it is referred to as direct or primary PCI. When fibrinolysis has failed to reperfuse the infarct vessel, or a severe stenosis is present in the infarct vessel, a rescue PCI can be performed. A more conservative approach of elective PCI can be used to manage acute STEMI patients only when spontaneous or exercise-provoked ischemia occurs, whether or not they have received a previous course of fibrinolytic therapy. Different Approaches for Angioplasty in AMI are given in Table C.4.

Table C.4: Different approaches for Angioplasty in AMI

<table>
<thead>
<tr>
<th>Primary (Direct):</th>
<th>Emergency PCI/Stent without prior thrombolytic therapy</th>
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<tr>
<td>Facilitated :</td>
<td>Reduced dose thrombolytic therapy with or without GPIIb/IIIa agents prior to emergency PCI</td>
</tr>
<tr>
<td>Rescue:</td>
<td>Emergency PCI for failed thrombolysis</td>
</tr>
<tr>
<td>Immediate:</td>
<td>PCI immediately after successful thrombolysis</td>
</tr>
<tr>
<td>Delayed:</td>
<td>PCI 1-7 days after thrombolysis</td>
</tr>
</tbody>
</table>

- **PRIMARY PCI:**

Primary PCI refers to angioplasty that is performed as a primary reperfusion strategy without prior thrombolytic therapy. The goal is to achieve reperfusion and salvage of myocardium. Primary PCI achieves TIMI-3 flow in over 90% of AMI patient, which is an important predictor of mortality and partly reflects the survival advantage associated with Primary PCI (Grines et al 1993, Zijlstra et al 2000). Current ACC/AHA guidelines favour primary PCI as the preferred reperfusion strategy in AMI patients if it can be done within 12 hours of symptoms onset, performed in timely fashion (PCI balloon inflation within 90 minutes of presentation), by skilled operators and supported...
by experienced personnel in an appropriate laboratory environment (Class I); in patients with 1) cardiogenic shock or severe heart failure, 2) contraindications to thrombolysis, 3) increased risk of bleeding and intracranial hemorrhage, and 4) symptom duration greater than three hours (Class I). It is also recommended within 12-24 hours, if ischemic symptoms persist, or patient develops CHF or hemodynamic instability (Class IIa). Primary PCI has been compared with fibrinolytic therapy in 22 randomized clinical trials (Antman et al 2004). An additional trial, SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock?) (Hochman et al 1999) that compared medical stabilization with immediate revascularization for cardiogenic shock, was included along with the above 22 trials in an overview of primary PCI versus fibrinolysis. These investigations demonstrate that PCI-treated patients experience lower short-term mortality rates, less nonfatal reinfarction, and less hemorrhagic stroke than those treated by fibrinolysis but have an increased risk for major bleeding (Keeley et al 2003). The C-PORT trial evaluated thrombolysis versus primary PCI in 454 AMI patients revealing superior results with primary PCI (Aversano et al 2002). The AIR PAMI trial investigated emergent transfer for Primary PCI versus onsite thrombolysis in high-risk STEMI patients. Inspite of early termination of the trial, primary PCI group showed non-significant reduction in the events (Grines et al 2002). DANAMI and PRAGUE-2 trials have reported comparable benefits with primary PCI & thrombolytic therapy (Andersen et al 2003, Widimsky et al 2003). Time from symptom onset to reperfusion is an important predictor of patient outcome. Two studies (Berger et al 1999, Cannon et al 2000) have reported increasing mortality rates with increasing door-to-balloon times. Other studies have shown smaller infarct size, better LV function and fewer complications when reperfusion occurs before PCI (Clements et al 1993, Brodie et al 2000, Stone et al 2001). An analysis of the randomized controlled trials comparing fibrinolysis with a fibrin-specific agent versus primary PCI suggests that the
mortality benefit with PCI exists when treatment is delayed by no more than 60 minutes. Mortality increases significantly with each 15-minute delay in the time between arrival and restoration of TIMI-3 flow (door to TIMI-3 flow time), which further underscores the importance of timely reperfusion in patients who undergo primary PCI (Juliard et al 2003). If the expected door-to-balloon time exceeds the expected door-to-needle time by more than 60 minutes, fibrinolytic treatment with a fibrin-specific agent should be considered unless it is contraindicated (Antman et al 2004). Randomized controlled trials evaluating the outcome of PCI for patients who present with STEMI but who are ineligible for fibrinolytic therapy have not been performed. Nevertheless, these patients are at increased risk for mortality (Cragg et al 1991), and there is a general consensus that PCI is an appropriate means for achieving reperfusion in those who cannot receive fibrinolytics because of increased risk of bleeding (Grzybowski et al 2003).

✓ Advantages Of Primary Angioplasty Strategy

1. Superior Restoration of blood flow:
Restoration of the epicardial coronary blood flow (achievement of TIMI 3 flow) and myocardial perfusion (achievement of Tissue Myocardial perfusion-TMP grade 3) is the goal of reperfusion strategy in AMI. The GUSTO-I trial confirmed the critical link between early establishment of TIMI-3 flow and myocardial salvage and subsequent survival (GUSTO Angiographic Investigators 1993). A relationship between TIMI-3 flow and survival has also been verified for primary angioplasty (Berger et al 1999). Catheter-based reperfusion techniques attain TIMI-3 flow in 93 to 98 percent of patients (Grines et al 1999, Stone et al 2002). Despite restoration of epicardial flow, many patients exhibit suboptimal tissue level perfusion (TMP grade less than 3). The impaired perfusion is associated with adverse left ventricular remodelling, heart failure, and reduced survival (Roe et al 2001, Rezkalla et al 2002). Although a significant proportion of patients
exhibit impaired perfusion (30 to 70 percent) (van 't Hof et al 1998, Gibson et al 2000) after successful restoration of infarct artery flow, there appears to be more preserved microvascular perfusion among patients undergoing primary angioplasty (Lane et al 2005).

2. treatment of the Inciting pathobiology in AMI

After successful thrombolysis, a significant residual stenosis remains in the majority of patients (Llevadot et al 2000). Treatment of the stenosis during primary angioplasty appears to lower the risk of recurrent ischemic events. In the meta-analysis of randomized trials, reinfarction was reduced to 3 percent with primary angioplasty compared with 7 percent for thrombolytic therapy (Keeley et al 2003). Stenting further reduces the risk of reocclusion and restenosis (Grines et al 2000)

3. anatomical definition and risk stratification

The angiographic and hemodynamic data obtained at the time of emergency catheterization impart valuable decision-facilitating information and more precise risk stratification. Stratification of patients into a low-risk group (age ≤ 70 years, LV ejection fraction > 0.45, one- or two-vessel disease, successful angioplasty, no persistent arrhythmias) at the time of the procedure facilitates rapid safe recovery

4. reduction in complication

Treatment with primary angioplasty appears to reduce the complications of myocardial infarct rupture. In a combined meta-analysis of the GUSTO-I and PAMI-I/II trials, primary angioplasty resulted in an 86 percent reduction in the risk of mechanical complications compared with that of patients undergoing thrombolysis (Stone et al 2000). Intracranial hemorrhage remains a serious complication of thrombolysis. One-third of the mortality reduction with primary angioplasty compared with thrombolysis has been attributed to curtailment of intracranial hemorrhage (Weaver et al 1997).
Interhospital Transfer For Primary PCI
To achieve optimal results, time from the first hospital door to the balloon inflation in the second hospital should be as short as possible, with a goal of within 90 minutes. Significant reductions in door-to-balloon times might be achieved by directly transporting patients to PCI centers rather than transporting them to the nearest hospital, if interhospital transfer will subsequently be required to obtain primary PCI (Antman et al 2004).

Primary Stenting for AMI
Stents have ascended to an essential role in interventional cardiology practice. A stent procedure is used along with balloon angioplasty. Stents are metallic mesh or coil splint, which are placed inside arteries to brace them, open and prevent collapse through dissections or elastic recoil. The stent is mounted on a balloon-tipped catheter, threaded through an artery, and positioned at the blockage. The balloon is then inflated, opening the stent. Then, the catheter and deflated balloon are removed, leaving the stent in place. The stent may be used to support and maintain a stretch of a diseased segment of the artery. It has been well demonstrated that there is improved procedural success with reduced long-term restenosis and a reduced need for coronary revascularization (Fischman et al 1994). The use of stents with PCI for MI is superior to the use of PCI without stents, primarily because stenting reduces the need for subsequent target-vessel revascularization (TLR) (Grines et al 1999). Three small trials in patients with AMI with vessels suitable for stenting have demonstrated a significant reduction with stenting in early (in-hospital or less than one month) recurrent ischemic events and in a late composite endpoint of death, recurrent AMI or repeat target vessel revascularization (TVR) by six months. Suboptimal results after primary angioplasty are predictive of recurrent ischemia or reocclusion (Grines et al 1995). Initial use of stents was restricted to "bailout" indications, but several studies demonstrated the feasibility...
and safety of stents in AMI (Stone et al 1998). Several randomized trials have been conducted comparing primary stenting with primary balloon angioplasty. The Stent-PAMI trial reported a reduction in the cardiovascular endpoints, recurrent ischemia and restenosis or reocclusion in the stent group (Grines et al 1999). CADILLAC trial showed similar benefits with primary angioplasty versus stenting with a lower target vessel revascularization rates in stent group (Stone et al 2002). A meta-analysis of the reported trials confirms the advantage of stent deployment (Zhu et al 2001). Thus, as with other PCI indications, stents are recommended to be routinely applied in AMI. In addition to the bare metal (stainless steel or cobalt-chromium alloy) stent, Drug-eluting stents (DES) is a major advancement in cardiology. DES contain pharmacological agent coated on the conventional bare metal stent. DES can maximize local drug effects and minimize the potential for systemic toxic effects. With proven efficacy in other therapeutic arenas, many drugs aimed at inhibiting cell proliferation (paclitaxel, sirolimus, tacrolimus and everolimus), cell migration (batimastat, a matrix metalloproteinase inhibitor) and abnormal healing (estradiol) are currently under clinical investigation. Currently available DES include Sirolimus coated coronary stents (CYPHER®, ABT-578 coated cobalt chromium alloy stent (ENDEAVOR®), Paclitaxel coated stents (TAXUS®) etc. Based on the various mechanisms of action of these agents, drugs released from these stents may be classified as immunosuppressive, anti-proliferative, anti-inflammatory, or pro-healing (Sousa et al 2003). The release of these agents further retard the risk of restenosis compared to bare metal stents. Preliminary reports suggest that compared with conventional bare metal stents, drug-eluting stents are not associated with increased risk when used for primary PCI in STEMI patients (Lemos et al 2004).
(C) Combining Thrombolysis And PCI As Reperfusion Therapy

- FACILITATED PCI

Facilitated PCI refers to a strategy of planned immediate PCI after an initial pharmacological regimen such as full-dose fibrinolysis, half-dose fibrinolysis, a GP IIb/IIIa inhibitor, or a combination of reduced-dose fibrinolytic therapy and a platelet GP IIb/IIIa inhibitor. A strategy of facilitated PCI holds promise in higher-risk patients when PCI is not immediately available (class IIb). Several randomized trials of facilitated PCI with a variety of pharmacological regimens are in progress which included 'Facilitated Intervention with Enhanced Reperfusion to Stop Events' (FINESSE) trial and Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-4 Trial comparing facilitated PCI with Primary PCI.

- RESCUE PCI

Rescue PCI refers to PCI within 12 hours after failed fibrinolysis for patients with continuing or recurrent myocardial ischemia. Patients with an occluded infarct artery (TIMI grade 0-1 flow) or suboptimal flow (TIMI grade 2 flow) 90 minutes after thrombolytic therapy have worse LV function, increased incidence of mechanical defects, and increased early mortality (Ross et al 1999). Rescue PCI performed in these patients with failed thrombolysis can establish reperfusion and may salvage myocardium, and improve prognosis. Few randomized trials including TAMI-5, RESCUE (Ellis et al 1994), GUSTO-III (Miller et al 1999) and MERLIN (Sutton et al 2004) have shown benefits with Rescue PCI following failed thrombolytic therapy. Persistence of ischemic chest pain, failure to resolve ST-segment elevation, rise of baseline/60 minutes biomarkers and hemodynamic or arrhythmic instability are generally indicators of failed pharmacological reperfusion and the need to consider rescue PCI. The current ACC/AHA guidelines recommend rescue PCI for STEMI patients with cardiogenic shock, hemodynamic or electrical instability, or persistent...
ischemic symptoms (class I). Patients requiring rescue PCI, however, remain at increased risk for reocclusion and early death, especially if the percutaneous revascularization procedure is unsuccessful.

- **PCI IMMEDIATELY AFTER SUCCESSFUL THROMBOLYSIS**
  A high-grade (>70%) residual stenosis is usually present following successful thrombolysis. However, trials of immediate PCI following successful thrombolysis demonstrated that routine PCI was associated with higher transfusion rates, increased need for bypass surgery, a trend toward increased mortality, and no improvement in predischarge LVEF (de Boer et al 1995, Gibbons et al 1993, Lieu et al 1996). Additional studies to confirm clinical benefits and determine the need or optimal timing for PCI are needed.

- **DELAYED PCI FOLLOWING THROMBOLYSIS**
  Delayed PCI refers to angioplasty performed electively (1-7 days following thrombolysis) in asymptomatic patients. As with rescue or immediate PCI, the goal of this approach was to reduce residual stenosis in the hopes of preventing reocclusion and recurrent ischemia, and augmenting the recovery of ventricular function. Trials of delayed PCI versus conservative therapy demonstrated no differences in death, reinfarction, or EF (The TIMI study Group 1989, Barbash et al 1990, The SWIFT investigators 1991, Van en Brand et al 1992, Lieu et al 1996). Despite concerns over infarct artery residual stenosis and late reocclusion, elective angiography and revascularization should be more targeted to post-STEMI patients with recurring symptoms, positive noninvasive stress tests, or other high-risk indicators (LVEF ≤0.40). Specifically, elective revascularization may be considered in patients with a history of prior MI, TIMI-2 flow, coronary stenosis ≥90% supplying a large amount of myocardium, and lesions documented to be physiologically significant by IVUS or Doppler.
(D) Acute Surgical Reperfusion:

CABG is also a treatment modality for ischemic heart diseases. In procedure, a blood vessel from another part of the body is used to bypass the blocked region. The saphaneous vein is used mainly for distal branches of right and circumflex coronary arteries and for sequential grafts to these vessels and diagonal branches. Internal mammary artery is used, which is remarkably free of atheroma, especially in patients under the age of 65 years. Emergency or Urgent Coronary Artery Bypass Graft (CABG) Surgery can be done for AMI for one of the following indications: persistent or recurrent chest pain despite fibrinolysis or PCI, high-risk coronary anatomy (e.g., left main stenosis) discovered at catheterization, or a complication of STEMI such as ventricular septal rupture or severe mitral regurgitation due to papillary muscle dysfunction (class I indication).

