Introduction
Among the many health predictions for the new millennium, cardiovascular disease (CVD) is emerging as a major cause of deaths all over the world. Coronary artery disease (CAD) is responsible for major disability in developed as well as developing countries (Enas et al 1995). CAD afflicts more than four million people in the U.S. and about 500,000 new cases are diagnosed each year. Heart failure is one of the most common reasons for hospitalization in U.S. (Garg et al, 2002). Feinleib et al (1982) demonstrated a declining trend of mortality rate from CAD, but this impressive 40% decrease in mortality rate is not a worldwide phenomenon. It is beyond doubt that the prevalence of CAD in the Indian subcontinent is higher than in other countries and that as an ethnic group, South Asian men and women are more prone to die of CAD than others. The predictions for India by 2015 show a steady increase in CAD prevalence since 1995 (Padmavati et al 2002). The CAD rates among overseas Asian Indians worldwide are 50% to 400% higher than people of other ethnic origin irrespective of gender, religion, or social class. The emigrant south Asian has myocardial infarction (MI) 2.5 to 5 times more frequently and 1.5 to 3 times higher from total CAD compared to the endemic population of Singapore, South Africa, England and U.S.A. (Marmot et al 1984). The present burden of CVD-related deaths indicates a need for effective prevention as well as management.

CAD among Indians has been found to be severe and more diffused and associated with serious complications and increasing mortality at younger age (Bulatao et al 1992). The higher rate of CAD among Indians cannot be explained by presence of conventional risk factor such as hypertension, smoking, diabetes and hypercholesterolemia alone and so are not helpful in explaining
increased rates. Instead, insulin resistance (Hughes et al 1990), hyperinsulinemia, impaired glucose tolerance, hypertriglyceridaemia, abdominal obesity (apple body configuration) and hypertension, the combination commonly referred to as “Metabolic Syndrome X”, is important in the Indian context. Evidence is emerging in favor of newer risk factors like low level of apolipoprotein A1 (apo A1), high levels of homocysteine (Hcy), apolipoprotein B (apo B), fibrinogen, intermediate density lipoprotein and LDL subclass pattern B (Kannel et al 1995).

CAD is a progressive disease, but the speed of progression varies tremendously, even among persons with similar risk factor levels and among arteries within the same individual. Among the wide spectrum of CAD, acute myocardial infarction (AMI), chronic refractory angina pectoris and heart failure (HF) are major disorders leading to high rates of morbidity and mortality in developed as well as developing countries. Patients suffering from these disorders require a more precise and holistic management and therapy. The current strategies includes management with various drugs as well as interventional procedures like percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG) involving use of various medical devices like stents, etc. Inspite of these, the treatment and management of these patients remain incomplete. Various advances are being done in the field of medical devices for prognosis, diagnosis and evaluating therapy is such patients. The present study was aimed to assess new medical devices for AMI, refractory angina and HF and utilize them to monitor the pharmacologic treatments, if applicable.

Acute ST segment elevation MI (STEMI or AMI) is a major health problem both in the developed, and developing countries like India. The mortality due to STEMI has however declined dramatically over the past three decades (Jose et al 2004). This decline has been attributed to the introduction of coronary care units, thrombolytic
therapy, percutaneous coronary interventions (PCI) and due to drugs such as aspirin, angiotensin converting enzyme inhibitors and beta blockers (Collins et al 1997). Thrombolysis is indicated to restore coronary patency in patients with AMI, thereby reducing the risk of death and subsequent long-term complications. The advantage of mechanical reperfusion over thrombolytic therapy is the more consistent restoration of brisk antegrade flow. When performed in a timely fashion, primary PCI results in reduced mortality and adverse cardiac events compared to thrombolytic therapy (Weaver et al 1997). The efficacy of primary angioplasty in AMI is well established (Keeley et al 2003). The infarct related artery (IRA) usually contains high burden thrombus formation (HBTF) (Yip et al 2001, Yip et al 2002) and lipid pool like contents (Gibson et al 2001, Tanaka et al 2002). This microvascular debris and/or platelet-thrombus embolizes into the distal microvasculature (Topol et al 2000, Prati et al 2003) ultimately leading to the no reflow phenomenon (Ito et al 1996, Topol et al 2000) during elective or primary percutaneous coronary interventions (PCI). This distal embolization of plaque or thrombotic debris during angioplasty in AMI results in infarct extension and high periprocedural mortality (Saber et al 1993). Several distal protection devices (DPD) have been developed to prevent distal embolization during angioplasty (Singh et al 2001) and their effectiveness has been reported (Grube et al 2001, Beran et al 2002). The PercuSurge GuardWire® Plus Temporary Occlusion and Aspiration System (Medtronic AVE, Santa Rosa, CA) is one of such devices designed to provide protection of the distal microcirculation during percutaneous intervention by temporarily occluding the distal vessel during angioplasty, thereby facilitating aspiration of dislodged atheromatous and thrombotic material before it reaches the arteriolar and capillary bed. There has been a clear cut benefit shown with this device as an adjunct to percutaneous intervention in saphenous vein graft (Baim et al 2002), carotid artery (Henry et al 1999) and renal arteries. Trials like SAFE and SAFER have already proved the efficacy of this device

