THERE ARE MANY THINGS IN LIFE THAT WILL CATCH YOUR EYE, BUT ONLY A FEW WILL CATCH YOUR HEART...PURSUE THOSE.

Abstract
World Health Organization has predicted that by 2020 up to three quarters of deaths in developing countries would result from non-communicable diseases wherein cardiovascular diseases (CVD) would be leading cause. Studies on prevalence of coronary artery disease (CAD) in India reveal disturbing trends. The prevalence of CAD in India is about 10% and it is four times higher as compared to US. Among the CVD, acute myocardial infarction (AMI), refractory angina and heart failure (HF) constitute higher risk manifestations presenting increasing treatment challenges. In spite of the phenomenal developments in the therapeutic and interventional strategies, these disorders remain a major cause of morbidity and mortality among CAD patients and a very few studies have been carried out to evaluate the efficacy of various drugs and medical devices for the treatment and management of patients with these conditions especially in India. We have evaluated efficacy of various drugs and specialized medical devices in patients with AMI, refractory angina and HF.

AMI is the first manifestation of CAD in approximately 50% to 70% of patients. Mechanical reperfusion by percutaneous coronary interventions (PCI) has been a successful modality in the restoration of the coronary patency in AMI. However, primary PCI for AMI, in lesions with large thrombus load has been reported to increase the procedural complication rates. Distal embolization of thrombus/plaque components during primary PCI may play a crucial role in limiting effective myocardial reperfusion and remains a challenge. PercuSurge GuardWire® Plus Temporary Occlusion and Aspiration System is a distal embolic protection device used as an adjunct to PCI for mechanical protection against distal embolization.
However, the device is underused due to the misconceptions that it is less user friendly, time consuming and not as efficacious as originally expected (EMERALD Trial). Hence, we evaluated the efficacy of this distal protection device (DPD) in AMI, primarily focusing on the actual procedural time involved in the PCI and a long term two year follow-up for the occurrence of major adverse cardiac events (MACE: i.e Death, Recurrent Myocardial infarction (ReMI), Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR), Emergent PCI or Coronary artery Bypass Graft Surgery (CABG)).

The evaluation of DPD was carried out in 67 prospective AMI patients undergoing primary/rescue PCI within 24 hours of the symptom onset. The patients were randomly divided into two groups: (a) Patients where PercuSurge GuardWire® was used (DPD group, n=30) and (b) patients were it was not used (Control Group, n=37). Use of the device was based on the economic affordability of the patients. The Institutional Review Board approved the protocol of the study. Along with conventional demographic and angiographic parameters including TIMI flow and TMP grade, incidence of slow/no reflow (NR) and usage of intracoronary vasodilators like adenosine, sodium nitroprusside, trinitroglycerin (NTG) and platelet glycoprotein IIb/IIIa (GP IIb/IIIa) receptor antagonists were recorded. The total procedural time as well as the time for individual steps of the PCI was evaluated in both the groups.

Use of DPD showed significantly greater achievement of TIMI III flow and TMP III grade (p<0.01). It significantly reduced the total procedural time for PCI (25.01 ± 2.17 min vs. 31.98 ± 2.52 min in control group, p<0.05). An additional time of 3.04 ± 0.57 minutes was consumed in the DPD group to inflate the distal balloon. Inspite of this, the time required after wire crossing to reach stent placement as well as to achieve TIMI III flow was significantly less with DPD. Further, its use significantly reduced the time after angioplasty balloon inflation/stent placement till optimal TIMI flow was achieved (17.37 ± 2.21 min vs. 24.41 ± 2.5 min in control group, p<0.05). This
is the critical time frame wherein distal embolization and NR tend to occur during the PCI. The incidences of NR were also significantly reduced (30% vs. 84% in control group, p<0.01), thus reducing requirement of intracoronary vasodilators and GP IIb/IIIa receptor antagonists. 90% patients were followed for 1 year and 80% for two years. At end of 2 years follow-up, 4 deaths were reported in the control group where device was not used while 1 death occurred in the DPD group. Thus, use of DPD reduces the total procedural time with better and faster optimal TIMI flow and TMP grade in primary/rescue PCI (as seen in RUBY registry). The device was associated with less long term cardiac events. More studies in focused and experienced centers may further explore its utility.

