RISK

THERE ARE NO SHORT CUTS
TO ANY PLACE WORTH GOING.

Discussion
In spite of phenomenal developments in therapeutic and interventional strategies, acute myocardial infarction (AMI), chronic refractory angina pectoris and chronic heart failure (CHF) remain major disorders leading to high rates of morbidity and mortality in developed as well as developing countries. Improved drug therapy and refinement and the development of invasive therapy modalities have greatly increased the life expectancy in these patients. Our study demonstrates a ray of hope with various new developments in the interventional procedures, medical devices and tailoring of the drug regimen in these patients of AMI, refractory angina and CHF.

**Efficacy of Distal Protection Device in AMI**

In the first set of our studies, we showed a beneficial effect of DPD in AMI patients. Microembolization may be a relatively frequent event among patients with acute coronary syndromes or after PCI. In the setting of primary angioplasty for AMI, the incidence of distal embolization is rather high, though it is not always observed angiographically. The benefit of primary PCI is limited by a 5% to 20% incidence of NR (Cura et al 2001, Yip et al 2003). NR phenomenon has been documented in ≥ 30% of patients after thrombolysis or PCI for AMI (Eeckhout et al 2001, Tanaka et al 2002), characterized by profound reduction in epicardial antegrade coronary flow without evidence of vessel dissection, thrombosis, or embolization. Embolization of atherosclerotic and thrombotic material in the distal microvasculature represents the likely cause of many of the silent or unexpected MIs following coronary intervention (Califf et al 1998). Distal embolization was related to reduced myocardial reperfusion, more extensive myocardial damage, and a poor prognosis (Henriques et al 2002, Stone et al 2002).
Mechanical embolic protection devices such as PercuSurge GuardWire® system have recently emerged as an attractive tool to prevent both embolization in the microvasculature and NR (Henry et al 1999, Belli et al 2000, Grube et al 2001). Preliminary results with PercuSurge® have been encouraging in the SAFER (Saphenous Vein Graft Angioplasty free of emboli randomized) trial which showed a significant reduction in MACE, MI and NR was reported in degenerated SV grafts (Baim et al 2002). SAFE study (Grube et al 2002) has also showed the efficacy of this device in patients with degenerated SVGs. However, very few studies have been done in AMI involving native coronaries. The preliminary results of RUBY (Revascularization Utilizing Balloon protection in acute coronary ischemic syndrome) registry have shown the efficacy of this GuardWire® in AMI and showed a high number of patients with TIMI III and low 30 day mortality using the device. Muller et al (2000) has shown that the PercuSurge GuardWire® system is a safe and effective device for the protection of distal embolization during interventions in degenerated aorto-coronary saphenous vein grafts and showed significant improvement in TIMI flow and TMP III grade. Huang et al (2003) has reported that no patient developed angiographic evidence of NR or distal embolization with DPD use. Similarly, in our study use of DPD was associated with achievement of TIMI III flow and TMP III grade in significantly more number of patients. In our study TMP grade 3 was achieved in 85% of patients which is similar to the study by Huang et al that show a Post procedural TMP grade 3 in 86.7% of its patients. Moreover, we also experienced significantly less incidences of NR with DPD use (30% in cases with PercuSurge use vs. 84% NR in patients without its use). A study by Kapoor et al (2005) limited to only 6 patients shows 100% procedural success with PercuSurge GuardWire® and brisk achievement of TIMI III flow. They did not observe NR in these patients. In our study we had 30 patients in which this distal protection system was successfully deployed, distal balloon occlusion established and aspiration completed without
any complications. Our study, having comparatively larger number of patients compared to Kapoor et al (2005) still complies with these encouraging results of this DPD. Pershad et al (2002) reported thrombus at the site of the GuardWire®'s distal occlusive balloon. However, no large-scale data is available in the line of this finding. In our study no procedural complications were observed. In our study, we achieved 100% device success and procedure success. This further supports the findings of Kapoor et al (2005) and Kalaria et al (2002) who showed that the technical success of the device without any complications.

EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris), a single, large scale GuardWire® trial in AMI patients has shown that the device was not associated with an improvement in the primary endpoints of post procedure ST resolution or infarct size. One of the major concerns over the use of the GuardWire® was longer procedure duration in the GuardWire® arm in this trial. Contrary to these results, our study show that the total procedural time is in fact significantly less with the use of the DPD. In our study, the time required after guide wire crossing to reach stent placement was significantly reduced with DPD use. Further, the time frame from PTCA balloon inflation/stent placement (in case of direct stenting) till optimal TIMI flow was also significantly with the device use.

In our study, we have considered the precise period from the guide catheter engagement till the last cine-indicating end of procedure as the total procedural time. This stringent time slot consideration may be responsible for our results, contrary to EMERALD trial. We also report for the first time that the total time required after lesion crossing by wire till achievement of TIMI III was significantly less with PercuSurge use. This time represents the slot when the atherothrombotic plaque is ruptured leading to distal microembolization and incidences of NR, thus complicating the procedure. Further, various agents such as GP IIb/IIIa inhibitors and Hetal Shah

202

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intracoronary vasodilators like adenosine, sodium nitroprusside, NTG, etc are employed to overcome these complications. All these may prolong the time of PCI as in cases where PercuSurge is not used. We found in our study that using PercuSurge provides distal protection against the microembolization and aspiration of the thrombotic debris, thus reducing the incidences of NR and thereby avoidance of various pharmacological interventions. Thus, our study shows that distal protection devices can be efficacious and may save time to TIMI III flow, in selected cases in AMI if carried out by experienced operators. Inspite of our study being limited by small size and lack of randomized set up; it supports the need of larger randomized trials continuously validating the efficacy of the device in native coronaries.

**Efficacy of Coronary Sinus Reducer Stent for treatment of Refractory angina**

CS Reducer® stent investigated in our study presents a new for the treatment of patients with refractory angina. Majority of patients suffering from ischemic heart disease can be adequately treated by drug therapy and revascularization procedures i.e CABG and PTCA. Improvement in pharmacological and interventional modalities has greatly improved the morbidity and mortality in ischemic heart disease patients in the last few decades. However, refractory angina remains a clinical problem that has not been fully recognized until recently. CS interventions are known to salvage ischemic myocardium, especially by limiting the infarct from its border. The primary goal of these approaches is not only to restore blood flow in the occluded vessels but also to salvage the damaged myocardium (Syeda et al 2004). Ido et al (2001) has shown that with intact vasomotor tone, CS occlusion increased the regional myocardial blood flow in ischemic region. These changes were significantly correlated with peak CS pressure during CS occlusion. We have shown that using the Neovasc Reducer® stent, a device that constricts the CS lumen can produce beneficial effect in patients with refractory angina. All the patients of
our study were implanted with the device without any complications. Evaluation of the device using CT angiography at 6 months revealed that all the stents were patent with no evidence of migration. Moreover, the CS wall was also found to be constricted along with the hourglass shape of the stent, thus leading to a reduction in the CS diameter with no evidence of blood flow around the narrowed mid-portion of the Reducer® stent. The successful reduction in the CS by the reducer stent can cause an increase the CS pressure and may have led to retroperfusion of the jeopardized myocardium according to the established theories of retroperfusion (Sato et al 1996). In our study, eight out of ten patients showed the improvement in ischemia in dobutamine stress echocardiography (DSE) at six months follow up. Stress perfusion test (SPECT) also revealed improvement in ischemia in six patients. All patients have completed one year clinical follow up without any events. Controlled coronary sinus occlusion was shown to retard necrosis of ischemic myocardium. It has been reported CS pressure elevation in beating heart may participate in augmenting collateral flow (Sato et al 1996). Mohl et al (2005) has evaluated optimization criteria investigating coronary venous flow data during PICS0. It was concluded that transient pressure elevation in the coronary venous system recruits collateral flow towards ischemic myocardium. CS pressure elevation by means of a partial or complete obstruction of the CS has been shown to reduce infarct size and acute mortality after myocardial ischemia (Gross et al 1937, Gregg et al 1938). It has been observed in various experimental models over years that increase in collateral flow to the ischemic region may be a necessary condition to effect the functional improvement. Collateral flow had an important role in salvaging the ischemic myocardium and is reported to be linked to CS pressure conditions (Toggart et al 1987). Conceivably, downstream venous pressure elevation increases coronary vascular impedance in the non ischemic bed as well as in the ischemic bed, and the collateral channels if any are present, will augment coronary flow from the non ischemic site to the ischemic site.
(Sato et al 1996). Our study demonstrates the successful reduction in the CS lumen using this new technique. The stent establishes a permanent and controlled narrowing of the coronary venous system, particularly at the CS, which is the "final pathway" of the cardiac venous drainage.