(E) Assessment of Reperfusion

Persistence of unrelenting ischemic chest pain, absence of resolution of the qualifying ST-segment elevation, and hemodynamic and/or electrical instability are generally indicators of failed pharmacological reperfusion and the need to consider rescue PCI. Assessment of Epicardial blood flow and myocardial perfusion following primary PCI is a direct evidence of the reperfusion achieved.

- Epicardial blood flow:

To provide a level of standardization for comparison of the various regimens, the blood flow in the infarct vessel is assessed angiographically according to the Thrombolysis In Myocardial Infarction trial (TIMI) grading system (Table C.5). TIMI grade 3 flow is considered to be the goal when assessing flow in the epicardial infarct artery following reperfusion (Gibson et al 2003). TIMI Frame count is a more quantitative index for the briskness coronary blood flow. It is the simple count of number of angiographic frames elapsed until the
contrast material arrives in the distal bed of the vessel (Gibson et al 1996).

- **Myocardial Perfusion:**

The goal of reperfusion therapy in AMI is not only the early, full, and sustained restoration of antegrade flow at the epicardial level but also the achievement of adequate reperfusion at the myocardial level (Roe et al 2001). Abnormalities of increasing myocardial perfusion as assessed angiographically by the TIMI myocardial perfusion (TMP) grade (Gibson et al 2000) (Table C.6) correlate with mortality risk even after adjusting for the presence of TIMI grade 3 flow or a normal TIMI frame count (Aneja et al 2002). Myocardial perfusion cannot be improved adequately without restoration of flow in the occluded infarct-related artery. However, even patients with TIMI grade 3 flow may not achieve adequate myocardial perfusion. Obstruction of the distal microvasculature by thrombi, microembolization, spasm of the distal microvasculature or reperfusion injury contributes to the tissue injury and inadequate myocardial perfusion. All this consequences may result in a phenomenon known as "No-reflow" which leads to failure to achieve myocardial reperfusion despite the presence of a patent coronary artery (Rezkalla et al 2002). Diagnostic techniques such as ST-segment resolution, angiographic blush, nuclear scintigraphy, myocardial contrast echocardiography, coronary Doppler, magnetic resonance imaging, and positron emission tomography have been used to assess the "no-reflow" phenomenon (Gibson et al 2004). The presence of no reflow in patients with AMI receiving reperfusion therapies has been associated with poor outcomes (Ito et al 1996).
Table C.5 TIMI Flow Grade Classification Scheme

<table>
<thead>
<tr>
<th>Flow Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No perfusion. No antegrade flow beyond the point of occlusion.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Penetration without perfusion. Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Partial perfusion. Contrast material passes across the obstruction and opacifies the coronary distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its flow into or clearance from comparable areas not perfused by the previously occluded vessel.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.</td>
</tr>
</tbody>
</table>

Table C.6 TIMI Myocardial Perfusion Grades

<table>
<thead>
<tr>
<th>Perfusion Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Minimal or no myocardial blush.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Dye stains the myocardium and this stain persists on the next injection.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Dye enters the myocardium but washes out slowly so that dye is strongly persistent at the end of the injection.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>There is normal entrance and exit of dye in the myocardium so that dye is mildly persistent at the end of the injection.</td>
</tr>
</tbody>
</table>
Keeping arteries open:

The "open artery" principle is considered a vital one in improving the outcome after myocardial infarction. The obstructed vessel should be unblocked as soon as possible, and patency should be maintained to improve the patient's prognosis and reduce morbidity. Remimer et al (1977) showed that early restoration of blood flow improved the subsequent function of the left ventricle. A more recent trial using graded outcomes determined by the thrombolysis in myocardial infarction trial (TIMI) showed that the higher the grade achieved, the lower the mortality at 30 days. Patients with TIMI grade 0 (complete occlusion) at 90 minutes had a 30 day mortality of 8.4%, whereas mortality was 4% in patients with TIMI grade 3 (GUSTO Angiographic Investigators 1993).

(F) No Reflow & Distal Embolization during PCI:

No-reflow (NR) describes the persistence of reduced flow and associated myocardial perfusion despite the removal of mechanical epicardial coronary occlusion. Ames et al (1968) first coined the term in their experimental work on cerebral ischemia. Coronary NR was also described first in an experimental setting (Kloner et al 1974) but was later noted to occur clinically as well (Bates et al 1986).

The exact pathophysiologic mechanism behind this phenomenon has not been identified. The epicardial vessel is patent and the flow impairment is the result of pathology in the microcirculation. This microvascular dysfunction usually follows a direct injury. Potential mechanisms of 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. Electron microscopy performed on animal experiments shows plugging of the capillaries with neutrophils, myocyte edema, and endothelial blistering (Kloner et al, 1974).
Capillary resistance to flow is thus increased. It has also been postulated that activated platelets secrete potent vasoactive substances that promote distal microvascular constriction, thus impeding flow. In addition, particles from plaques or thrombi that are dislodged and embolized downstream by the revascularization procedure can lead to microvascular spasm. It is important to keep in mind that the responses of the endothelium of the distal microvasculature to these vasoactive substances may not be identical to those of intact endothelial cells. In other words, endothelium dependent vasoactive substances may lead to incomplete or even paradoxical responses once exposed to injured endothelium. No reflow in AMI may result due to the ischemia reperfusion injury following the reperfusion of the infarcted artery.

Another most challenging scenario encountered in AMI is the presence of thrombus, and the subsequent distal embolization due to mechanical disruption of the culprit lesion (Topol and Yadav 2000), a scenario occurring during primary/Rescue PCI. Resultant epicardial vessel and microvascular impedance to flow contributes to long-term LV dysfunction, CHF and death (Ito et al 1996, Henriques et al 2002, Morishima et al 2000). Embolization, either spontaneous or following percutaneous coronary intervention (PCI) has an important role in the development of the no-reflow phenomenon after AMI (Rezkalla et al 2002).

- **Management of No-reflow & Distal Embolization**

  The best approach for management of no-reflow phenomenon is probably to avoid it altogether. Therefore, strategies aiming at reducing the risk of its occurrence are perhaps the most effective. Treatment of established no-reflow phenomenon is mainly pharmacologic. The response of the coronary microvasculature to vasoactive substances varies with the location of the vascular bed. In general, sub-endocardial blood flow increases more than sub-
epicardial blood flow in response to endothelium dependent vasodilators like acetylcholine, adenosine triphosphate, and arachidonic acid (Quillen and Harrison 1992). The response of the coronary microvasculature to endothelium-dependent factors is reduced after ischemia-reperfusion (Quillen et al 1990). Endothelium independent substances like sodium nitroprusside are equivalent in the two regions of myocardium.

Drugs for the treatment of No-reflow:

Nitroglycerin: Intracoronary (IC) NTG has been used as a mainstay in the treatment of no-reflow. Although NTG is a potent vasodilator of the epicardial coronary artery, it has weak effects as a microvasculature/arteriolar vasodilator.

Sodium nitroprusside: IC nitroprusside may also effectively treat no-reflow. This agent probably works via its action as a NO donor at the arteriolar level. The drug is most often administered via the distal lumen of a balloon catheter or on infusion catheter.

Adenosine: Adenosine is perhaps the most potent arteriolar vasodilating drug available to reverse no-reflow in degenerated SVG. Adenosine is generally considered an endothelium independent vasodilator. It is secreted locally to purinergic receptors and causes relaxation by activating adenylate cyclase. Adenosine is considered a possible auto-regulator of coronary blood flow. In the setting of intervention in AMI, adenosine has been found to decrease the incidence of no-reflow by four-fold.

Calcium Channel Blockers: CCB, however, appears to have substantial efficacy in reversing no-reflow. Verapamil, diltiazem and nicardipine have all been used successfully to reverse no-reflow. The mechanism of action of verapamil is most likely a direct effect on arteriolar smooth muscle cells that promotes relaxation and consequently cases spasm.

Papavarine: The reasoning behind the use of papavarine is that ischemia induces spasm, which, in turn, contributes to the development of no-reflow, thus perpetuating ischemia and tissue...
injury. Papavarine would break the ischemia-spasm cycle and thus help resolve no-reflow. Care must be taken though because papavarine may lead to QT-segment prolongation and has been known to cause Torsades de Pointes.

**Antioxidants:** Antioxidants such as superoxide dismutase and allopurinol (to decrease reperfusion injury) and mannitol (to reduce myocardial edema) have been studied in experimental MI, but their value for no-reflow is unknown.

**Platelet GP IIb/IIIa antagonists:** The use of potent platelet receptor antagonist for preventing or reversing no-reflow is controversial. They may play a role in the prevention of no-reflow in SVG intervention and in AMI. The use of GP IIb/IIIa antagonists is indicated in high-risk coronary interventions. They are probably not best used as a treatment once no-reflow is established. Presently, there is relatively little data regarding the use of GP IIb/IIIa inhibitors in this setting.

**Devices for Prevention of No-Reflow:**

There are a number of devices that are either approved or under investigation for the treatment of IC thrombus and/or the prevention of no-reflow during coronary interventions. The major ones include Angiojet Rheolytic Thrombectomy System, Acolysis device and distal embolization protection device (DPD). Multiple devices of this type are in development and testing at Cordis/J&J, Microvena, Boston Scientific, and other companies. The filter devices, a kind of DPD has the potential advantage of allowing distal blood flow while the larger embolic debris is collected. Atherectomy and stenting may also cause no reflow. The best strategy is to avoid its occurrence by the use of DPD like PercuSurge GuardWire® system. Platelet GP IIb/IIIa antagonists can be concomitantly used when indicated, although definitive data demonstrating their benefit in no reflow situations is lacking at the time. If no-reflow does occur, there are number of pharmacologic options that appear to be effective in reversing no-reflow and to relieve the element of spasm in the microcirculation in
an attempt at breaking the cycle of continued microvascular injury. Rapid boluses of IC adenosine with or without adjunctive IC nicardipine, IC verapamil, diltiazem and nitroprusside appear to be effective agents. In high-risk thrombus-laden lesions, prevention of no-reflow may be feasible with clot debulking devices such as the angiojet and acolysis. Comparing drugs with mechanical devices should be carefully assessed in future clinical trials.

- **Management of Distal Embolization**

  Distal embolization of thrombus/plaque components during primary PCI may play a crucial role in limiting effective myocardial perfusion (Limbruno et al 2003), thus it can be hypothesized that mechanical prevention of distal embolization might prevent no-reflow during PCI.

The use of protection devices during stenting of stenotic venous grafts intended to prevent distal embolization appears feasible and may confer a potential role of these devices in the improvement of patient outcomes. Several new devices have been developed to prevent embolic particles from passing into the distal microcirculation during intervention. These are divided broadly into two categories: balloon occlusion devices and filter devices. Currently only 2 are approved by the FDA for use in PCI (Schomig et al 2005): the PercuSurge GuardWire (Medtronic Corp, Santa Rosa, Calif) and FilterWire-Ex (Boston Scientific, Santa Clara, Calif). Early methods included using two guiding catheters and occluding the distal vessel with a balloon catheter and performing an aspiration thrombectomy using an aspiration device while a balloon was inflated within the vessel (Stein et al 2000).

The PercuSurge GuardWire® system works by temporary inflation of a low-pressure occlusion balloon distal to the PCI site, followed by use of an aspiration catheter to remove debris released.
from the treated lesion after which the balloon is deflated and antegrade flow is reestablished. In the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial, the use of the PercuSurge GuardWire® was associated with a 42% relative reduction in major adverse cardiac events and a significant reduction in the occurrence of the no-reflow phenomenon compared with stenting without distal embolic protection; however, no significant difference in mortality was observed (Baim et al 2002). More recently, another randomized study with a patient population similar to that of the SAFER study and designed to assess the noninferiority of a filter-based protection device compared with the balloon occlusion and aspiration system reported similar rates of major adverse cardiac events with both devices (Stone et al 2003).

As an alternative to occlusion devices, a number of porous membrane filters mounted on the tip of coronary guidewires have been developed to capture and retrieve embolized materials during intervention. These include devices like Angioguard®, Filterwire-Ex system and may other filters. The Filter Wire-Ex system is an intravascular filtration device that is placed distal to the PCI site without impeding antegrade blood flow. Distal filters allow perfusion and contrast injection, thus ensuring better angiographic control during angioplasty and stent deployment. However the filters may fill with particulate debris and reduce anterograde flow. Simply removing the filter wire without aspiration may release a column of static particulate debris into the distal microcirculation—in this circumstance, aspiration of the column of material with an aspiration catheter before filter removal may be useful. The recent, large, randomized FIRE trial compared distal balloon protection with a distal filter during SVG interventions. In this study the device success and the incidence of myocardial infarction were reported to be similar (Rogers and Stone 2002).
As the market for embolic protection devices has increased, the spectrum of application of embolic protection devices has expanded to include primary PCI for AMI. There have been observations suggesting a beneficial impact of distal protection devices that have encouraged their use in patients with AMI in many centers (Limbruno et al 2003, Huang et al 2003, Yip et al 2003, Orrego et al 2003, Nakamura et al 2004, Taguchi et al 2005), but randomized clinical trials of the value of these devices in this setting have not been conducted.

C.2.3.7 Ancillary Therapy to Reperfusion Therapy
Reperfusion therapies including fibrinolysis and primary PCI attempt to rapidly obtain and sustain optimal flow in the infarct related artery. Adjunctive therapies are used along with thrombolysis or primary PCI to enhance the coronary reperfusion or alternatively to minimize the extent of ischemic myocardial injury. These include antiplatelet agents, nitrates (described above), beta blockers, Calcium channel antagonists, ACE inhibitors and many more.

(A) Anti-thrombin Agents:
- Unfractionated Heparin:
Unfractionated heparin is recommended in all the patients undergoing percutaneous or surgical revascularization (Class I). It forms a chemical complex with antithrombin III. This complex inactivates both free thrombin and factor Xa; thus acting as an indirect thrombin inhibitor. The desired clinical effect of heparin is the inhibition of additional formation and propagation of thrombi. Unfractionated heparin is beneficial until the inciting thrombotic cause (ruptured plaque) has completely resolved or healed. Intravenous unfractionated heparin is recommended in patients with a MI who undergo percutaneous revascularization or fibrinolytic therapy with alteplase. It is also recommended in patients with AMI who receive fibrinolytic therapy with a non-selective fibrinolytic agent (urokinase,
streptokinase, anistreplase) and are at increased risk for systemic emboli (prior embolic event, large or anterior wall infarction, known left ventricular thrombus, or atrial fibrillation) (Ryan et al 1999).