While the survival of patients with primary coronary events continues to increase, there is a group of patients with severe disabling angina and CAD who are refractory to conventional forms of treatments including revascularization techniques and medical therapy. Earlier reports reveal that increase in coronary sinus (CS) pressure redistributes collateral blood flow into ischemic territories of the myocardium, reduces ischemic damage and infarct size. Thus, CS narrowing might offer an alternative treatment for patients with refractory angina who are not candidates for revascularization. The CS Reducer® is a percutaneous implantable stent-like device, designed to establish CS narrowing and to elevate CS pressure. The Reducer® is a stainless steel mesh, balloon expandable stent. After implantation, it has an hourglass shape with a diameter of 3.0 mm at its center and 8-12 mm at both ends. Pre-clinical experiments on implantation of the Reducer® stents were reported to be safe and associated with reduced mortality and improved ischemic and cardiac functional parameters. However, no study has been conducted on the safety and efficacy of this device in patients with refractory angina. We have evaluated the safety and efficacy of this device for the first time in the world in refractory angina patients.
The study was a first-in-man, single-arm, safety and feasibility study in ten patients with refractory angina. Patients with Canadian cardiovascular society (CCS) angina class III, objective evidence of reversible myocardial ischemia by stress echocardiography or myocardial perfusion test, and left ventricular ejection fraction (LVEF) >30% were included. CS Reducer® stent was implanted in all patients percutaneously through the internal jugular vein. All patients were followed at the end of 1, 3 and 6 months with multi-slice computed tomography angiography (MSCT), stress echocardiography, myocardial perfusion test (SPECT), and angina/quality of life (QOL) questionnaire. One year Clinical follow up was also taken for all the patients.

All the ten refractory angina patients tolerated the CS Reducer® implantation procedure well. Immediate procedural and peri-procedural success rate was 100%. CS as well as the stents were very well visualized in the non-invasive MSCT evaluation. All were at the exact site of implantation in the CS without migration. All Reducers® were patent with no evidence of thrombosis throughout the follow up period. The mean diameters of the stents as measured in the post implantation MSCT were: proximal 11 ± 2 mm; distal 7.2 ±1mm and mid 3.0 ±0.2mm. The CS wall was constricted along with the hourglass shape of the stent, thus leading to a reduction in the CS diameter. No blood flow around the narrowed mid-portion of the stent was seen at 3 and 6 months follow-up. The transverse sections of the CS in MSCT showed open lumen in all stents. This suggested the ability of the device to cause CS narrowing which may increase the CS pressure. During a follow up period of 1-6 months no MACE was recorded. There was no evidence of migration of the device, thrombosis or occlusion of the CS. Six months evaluation showed a significant improvement in the mean angina class of the patients (3.0±0.15 at baseline vs. 1.4 ±0.2 at 6 months; p<0.01). There was a significant improvement in ischemia at the end of six months as evident by stress echocardiography (mean ischemia score 1.4 ±0.3 at
baseline vs. 0.67 ±0.3 at 6 months; \( p<0.05 \) and SPECT (mean ischemia score 2.0±0.0 at baseline vs. 1.4±0.5 at 6 months; \( p=0.057 \)). The quality of life and exercise tolerance also improved in the patients. One year clinical follow up in all the patients was free of any adverse clinical events. Implantation of the CS Reducer\textsuperscript{®} stents was thus, feasible and safe. It presents a novel effective tool for patients with refractory angina who presently have ischemic symptoms uncontrollable by medical therapy and are also not candidates for revascularization.