Our working hypothesis was that in the setting of obstructive CAD - by increasing coronary sinus pressure, perfusion of the myocardium and non-ischemic areas will be enhanced, and consequently hemodynamic parameters will improve. Pre-clinical, experimental studies using pig model of reversible myocardial ischemia, implantation of this stent led to an improvement in ischemia parameters, pressure elevation of CS and reduced mortality. This first experience in man shows that the implantation of the device was safe and free of any short or long-term complications. The improvement in ischemic parameters in the DSE and SPECT scan reflect the efficacy potential of this device. Six months follow up showed a significant improvement in the CCS angina class of the patients. In our study, ST segment depression also disappeared or improved over six months. Five out of seven patients who showed severe ischemia in DSE prior to implantation showed improvement in ischemia on 6 month follow up and six patients showed improvement in the SPECT test.

A few patho-physiologic explanations are proposed to explain the mechanisms of action of this novel treatment approach. Increased CS and coronary venules pressure might enhance redistribution of collateral blood flow from non-ischemic to ischemic territories of the myocardium by the enlargement of already open and existing small vessels and by opening of pre-formed collaterals. Also, the increased capillary perfusion and pressure may result in an increase in cardiac oxygen consumption and cardiac contractility (the Gregg phenomenon). The Reducer® stent possibly works with a similar mechanism. The improvement in ischemia during SPECT as well as DSE can be attributed to redistribution of collateral blood from non-
ischemic to ischemic territories of the myocardium. Collateralization also plays a role in improvement in exercise capacity (Tayebjee et al 2004). Due to myocardial ischemia, the action potential duration is shortened, and electrical gradients are created, resulting in ST segment depression or elevation. At the molecular level, activation of sarcolemmal K\textsubscript{ATP} channels by ischemic ATP depletion may play a role. Increased myocardial oxygen demand associated with a failure to increase or an actual decrease in regional coronary blood usually causes ST segment depression (Armstrong et al 2005, Udelson et al 2005). In our study, though there is no significant improvement in METs and exercise time, the Double product and ST changes have significantly improved. This indicates the improvement in myocardial ischemia in these patients. The angina class as well as the quality of life questionnaire has also shown improvement at six months. The event free one-year follow up further, substantiates the efficacy and safety of the device.

MSCT has become an important tool for noninvasive evaluation of cardiovascular structures (Roper et al 2003). Jongbloed et al (2005) report successful evaluation of the CS and its tributaries by MSCT. In our study, pre-implantation MSCT was performed for the measurement of the CS diameter, which correlated well with the results from invasive angiography. Post implantation evaluation of the Reducer\textsuperscript{®} stent done by MSCT clearly demonstrated the patency of the stent as well as the construction of the CS wall which is responsible for the mechanism of stent. The mechanism of action of CS reducer stent thus appears to justify the retroperfusion of the ischemic myocardium with involvement of collaterals. This can be further studied by investigating the growth factors and development of collaterals in these patients. Implantation of CS Reducer\textsuperscript{®} stent was safe and feasible and the stent patent and functional throughout the follow up period. It demonstrates a new concept for management of refractory angina patients who are not eligible for revascularization by the CS Reducer stent.
Safety and Functionality of the implantable device for non-invasive monitoring of pulmonary artery pressure in CHF