• **Low-molecular-weight Heparin (LMWH)**

LMWH are considered as an accepted alternative to UFH in AMI patient receiving thrombolytic therapy (Class IIb). This class includes agents like enoxaparin, fondaparinux, etc. LMWH are formed by controlled enzymatic or chemical depolymerization, producing glycosaminoglycans of various length and less molecular weight than UFH (Antman et al 2001). Compared to UFH, the rate of early reperfusion is not enhanced by LMWH, but the rates of reocclusion of the infarct artery, reinfarction, or recurrent ischemic events appear to reduce with LMWH (Ross et al 2001, Simoons et al 2002, Antman et al 2002). LMWH can be administered to MI patients not treated with fibrinolytic therapy that have no contra-indication to heparin.

• **Direct Thrombin Inhibitors:**

UFH and LMWH are indirect inhibitors of thrombin and hence to overcome their limitations, direct thrombin inhibitors are being investigated (Antman et al 2001). These agents are recommended in case of known heparin induced thrombocytopenia in AMI patients as an alternative to heparin (class IIa). The principal direct thrombin inhibitors are hirudin, bivalirudin, argatroban and lepirudin; however have not shown to reduce mortality compared to heparin when used as adjuncts to fibrinolytics (Direct Thrombin Inhibitor Trialists' Collaborative Group 2002). Efficacy of hirudin and bivalirudin in comparison to heparin is investigated in many trials. One unique advantage of these agents is that fact that they donot cause or worsen heparin induced thrombocytopenia. HERO-2 trial tested bivalirudin versus heparin as adjunctive therapy to streptokinase, but did not reveal significant benefits (White et al 2001).
(B) Antiplatelet Agents:
The pathology of an occlusive coronary thrombus is the adhesion of a small collection of activated platelets at the site of intimal disruption in an "unstable" atherosclerotic plaque.

- **Aspirin:**
The rationale for the use of aspirin along with thrombolytic therapy lies in the relatively high risk of re-occlusion of 5-30% and a rate of re-infarction of about 4% when aspirin is not used (Fuster et al 1993). Aspirin, proved to be beneficial in AMI (ISIS-2 collaborative group 1988), is given in a dose of at least 150 mg and up to 325 mg immediately on recognition of MI signs and symptoms and continued daily indefinitely (Class I, Antman et al 2004).

- **Adenosine Di-Phosphate (ADP) Receptor Antagonists:**
Other antiplatelet class of drugs namely thienopyridines—including clopidogrel, ticlopidine block the Adenosine Diphosphate (ADP)-mediated activation of platelet glycoprotein IIb/IIia (GP IIb/IIia) receptor and led to irreversible inhibition of platelet aggregation. Clinical studies indicate that clopidogrel is at least as effective as aspirin in reducing vascular events (The CAPRIE Steering Committee 1996) and the combination appears to be more beneficial than aspirin alone (Yusuf et al 2001). Clopidogrel combined with aspirin is recommended for STEMI patients who undergo coronary stent implantation (Class I). There are no safety data available regarding the combination of fibrinolytic agents and clopidogrel, but ongoing trials will provide this information in the future. However, in patients in whom aspirin is contraindicated because of aspirin sensitivity, clopidogrel is probably useful as a substitute for aspirin to reduce the risk of occlusion (Patrono et al 2004).
Review of Literature

- **GP IIb/IIIa Receptor Inhibitors:**
  Whatever the pathway of platelet activation, platelet-platelet interaction and thrombus formation is ultimately regulated by the GP IIb/IIIa receptor. Abciximab, eptifibatide and tirofiban are intravenously administered agents that block the platelet GP IIb/IIIa receptors inhibiting crosslink formation between platelets and fibrinogen as the final common pathway of platelet aggregation. Efficacy of these agents in AMI has been extensively investigated (Katritsis et al 2003). The use of intravenous glycoprotein IIb/IIIa inhibitors during PCI and in patients with MI and ACS has been shown to reduce the composite endpoint of death, reinfarction, and the need for target-lesion revascularization at follow up (Brener et al 1998). GUSTO V trial has reported the efficacy of abciximab in combination with half dose of streptokinase versus full dose streptokinase in AMI (Topol et al 2001). Adjunctive abciximab and tirofiban therapy have been investigated in the setting of primary PCI. Clinical results are more favorable in the ADMIRAL trial in AMI in which abciximab was administered during primary PCI. However, the largest randomized trials of primary PCI or stenting, CADILLAC, did not demonstrate a benefit of abciximab with regards to angiographic and clinical endpoints (Stone et al 2002). The current ACC/AHA guidelines state that it is “reasonable” to administer abciximab (class IIa) or tirofiban/eptifibatide (class IIb) prior to primary PCI (Antman et al 2004). Oral GP IIb/IIIa inhibitors are also under investigations.

**(C) Nitrates:**
Nitrates provide nitric oxide to vascular smooth muscles, thereby inducing vasodilation, and they likely have significant antiplatelet effects. Nitrates vasodilate coronary arteries and reduce coronary vasospasm, thereby increasing myocardial oxygen delivery (GISSI-3 investigators 1994). Two large placebo controlled trials, GISSI-3 and ISIS-4 have shown mortality benefits with Trinitroglycerin therapy as adjunctive to fibrinolysis (GISSI-3 Investigators 1994, ISIS-4
Collaborative group 1995). Low BP, headache, and tachyphylaxis limit the use of nitroglycerin. Nitrate tolerance can be overcome either by increasing the dose or by providing a daily nitrate-free interval of 8-12 hours (Ryan et al 1999).

(D) Beta-blockers:
Beta-blockers or beta-adrenergic antagonists reduce myocardial damage by decreasing the components of myocardial oxygen demand. In patients with AMI, they reduce infarct size, ventricular arrhythmias, and recurrent ischemia (Gheorghiade et al 2002). During the acute phase of a MI, beta-blocker therapy may be initiated intravenously; later patients can switch to oral therapy for long-term treatment. This β-1 selective agents like metoprolol, atenolol, timolol, isomolol, acebutolol etc. that have beneficial effects in AMI. Various trials (ISIS-1, BHT, MIAMI and CAPRICON) have proved mortality benefits in AMI with beta-blocker therapy.

(E) Inhibitors of Renin Angiotensin Aldosterone system:
Oral angiotensin converting enzyme inhibitors (ACEi) are recommended in MI patients within the first 24 hours of symptom onset, if no contra-indications exist (Class I). The beneficial effects of ACE inhibitors in AMI are particularly large in hypertensive (Borghi et al 1999) and diabetic (Zuanetti et al 1997, Gustafsson et al 1999) patients. ACE inhibitors tilt the fibrinolytic balance toward a profibrinolytic state by reducing plasma levels of PAI-1 (Brown et al 1999) and improve endothelial vasomotor dysfunction in patients with CAD (Mancini et al 1996). HOPE study demonstrated that patients who were at high risk of cardiovascular events benefited considerably from treatment with ACEi (Yusuf et al 2000). The potentially beneficial effects of ACEi include a reduction in left ventricular hypertrophy, vascular hypertrophy, and progression of atherosclerosis, plaque rupture and thrombosis, in addition to a potentially favorable influence on myocardial oxygen supply/demand relationships, cardiac
hemodynamics and a reduction of sympathetic activity (Lonn et al 1994). Post-AMI ACE inhibition is also found to be associated with hypotension, renal insufficiency, and cardiogenic shock. Angiotensin Receptor blockers (ARBs) like Valsartan, Losartan, Telmisartan, Candesartan are used as an alternative method in AMI patients intolerant to ACEi (Class I). However, use of ARBs has not been explored as thoroughly as ACEi in AMI.

**(F) Calcium Channel Blockers (CCBs):**
CCBs lower Blood pressure (BP), prolong treadmill exercise tolerance, and reduce myocardial ischemia episode in stable CAD patients. Multiple studies have been conducted with verapamil, diltiazem, and nifedipine in the AMI setting. Verapamil and diltiazem are recommended in AMI patients in whom beta-blockers are ineffective or contraindicated (Class IIa). Short acting Nifedipine is contraindicated in AMI as it increased mortality risk.

**(G) Lipid lowering agents:**
Recent clinical trials demonstrate that lipid-lowering therapy reduces total mortality, CV mortality, coronary events, and stroke in persons with AMI or established CHD. Treatment with statin drugs (3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase inhibitors) including agents like simvastatin, atorvastatin, rosuvastatin, pitavastatin has shown impressive benefit post-AMI. Various trials (4S, CARE, MIRACL) have demonstrated the benefits of these drugs.

**(H) Miscellaneous agents:**
The indications for long-term anticoagulation after STEMI remain controversial and are evolving. Although the use of warfarin has been demonstrated to be cost-effective compared with standard therapy without aspirin, the superior safety, efficacy and cost-effectiveness of aspirin has made it the antithrombotic agent of choice for secondary prevention (Cairns et al 1995).
Several investigators have attempted to reduce myocardial necrosis postinfarction with metabolic modulation and agents designed to conserve myocardial intracellular adenosine triphosphate and other energy stores. Infusion of high- or low-dose glucose-insulin-potassium (GIK) versus usual care was studied in the ECLA GIK pilot trial, which revealed that high-dose GIK infusion had a neutral effect on mortality, cardiac arrest, and cardiogenic shock in patients with acute STEMI (Mehta et al 2005). Magnesium produces coronary vasodilatation, reduces platelet aggregation, stabilizes myocardial cell membranes and possibly limits catecholamine and reperfusion related myocardial necrosis. Few reports including LIMIT-2 trial and ISIS-4 study have investigated the benefits of Magnesium in AMI.

Intra-aortic balloon pump:
Counter pulsation is preserved for AMI patients with severe refractory ischemia or with hemodynamic instability in patients before or after coronary angiography.

C.3.3 DIAGNOSTIC MODALITIES IN REFRACTORY ANGINA

The European society of cardiology (ESC) Joint Study Group (Mannheimer et al 2002) defines refractory angina pectoris as follows:

"Refractory angina pectoris is a chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. The presence of reversible myocardial ischemia should be clinically established to be the cause of the symptoms. Chronic is defined as a duration of more than 3 months".

A system of grading the severity of angina pectoris proposed by the Canadian Cardiovascular Society (CCS) has gained widespread acceptance (Table C.7) (Campeau et al 1976). Two criteria are required to confirm the diagnosis for refractory angina pectoris: objective ischemia must produce severe symptoms, and all known conventional
therapies must be exhausted. Patients with refractory angina have either marked limitation of ordinary physical activity or are unable to perform any ordinary physical activity without discomfort (CCS functional class III or IV). There must be some objective evidence of ischemia, as demonstrated by exercise treadmill testing, stress imaging studies or coronary physiologic studies.

C.7 Canadian Cardiovascular Society (CCS) grading for severity of angina

<table>
<thead>
<tr>
<th>Class</th>
<th>CCS Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight in normal conditions.</td>
</tr>
<tr>
<td>IV</td>
<td>Inability to carry on any physical activity without discomfort- anginal syndrome may be present at rest.</td>
</tr>
</tbody>
</table>

C.3.3.1 Non-invasive testings

(A) Biochemical tests:
In patients with chronic angina, metabolic abnormalities that are risk factors for the development of CAD are frequently detected. These abnormalities include hypercholesterolemia and other dyslipidemias, carbohydrate intolerance, and insulin resistance. All patients with established or suspected CAD warrant biochemical evaluation of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and fasting blood glucose (NCEP ATP III 2001). Several other biochemical
markers have been shown to be associated with higher risk of future cardiovascular events which includes Lp(a), apoprotein B (Lamarche et al 1998), small dense LDL, homocysteine (The Homocysteine Studies Collaboration 2002), hs CRP (Ridker et al 2003), fibrinogen etc. Blood levels of cardiac markers of necrosis (e.g., cardiac troponin) are normal in patients with chronic stable angina, which serves to differentiate them from patients with acute myocardial infarction. Novel biomarkers of myocardial ischemia are currently under study and may ultimately prove valuable in the noninvasive detection of ischemia in patients with stable CAD (Morrow et al 2003).

**(B) Resting ECG**

The resting ECG is normal in approximately half of patients with chronic angina pectoris, and even patients with severe CAD may have a normal tracing at rest. The most common ECG abnormalities in patients with chronic CAD are nonspecific ST-T wave changes with or without abnormal Q waves.

**(C) Exercise ECG:**

The exercise ECG is particularly helpful in patients with chest pain syndromes who are considered to have a moderate probability of CAD and in whom the resting ECG is normal, provided that they are capable of achieving an adequate workload. The main types of exercise are isotonic or dynamic exercise, isometric or static exercise, and resistive (combined isometric and isotonic) exercise. Cycle ergometer, treadmill devices and the six minute walk test are used for exercise testing. Although cycle ergometers have important advantages, fatigue in the quadriceps muscles in patients who are not experienced cyclists usually makes them stop before reaching their maximum oxygen uptake. As a result, treadmills are more commonly used.
(D) Exercise Treadmill Testing:
The standard Bruce protocol is popular, and a large diagnostic and prognostic data base has been published using this protocol (Ellestad et al 1996, Froelicher et al 2000, Fletcher et al 2001) The Bruce multistage maximal treadmill protocol has 3-minute periods to allow achievement of a steady state before workload is increased. Pharmacological agents like digoxin, beta blockers, anti-hypertensives and vasodilators are withdrawn prior to the test, since they may interfere with the ischemic responses during the test. Interpretation of the exercise test includes consideration of the exercise capacity (duration in minutes and metabolic equivalents (METs)) and clinical, hemodynamic, and ECG response. One MET is the standard basal oxygen uptake of 3.5 ml per kg per min. The occurrence of ischemic chest pain consistent with angina leading to termination of the test, is important, abnormalities in exercise capacity, systolic blood pressure response to exercise, and heart rate response to exercise are important findings. The most important ECG findings are ST depression and ST elevation. The most commonly used definition for a positive exercise test is greater than or equal to 1 mm of horizontal or downsloping ST-segment depression or elevation for greater than or equal to 60 to 80 ms after the end of the QRS complex, either during or after exercise (Gibbons et al 2002). The abnormal responses in ischemic patients are due to increased myocardial oxygen demand associated with a failure to increase or an actual decrease in regional coronary blood flow usually causes ST segment depression; ST segment elevation may occasionally occur with more severe coronary flow reduction.