Inspite of recent advances in understanding the pathophysiology and treatment of HF, this end stage of all heart diseases continues to result in significant morbidity and mortality. The left ventricular end diastolic pressure (LVEDP), a critical hemodynamic parameter serves as the basis for most decompensation events in chronic HF (CHF). Frequent monitoring of pulmonary artery (PA) pressure (PAP) supplies feedback loop for the direction of therapy, which can be performed by right heart catheterization (also known as PA catheterization or Swan-Ganz catheterization). However, the invasive nature of this modality is inconvenient and hence limits its application only to hospitalized patients. Remon CHF System (ImPressure\textsuperscript{®}) is a new device that has been developed to measure the PAP waveform based on non-invasive acoustic activation and communication, as frequently as necessary. Based on the successful animal studies, we have carried out the first-in-man pilot study to evaluate its delivery system and its safety and functionality in ambulatory patients.

The evaluation of the safety and functionality of this pressure monitoring device (ImPressure\textsuperscript{®}) was carried out in ten New York Heart Association (NYHA) class III/IV HF patients. Baseline hemodynamic assessment was obtained prior to implantation of this device by right heart catheterization. A control pressure measurement
was also performed using a Millar catheter. The ImPressure® device (3mm x 3mm x 16mm), made of titanium case, encapsulating an energy exchanger, control chip, pressure sensor and energy reservoir with ultrasonic capabilities was 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 device 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. PAP was measured using the device till 6 months. Right heart catheterization with Millar catheter was repeated at 6 months for authenticating the ImPressure®'s functionality and accuracy. The functionality of the device was also verified at one year of implantation.

The ImPressure® device was successfully deployed in the right PA in all the ten CHF patients with no clinical adverse events. Pressure measurements were successfully obtained from all implanted devices immediately following implantation and at all follow ups till one year. ImPressure®'s functionality and accuracy were comparable to the control pressure measurements from Millar Catheter at baseline and 6 months. The pressure curves, collected simultaneously from the Remon CHF system and the Millar pressure catheter, were almost identical and equivalent for clinical purposes. One-year follow up was free of any clinical events. Thus, the implantable monitoring device presents a novel concept for non-invasive monitoring of PAP in CHF. Its unique telemetric technology enables easy repeated non-invasive measurement of the PAP waveform and PA fiastolic pressure in ambulatory patients. Such frequent noninvasive monitoring of PAP may improve the prognosis and management of CHF patients.
Limited studies have been reported with respect to physiological changes like diurnal variation, variation in PAP following exercise and uptitration of beta-blockers with frequent and repeated hemodynamic monitoring in CHF. Diurnal variation and more importantly nocturnal rise in PAP increase the risk of developing paroxysmal nocturnal dyspnoea in CHF patients. Moreover, increase in LVEDP, PAP on exercise and limitation of exercise capacity are common findings in CHF. Hence, following the successful implantation of the implantable PAP monitoring device, we investigated the diurnal variation in PAP, exercise capacity and subsequent variation in PAP following exercise in these CHF patients using the device.

Following the implantation till one month, all the patients were monitored ambulatory for the changes in PAP and other related hemodynamic parameters over a 24-hour cycle every week to evaluate the diurnal variation in PAP. PA systolic and diastolic pressure was monitored non-invasively using this device every 2 hours during daytime and every 3 hours during night. All patients received 1mg/2mg Lorazepam (Ativan®) at bedtime along with the conventional CHF therapies. Time frame from 8:00 hours to 20:00 hours comprised the daytime and 22:00 hours to 6:00 hours comprised night time for analysis. Average of the four diurnal cycles was taken for analysis. At end of one month, all these patients underwent Treadmill Exercise test (TMT) according to the standard Bruce Protocol. PAP was measured immediately before and after the exercise and on recovery using the noninvasive monitoring device.