The Remon CHF system investigated in this study monitors PAP in CHF patients non-invasively and frequently. Despite major advances in medical therapy, the appropriate diagnosis and management of CHF continues to offer many clinical challenges (Magalski et al 2002). Right heart pressures provide diagnostic, therapeutic and prognostic information in the treatment of CHF (Stevenson et al 1991). It has been recognized that PA end diastolic and pulmonary artery wedge pressures are comparable in value to LVEDP and, hence are acceptable variables of LV preload in a majority of physiologic and pathophysiologic states (Braunwald et al 1961, Fishman et al 1963, Kaltman et al 1966, Jenkins et al 1970, Reynolds et al 1995). Hemodynamic measurements have traditionally been restricted to cardiac catheterizations laboratories and intensive care units. Measurements cannot be made easy in ambulatory settings and repeated catheterizations, are limited by cumulative cost and risk (Ohlsson et al 2001). The Results from our implantable device study thus introduces a new concept for long-term non-invasive and frequent monitoring of PAP with the implant, which may reveal information of assistance in the management of CHF patients. Our study was a first-in-man and thus was limited to 10 patients. It showed that implantation of this device was feasible, safe and functionality was available for the period of follow up. Ten CHF patients were successfully implanted with this device without any complications. All devices were patent and well visualized in the CT angiography during the following six months. Functionality and accuracy of the device was available at six months follow up and the diastolic pressures correlated well with the standard control Millar catheter. Communication of the implant and the external system is successfully evaluated till one year follow up. Our study showed that long-term wireless communication with this deeply implanted miniature sensor is feasible, safe, and accurate in HF patients. Such a
device may be of substantial clinical value in detecting marked PA diastolic pressure variability that can help in correlating PA pressure with clinical condition. The device provides easily repeated measurements of PAP waveform.

Right heart or Swan Ganz catheterization has been used to guide therapy in multiple settings (Steimle et al 1997), but recent studies have raised concerns that Pulmonary artery catheterizations may lead to increased mortality in hospitalized patients. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial has shown that the 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 catheterization (The ESCAPE Investigators 2005). The study also showed that invasive monitoring using catheterization increased the anticipated adverse events in these patients. It raised a concern against need of noninvasive assessments. Several other implantable systems are under evaluation to monitor patients with heart disease. The Chronicle system measures right ventricular pressure in patients with CHF (Steinhaus et al 1996). Continuous hemodynamic monitoring with this device was technically feasible and provided information during normal activity (Ohlsson et al 1998, Braunschweig et al 2002). Another system that records intramyocardial electrocardiogram to detect rejections after cardiac transplantation has also been evaluated (Hetzer et al 1998). In both the cases a wire (lead) is required to transfer data to a superficially implanted module, similar to a pacemaker, that is then interrogated using electromagnetic communication. Moreover, the Chronicle® implantable hemodynamic monitor provided right ventricular pressure from which diastolic PAP can only be estimated. Using the Bland-Altman method (Bland et al 1986), Reynolds et al (1995) validated the algorithm for the estimation of PA diastolic pressure from right ventricular pressure and Magalski et al (2002) demonstrated that their sensor remained stable in the right ventricle for more than one year.
Estimating PA diastolic pressure from right ventricular pressure is not likely to be as accurate as direct measurement. In our study, the Remon CHF system's implant is much smaller, the procedure has been simple and only minimally invasive and the system has added benefit of being wireless. Moreover, it measures the systolic and diastolic PAP directly. These diastolic pressures were correlated well with the gold standard pressures from Millar catheter. The Bland-Altman analysis for this device compared to Millar catheter showed a better correlation, thus exhibiting accuracy of the device. Initial clinical experience with abdominal aortic aneurysm endovascular therapy showed intrasac pressure monitoring using this technique was similarly safe and efficacious (Ellozy et al 2004). MSCT results showed the placement and patency of the anchors of the device. The device showed functionality with accuracy at 6 months follow up and continues to be functional at 1 year follow up. The study, thus demonstrated a non-invasive modality for hemodynamic monitoring in CHF patients. However, long term functionality and data accuracy from implanted device remains essential for clinical utility.