(E) STRESS IMAGING STUDIES: Echocardiographic & Nuclear
A variety of methods can be used to induce stress: 1) exercise (treadmill or upright or supine bicycle and 2) pharmacologic techniques (either dobutamine or vasodilators). When the patient can exercise to develop an appropriate level of cardiovascular stress (e.g.,
6 to 12 min), exercise stress testing (generally with a treadmill) is preferable to pharmacologic stress testing (Class 1 indication). However, when the patient cannot exercise to the necessary level or in other specified circumstances (e.g., when stress echocardiography is being used in the assessment of myocardial viability), pharmacologic stress testing may be preferable. Three drugs are commonly used as substitutes for exercise stress testing: dipyridamole, adenosine, and dobutamine. Dipyridamole and adenosine are vasodilators that are commonly used in conjunction with myocardial perfusion scintigraphy, whereas dobutamine is a positive inotropic (and chronotropic) agent commonly used with echocardiography. During exercise stress, the increase in myocardial oxygen demand and limitation of oxygen supply create a supply-demand mismatch often resulting in cellular ischemia. Double product, defined as the product of Maximum heart rate with maximum systolic blood pressure, reflects the exercise capacity during stress testing. With pharmacological stress, the perfusion defect may represent merely the heterogeneity in coronary flow reserve. "Demand" may change little during pharmacological stress; there is often a reduction in blood pressure accompanied by a reflex although modest increase in heart rate, so that double product de, reflecting oxygen demand, changes little during the vasodilator "stress." Thus, a supply-demand mismatch may not occur and cellular ischemia may not be present despite vasodilator-induced perfusion defects.

a) Stress Echocardiography:
Stress echocardiography is a family of examinations in which two-dimensional echocardiographic monitoring is undertaken before, during, and after cardiovascular stress. The form of cardiovascular stress can include exercise with treadmill or bicycle ergometry. For patients incapable of physical exercise, pharmacological stress, employing a dobutamine infusion is used. Numerous studies have shown that exercise echocardiography can detect the presence of CAD with an accuracy that is similar to that of stress myocardial perfusion.
imaging and superior to exercise ECG alone (Fleischmann et al 1998). Patients with significant obstructive coronary disease develop regional wall motion abnormalities identical to those seen during physical stress. The most well studied and clinically available method is dobutamine stress echocardiography (DSE). Dobutamine increases both the heart rate and contractility and produces diagnostic changes in regional wall motion and systolic wall thickening as ischemia develops. Low-dose dobutamine infusion (5 to 10 µg/kg/min) is also valuable for assessing contractile reserve in regions with hypokinetic or akinetic wall motion at rest as a means of identifying viable myocardium that may improve in function after revascularization (Bax et al 1999). Dobutamine in high doses (20 to 40 mcg/kg/min) increases the three main determinants of myocardial oxygen demand, namely, heart rate, systolic blood pressure, and myocardial contractility, thereby eliciting a secondary increase in myocardial blood flow and provoking ischemia. Atropine increases the accuracy of DSE in patients with inadequate heart rate responses, especially those taking beta-blockers and those in whom second-degree heart block develops at higher atrial rates. The safety record of dobutamine has been excellent, and its accuracy appears equivalent to that of exercise echocardiography. Doppler tissue imaging, which allows quantification of intramural myocardial velocities, provides a more direct measure of myocardial function during stress and may provide objective, quantitative evidence of induced ischemia during stress echocardiography (Voigt et al 2003) Usually DSE is performed transthoracic, but when not feasible transesophageal imaging is also done (Gibbons et al 2003). Dobutamine stress imaging achieves diagnostic accuracy comparable to that of exercise echocardiography. Echocardiographic findings suggestive of myocardial ischemia include 1) a decrease in wall motion in at least one LV segment with stress, 2) a decrease in wall thickening in at least one LV segment with stress, and 3) compensatory hyperkinesis in complementary (nonischemic) wall segments (Cheitlin et al 1997).
b) Nuclear Imaging: Stress myocardial perfusion imaging

Exercise perfusion imaging with simultaneous ECG is superior to exercise ECG alone in detecting CAD, in identifying multivessel disease, in localizing diseased vessels, and in determining the magnitude of ischemic and infarcted myocardium. In patients with suspected or known chronic stable angina, the largest accumulated experience in myocardial perfusion imaging has been with the tracer Thallium-201 (201-Tl), but the available evidence suggests that the newer tracers 99mTc sestamibi and 99mTc tetrofosmin yield similar diagnostic accuracy (Maddahi et al 1993, Verani et al 1993, Sridhara et al 1993, Zaret et al 1995). Thus, 201T1, 99mTc sestamibi, or 99mTc tetrofosmin are used interchangeably with similar diagnostic accuracy in ischemic heart diseases. Myocardial perfusion imaging may use either planar or single-photon emission computed tomographic (SPECT) techniques and visual analyses (191-194) or quantitative techniques (Nohara et al 1984, Fintel et al 1989). The published results of exercise SPECT imaging show high specificity and sensitivity of the test (Gibbons et al 2003). As with exercise ECG, beta blockers are recommended to be withheld for almost 48 hrs before stress imaging studies.

(F) Computed Tomography (CT) angiography

The use of CT to perform coronary angiography non-invasively is progressing rapidly. Initially electron beam CT was the technique of choice due to excellent temporal resolutions. Multi Slice Cardiac CT (MSCT) technology with atleast 16 detectors is now becoming more widely available and temporal and spatial resolution is improving. MSCT has evolved to enable reliable non-invasive coronary angiography and is now available with 40 and 64 slices. Cardiac CT can demonstrate the morphological consequences of ischemic heart disease, can assess ventricular function and perfusion, and is applied with increasing success to visualizing coronary arteries (Achenbach et al 2005).
C.3.3.2 Invasive diagnostic procedures

(A) Coronary Angiography
This invasive technique for imaging the coronary artery lumen remains the most accurate for the diagnosis of clinically important obstructive coronary atherosclerosis and less common nonatherosclerotic causes of possible chronic stable angina pectoris, such as coronary artery spasm, coronary anomaly, Kawasaki disease, primary coronary artery dissection, and radiation-induced coronary vasculopathy (Mark et al 1984, Hillis et al 1978, Roberts et al 1986). Coronary angiography is recommended for refractory angina Patients, who have disabling angina despite medical therapy (Class I indication). Coronary angiography is required to confirm the diagnosis of refractory angina and non-feasibility of any revascularization procedures.

C.3.4 TREATMENT MODALITIES IN REFRACTORY ANGINA

In addition to improvement in lifestyle, the conventional way to improve myocardial ischemia is by either reducing the oxygen demand (beta blockers, calcium channel blockers) or by improving the supply (nitrates, revascularization procedures such as PTCA or CABG). Additive measures include lipid lowering, inhibition of platelet aggregation, and interference with the renin-angiotensin system which are used for the treatment of angina (Table 2). The first step in the therapy for refractory angina is a critical re-evaluation of these antianginal drug regimens. Studies in patients with seemingly refractory unstable angina (Grambow et al 1992) or severe chronic angina (Naegele et al 1997) have shown that a considerable proportion of patients improve after the dosage of antianginal drugs has been increased and/or their combinations optimized.
C.3.4.1 Beta Blockers

*Beta blockers* remain the first line of treatment for angina pectoris. Beta blockers decrease myocardial oxygen demand by decreasing heart rate and contractility during stress. A slower heart rate also increases the diastolic filling time available for coronary perfusion. Beta blockers thereby increase exercise tolerance and reduce the frequency of anginal attacks. It is recommended that the dosage of beta-blockers should be increased to reduce resting heart rates to 55–60 beats/min.

C.3.4.2 Calcium Channel blockers:

These agents act as pure arterial vasodilators, with variable effects on cardiac conduction and contractility. Phenylalkylamines, such as verapamil, and benzodiazepines, such as diltiazem, have negative inotropic and chronotropic effects. Thus, verapamil and diltiazem retard the increase in myocardial oxygen demand at submaximal work loads, resulting in an increase in the anginal threshold. Dihydropyridines, such as nifedipine, produce negligible decreases in myocardial oxygen demand; instead, they increase myocardial oxygen supply by increasing coronary blood flow through changes in vascular tone. By combining beta-blockers with one of the long-acting dihydropyridine calcium antagonists such as amlodipine (Knight et al 1998) or felodipine (Dunselman et al 1997, Emanuelsson et al 1999), a significantly better therapeutic response can be achieved. The calcium inhibitor bepridil has also been suggested as an alternative drug for symptom relief in severe angina, despite a rather unfavourable side-effect profile (Hollingshead et al 1992, Narahara et al 1992, Zusman et al 1993).

C.3.4.3 Nitrates

Nitrates, another class of antianginal drugs are endothelial-independent vasodilators. They dilate vascular smooth muscles even in vessels without endothelium. At therapeutic doses, nitrates exert
their most prominent vasodilatory effects on systemic veins and conductance arteries. Venodilation leads to decreased left ventricular volume and thus diminished systolic wall stress and oxygen requirements. Furthermore, nitrates have been shown to cause modest stenosis dilation and to relieve coronary vasoconstriction related to endothelial dysfunction. Flow through collateral channels feeding ischemic myocardial regions is also increased. Clinically, exercise tolerance increases and anginal attacks decrease. The use of nitrates may be limited by tolerance development. Molsidomine or nicorandil can be tried instead of long-acting nitrates or added to bridge the recommended 6-8 h nitrate-free period (Ciopor et al 1997).

C 3.4.4 Antiplatelet agents:
Aspirin is recommended for all patients with known CAD. It irreversibly acetylates platelet cyclooxygenase, thereby limiting the production of proaggregatory thromboxane A2. Although aspirin use is widespread among patients treated with CAD, platelet inhibition is only attenuated, and coronary events continue to occur. Agents like Clopidogrel and ticlopidine are thienopyridine derivatives that blocks adenosine diphosphate-mediated platelet aggregation are also recommended as antiplatelet therapy. In patients allergic to aspirin, clopidogrel or ticlopidine can be used as antiplatelet therapy.

C 3.4.5 Lipid Lowering agents:
Several studies have demonstrated that cholesterol reduction improves ischemic symptoms and ST-T changes on the ECG when added to conventional antianginal therapy (van Boven et al 1996, Andrews et al 1997). Reduction in LDL cholesterol has an anti-ischemic effect that is attributable to improved endothelial function at the level of the epicardial conductance vessels (Leung et al 1993, Egashira et al 1994, Anderson et al 1995, Gotto et al 1995, Treasure et al 1995). Statins are a widely used class of lipid lowering agents. Besides reducing LDL cholesterol, these hepatic hydroxymethyl
glutaryl coenzyme A reductase inhibitors (statins) possess anti-inflammatory and plaque-stabilizing properties (Albert et al 2001). Recently, the Atorvastatin Versus Revascularization Treatment (AVERT) trial, using high-dose atorvastatin in patients with mild to moderate anginal symptoms, showed a reduction in recurrent coronary events, as compared with patients treated with conventional lipid-lowering therapy and elective angioplasty (Pitt et al 1999). It is not known what level of LDL cholesterol reduction is optimal in refractory angina, nor has any study been performed on the efficacy of lipid lowering in patients with such chronic symptoms.

C.3.4.6 Angiotensin Converting Enzyme Inhibitors (ACEi)
With the report of the Heart Outcomes Prevention Evaluation (HOPE) study (HOPE Investigators 2000), ACEi have received renewed interest as an anti-ischemic medication. This large, randomized, placebo-controlled trial demonstrated a significant 22% decrease in mortality and recurrent ischemic events in patients with known vascular disease or diabetes plus one other cardiovascular risk factor and normal left ventricular function who received the ACEi ramipril versus placebo. Two similar multicenter studies—the Prevention of Events with ACE inhibition (PEACE) and European Trial on the Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA)—are also evaluating the anti-ischemic effects of ACE inhibitors in patients with CAD and normal left ventricular function.

C.3.4.7 Adjunctive Treatments for Refractory Angina
Despite all the therapeutic measures discussed above, refractory angina patients remain severely incapacitated by their chest pain. There are various reasons making these patients unsuitable for revascularization strategies (Table C.8). In such cases, other therapeutic options need to be considered (Table C.9, Figure C.6). These includes application of additional medications, treatments aimed at improving myocardial perfusion, modulation of the nervous system and treatments aimed at vessel formation.
Table C.8 The most common reasons why further revascularization procedure is not possible for refractory angina patients

- Unsuitable anatomy, such as diffuse coronary sclerosis, often with well-preserved left ventricular function. Sometimes called end-stage angina.
- One or several previous CABGs and/or PTCA, which exclude further benefit or possibility of further revascularization.
- Lack of graft material.
- Impaired left ventricular function in patients with previous CABG and/or PTCA.
- Extracardiac diseases, which increase perioperative/postoperative morbidity or mortality, such as general arteriosclerotic disease, renal insufficiency, carotid stenosis and pulmonary disease.
- Age—often in combination with the above mentioned factors

Table C.9 Therapeutic Options for Refractory Angina Pectoris

1. Pharmacologic therapy—additional antiplatelet agents, thrombolytic therapy, low-molecular-weight heparins, partial fatty acid oxidation inhibitors
2. Neurostimulation
3. Enhanced extracorporeal counterpulsation
4. Laser revascularization (surgical and percutaneous)
5. Gene therapy
6. Percutaneous in situ coronary venous arterialization
7. Chelation therapy
8. Heart transplantation

Figure C.6:
Schematic representation of additional therapeutic options for patients with chronic refractory angina pectoris.