For the whole group, the mean daytime PAP was 28.8±2.6 mmHg systolic and 14.2±1.8 mmHg diastolic. During the night, PAP significantly (p<0.05) rose to 31.6±3.0 mmHg systolic and 16.1±2.1 mmHg diastolic. In seven out of ten patients, there was a rise in the PAP at night. The mean increase from day to night in systolic pressure was 2.8±1.1 mmHg and in diastolic pressure was 1.9±0.6 mm Hg. The systemic blood pressure (BP) and heart rate (HR) did not show any significant variation during the night. Thus, CHF patients do show
diurnal variation in PAP. Nocturnal rise in PAP may be responsible for the worsening of these patients' symptoms at night or early morning. Noninvasive measurements by this novel implantable device may assist the daily monitoring of these patients including their nocturnal changes and adjustment of therapy.

All the patients finished the symptom limited baseline TMT with a peak heart rate (HR) of >90% of targeted heart rate (THR). The mean exercise time was 6.4±0.7 minutes, corresponding to 7.9 ± 0.7 metabolic equivalents (METS). Resting PAP were 32.7±3.5 mmHg systolic and 17.1±2.5 mmHg diastolic. Post TMT, PAP significantly (p<0.05) rose to 49.0±5.7 mmHg systolic and 24.1±3.6 mmHg diastolic. The BP pre-TMT was 111±6/71±3 mmHg which post TMT rose to 144±9/82±3 mmHg (p<0.01). The mean increase in the PAP due to exercise was 16.3±3.2 mm Hg systolic and 6.9±1.8 mm Hg diastolic (p<0.01). Thus, the study showed significant rise in PA pressure and more importantly, PA diastolic pressure following exercise in CHF patients limiting their exercise capacity. This increase in PA pressure may be secondary to either ischemia or Left ventricular dysfunction or both. Management of these patients should be tailored to avoid this exertional rise in PA diastolic pressure either by avoiding ischemia or by improving Left ventricular dysfunction.

Beta-blockade improves survival, reduces hospitalizations for HF, and improves left ventricular function when given over a long period of time in CHF. However, there have been concerns that beta-blockade may lead to worsening heart failure when the therapy is initiated. Metoprolol Extended Release (MXL) is a β₁-selective agent that has been reported to improve survival and reduce hospitalization in CHF patients. There is limited information on variations in PAP after the use of beta-blockers in ambulatory CHF patients. Thus, we evaluated the uptitration of MXL and its effect on PAP using the pressure-monitoring device. We also evaluated the effect of MXL on
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diurnal variation, on exercise capacity and subsequent variation in PAP in these patients.

All the patients received other conventional CHF therapy except beta-blockers for the first month. After investigating the diurnal and exercise induced variation in PAP in these patients, all the patients were then loaded with MXL 25mg/day and uptitrated two weekly using the MERIT-HF criteria to reach a target dose of 200mg/d. PAP was monitored at baseline and at each uptitration follow-up till 6 months and till 1 year. Further, all patients were non-invasively monitored for PAP every 2 hours in day time and every 3 hours during night for a 24 hrs cycle after reaching 100mg/d and 200mg/d MXL to evaluate the effect of MXL on nocturnal rise in PAP. All the patients also underwent TMT at each uptitration visit. Along with the exercise capacity, PAP was monitored non-invasively using the device before and after each TMT to evaluate the effect of MXL in these CHF patients.

MXL was successfully uptitrated to the target dose of 200mg/d in 8 out of the 10 CHF patients. For these 8 patients taken into analysis, the baseline (no MXL) PAP was 30.6±3.9 mmHg systolic and 16.1±2.8 mmHg diastolic. The BP and HR were 112±7/70±2 mmHg and 83±5 beats/min respectively. After 2 weeks of loading MXL 25 mg/d, PAP slightly rose to 32.5±2.0 mmHg systolic and 16.6±2.2 mmHg diastolic. Further uptitration to 50mg/d MXL increased the systolic PAP significantly to 35.8±2.7 mmHg (p<0.05) and diastolic to 19.0±2 mmHg. On reaching 100mg/d MXL dose, the PAP was lowered back to 33.0±3.7 mmHg systolic and 15.6±2.3 mmHg diastolic. Uptitration to the target dose of 200mg/day MXL was successful without any further significant changes in PAP. At end of this, systolic PAP was 34.6±4.1 mmHg and diastolic was 15.9±2.4 mmHg. The mean systemic BP and HR decreased with the increase in MXL dose. Thus, uptitration of MXL with simultaneous PAP monitoring was achieved successfully with minor variation in PAP. However, one diabetic female patient out of the ten could not tolerate MXL.