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with reduction in MACE, MI and mortality in patients with SVG lesions (Grube et al 2002, Biam et al 2002). However, there is a difference in opinion for the use of this device as far as intervention in coronaries is concerned. On one hand, interim conclusions from RUBY registry have shown that the device has a high delivery success rate and high number patients were found to achieve TIMI III after the procedure. On the other hand, the results from EMERALD trial (Stone et al 2004), which is the largest trial in AMI, failed to show a beneficial effect from the use of distal embolic protection devices in AMI patients. On the contrary, it showed that the DPD was not associated with an improvement in the primary endpoints of post-procedure ST resolution or final infarct size. Further, it concluded that the Procedural duration was significantly longer in the GuardWire® arm as compared to the procedures without its use. Thus, there is a possibility that using these devices make the intervention more complicated as compared with conventional PCI and is suspected to be time consuming. Interestingly, recent report by Kapoor et al (2005) has shown encouraging results with the use of PercuSurge GuardWire® in primary PCI. The study aims to investigate the efficacy of this device in the setting or primary/rescue PCI in AMI; the time consumption in the procedure with and without the use of PercuSurge GuardWire® and long term clinical events.

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. It has been recognized that there is a group of patients with severe disabling angina and CAD who are refractory to conventional forms of treatments (Mannheimer et al 2002); the diagnosis termed as ‘chronic refractory angina pectoris’. Such a population includes patients with diffuse CAD, distal vessel CAD, small vessel CAD, patients with failed PCI / CABG, untouchable aorta with diffuse disease and high risk...
patients. Refractory angina has become an increasingly challenging problem in clinical practice. Several forms of treatment have been tried, but results emerging from clinical studies suggest that spinal cord stimulation and enhanced external counterpulsation present the most favourable risk/cost to benefit profile.