ECCP- enhanced external counterpulsation
SCS- spinal cord stimulation
TENS- transcutaneous electrical nerve stimulation
VEGF- vascular endothelial growth factor
First, the application of additional medication, administered either systemically such as cordarone, chelation, opioids, and (intermittent) urokinase, or locally, such as intrathecally applied anaesthetics or opioids. If the measures mentioned above remain unsuccessful and patients still suffer from frequent episodes of angina, long-term intermittent therapy with urokinase is proposed as a therapeutic option (Leschke et al 1996, Schoebel et al 1997). It is reported that the therapeutic effectiveness of urokinase is at least in part mediated by the improved rheological properties of the blood with consequent increases in blood flow in the myocardial microcirculation. Currently, intermittent administration of thrombolytic therapy for the treatment of refractory angina appears safe. Fibrinogen levels are reduced, leading to decreased red blood cell aggregation and plasma viscosity. Clinically, exercise capacity is increased and subjective anginal episodes are also decreased. However, because of the small number of patients studied and the lack of a placebo control group, the value of thrombolytic therapy in patients with refractory angina is uncertain. Opioids can be used in refractory angina in selected cases where other therapies fail. Hormone replacement therapy is recommended to be considered in post-menopausal women who have hyperlipidemia with poor control by lipid-lowering drugs without contraindication for hormone replacement therapy, as recently advised by the European Society of Cardiology (Schenck-Gustafsson et al 2000). In general, the use of adjunctive medication for long term treatment is withheld because of its drawbacks (opioids), because it is only suitable for short term application (intrathecally applied anaesthetics), it is costly (urokinase), or it has not proven to be effective for this indication (chelation, cordarone). Medications targeting inflammation and thrombosis are considered to be more potent options in the near future.
• Second, treatments aimed at improving myocardial perfusion, by means of a rehabilitation programme or by affecting the hemodynamic system. The trade-off of the beneficial effects of cardiac rehabilitation programmes on cardiac performance is the need for continuation of the programme (Linxue et al 1999). Angina pectoris may also be treated by enhanced external counterpulsation (class IIb indication). This method is directed at diastolic augmentation of blood flow in the coronary arteries through an increase in aortic retrograde blood flow, induced by compression of cuffs that are wrapped around the legs. Recently, enhanced external counterpulsation has been reported to be effective in improving myocardial perfusion during stress in patients with chronic stable angina (Stys et al 2002). However, experience is limited and the equipment costly.

• Third, modulation of the nervous system. The nervous system can be modulated through spinal cord stimulation or transcutaneous electrical nerve stimulation. Neuromodulation appears to be one of the most successful adjunctive treatments. It is a reversible therapy and has been reported to be effective, without concealing angina pectoris during an acute myocardial infarction. The beneficial effects of neuromodulation, expressed in a reduction in the number and severity of anginal attacks in conjunction with an improvement in exercise capacity and quality of life, have been reported to last for several years. Evidence that spinal cord stimulation exerts an additional anti-ischemic effect is provided by studies on exercise testing, ambulatory ECG monitoring, positron emission tomography, and coronary flow measurements. The explanation for the reduction in myocardial ischemia may be a homogenisation of the myocardial perfusion (DeJongste et al 1999). Spinal cord stimulation has been proposed as a method for providing analgesia for patients with chronic angina pectoris refractory to medical, catheter interventional, or surgical (Class IIb). There is evidence that electrical stimulation of the dorsal aspect of the spinal cord stabilises the intrinsic cardiac nervous
system and may therefore prevent deleterious consequences, such as electrical instability of the ventricles (Foreman et al 2000). Research performed by Kanno and colleagues in 1999 may shed new insights into the influence of electrical stimulation on the concentration of vascular endothelial growth factor (VEGF). From this investigations on low intensity (10% of contraction threshold) electrical stimulation in ischemic hind paw muscles of rabbits and in muscle cells in vitro it may be concluded that VEGF mRNA concentration after stimulation is increased significantly. Denervation of the heart by endoscopic transthoracic sympathectomy has also been reported in a very limited number of publications over the last decade. The drawback of these destructive experimental treatments is a relatively high mortality and morbidity, ranging from 5–10% (Wettervic et al 1995).

- Fourth, treatments aimed at vessel formation through upregulation of vascular endothelial growth factors inducing angiogenesis, making use of stem cells, or applying either transmyocardial (Transmyocardial Revascularization-TMR) or percutaneous laser (Percutaneous Myocardial revascularization-PMR). Surgical laser transmyocardial revascularization is indicated in patients with refractory angina (Class IIa). Restoration of function by means of angiogenesis is a stepwise experimental procedure, best studied by making use of gene therapy. Gene therapy can be applied by direct intramyocardial injection of naked DNA encoding for VEGF, a heparin binding glycoprotein, as well as adenoviral transfection with VEGF. Regulation of VEGF mainly takes place via oxygenation of tissues. Ischemia enhances both the expression and production of VEGF. Furthermore, since an increased concentration of VEGF mRNA has been demonstrated in ischemic tissues, this suggests a negative feedback system. When oxygen concentration in the tissues increases, VEGF gets down regulated. At the onset of the angiogenesis process, endothelial cells produce metalloproteinases to digest the basement membrane. Next, the endothelial cells may disconnect from the basement membrane, and
are able to migrate, proliferate, and form a network of "endothelial tubes". To become functionally important the vessels then need to mature. During the following arteriogenesis, nascent vessels become extensively covered by a muscular coat creating blood vessels with viscoelastic and vasomotor properties (Carmeliet et al 2000). Studies on gene therapy have demonstrated a remarkable improvement in flow to ischemic areas in peripheral arteries as well as in the heart (Tio et al 1999). Although the clinical results are encouraging, a need for further validation in placebo controlled trials remains. With respect to angiogenesis most concerns relate to the vehicle, usually a genetically manipulated virus, delivering growth factor.

In conclusion, gene therapy induced new blood vessel formation, making use of angiogenetic growth factors, is and promising development. TMR and PMR are meant to improve the flow through myocardium by channelling with laser beams. Mirhoseini was the first to advocate direct laser therapy of myocardium as a treatment for refractory angina, in 1981. The idea initially was to create transmural channels from the left ventricular cavity into the myocardial muscle improve myocardial perfusion. Although some animal studies have suggested patency of lasered channels, most studies and necropsy reports showed occlusion of the lasered channels within one day, making neo-"revascularisation" a mechanism of action unlikely. Also denervation of the heart or laser induced angiogenesis with subsequent collateralization causing improvement of perfusion is not proven. Initially the myocardium was lasered from the epicardial side heart surgery, both as an adjunct to bypass surgery and as a stand alone procedure. Early studies showed a high postoperative mortality. Randomized controlled studies comparing laser therapy with medical treatment reported inconsistent findings. The majority showed a reduction anginal complaints, some an improvement in exercise capacity, and only one study demonstrated an improved perfusion. Developments in catheter based technology it possible to deliver the laser energy from the endocardial
Preliminary data show that efficacy is the same as surgical based laser therapy. However, in view of unknown underlying mechanism of action, to date therapy is not recommended for this subset of patients. Finally, heart transplantation is not considered a feasible treatment for this group of patients. Some of the discussed adjuvant treatments have class IIa or IIb indications, according to the recent AHA/ACC guidelines (Gibbons et al 2003).

Percutaneous in situ coronary venous arterialization (PICVA) is a percutaneous approach to CABG that redirects arterial blood flow from the occluded, offending artery into an adjacent coronary vein, thereby arterializing the vein and providing retroperfusion to ischemic myocardium. Even in the most severe cases of CAD, the venous system is generally free of atherosclerosis, and the individual veins are dispensable, owing to a redundant venous system. Anecdotal reports documenting relief from angina using coronary retroperfusion from the 1940s to the 1970s inspired the modern-day revival of this technique (Kay et al 1975). Percutaneous in situ coronary artery bypass (PICAB) is also an advancing technology for this group of patients with refractory angina in whom arterial blood flow is redirected from a diseased artery to an adjacent coronary vein, and then rerouted back to the artery after the lesion (Fitzgerald et al 1999). Although the potential for PICVA and PICAB, as treatment for patients with poor anatomy for traditional revascularization procedures, is enormous, currently these technologies are considered experimental.

Patients with chronic refractory angina, thus differ from ordinary angina patients in three ways: a) refractory angina patients maintain their left ventricular function despite severe three vessel disease; b) they do not experience severe arrhythmias and therefore mortality is only about 5%; and c) their angina debilitating. Thus, this population is known as “No-Options” patients as neither optimal pharmacological therapy nor revascularization therapy (PCI/CABG) is suitable for treatment. The alternative therapies proposed are less well...
documented and/or have unfavourable documentation with conflicting results or serious adverse effects and thus have limited feasibility. Currently, the management of refractory angina is limited to the anti-anginal therapies available. New and often promising modalities of treatment and research in this area is required.

C.3.5 DIAGNOSTIC MODALITIES IN HF

HF generally refers to the chronic syndrome, or chronic HF (CHF). New York Heart Association (NYHA) classification is the commonly used functional and therapeutic classification of HF and used to assess the severity of functional limitations (Table C.10). The ACC/AHA classification of HF based on stages of the syndrome is also applicable (Table C.11) (Hunt et al 2005).

Table C.10 New York Heart Association classification for HF

<table>
<thead>
<tr>
<th>Class</th>
<th>NYHA Functional Classification</th>
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<tr>
<td>I</td>
<td>Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea</td>
</tr>
<tr>
<td>II</td>
<td>Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnea</td>
</tr>
<tr>
<td>III</td>
<td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation or dyspnea</td>
</tr>
<tr>
<td>IV</td>
<td>Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
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</tbody>
</table>
Table C.11 ACC/AHA Classification of CHF

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for developing HF</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic HF</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>D</td>
<td>Refractory end-stage HF</td>
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The initial evaluation of new onset HF should include an electrocardiogram, chest radiograph, Echocardiography and B-type natriuretic peptide assay.

C.3.5.1 Electrocardiogram

The cardiac rhythm may be normal sinus, sinus tachycardia, or atrial fibrillation. Left ventricular hypertrophy, left bundle branch block, intraventricular conduction delay, and non-specific ST segment and T wave changes support a diagnosis of heart failure. Q waves in contiguous leads strongly implicate a previous myocardial infarction and coronary atherosclerosis as the etiology.

C.3.5.2 Chest Radiograph

Chest radiographic findings of HF include cardiomegaly, pulmonary vascular redistribution, pulmonary venous congestion, alveolar edema, and pleural effusions.

C.3.5.3 Echocardiography

Echocardiogram serves as the most useful diagnostic test for heart failure. Echocardiography can distinguish between systolic and diastolic dysfunction. If systolic dysfunction is present, regional wall motion abnormalities or left ventricular aneurysm suggest an ischemic basis for heart failure, whereas global dysfunction suggests a non-ischemic etiology. Echocardiography measures left ventricular systolic function more precisely, which is important from a prognostic...
standpoint (Cintron et al 1993, Cohn et al 1993) and for monitoring the response to beta blocker therapy, a treatment that favorably affects systolic function (Eichhorn et al 1996). Echocardiography is helpful in determining other etiologies such as valvular heart disease, cardiac tamponade, and pericardial constriction, and provides useful indications about infiltrative and restrictive cardiomyopathies (Bristow et al 2005). Echocardiography can also provide meaningful prognostic information about diastolic function, severity of hypertrophy, chamber size, and valvular abnormalities. In many cases however, the exact etiology for heart failure cannot be discerned from the echocardiogram.

Diastolic dysfunction, on the other hand, reflects near-normal systolic function and unequivocal evidence of HF. This includes acute decompensation episodes (pulmonary edema on chest radiograph with breathlessness or right sided heart failure) or chronic myocardial dysfunction resulting in high filling pressures, decreased cardiac output and impaired functional capacity.

C.3.5.4 Cardiac Catheterization:

*Coronary angiography* may aid diagnose the coronary atherosclerosis as the cause of HF. Left ventriculography documents the severity of left ventricular systolic dysfunction and mitral valve regurgitation.

*Radionuclide ventriculography* provides objective data about right and left ventricular systolic function (de Groote et al 1998). No assessment of diastolic function or valvular function can be obtained by this test so it is performed less frequently than echocardiography.

Magnetic resonance imaging (MRI) is useful in assessing for arrhythmogenic right ventricular dysplasia, myocardial viability, and infiltrative cardiomyopathies.

Objective information about functional capacity can be obtained from metabolic exercise testing. This can distinguish ventilatory from cardiac limitations in patients with exertional dyspnea. A peak oxygen consumption >25 ml/kg/min is normal for middle-age adults, but a
value <14 ml/kg/min is indicative of severe cardiac limitation and poor prognosis (Myers et al 1998).

C.3.5.5 Serum B-type natriuretic peptide (BNP) assay

BNP and N-terminal pro-BNP estimations has emerged as a useful diagnostic test for the detection of heart failure (Dao et al 2001, Kazanegra et al 2001). However, the use of BNP measurements to guide the titration of drug doses has not been shown to improve outcomes more effectively than achievement of the target doses of drugs shown in clinical trials to prolong life (Tang et al 2003). Ongoing trials will help to determine the role of serial BNP measurements in both diagnosis and management of HF.

C.3.6 TREATMENT MODALITIES IN HF

The goals of treatment for CHF are to (1) relieve symptoms and improve functional capacity, (2) reduce disability and hospitalizations, (3) delay progression of or reverse remodelling and myocardial dysfunction, and (4) reduce mortality. Depending on the stage of HF, one or more of these goals may be important which accordingly dictates the type of pharmacological agents to be used (Table C.12).

C.3.6.1 Non-Pharmacological Therapies & General Measures:

- Dietary sodium and fluid restrictions is recommended to all heart failure patients. Limiting patients to 2 gm per day of dietary sodium and 2 liters per day of fluid will lessen congestion and lower the need for diuretics.
- Cardiac rehabilitation may improve symptoms and exercise tolerance in patients with heart failure. This will also reduce or prevent skeletal muscle atrophy that may worsen exercise tolerance. Weight loss in encouraged in obese patients. Smoking cessation and other life style modifications are recommended.
- For stage A HF, the ACC/AHA guidelines strongly recommends (Class I indication) control of risk factors for CAD and other cause of cardiomyopathy, including hypertension, hyperlipidemia, diabetes, alcohol abuse, cigarette smoking and hyperthyroidism.
Table C.12
Stages in the development of heart failure/recommended therapy by stage

FHx CM indicates family history of cardiomyopathy;
ACEI, angiotensin converting enzyme inhibitors; and
ARB, angiotensin receptor blocker

FHx CM indicates family history of cardiomyopathy; ACEI, angiotensin converting enzyme inhibitors; and ARB, angiotensin receptor blocker.
C.3.6.2 Pharmacological therapy for CHF caused by systolic dysfunction

(A) Angiotensin Converting Enzyme Inhibitors (ACEi)

ACE inhibitors is recommended for stage B HF since the goal is to reduce the risk of further damage to the left ventricle and to minimize the rate of progression of LV dysfunction (class I indication from Stage B to D HF). Afterload reduction and neurohormonal modulation with ACE inhibitors improve mortality, heart failure symptoms, exercise tolerance, left ventricular ejection fraction as well as reduce emergency room visits and hospitalizations (Cohn et al 1986, Pitt et al 1991, Yusuf et al 2000). The dose of ACE inhibitors should be titrated to the maximum that can be tolerated symptomatically (Packer et al 1999) or as per the recommended target dose. The main side effect from ACE inhibition is cough, which may necessitate change either to an angiotensin-II receptor blocker (ARB) or the combination of hydralazine and nitrate. However, it is found at times that most patients cough on ACEi because of congestive heart failure rather than ACE intolerance, and may improve with further diuresis. Two uncommon side effects of ACEi are angioedema and acute renal failure (because of bilateral renal artery stenosis), both necessitating immediate cessation of the drug.