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Uptitration of MXL showed a marked deterioration in PAP leading to hospitalization where intravenous diuretics were administered. Reloading of MXL repeatedly showed deterioration in PAP as monitored non-invasively using the device. Hence, Loading MXL in CHF patients using the recommended protocol is feasible but may be associated with minor insignificant changes in PAP. However, some patients may show beta blocker intolerance and hence slow and careful uptitration may be preferred. Non-invasive monitoring may assist the tailoring of therapies in CHF.

The mean baseline daytime PAP for the eight uptitrated patients was 25.2±0.5 mmHg systolic and 14.1±0.2 mmHg diastolic. During night, pressure significantly (p<0.001) increased to 27.8±0.2 mmHg systolic and 16.0±0.2 mmHg diastolic suggesting a nocturnal rise in PAP as already observed. Uptitration of MXL to 100mg/d caused an initial increase (p<0.05) in daytime PAP to 32.5±0.5 mmHg systolic and 15.3±0.5 mmHg diastolic, with a further increase in nocturnal PAP; 35.7±0.6 mmHg systolic and 17.7±0.4 mmHg diastolic at night (p<0.01 for both, compared to respective daytime and baseline night pressures). Further uptitration to 200mg/d showed a significant rise in daytime PAP to 34.0±0.4 mmHg systolic and 15.6±0.6 mmHg diastolic (p<0.05) as compared to baseline. However, contrary to the nocturnal rise with initial uptitration, at night, systolic and diastolic PAP significantly dropped to 27.8±0.9 mmHg (p<0.01 as compared to daytime) and 14.0±0.3 mmHg (p<0.05 compared to respective daytime and baseline) respectively. Slow and careful uptitration of MXL upto 200 mg/d may prevent this nocturnal rise as evident from the non invasive frequent monitoring by ImPressure® device.

All the 8 patients had symptom limited TMT. The mean baseline exercise time for this group was 6.8±0.7 mins and 8.4±0.7 METS. After 2 weeks of loading 25mg/d MXL, the exercise time was 7.0±0.8 mins and METS 8.6±0.8. The post TMT PAP rose significantly to 51.6±5.6 mmHg systolic (p<0.05) and 23.7±3.7 mmHg diastolic. On 50mg/d MXL dose exercise time and METS increased to 7.9±1.0 mins.
(p=0.09) and 9.4±0.9 respectively. No significant change was observed in the hemodynamic or exercise parameters on reaching 100mg/d MXL. On achieving the target dose of 200mg/d MXL, the exercise time and METS increased significantly to 8.0±0.9 mins and 9.7±0.9 respectively (p=0.03 for both) with no significant change in post TMT PAP (52.1±6.3 mmHg systolic and 23.6±3.1 mmHg diastolic). Post TMT HR decreased significantly from 106±3 per min at baseline to 89±5 per min at 200mg/d MXL (p=0.01). Thus, MXL treatment may produce a slight insignificant increase in systolic PAP but may improve the exercise capacity in selected patients.

One year follow up with echocardiographic evaluation of these CHF patients revealed significant clinical improvement. Six out of ten patients showed significant improvement in LVEF. The mean LVEF of the patients improved from 23.7±0.9 % prior to the device implantation to 29.9±1.8% at one year follow up (p<0.01). Thus, management of CHF and titration of CHF therapy aided by such non-invasive monitoring may show significant clinical improvements in such patients.