The concept of arterialization of the cardiac venous system to increase the flow of oxygenated blood to ischemic myocardial tissue was suggested more than 100 years ago and has since been modified with the development of new technologies (Pratt et al 1898). The retrograde treatment of myocardial ischemia via the coronary venous system has been investigated in relation to acute myocardial infarction, coronary revascularization and open heart surgery (Mohl et al 1984, Berland et al 1990, Incorvati et al 1993). Initial attempts of permanent retroperfusion of the CS by means of anastomosis to an arterial vessel were discontinued because of ultrastructural damage of the wall of the CS caused by drainage disruption (Baskt et al 1956, Hahn et al 1952). Intermittent CS occlusion (ICSO), pressure controlled intermittent CS occlusion (PICSO), synchronized retrograde perfusion and simplified retroperfusion have all been described to be effective in salvaging ischemic myocardium in several experimental models of coronary artery occlusion (Aldea et al 1996, Ikeoka et al 1990), however the mode of action of these interventions remain speculative. Clinical application of PICSO during the early reperfusion period has showed improvements in regional myocardial function (Mohl et al 1988). It has been demonstrated that following CS occlusion, there was a tremendous increase in antegrade flow (Mohl et al 1984). Increasing the coronary sinus (CS) pressure improves perfusion of ischemic myocardium by distributing collateral blood flow in ischemic territories (Ido et al 2001) and by reducing ischemic damage and infarct size (Mohl et al 1984, Sato et al 1996). Literature demonstrates the potential anti-ischemic effect of intermittent CS occlusion (Syeda et al 2004). Intermittent CS occlusion decreases ischemic damage during coronary occlusion by 29-39% (Syeda et al
2004). A new stent like device named the Neovasc Reducer® stent (Neovasc Medical Ltd, Israel) is designed to establish a permanent and controlled narrowing of the coronary venous system, particularly at the coronary sinus, which is the "final pathway" of the cardiac venous drainage. By increasing the CS pressure, this CS reducer stent enhances the retrograde perfusion and coronary collateral flow to ischemic myocardium. Due to the Gregg phenomenon, the increased capillary perfusion may cause an increase in cardiac oxygen consumption and cardiac contractility (Faxon et al 1985). It is expected that due to rise in CS pressure due to this device, the already open and existing small vessels may enlarge and there would be improved extraction of the oxygen from the venous blood. Hence, this new CS reducer stent might represent a unique opportunity for relieving otherwise untreated IHD symptoms and improve myocardial function for a short and long term. In pre-clinical experiments, this stent was implanted in 30 pigs' heart, with or without myocardial ischemia. Post implantation angiography of all 30 implanted pigs revealed proper implantation at the designated location within the CS, as well as patency of the CS and the stent with blood flow through the 3mm diameter lumen at the center portion of the Reducers. The procedure was uneventful in all, with no adverse events like CS rupture, dissection, thrombosis or occlusion observed in any of the treated pigs. In pigs with documented reversible myocardial ischemia, implantation of this CS stent caused improvement in ischemia parameters, pressure elevation in CS and reduced mortality. Experimental studies, thus suggested that implantation of the CS reducer stents was feasible and safe, and carried on short or long term complications (Unpublished experimental Data from Neovasc Medical Ltd, Israel). Based on these experimental findings, this study was conducted to evaluate this novel CS Reducer stent as a potential alternative therapy for patients with refractory angina who were not candidates for revascularization.
Heart failure, the most critical and chronic presentation of CVD is the end stage of all diseases of the heart and is a major cause of morbidity, mortality (Davis et al 2000) and hospitalization worldwide (Khand et al 2000, Llyod-Jones et al 2002). HF affects an estimated 4.6 million individuals in the US and its prevalence increases with age (AHA update 1997). The syndrome of heart failure is a dynamic process that results from a complex interaction between impaired cardiac function, neurohormonal activation, and compromised vascular endothelial function. Chronic HF (CHF) is typically the manifestation of left ventricular (LV) dysfunction, which is a condition where the LV muscle is weakened. The physiological disturbances in CHF are complex, but a common feature is impairment in the performance of the heart as a pump. Effective therapy can reduce symptoms, mortality and rehospitalization rates (Cleland et al 2003, Nohria et al 2002). 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. While heart catheterization is the most accurate way to define the hemodynamic condition, the invasive nature of this procedure limits its use to patients with severe decompensation (Shah et al 2005, Binanay et al 2005). Since clinical deteriorations are often preceded by elevation of LV filling pressures and increase fluid volumes in the lung, the noninvasive detection of these changes might be helpful to further improve the care of these patients (Friedman et al 1997, Yu et al 2005). A recent study (Presented at ACC 2005, Bourge et al) demonstrated that HF management strategies based on continuously monitored intracardiac pressures in patients already receiving best available therapy improved patient morbidity. Intracardiac pressure monitoring in this study was achieved using the Medtronic Chronicle™ system, a programmable pacemaker-like memory device placed in the pectoral area and connected to a transvenous lead carrying a pressure sensor.
in the right ventricular outflow tract (Steinhaus et al 1996). Volume status using this system is estimated from pulmonary artery (PA) diastolic pressure, indirectly derived using measured right ventricular pressure. The clinically available systems for accurate monitoring of patients with heart disease use electromagnetic energy to communicate with sensors in the heart (Steinhaus et al 1996, Hetzer et al 1998, Yu et al 2005). However, limited penetration by radiofrequency energy renders it useful mainly for interrogating superficial implants.

A new device, Remon CHF system (Remon ImPressure®; Remon Technologies Ltd., Israel) is a novel system designed for non invasive monitoring of PA pressure (PAP) in HF patients. The system comprises an implant and an external communication/analysis unit. The ImPressure® implant (3mm x 3mm x 16mm), is made of titanium case, encapsulating an energy exchanger, control chip, pressure sensor and energy reservoir with ultrasonic capabilities. It is intended to be percutaneously implanted, using a delivery system (internal jugular approach) in the Right PA. When interrogated by the desktop system, through a handheld transducer, in contact with the chest, the implant is activated. The energy exchanger (piezoelectric transducer) converts applied external ultrasonic pressure to electrical energy. Once energized, the control chip interrogates the pressure sensor and ultrasonically transmits the digital reading to an external receiver thus providing a waveform for PAP. In preclinical experiments, the device was implanted in 8 pigs. The implantation was successful with no adverse events till 6 months. Fluoroscopy and macroscopic observation verified that the implant was at the desired location in all animals and PAP was easily obtained after implantation till 6 months (Unpublished data from Remon Technologies Ltd, Israel). Initial clinical studies using this device were done in abdominal aortic aneurysm. This initial clinical experience in abdominal aortic aneurysm endovascular therapy showed that intrasac pressure monitoring using this technique was similarly safe and efficacious.
Based on these experimental results and clinical experience, the present study was conducted to evaluate the safety and functionality of this implantable device in patients with HF.