Diurnal Variation in pulmonary artery pressure in CHF

After showing that frequent and non-invasive monitoring with the implantable device was technically feasible, we extended our study to get the information on physiologic conditions and medical interventions. There is only limited information about normal diurnal variation of PAP in CHF patients. In ten normal individuals who underwent polygraphic monitoring of PAP showed a rise in PAP at night (Lugaresi et al 1978). Donald et al (1953) has shown a significant rise in PAP during sleep in normal individuals. In other report, diurnal variation in diastolic PAP in patients with chest pain showed a significant rise in between midnight and 6:00 hrs (Levy et al 1987). In our study, we found considerable variability in PAP through the day and within the group. Seven out of ten patients showed a rise in the PAP at night in our study. The mean systolic as well as diastolic
PAP for the whole group significantly increased at night (p<0.05). The mean increase in systolic pressure from day to night was 2.8 \pm 1.1 \text{mmHg} and diastolic pressure was 1.9 \pm 0.6 \text{mmHg}. Gibbs et al (1989) had shown a nocturnal rise in PAP in CHF patients. However, it was an invasive investigation wherein all the patients were hospitalized for 24-48 hrs and continuous monitoring was done using right heart catheterization. In our study, this 24 hrs monitoring was done non-invasively using the device. Our results of diurnal variation in PAP comply with this study showing a nocturnal rise in PAP. In our study, for the whole group the mean systolic and diastolic PAP at rest were variably higher during the day since these were NYHA class III/IV patients, and further showed a deteriorating rise in PAP at night. PAP may be affected by left ventricular function (Scheinman et al 1973, Kaltman et al 1966), exercise, effects on diuretics (Dikshit et al 1973), meals (Cornyn et al 1986, Siemienczuk et al 1984), respiratory pattern (Tilkian et al 1976), autonomic effects such as fear (Lewis et al 1960) and temperature (Burch et al 1957). Report by Brigden et al (1995) suggests that patients with heart failure and angina show a nocturnal rise in PAP accompanied with a fall in systemic pressure. Our study results comply with the nocturnal rise in PAP; however the insignificant change in systemic pressure in our study may be attributed to limited small number of patients. It can however be suggested that the nocturnal pressure rise cannot be explained entirely by posture.

Sleep itself is probably not responsible for the pressure changes because hypnosis had no effect on cardiac output or pulmonary vascular pressures (Arvidsson et al 1970). The rise in pressure at night in our study was not always sudden and it varied considerably. Two patients did not show considerable rise in PAP and one patient in fact, showed an insignificant decrease. However, patients with CHF and nocturnal rise in PAP may be at increased risk of developing paroxysmal nocturnal dyspnoea. Diurnal variations and positional changes in pressures are important factors, and since this type of
implantable device allows frequent and non-invasive recording of PAP, may provide insights into how the physiologic system responds to activities of daily living.

**Exercise capacity and exercise induced variation in pulmonary artery pressure in CHF**

Impairment of lung mechanics, increase of PAP and limitation of exercise capacity are common findings in CHF. Exercise testing is often used to assess functional impairment of patients with CHF. Exercise capacity may be limited for a variety of reasons in HF patients including abnormality in central and peripheral cardiovascular functions (Pina et al 2003). Exertional dyspnoea is a frequent limiting symptom in CHF patients (Hasuda et al 2005). Little information is available about the changes in PAP during exercise in CHF patients. Gibbs et al (1990) reported a poor correlation between symptoms and PAP during maximal exercise and during single episodes of daily activity in heart failure patients. In our study, all patients finished the symptom limited TMT with a peak HR of >90% THR. The mean systolic and diastolic PAP rose significantly post exercise along with the systemic BP and mean HR.

Agostoni et al (2002) reported a significant linear correlation between the respiratory function and pulmonary vascular pressure changes during exercise in heart failure. Impairment in exercise capacity is one of the hallmarks of CHF, and it has been shown to strongly correlate with the severity of the disease (Nieuwland et al 1998). Raeside et al (2000) has shown that pulmonary hemodynamic on exercise can be measured by micromanometer-tipped pulmonary artery catheters, and that these hemodynamic correlate with ventilatory equivalents for oxygen and carbon dioxide measured non-invasively during a simultaneous cardiopulmonary exercise test. The report proposed that accurate measurements of PAP on exercise in patients with mild resting pulmonary hypertension, or normal PAP who are symptomatic on exercise might help identifying the risk of
clinical deterioration in these patients. Our study reports the variations in PAP due to exercise in heart failure by non invasive monitoring. This rise in PAP may be responsible for limiting the exercise capacity in these patients, detecting which may help the management of such patients. *Thus, the study demonstrated that non-invasive monitoring of PAP during exercise in CHF patients was feasible using the device. Monitoring such hemodynamic changes over extended periods of time may be useful in the management of these patients.*