(B) Angiotensin Receptor Blockers (ARBs)

These agents block the effects of angiotensin-II at the receptor level. In clinical trials, these agents were superior to placebo but not better than ACEi in improving mortality. They improve morbidity when added to ACE inhibitors and have fewer side effects (Cohn et al 2001). Angiotensin receptor blockers (ARBs) are recommended as second-line therapy in patients who are intolerant to ACE inhibitors because of cough or angioedema (Class I indication for Stage B, C, D HF). ARBs can reduce the combined endpoint of cardiovascular mortality and HF hospitalizations when administered on top of ACEi in stage B patients with preserved blood pressures (Cohn et al 2001, McMurray et al...
2003) mostly by reducing HF hospitalizations. However, Val-Heft trial showed an increased mortality-in patient treated with ARB Valsartan on top of ACE inhibition and beta blockade (Cohn et al 2001), This adverse effect was not found in the CHARM-Added trial, which investigated the ARB Candesartan (McMurray et al 2003). In both trials ARBs were effective in lowering mortality and HF morbidity in patients intolerant of ACE inhibitors (Granger et al 2003). Further, ARBs may be useful for the treatment of diastolic heart failure (Yusuf et al 2003).

(C) Beta-blockers

The chronically increased adrenergic drive present in the failing human heart delivers adverse biological signals to the cardiac myocyte through \( \beta_1 \), \( \beta_2 \), and possibly \( \alpha_1 \)-adrenergic receptors. Elimination of these adverse signals is the fundamental reason for using antiadrenergic agents in the treatment of chronic HF (Bristow et al 2000). Because of their clinical availability, beta-adrenergic blocking agents were the first antiadrenergic agents used to treat chronic HF (Waagstein et al 1975). Although three classes of beta blockers are now available for clinical use, only the "second-generation" \( \beta_1 \) receptor-selective antagonists (metoprolol, bisoprolol) or the "third-generation" beta blocker-vasodilators (carvedilol) are tolerated to an acceptable degree by subjects with chronic HF (Eichhorn et al 1997). Second-generation compounds are tolerated because they do not block cardiac pre- or postjunctional \( \beta_2 \) receptors (Newton et al 1999, Bristow et al 2000), and third-generation compounds are tolerated because their afterload-reducing properties mitigate the cardiac output-reducing effects of beta-adrenergic withdrawal (Gibeline et al 1993). The exact mechanism of beta-blocker action is unclear, but likely involves anti-arrhythmic, anti-ischemic, anti-remodelling, and anti-apoptotic properties as well as improved beta-receptor pathway function. Myocardial oxygen consumption is reduced with beta-blockers, primarily due to a reduction in heart rate. Both second- and third-generation beta-blocking agents improve intrinsic systolic...
function and reverse remodelling in primary or secondary cardiomyopathy in a time-dependent fashion that begins after an initial period of myocardial depression related to withdrawal of beta-adrenergic support (Bristow et al 1997). However, these effects are not uniform across all treated subjects, and some subjects may deteriorate and have an adverse clinical response to beta blockade (Lechat et al 1997). The specific mechanism by which beta blockers produce a time-dependent improvement in systolic function and reversal of remodelling has also been investigated (Lowes et al 2002, Abraham et al 2002). In the failing, remodelled human heart, both second- and third-generation beta-blocking agents produce changes in myocardial gene expression that would be expected to increase systolic function and reverse remodelling (Lowes et al 2002). Unlike members of the ACEi, ARB, and aldosterone antagonist classes of neurohormonal inhibitors, beta-blocking agents are more diverse in their pharmacological effects. Three beta-blockers, carvedilol, metoprolol succinate and bisoprolol have been shown to improve survival in patients with heart failure (Packer et al 1996, Hjalmarson et al 2000, The CIBIS-II Study 1999). Regardless of the type of beta-blocking agent used, the treatment approach that must be taken in subjects with chronic HF is to start with extremely low doses (1/8 to 1/16 of the target dose) and gradually increase the dose every 1 to 2 weeks until full beta-blocking doses are achieved (Eichhorn et al 1997). Beta-blockers are recommended along with ACEi in stage B, C, D HF (Class I indication). They are also recommended in NYHA Class IV patients who are euvolemic, based on the findings from the COPERNICUS study (Packer et al 2001).

**Metoprolol** is a second-generation β₁ receptor-selective blocking agent with an approximately 75-fold higher affinity for human beta₁- than beta₂-adrenergic receptors. Metoprolol, in its long-acting, controlled-release/extended release form (Metoprolol succinate, CR/XL), is approved for the treatment of HF. The first placebo-controlled multicenter trial with a beta-blocking agent was the Metoprolol in
Dilated Cardiomyopathy (MDC) trial, which used the shorter acting tartrate preparation at a target dose of 50 mg three times a day (Waagstein et al 1993). Despite the salutary clinical effects demonstrated for metoprolol tartrate in MDC, the preparation was limited due to its short elimination and pharmacological half life leading to more likelihood of "beta withdrawal syndrome" occurrence especially if dose is missed or delayed. Hence more efficacious controlled release/extended release preparation was developed (Metoprolol Succinate CR/XL), which was evaluated in the metoprolol CR/XL Randomized Interventional Trial in Congestive Heart Failure (MERIT-HF) trial (The International Steering Committee MERIT-HF 1997). MERIT-HF was stopped prematurely because of a 34 percent reduction in mortality in the Metoprolol arm (Kukin et al 2000). The CR/XL preparation used in MERIT-HF produces a relatively constant blood level of metoprolol for 24 hours, but the bioavailability of the CR preparation is approximately 70 percent that of the conventional formulation. Metoprolol CR/XL is recommended to be started at a dose of 25 mg/day (half dose for class III/IV) and uptitrated to a target dose of 200mg/d (MERIT-HF Study Group 1999).

**Bisoprolol** is another second generation beta\textsubscript{1} receptor-selective blocking agent investigated in heart failure. CIBIS-I and CIBIS-II trials have reported the efficacy of bisoprolol in patients with cardiomyopathy (CIBIS Investigators and Committees 1994, CIBIS-II Investigators 1999).

**Carvedilol**, currently approved for the treatment of chronic heart failure, is a minimally \(\beta\textsubscript{1}\) receptor-selective beta-blocking agent that has high affinity for \(\alpha\textsubscript{1}\)-adrenergic receptors as well as ancillary antioxidant action (Noguchi et al 2000). The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial in "severe" HF with no documentation of NYHA functional class showed efficacy of carvedilol in reducing the risk of mortality, death or HF hospitalization (Packer et al 2002). Carvedilol has also been evaluated in a post-myocardial infarction trial in which patients had to exhibit LV
dysfunction, the CAPRICORN trial. Although carvedilol did not reduce the primary endpoint of mortality plus cardiovascular hospitalization, it did reduce significantly the total mortality, cardiovascular mortality and nonfatal myocardial infarction (Australia/New Zealand Heart Failure Research Collaborative Group 1997). **Bucindolol** and **Nebivolol** are other third generation beta blocker-vasodilators with limited but favourable experience in heart failure trials. (Wisenbaugh et al 1993, BEST trial investigators 2001)

A mortality trial (Carvedilol or Metoprolol European Trial [COMET]) comparing metoprolol tartrate with carvedilol demonstrated greater mortality reduction in favor of carvedilol, with respective mean daily doses of the two beta blockers being 85 and 42 mg (Poole-Wilson et al 2003). This relatively low average dose of metoprolol also produced less heart rate or blood pressure reduction than carvedilol (Poole-Wilson et al 2003). However, in MERIT-HF the degree of mortality reduction produced by metoprolol CR/XL in the entire cohort (MERIT-HF Study Group 1999) as well as in a subpopulation with "severe HF" (Goldstein et al 2001) was essentially identical to that produced by carvedilol in the COPERNICUS (Packer et al 2002) trial. It thus appears, at least some of the differential efficacy of carvedilol and metoprolol in COMET was probably due to the lower beta<sub>1</sub>-blocking doses of immediate-release metoprolol tartrate rather than to an absolute difference in efficacy between metoprolol and carvedilol (Bristow et al 2003). Although data indicating that carvedilol is superior to metoprolol have been generated in direct comparison trials (Poole-Wilson et al 2003, Metra et al 1994), these trials were flawed by the use of a lower beta<sub>1</sub>-blocking dose of the formulation of metoprolol in comparison with carvedilol (Bristow et al 2003). Therefore, lower doses of shorter acting beta<sub>1</sub>-selective blocking agents such as metoprolol tartrate or atenolol (for which there is no controlled experience in HF) cannot be recommended as equivalent to therapy with higher doses of carvedilol, metoprolol CR/XL, or bisoprolol. The possibility that carvedilol is truly superior to beta<sub>1</sub>-
selective agents delivered to the same degree of $\beta_1$ receptor blockade still remains, but no study demonstrating this has been conducted. Because of the pharmacological heterogeneity among beta-blocking agents, the degree of polymorphic variation in key components of adrenergic mechanisms, and the clinical diversity of HF subpopulations, there remains an excellent possibility that antiadrenergic therapy with beta-blocking agents will evolve to a more tailored and targeted approach involving individual types of agents being more effective for subsets of polymorphic receptor variants or other determinants of antiadrenergic response, or both (Torp-Pedersen et al 2002).

(D) Digoxin

Digoxin is a weak oral inotrope whose main effect in heart failure is neurohormonal modulation of centrally mediated sympathetic activity. A large randomized controlled trial showed that the use of digoxin reduces the rate of hospitalization for heart failure, but has no effect on mortality (The Digitalis Investigation Group 1997). Digoxin is renally excreted and so dose adjustment is necessary in renal failure. A low dose of digoxin (0.125 mg daily) should be prescribed to most patients, especially women. Digoxin currently is recommended in the ACC/AHA guidelines for patients with left ventricular systolic dysfunction who remain symptomatic while receiving standard medical therapy, particularly if they are in atrial fibrillation (Class IIa indication for Stage C HF).

(E) Diuretics

Along with ACEi and Beta blockers, Diuretics and salt restriction is strongly recommended in Stage C of the HF (Class I indication). Diuretics are useful in relieving congestion and treating hypertension (Brater et al 1997). Most patients with heart failure have some degree of symptomatic congestion and benefit from diuretic therapy. Usually a loop diuretic is required, with the addition of a thiazide diuretic in patients refractory to the loop diuretic alone Inspite of lack of large-scale trials, loop diuretics are a cornerstone of symptomatic HF
treatment beginning in stage B (Taylor et al 2000). The goals of diuretic therapy are to reduce congestive symptoms, reduce wall stress, and attenuate the harmful signaling of remodelling/dysfunction mechanisms. Although useful for symptomatic relief, diuretics have not been shown to improve survival and may cause azotemia, hypokalemia, metabolic alkalosis and elevation of neurohormones.

**(F) Aldosterone Antagonists**
The aldosterone antagonist, K⁺-sparing minimal diuretic Spironolactone, has been shown to lower mortality in stage C HF patients, and results with the newer aldosterone antagonist Eplerenone in a post-myocardial infarction setting (Pitt et al 2003) suggest that aldosterone inhibition added to an ACE inhibitor would be effective in lowering mortality and morbidity in stage B HF. The RALES trial was a randomized controlled study that reported a significant mortality benefit of spironolactone, when added to standard therapy in patients with advanced heart failure (Pitt et al 1999). Aldosterone inhibition may prevent sodium and water retention, endothelial dysfunction and myocardial fibrosis. With spironolactone therapy, diligent monitoring of serum potassium levels is mandatory, as patients may develop hyperkalemia. Since data in mild heart failure are lacking, and the drug is reserved for patients with moderately severe-severe heart failure. The EPHESUS study reported a 15% reduction in the risk of death and hospitalization in patients with heart failure and LVEF <40% after a myocardial infarction, who were treated with the selective aldosterone receptor antagonist, eplerenone (Pitt et al 2003)

**(G) Hydralazine and Nitrates:**
Hydralazine and nitrates in combination are effective afterload and preload reducing agents used in ACE-intolerant patients. ACEi had a mortality benefit over hydralazine and nitrate in a large randomized controlled trial and thus recommended as the agent of choice (Cohn et al 1991). Hydralazine and nitrates may be added to ACE inhibitors
when additional vasodilation is needed or pulmonary hypertension is present (Class IIa indication).

(H) Other Medical Therapies
It is recommended that patients with known CAD should be treated with aspirin and a statin to lower the LDL to 70 mg/dl. Calcium channel antagonists have not been proven to be beneficial in heart failure patients (Hunt et al 2005). Short-acting calcium channel antagonists such as nifedipine are contraindicated because they increase mortality, elevate neurohormones, and worsen heart failure. Dihydropyridines such as amlodipine have a neutral effect on heart failure and may be useful for treating concomitant hypertension or angina pectoris (Packer et al 1996).

The use of warfarin to prevent cardioembolic strokes remains controversial in the absence of atrial arrhythmias, since the risk appears to be relatively low. Warfarin therapy is recommended in patients with atrial arrhythmias, left ventricular thrombi, or left ventricular aneurysms (Dunkman et al 1993, Baker et al 1994).

Specific therapies for treating atrial fibrillation, sleep apnea, anemia, obesity, and thyroid diseases may improve the symptoms and functional limitations of heart failure.

(I) Intravenous Inotropes and Vasodilators:

Dobutamine
Dobutamine is a useful inotropic agent for moderately decompensated heart failure (Leier et al 1992). It enhances contractility by directly stimulating cardiac beta-1 receptors (Felker et al 2001). Intravenous dobutamine infusions, sometimes guided by hemodynamic monitoring, may be useful in selected patients with acute exacerbations of hypotensive heart failure or shock. Dobutamine reduces aortic impedance and systemic vascular resistance, thus reducing afterload and improving ventricular-vascular coupling by reducing aortic impedance (Leier et al 1978, Leier et al 1992). The LV afterload-reducing effects are also responsible for the reduction in functional mitral regurgitation often observed concomitantly with
dobutamine infusions in patients with large dilated ventricles and high LVEDP (Keren et al 1989). The dose of dobutamine is recommended to be titrated to the lowest dose compatible with hemodynamic stability in order to minimize adverse events.