Diurnal variation in left ventricular end diastolic pressure (LVEDP) has important consequences in patients with CHF. CHF patients show diurnal variation in the PAP (Gibbs et al 1989), and more importantly a nocturnal rise in these pressures, which may increase the risk of developing paroxysmal nocturnal dyspnoea. Previous observations have suggested that PAP, an indirect measure of left ventricular filling pressures rises during sleep, whereas systemic artery pressure falls (Brigden et al 1995). Very few studies have investigated diurnal variations in PAP in ambulatory CHF patients. Similarly, increase in LVEDP, PAP and limitation of exercise capacity are common findings in CHF. The reduction of exercise capacity with early occurrence of fatigue and dyspnoea is a hallmark of heart failure syndrome. There are objective similarities between heart failure and muscular deconditioning (Piepoli et al 2006). The hemodynamic response to exercise in CHF patients is however not extensively studied. Thus, in the present study, we evaluated diurnal variation and the effect of exercise on PAP in CHF patients using non-invasive monitoring by the implanted device.

Management of the CHF patients is a complex task that involves titration of several drugs, which may interact with each other, and trigger undesired results. The primary medications used to treat CHF patients are diuretics, inhibitors of the renin-angiotensin system, \(\beta\)-Blockers, inotropes (digitalis), and vasodilators. It has been proposed that \(\beta\)-blocker therapy may interrupt the cycle of sympathetic nervous system activation characteristic in patients with deteriorating left ventricular function (Sackner-Bernstein et al 1995). In controlled clinical trials, various beta-blockers have been demonstrated to improve exercise capacity and left ventricular function and decrease
symptoms in patients with HF (Waagstein et al 1975, Gilbert et al 1990, Fisher et al 1994, Packer et al 1996). Survival benefits with beta-blocker therapy have also been demonstrated in various studies (Packer et al 1996, CIBIS II Investigators 1999, Goldstein et al 1998). Metoprolol XL (metoprolol succinate extended-release tablets) is a \( \beta_1 \)-selective agent that improved survival and reduced hospitalization among patients with New York Heart Association class II-IV HF in a randomized trial (Hjalmarson et al 2000). It has been observed that despite their long-term beneficial effects, a short term \( \beta \)-blockers have the potential to exacerbate the symptoms of HF (Marrick et al 1999, Chavey et al 2003). There has been concern that beta blockade may lead to worsening HF when the therapy is initiated (Gottlieb et al 2002). To minimize the risks, it is recommended that the drugs be started at low doses and slowly titrated to effective doses. However, the frequency of increased symptoms during titration, identification of the patients at greatest risk, and the time course of any possible deterioration have not been reported for any of the large beta blocker trials. Moreover, there is limited information on effect of beta-blockers on PAP in CHF patients. \textit{The present study thus aims to evaluate the titration of metoprolol XL in CHF patients undergoing non-invasive monitoring of PAP by the implanted device.}

There is a lack of extensive information on effect of beta blockade on diurnal variations or hemodynamics following exercise in CHF. Beta-blockade usually causes a slight reduction in exercise capacity among healthy subjects, while more variable results have been observed in chronic heart failure (CHF) (Gullestad et al 2001). \textit{Thus, we also evaluated the effect of Metoprolol XL on diurnal variation, exercise capacity and exercise induced variation in PAP in these CHF patients using the device. Clinical improvement in these CHF patients due to non-invasive monitoring aided management at one year was also evaluated.}
OBJECTIVES OF THE STUDY:

✓ To evaluate the efficacy of the DPD (PercuSurge GuardWire® system) as an adjunct to PCI in AMI patients with special emphasis on procedural time.

✓ To compare the use of adjunctive therapy like vasodilators, GP IIb/IIIa inhibitors during PCI with and without use of DPD in AMI patients.

✓ To evaluate the safety and efficacy of the CS stent (Neovasc Reducer® stent) for treatment of patients with refractory angina pectoris.

✓ To evaluate the safety and functionality of Remon ImPressure® device for non-invasive monitoring of pulmonary artery pressure in CHF patients.

✓ To study the diurnal variation in pulmonary artery pressure in CHF patients using non invasive monitoring by the implanted device.

✓ To study the exercise capacity and variation in pulmonary artery pressure during exercise in CHF patients using non invasive monitoring by the implanted device.

✓ To evaluate the dose titration of Metoprolol XL in CHF patients using hemodynamic monitoring by the implanted device.

✓ To evaluate the effect of Metoprolol XL uptitration on pulmonary artery pressure and its diurnal variation in CHF patients using non-invasive monitoring by the implanted device.

✓ To evaluate the effect of Metoprolol XL uptitration on exercise capacity and subsequent variation in pulmonary artery pressure in CHF patients monitored non-invasively using the implanted device.

✓ To evaluate the clinical improvement in the CHF patients following management aided by non-invasive monitoring using the device.