**Uptitration of Metoprolol XL and its effects on pulmonary artery pressure and related physiological changes in CHF**

Further, to the physiologic changes in PAP, we studied the efficacy and uptitration of Metoprolol XL (MXL) in these CHF patients. The pattern of medications used in patients with HF has changed dramatically in the last two decades (Young et al 1995, Bart et al 1999). Currently, the medical management of CHF patients is done by frequent physician examinations and close monitoring of the patient’s clinical status to maintain optimal volume or ventricular performance. One of the major controversial drugs used in CHF is a beta-blocker. Use of beta-blockers improves survival, reduces hospitalizations for heart failure and improves left ventricular function when given over a long period of time to CHF patients (MERIT-HF study group 1999). Controlled clinical trials have shown that beta-blockers produce consistent benefits in patients with CHF (Packer et al 1996, CIBIS II investigators 1999, MERIT-HF Study group 1999). As a result, these agents are now recommended for use in all patients with mild to moderate heart failure caused by LV systolic dysfunction that do not have contradictions (Packer et al 1999). However, there has been concern that beta blockade may lead to worsening heart failure when the therapy is initiated (Gottlieb et al 2002). Beta-blockers require careful initiation and titration when used in patients with HF. Some patients tolerate beta-blocker therapy initiation without difficulty, whereas in other patients this period presents clinical challenges...
Recent study by Butler et al (2006) showed that beta-blocker therapy before and during hospitalization for CHF is associated with improved outcomes. Catheterization was done in these patients and it was found that there were no significant differences in any of the hemodynamic measures including PCWP among patients in whom beta-blocker therapy was continued or not during the hospitalization. However, during hospitalization in acute decompensated HF, the adjustment of medications does not normally rely on close hemodynamic monitoring in these patients. To best of our knowledge there is no data available on the effect of beta-blockers on PAP in CHF patients managed on the outpatient basis. 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. Our study has been unique as it demonstrates the uptitration of the β₁ selective blocker MXL, with simultaneous non-invasive monitoring of PAP in CHF patients.

The dose adjustment was done on a conservative level depending on clinical status. Therefore, after the device implantation, all patients were discontinued for a small period of 4 weeks and then MXL was uptitrated depending on the PAP. The non-invasive PAP measurement served a precise tool for monitoring beta blocker therapy in these patients. In our study, eight out of 10 patients were uptitrated to the target dose of 200mg MXL/day over a period of six months. In our study, there was a trend towards rise in PAP during initial uptitration of MXL. However, this rise was followed by a subsequent fall on reaching the target MXL dose. Further, in our study the systolic BP and HR decrease as expected with MXL treatment. This initial rise in PAP justifies the indication for slow and careful uptitration of beta blockers in HF. The device thus served a useful tool for the monitoring of the therapy in these patients.
CIBIS II has already shown benefits of \( \beta_1 \) selective blocker bisoprolol in worsening heart failure (CIBIS II investigators 1999). Hjalmarson et al (2000), in the landmark trial MERIF-HF has shown the survival benefit in CHF patients with metoprolol. The study demonstrated improved survival, reduced need of hospitalization due to worsening HF, improved NYHA functional class and beneficial effects on patients well being by metoprolol CR/XL in symptomatic HF. In our study, the patients were thus uptitrated using this MERIT-HF criterion, every two weekly to reach the target dose of 200 mg MXL per day. The mechanisms involved in the beneficial effects of \( \beta_1 \) blockade in CHF patients are not completely known. However, it is well established that in patient with CHF due to systolic dysfunction of various etiologies, metoprolol has favorable effects on left ventricular geometry and function, myocardial energy balance and exercise capacity (Andersson et al 1991, Waagstein et al 1993, Waagstein et al 1998). However, there are no reports on the effect of MXL on PAP in such patients. The present study investigated the variation in PAP occurring while uptitrating MXL in these patients.