**Milrinone**

Milrinone is a phosphodiesterase-III inhibitor that increases intracellular cyclic adenosine monophosphate (cAMP) and enhances contractility. Milrinone is useful in patients with hypotensive, low output heart failure and pulmonary hypertension, since it is a more potent pulmonary vasodilator than dobutamine. Milrinone, in contrast to dobutamine, is also useful in patients on chronic oral beta-blocker therapy who develop decompensated heart failure. The OPTIME study, involving the intravenous infusion of milrinone for 48 hours during hospitalization for decompensated heart failure, failed to show symptomatic benefit, and was associated with an increased risk of atrial arrhythmias and hypotension (Cuffe et al 2002).

**Nitroglycerin**

Nitroglycerin is a nitric oxide donor that increases the intracellular concentration of cGMP in endothelial and smooth muscle cells causing vasodilation. It is predominantly a venodilator, and to a lesser extent, an arterial vasodilator that reduces cardiac preload and alleviates pulmonary congestion. Intravenous nitroglycerin is recommended in the ACC/AHA guidelines for the management of patients with acute pulmonary edema.

**Sodium Nitroprusside**

Sodium nitroprusside is a nitric oxide donor and a potent short-acting arterial and venous vasodilator. It is useful as an afterload reducing agent in patients with acute decompensated heart failure and adequate systemic blood pressure. It has balanced effects on afterload and preload, and ventricular filling pressures are rapidly reduced by an increase in venous compliance (Risoe et al 1992). During nitroprusside infusions, patients are converted to oral vasodilators such as ACE inhibitors, ARBs, or hydralazine/nitrates. Nitroprusside
should be avoided in patients with active ischemia due its potential for "coronary steal syndrome" which shunts blood away from the ischemic myocardium to well-perfused muscle (Cohn et al 1982). Nitroprusside infusions are generally reserved for patients in an intensive care unit and require invasive hemodynamic monitoring.

**Nesiritide**
Nesiritide, synthetic B-type natriuretic peptide, is an arterial and venous vasodilator with modest diuretic and natriuretic properties (Iyengar et al 2004). Nesiritide increases cardiac output by reflex vasodilation without increasing heart rate or oxygen consumption. It modulates the vasoconstrictor and sodium retaining effects of other neurohormones. In clinical trials involving patients hospitalized for decompensated heart failure, nesiritide has been shown to improve hemodynamic and clinical status (Colucci et al 2000, Mills et al 2002).

**Other novel Agents:**
Phosphodiesterase inhibitors like milrinone, amrinone, enoximone are being evaluated in HF. Other new class of drugs currently under investigation as future HF therapy includes Neutral endopeptidase inhibitors/vasopeptidase inhibitors (eg. Omapatrilat, Candoxatril, ecadotril), calcium sensstizers (eg. Levosimendan, Pimobendan), cardiac natriuretic peptides and vasopressin 2 receptor blockers (eg. conivaptan, tolvaptan).

C.3.6.3 Pharmacological therapy for CHF caused by Diastolic Dysfunction
Unlike systolic dysfunction, no medical treatment that reduces mortality in diastolic dysfunction is available. The cornerstone of treatment is careful regulation of ventricular filling pressure by diuretics, in a range that prevents excessive dyspnea and liver congestion but allows for adequate cardiac output. ACEi and/or spironolactone may make diuretic management easier by preventing excessive activation of the RAAS. In addition, some evidence indicates that ACEi improve ventricular relaxation (Friedrich et al 1994), but
this improvement does not seem to be translated into benefit in subjects with diastolic HF. A large clinical trial (CHARM-Preserved) (Yusuf et al 2003) comparing an ARB (candesartan) to placebo demonstrated a small (18%) reduction in HF hospitalizations, without a beneficial effect on the primary endpoint (cardiovascular death or HF hospitalizations) or on mortality. In patients with tachycardia (resting heart rates >90 beats/min) beta blockers may be used to slow the heart rate and prolong filling time, and beta blockers or amiodarone may be required to control and prevent supraventricular arrhythmias. Finally, phosphodiesterase inhibitors (PDEIs) have been shown to improve diastolic function acutely (Mitrovic et al 1996), but there has been no controlled experience with these agents in chronic therapy.

C.6.3.4 Hemodynamic Monitoring to Tailor CHF therapies:

Management of the CHF is a complex task that involves titration of several drugs, which may interact with each other, and trigger undesired results. The titration of the drugs needs to be optimized for achieving the best results (Hunt et al 2005, Swedberg et al 2005). The medical treatment of CHF is in essence, an art of balancing the hemodynamic status of the patient in a state of compensation, such that the compensatory mechanisms and thus progression of the CHF is minimized. Even once balanced (sometimes directed by invasive hemodynamic measurements during hospitalization events), decompensation may often occur. The LVEDP and PCWP are critical hemodynamic parameters, which are the basis for most decompensation events. The LVEDP is obtained clinically from the pulmonary artery wedge pressure, which correlates with the pulmonary artery diastolic pressure (PADP). Frequent, readily available, monitoring of LVEDP, PCWP or PAP, supplies the necessary feedback loop for direction of therapy. There is evidence that a tailored, hemodynamic approach to treatment has an important impact on outcome (Yancy et al 2003). Presently, Hemodynamic monitoring is traditionally restricted to invasive pulmonary artery
catheterization (also known as Swan Ganz Catheterization) which involves a balloon tipped flow guided pulmonary artery catheter for measurements of these critical parameters. The recent ESCAPE trial, however failed to show the benefits of pulmonary artery catheterization in hospitalized patients (The ESCAPE investigators 2005). The invasive nature of the hemodynamic monitoring leaves the current outpatient uptitration of CHF therapy limited to clinical evaluation. Many non-invasive hemodynamic monitoring devices are currently under investigation to overcome this limitation.

C.3.6.5 Device Therapies for Heart Failure:

(A) Cardiac Resynchronization Therapy

Multiple clinical trials have shown the potential benefit of cardiac resynchronization therapy in patients with severe symptomatic heart failure, and a wide QRS complex (Cazeau et al 2001, Abraham et al 2002). With cardiac resynchronization therapy, a third electrode is implanted in a left cardiac vein via the coronary sinus so that the right and left ventricles can be activated simultaneously. Optimal synchronization of atrial and ventricular contraction is achieved with echocardiographic guidance. It is also known as biventricular pacing strategy and is based on the fact that most subjects with intraventricular conduction delay have dyssynchronous left ventricular contraction, which results in a reduction in ventricular performance and unfavourable myocardial energetics (Kass et al 1999). The COMPANION Trial CRT or CRT + ICD with optimal pharmacological therapy were compared to only optimal pharmacological therapy for effects on survival and hospitalizations (Buxton et al 1999). It was found that both CRT and CRT+ICD reduced the incidence of the primary endpoint of all-cause mortality or all-cause hospitalization by 19 to 20 percent (p<0.02), secondary to an favorable effects on mortality and HF hospitalizations (Bristow et al 2004).
(B) Defibrillator Therapy

Approximately half of the patients with heart failure die suddenly. Implantation of an internal cardioverter defibrillator (ICD) may improve survival in certain subsets of heart failure patients and has been shown to be superior to anti-arrhythmic drug therapy in preventing sudden death (Gollob et al 2002, Moss et al 2002). Current indications for defibrillator therapy include patients with LV dysfunction who have survived sudden cardiac death (Falk et al 1992), have symptomatic sustained ventricular tachycardia (MADIT Investigators 1996), have asymptomatic nonsustained but inducible ventricular tachycardia (Buxton et al 1999), or have an ischemic cardiomyopathy with an LVEF less than 30 percent (Moss et al 2002). An ICD implanted in patients with dilated cardiomyopathy and at least NYHA Class II CHF may improve survival over optimal medical care and/or anti-arrhythmic drug therapy (Kadish et al 2004). Cardiac resynchronization therapy can be combined with an ICD as a single device if a patient meets criteria for both devices.

(C) Left Ventricular Assist Devices (LVAD):

Certain patients with cardiogenic shock unresponsive to intra-aortic balloon counterpulsation and intravenous inotrope therapy are referred to a tertiary care center for mechanical circulatory support (Rose et al 2001, Delgado et al 2002). The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) evaluated one device (Heartmate vented electric device) in patients who were not transplant eligible. The device therapy caused a 48% reduction in death and improved quality of life (Rose et al 1999, Rose et al 2001). Presently, LVADs are best used as a bridge to cardiac transplantation in patients who are appropriate transplant candidates. The inflow cannula for an LVAD is connected to the apex of the left ventricle. Blood is mechanically pumped by the device via the outflow cannula to the aorta. FDA-approved LVADs include the Heartmate, Novacor, Thoratec, and Abiomed devices. Complications
following LVAD implantation are common and often life-threatening: stroke, infection, peri-operative coagulopathy and bleeding, multi-system organ failure and bioprosthetic valve insufficiency. LVADs may be used as permanent implants (destination therapy), but many obstacles presently prevent widespread implementation.

C.3.6.6 Surgical Therapies for HF:

(A) Ventricular Reconstruction Surgery
Ventricular reconstruction surgery, also called ventricular remodelling surgery or a Dor procedure, is performed for heart failure secondary to ischemic cardiomyopathy (Mickleborough et al 2004). It consists of several components: coronary artery bypass grafting, mitral and tricuspid valve repair, resection of left ventricular scar or aneurysm, reshaping the left ventricle from a spherical to an elliptical shape, and epicardial left ventricular pacing lead placement. Patients suitable for this procedure have coronary artery disease, extensive ischemia or hibernating myocardium, severe left ventricular dysfunction with akinetic or dyskinetic ventricular segments, and mitral/tricuspid regurgitation. A trial investigating the addition of surgical anterior ventricular restoration (Athanasuleas et al 2001) to CABG (the STICH Trial) is currently being conducted.

(B) Cardiac Transplantation
Cardiac transplantation is reserved for otherwise healthy patients with end-stage heart failure with severely impaired function despite optimal medical therapy (Hunt et al 1998). Survival after transplantation is superior to that with pharmacological or pharmacological + device therapy. However, as can be observed in the COMPANION Trial CRT-D patients (Bristow et al 2004), survival with the combination of pharmacological and device therapy is improving and with another incremental improvement it will be more preferable than transplantation for stage C patients. The biggest limitation of transplantation is limited supply of donors. Thus, it is reserved for subjects who have reached stage D or late stage C HF and is

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116

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progressing despite application of all medical therapy of proven benefit. Complications that limit survival include rejection, infection, transplant coronary vasculopathy, and malignancy. Following cardiac transplantation, patients are subjected to lifelong immunosuppression to prevent rejection that renders them susceptible to various opportunistic infections and malignancies.

**(C) Mitral Valve Reconstruction In Left Ventricular Dysfunction**

Mitral regurgitation occurs to a greater or lesser degree in the remodelled, dilated ventricle. During the past decade surgical approaches to correction of mitral regurgitation without valve replacement have been applied to the failing, remodelled ventricle with low operative mortality and impressive early clinical outcomes (Bolling et al 1998). However, no prospective controlled, randomized studies have compared mitral valve reconstruction with the best available medical therapy, which itself can reverse remodelling in patients with mitral regurgitation.
C.4 CHANGING TRENDS IN THE MEDICAL DEVICES USED IN CARDIOLOGY

C.4.1 Advances in Medical Devices in Interventional Cardiology

The potential efficacy of new devices relative to PTCA may be two-fold. These devices, overcome the high incidences of restenosis with PTCA. Many new devices have been approved by FDA since 1990 and a number of others are in various stages of review which includes coronary atherectomy (direct coronary atherectomy, rational atherectomy, transluminal extraction atherectomy), Intra Coronary (IC) stents, use of lasers and other ablative energy (thermal balloon angioplasty, laser angioplasty) out of which IC stent placement is very widely used now-a-days.

C.4.1.1 Coronary Stent Systems

The chief limitation of coronary stenting is subacute thrombotic occlusion, which occurs in about 4 percent of patients within 2 to 14 days after stent implantation and almost always results in a myocardial infarction or death (Bittl et al 1979). Currently, some predominant technological advancement is focused on the development of stent technology. Drug Eluting stents (DES) were thus introduced to overcome the high restenosis rates with bare metal stents. Drug-eluting stents have been highly successful and have prevented complications such as restenosis and thrombus - conditions that are associated with the use of bare metal stents. DES currently in use comprise of Sirolimus eluting and paclitaxel eluting stents. Recently, Zotorolimus eluting cobalt alloy stent is also introduced. However, latest updates for the European Society of Cardiology Meet in 2006 have provoked late stent thrombosis issues with these DES. Newer advances include Bio-absorbable stents, and stents coated with bioengineered surfaces which are expected to dominate the market for interventional cardiology.
C.4.1.2 Atherectomy

Atherectomy may be an option for certain patients who cannot have balloon angioplasty. Directional atherectomy has been another attempt to solve the problem of re-occlusion of the blood vessels. A balloon catheter is inserted for determining position; then, a tiny cutter spinning at 2,500 rpm removes plaque fragments from the arterial walls. The use of angioplasty with the coronary artery stent, however, is proving to be safer and more effective. Rotational Atherectomy uses the Rotablator to remove atheromatous plaque by rapid spinning burr advanced through the narrowed artery.

C.4.1.3 Ablative laser assisted Angioplasty:

Lasers have been used with both PTCA and CABG procedures but the risks have been high and the treatment is expensive. Laser ablation uses a catheter that has a metal or fiber-optic probe on the tip. The laser uses light to burn away plaque and open the vessel enough so that a balloon can further widen the opening. One laser procedure called Transmyocardial Laser Revascularization (TMLR) applies laser energy directly to areas in the heart where blockage has occurred and creates 10 to 50 tiny channels. These perforations become channels for blood to flow to oxygen-starved areas of the heart. It has been approved for patients with severe angina who do not respond to other treatments. A number of studies are showing that the procedure improves quality of life and reduces anginal pain. Experience with this procedure is still limited, and more studies are required to determine if TMLR is any more effective than medications. The procedure itself carries some risks for complications, including some that can be life threatening. New laser techniques may help reduce these problems.

C.4.1.4 Ultrasound Thrombolysis

The device is developed as a potential alternative to angioplasty that uses high frequency sound waves to dislodge and dissolve the fatty plaques on the walls of coronary arteries. A long probe with three
wires at the tip that transmit the ultrasound waves is inserted into the artery through a standard angioplasty catheter. High-power pulses of high frequency ultrasound waves are delivered three times at one-minute intervals. Initial experiments have found that this treatment effectively reopens clogged arteries with a relatively low restenosis rate.