Out of the ten, one patient discontinued due to deterioration in hemodynamic conditions on uptitration while other patient got delayed in the titration due to irregular follow up. The patient deteriorating on MXL uptitration presented with initial symptoms of continuous coughing; later on detected as decompensation event by the non invasive monitoring of PAP with the ImPressure\textsuperscript{®} device. The patient was hospitalized and stabilized with intravenous diuretics. Subsequent attempts to uptitrate or load minimum dose of MXL led to repetitive deterioration as reflected by rise in PAP. This small but important observation supports the evidence of metoprolol and hence beta-blockers intolerance is selective CHF patients. Repeated attempt to load MXL lead to increase in PAP subsequently stabilized with diuretic treatment. The patient was ultimately discontinued of any beta-blocker therapy.
Various reasons may have accounted for the intolerance of MXL in this patient. The patient was the only female and diabetic in the group having idiopathic dilated cardiomyopathy. It was found that this diabetic patient had higher systolic and diastolic PAP as compared to rest non diabetics. There are considerable reports showing beneficial effects of beta-blockers in diabetic HF. In an experimental study by our institute (Shah et al 2005 unpublished results), we observed that metoprolol in comparison to atenolol had some beneficial effects with respect to cardiovascular complications associated with diabetes in streptozotocin induced diabetic rats. Cruickshank et al (2002) commented that beta-blockers have a poor image as a potential therapy due to apparent adverse effect on surrogate end points such as insulin resistance. The report recommended that beta-blockers, which were severely under prescribed, should be considered as a first line therapy option for all diabetics with IHD. Subgroup analysis from MERIT HF trials showed that HF patients with diabetes well tolerated MXL therapy (Deedwania et al 2005). Contrary to these reports, the diabetic patient in our group deteriorated on MXL uptitration while she was on other stable conventional CHF medications. Despite several studies, the effect of beta-blockers on glucose metabolism is still controversial because of the different actions of different blockers. Beta-receptor stimulation results in an increase in liver glycogenolysis and gluconeogenesis, an increase in muscle glycogenolysis, and stimulation of insulin release. In several studies, it was demonstrated that selective and nonselective beta-blockers reduce the uptake of glucose from peripheral muscles inducing a mild increase in plasma glucose and compensatory hyperinsulinemia. Selective beta-blockers like atenolol or metoprolol can decrease glucose uptake by about 25%, and the decrease in sensitivity to insulin is associated with increases in plasma insulin (Assal et al 2004). Gotzshce et al (1983) investigated the myocardial beta receptor adenylate cyclase system in short term streptozotocin diabetic rats. Since it was found that the beta-receptor number and affinity was identical in control and diabetic animals, it
was proposed that a functional uncoupling of the myocardial beta-receptor from productive adenylate cyclase activation might exist in experimental diabetes. The study indicated a possibility of catecholamine induced desensitization in diabetics, however was not extrapolated to human diabetes mellitus. Use of third generation beta blocker such as carvedilol, which, through its $a_1$ blockade has the advantages of vasodilatation and lowering of insulin resistance in addition to its proven efficacy in HF, may provide distinct advantage in such diabetic patient (Bell al 2002). Patients with idiopathic cardiomyopathy are reported to receive benefits from beta-blocker therapy. A Study by Engelmeier et al (1985) has reported an occasional worsening of HF symptoms during MXL uptitration in patients with dilated cardiomyopathy. In dilated cardiomyopathy, significant selective downregulation of $\beta_1$ receptors have been reported resulting in a marked alteration of $\beta_1;\beta_2$ receptor density ration in the subendocardium. Treatment with the $\beta_1$-selective antagonist Metoprolol has been shown to increase beta-adrenergic receptor density in some patients with idiopathic dilated cardiomyopathy (Beau et al 1993). The MERIT-HF trial has already showed benefits with metoprolol CR/XL in patients with and without cardiomyopathy. In a study comparing treatment of carvedilol with metoprolol in patients with dilated cardiomyopathy (Hirooka et al 2001), drug intolerance occurred more with metoprolol than carvedilol treatment. It has also been proposed that a substantial proportion of patients with dilated cardiomyopathy have circulating autoantibodies directed against the cardiac beta-adrenoceptor. This induce downregulation by interfering at several steps in the cycling of beta-receptors. These effects would contribute to the reported decline in beta-receptor responsiveness in cardiomyopathic myocardium (Limas et al 1991). Since in our study it was only one patient with dilated cardiomyopathy who showed intolerance, further investigations are required to support such reports. Further, there have been numerous studies relating to particular polymorphisms in adrenergic-receptor
genes to disparate disease outcomes or to differential responses to drugs (Wagoner et al 2000, Hajjar et al 2002). Maack et al (2001) showed intolerance in MXL treated patients due to CYD2d6 polymorphism. A recent study (Lanfear et al 2005) has shown that polymorphisms of beta-receptors may be responsible for ill effects in certain patients. The study shows that in acute coronary syndrome patients, beta-blocker therapy have differential survival benefits associated with their beta receptor genotypes. Terra et al (2005) has reported that patients with beta-receptor polymorphism may be responsible for intolerance to the therapy during uptitration. This small but important finding of our study emphasizes the intolerance of beta-blockers in selective patients, where in careful uptitration is recommended. This may be a cause of intolerance and worsening with MXL therapy in CHF patients needs to be deeply investigated.

Our study also investigated the effect of MXL uptitration on the nocturnal rise in PAP and variation in PAP by exercise in these patients. As discussed earlier, the uptitration of MXL needs to be monitored. In spite of the initial deterioration and controversy prevailing with benefits of beta-blockers, MERIT-HF study (Hjalmarson et al 2000) has shown improved survival and reduced events with beta-blockers use in CHF. Our results of MXL effect on diurnal variation may indicate reasons this long-term benefits. Uptitration of MXL to 100mg/d caused an initial increase (p<0.05) in daytime systolic and diastolic PAP and a continuing deterioration in nocturnal PAP. Further uptitration to 200mg/d showed a significant rise in daytime but contrary to the previous nocturnal rise, achieving this target dose caused a significant drop in the night PAP as compared to initial uptitrations.

On loading 25mg/d MXL, there were no significant changes in exercise time and METS but a significant rise in post TMT PAP. On 50mg/d MXL dose exercise time and METS increased without any changes in post TMT PAP. On the target dose of 200mg/d MXL, the
Exercise time and METS increased significantly without any considerable change in post TMT pressures. Improved exercise capacity in CHF has been attributed to restoration of endothelial function. ACE inhibitors as well as beta-blockers have previously been shown to enhance endothelial function and exercise capacity. Engelmeier et al. (1985) reported that long-term beta blockade improves functional class and exercise capacity. The study showed a significant improvement in the mean MET score with metoprolol treatment as compared to placebo in patients with CHF from dilated cardiomyopathy (Engelmeier et al 1985). In our study, we reported the effect of MXL therapy on the PAP before and after the TMT. Poelzl et al (2006) reported that short-term improvement of submaximal exercise capacity in CHF patients following optimized therapy with ACE inhibitors and beta blockers is associated with restoration of endothelial function in conduit arteries. It has been reported that there is a greater LV parameters improvement with carvedilol as compared to metoprolol with a greater increase in exercise capacity with metoprolol (Di Lenarda et al 1999, Kukin et al 1999, Sanderson et al 1999). Metra et al (2000), in a randomized, double blind comparison of long term effect of metoprolol and carvedilol showed that carvedilol produced a greater decrease in PAP both at rest and during exercise than metoprolol. Further, contrary to this, metoprolol group showed greater increase in maximal exercise capacity than carvedilol. This study proposed that the greater reduction in peak exercise HR with carvedilol might have impaired the increase in exercise capacity that would have been expected to accompany an improvement in cardiac performance. Our results comply with these beneficial effects of MXL on exercise capacity in CHF patients. In our study, the % THR and peak exercise HR were not significantly altered by MXL uptitration. This may justify the improvement in exercise capacity in these patients as reflected by exercise time and METS improvement. Moreover, the check on rise in PAP post TMT as demonstrated by MXL may reflect the benefits observed.
Previous studies have clearly demonstrated the beneficial effect of beta-blockers in patients with stable HF. Beta-blockers improve LVEF and reduce cardiac mortality (de Groote et al 2005). One-year follow up of these CHF patients implanted with the device was free of any clinical adverse events or device related complications. Moreover, there was significant improvement in the ejection fraction of the patients. It may be proposed that uptitration of beta-blocker along with management of these patients assisted by non-invasive monitoring using this device may account for the improvement in the patients.

The studies thus showed that non-invasive monitoring of PAP may assist the management of CHF patients on routine basis. The CHF therapy can be tailored according to the precise hemodynamic assessment available by such implantable device. The study was limited by no. of subjects because of its pilot nature, however, has demonstrated beneficial effects of MXL in CHF patients. MXL and thus other beta-blockers may require a slow and careful uptitration in such patients and precise PAP monitoring may facilitate tailoring the CHF medications to individual patient’s profile. Beneficial effects of MXL on nocturnal rise and exercise-induced variation in PAP reflect the preliminary causes for its long-term efficacy. This small, short term beneficial effects may support the expanding role of beta blockade in management of CHF.