C.4.1.5 Mechanical Thrombectomy
Mechanical thrombectomy with AngioJet rheolytic thrombectomy catheter has been investigated. This device utilizes high-velocity saline jets to create a low-pressure zone at the catheter tip through a Bernoulli effect, allowing fragmentation and aspiration of thrombus. Randomized trial examining routine application of AngioJet thrombectomy during catheter-based reperfusion in AMI is in progress.

The X-sizer device employs helical thrombectomy and vacuum aspiration. It was found to be beneficial in a trial of primary stenting (Napodano et al 2003). Other thrombus removal devices using vacuum-assisted aspiration through specialized catheters have also been successfully utilized in myocardial infarction (van Ommen et al 2001).

C.4.1.6 Distal embolic protection devices
The distal embolization of atherosclerotic debris is a potential cause of myocardial necrosis after PCI. It is a major cause of no reflow and in adequate myocardial perfusion, especially following interventions in high thrombus burden scenario like AMI. Three classes of embolic protection devices are being evaluated in various settings including PercuSurge GuardWire® System and Angioguard® filter device which are currently in use.
(A) **Distal Occlusion Systems:** Systems that use a low-pressure balloon to occlude flow during intervention

PercuSurge GuardWire® temporary occlusion and aspiration system (Medtronic, USA) is a low profile system for the aspiration of liberated debris (Baim et al 2002). It consists of a 210 cm angioplasty wire constructed using a 0.014-inch nitinol hypotube with a distal 35-mm radiopaque, shapeable, steerable tip (Oesterle et al 1999). A 5.5-mm elastomeric balloon inflatable between 3.5 and 5.0 mm is positioned at the distal portion of the wire. The GuardWire® tip is advanced across the stenosis and the balloon inflated in a segment that is relatively free of disease to block the blood flow into the distal portion of the vessel. Balloon angioplasty and stent placement are then performed over the GuardWire®. After stent deployment and after dilation, an export aspiration catheter is used to remove the particulate debris. A 20-ml locking syringe is attached to the aspiration catheter to generate a vacuum and to serve as the collection chamber. After aspiration of the microparticulate debris, the GuardWire® balloon is deflated and distal flow to the vessel restored (Webb et al 1999). Some studies reported favorable results with this device as an adjunct to percutaneous intervention in saphenous vein graft (Muller et al 2000, Baim et al 2002), carotid artery (Henry et al 2002), or renal artery (Henry et al 2001). There have been concerns that DPD use during primary PCI might delay reperfusion. One of the most important limitations of this distal balloon occlusion device is that it may cause distal ischemia that may not be tolerated by some patients. In addition, filter preparation is cumbersome and angiography cannot be performed while the distal balloon is inflated, making assessment of the artery and stent placement more difficult. Preliminary results from the first 188 patients undergoing PCI using the GuardWire® in the RUBY registry have suggested that direct device delivery was possible in 87% cases with favourable angiographic and electrocardiogram characteristics and low clinical rates (Gorog et al 2005).
Huang et al (2003) reported that the use of PercuSurge GuardWire® was feasible, safe and effective for distal protection during primary PCI in AMI. PercuSurge GuardWire® utilization during primary PCI yielded a substantially higher rate of immediate final TIMI 3 flow in epicardial vessels and increased the integrity of the microvasculature (Wu et al 2005). However, a recent Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) randomized trial failed to show beneficial effects with GuardWire® in AMI. The trial reported that PercuSurge GuardWire® system effectively retrieves embolic debris in most patients with acute STEMI undergoing emergent PCI. However, it did not result in improved microvascular flow, greater reperfusion success, reduced infarct size, or enhanced event-free survival (Stone et al 2005). It was inferred that placement of the protection device and inflation of the distal occlusion balloon prolonged the time to reperfusion, thus having the potential to abrogate the beneficial effects of rapid mechanical revascularization (Schomig et al 2005). Numerous explanations have been given for the surprising lack of efficacy of the DPD used in this study (Stone et al 2005). PercuSurge GuardWire® System is presently the best available option for preventing distal embolization and no reflow in PCI, particularly in high thrombus burden conditions like AMI.

- The EXPORT aspiration catheter which is part of the PercuSurge system is also found to be effective as a stand alone device for thrombosuction during PCI in AMI (Wang et al 2002). A large randomized multinational EXPORT study is currently investigating the efficacy of this aspiration catheter in PCI for AMI.

- The TriActiv® (Kensey Nash, Exton, Pennsylvania) system has a distal balloon that is inflated with CO₂, allowing more rapid balloon inflation and deflation. The device is under investigation in PRIDE trial for SVG disease.
(B) Embolic entrapment filters

The advantage of the filters over distal occlusion devices is that antegrade flow is maintained during the procedure, allowing intermittent contrast injection to visualize underlying anatomy and assist in precise stent placement. The device is a porous membrane filter mounted on the tip of coronary guidewires to capture and retrieve embolized materials during interventions. In general, the porous membrane filters are supported by an array of super elastic nitinol, which is restrained by an outer delivery sheath until the tip is delivered across the lesion. After retraction of the delivery sheath, the self-expanding filters support the filter against the wall of the vessel. Although liberated particles larger than the filter pore size are trapped within the filter, histological examination of the retrieved material suggests that particles smaller than the pore size may also be removed, likely due to the creation of fibrin strands within the filter. Once the intervention has been completed, a recovery sheath is advanced to close the filter structure, trapping any collected debris and reducing the filter diameter sufficiently to allow recovery back into the guiding catheter.

- The EPI Filterwire (Boston Scientific, Massachusetts) contains an elliptical polyurethane filter with 100 micron pores. It was compared against PercuSurge GuardWire system and was found to have equivalent benefits (Stone et al 2002).
- The Emboshield Filter (Abbott Laboratories, Chicago, Illinois) contains a floating filter along with the guidewire. This cardioshield filter is undergoing clinical evaluation in the CAPTIVE trial.
- The eV3 Filter (eV3, Minnesota) is undergoing clinical evaluation in patients with SVG disease in the SPIDER trial. Interceptor Filter (Medtronic Vascular, Santa Rosa, California) is a distal wire filter. The Rubicon Filter is an integrated wire filter and guidewire that does not require a delivery sheath for deployment.
- The AngioGuard® Filter (Cordis Corp, J&J, USA) is an approved embolic protection device during SVG intervention.
(C) Proximal Occlusion Devices

This third type of DPD involves the proximal occlusion of the treated vessel with a balloon on the tip or just beyond the tip of the guiding catheter. With inflow occlusion, the retrograde flow generated by distal collaterals or infusion through a “rinsing” catheter should propel any liberated debris back into the lumen of the guiding catheter. Although such devices have undergone limited clinical testing, they have the advantage of providing protection even before the first wire is advanced across the target lesion.

C.4.1.7 Chronic Total occlusion (CTOs) Crossing wires

The inability to pass a guidewire through an occluded segment into the distal lumen is a major cause of failure in CTOs. Several alternative devices have been evaluated as adjuncts to conventional wires in patients with CTOs which includes excimer laser tipped wire, The safe-cross wire®, LuMend Frontrunner® Wire and FlowCardio CROSSER Ultrasound device (Turi et al 2003)

C.4.2 Advances in Medical Device & Technologies for Management of Angina

C.4.2.1 Enhanced External Counterpulsation

A non-invasive technique called Enhanced External Counterpulsation (EECP) has been used successfully by over a million people in China and is currently in trials in the U.S. external counterpulsation involves the use of a device with inflatable cuffs that surround the lower limbs and inflate and deflate in synchronization with the cardiac cycle. The device is designed to reduce loading conditions in systole while increasing coronary perfusion pressures in diastole (Michaels et al 2002). External counterpulsation has been shown to reduce the frequency and severity of anginal attacks in patients with symptomatic coronary artery disease (Arora et al 1999). EECP will not be likely to replace PTCA or CABG, but it may reduce the need for nitrates and is proving to provide long lasting benefits. This therapy as
discussed in section C.3.4.7 is indicated for patients with refractory angina who cannot be managed adequately by medical therapy and who are not candidates for revascularization (interventional and/or surgical). Early trials of this therapy in patients with HF and low EF have been encouraging, and a randomized trial has been completed recently (Soran et al 2002).

C.4.2.2 Endoscopic Transthoracic Sympathicotomy
It is considered one of the last resorts for people with severe untreatable refractory angina. Endoscopic transthoracic sympathecotomy is not suitable as a primary alternative for the treatment of refractory angina pectoris. This operation blocks the nerves that cause chest pain and, in one European study, proved to be very beneficial in relieving angina. Because such patients no longer experience any chest pain, however, they may not experience important symptoms of heart attack if they occur. Endoscopic transthoracic sympathecotomy is still to be considered as an experimental therapy modality with an unfavourable profile of mortality, morbidity and complications.

C.4.2.3 Multislice Computed Tomography:
Multislice computed Tomography (MSCT) has become an important tool for non-invasive evaluation of cardiovascular structures (Ropers et al 2003). It has been investigated for the visualization of coronary venous anatomy (Jongbloed et al 2005) as well as coronary artery stents (Mahnken et al 2005). Although the excellent spatial resolution of multislice spiral computed tomography (MSCT) enables the coronary arteries to be visualized, its limited temporal resolution results in poor image reproducibility because of cardiac motion artifact and hence limits its widespread clinical use (Sato et al 2003). The technique is continuously being investigated for updation and explorations of its clinical applications, especially for evaluation of cardiac devices.
C. 4.3 Advances in medical Devices in Heart failure management

Newer devices and technologies in the management of heart failure, such as implantable hemodynamic monitors and internal cardiac support devices, external counterpulsation, treatment for sleep-disordered breathing, myocardial growth factors and stem cell transplantation, and devices to achieve intravascular volume reduction are under active investigation.

C.4.3.1 Techniques for Respiratory Support

Patients with HF frequently exhibit abnormal respiratory patterns, including Cheyne-Stokes breathing and sleep-disordered breathing. The use of nocturnal oxygen and devices that provide continuous positive airway pressure has been reported to produce symptomatic improvement (Tkacova et al 1998, Javaheri et al 2000). Although there is no direct evidence that treatment of sleep-disturbed breathing prevents incident HF, treatment of established LV dysfunction with continuous positive airway pressure breathing has been shown to improve LV structure and function in patients with either obstructive or central sleep apnea disturbed-breathing syndrome (Malone et al 1991). Additional studies are in progress to evaluate the efficacy of these interventions.

C.4.3.2 Cardiac support devices

There is developing experience with surgical devices that are designed to alter physical stresses on the LV; theoretically, the devices may improve performance or attenuate further ventricular dilatation. One such device now being evaluated clinically is a cardiac wrapping device made from bidirectional woven polyester that allows for shortening but resists circumferential expansion beyond the limits of the wrap (Chaudhry et al 2000). Clinical trials in Europe (Raman et al 2001) and the United States are currently under way to evaluate the safety and efficacy of this device in patients. Other ventricular constraint or support devices are also under investigation in Europe and the United States.
C.4.3.3 Mechanical Circulatory support Devices

Long-term mechanical circulatory support continues to be a source of intense research and development. The obstacles of thrombogenicity (and embolization), device infection, and immunological sensitization remain a target of ongoing research for the currently available Ventricular Assist Devices (VADs). The potential of VADs as destination therapy has further tested the limits of device durability. Current developments are focused on miniaturization of pump design to allow complete implantability and pediatric applications. Years after the invention of centrifugal pumps, researchers are re-evaluating these pumps as the third generation of implantable circulatory assist devices. The Levitronix LVAS (Levitronix, Waltham, MA) is one such pump built on the "maglev" (magnetic levitation) concept, which allows the motor to levitate the rotor magnetically so that rotation is achieved without friction, with less thrombogenicity, with minimal noise and vibration, and with anticipated long-term durability because of lack of metal-to-metal contact. The DuraHeart (Terumo, Ann Arbor, MI), based on a similar concept and design and, the Cor-Aide device (Cor-Aide, Cleveland, OH) have been operated without anticoagulation in animal trials. Clinical applications of these strategies are presently unknown. Pediatric Assist Devices for children with end stage heart failure are also under investigations.

C.4.3.4 Implantable Hemodynamic Monitors (IHM)

Traditional hemodynamic evaluation by Swan Ganz Catheterization or Pulmonary artery catheterization (PAC) is limited by its invasive nature and need of hospitalization. Continuous hemodynamic monitoring may assist the tailoring of CHF therapy, but however is inconvenient on daily basis. It has been long recognized that PA end diastolic pressure and PCWP are comparable in value to LVEDP and hence are acceptable variables of LV preload in majority of physiologic and pathophysiologic states (Reynolds et al 1995). Long term monitoring of LV preload, including monitoring in the ambulatory setting, might be very useful but is currently limited by technologic...
and conceptual constraints. It is reported that right ventricular pressures at its maximal first derivative which is easily measured if it occurs at or near pulmonary valve opening provides accurate estimation of PA end diastolic pressure (Reynolds et al 1995).

Several implantable systems are in development for the chronic, remote, outpatient monitoring of ventricular filling pressures and other hemodynamic and clinical variables in HF patients. One such IHM system (Chronicle®, Medtronic, Minneapolis, IN) has completed phase I and II study and currently being evaluated in a phase III randomized outcomes trial. The hypothesis underlying this approach suggests that changes in therapy to optimize LV filling pressure may improve outcomes in HF patients (Magalski et al 2002, Adamson et al 2003). The Chronicle® consisted of an implantable memory system, similar to the pulse generator of a pacemaker, which is implanted subcutaneously in the prepectoral area. The pressure sensor was similar to a modified pacemaker lead, was positioned in the right ventricle. The system detects heart rate, right ventricular systolic and diastolic pressures and the maximum rate of pressure increase or decrease. With previous validated algorithms, PA diastolic pressure is derived from this data. Ohlsson et al (1998) investigated the feasibility of this long term ambulatory implantable hemodynamic monitoring system. In the multicentric 12 months follow up study, this IHM and a standard reference pressure system recorded comparable data in patients with CHF (Magalski et al 2002).

The recent ESCAPE trial concluded that therapy to reduce volume overload during hospitalization for heart failure led to marked improvement in signs and symptoms of elevated filling pressures with or without the PAC. Addition of the PAC to careful clinical assessment increased anticipated adverse events, but did not affect overall mortality and hospitalization (The ESCAPE investigators 2005). Hence, Future trials to test noninvasive assessments with specific treatment strategies that could be used to better tailor therapy for both survival time and survival quality as valued by patients are required.