IN THE CONFRONTATION BETWEEN THE STREAM AND THE ROCK, THE STREAM ALWAYS WINS...NOT THROUGH STRENGTH, BUT THROUGH PERSISTENCE.

PERSISTENCE

Materials & Methods
The Studies were carried out at The Heart Care Clinic, Sterling Hospital, SAL Hospital and Apollo Hospitals, Ahmedabad, India. All the interventional procedures were performed by the team of interventional cardiologists of the Heart care Clinic, led by Dr Keyur Parikh. Good Clinical Practices were followed upon as per ICMR and ICH guidelines. The protocols were approved by the corresponding Institutional Review Boards. All the patients gave written informed consent before participation in the study. Case Report Forms were filled for all the patients. Baseline demographic details as well as biochemical and hematologic parameters were collected. Vital signs like systemic blood pressure, heart rate were collected. Patient's history for diabetes, hypertension, CAD, etc were also recorded.

D.1 EFFICACY OF DISTAL PROTECTION DEVICE (PercuSurge GuardWire®) IN AMI

D.1.1 Study Population:
67 consecutive AMI patients angiographically detected of thrombotic lesion and undergoing primary/rescue PCI (having indication for DPD use) within 24hrs of onset of chest pain were enrolled for the study from September 2003 to Feb 2004 at Sterling Hospital, Ahmedabad. The patients were randomly divided into two groups depending on whether DPD (PercuSurge®) was used or not during PCI inspite of its indication. Use of DPD was based on the economic affordability of the patients. In all, DPD was used in 30 patients (Group I; DPD); whereas the rest of the 37 patients formed the control group (Group II).

D.1.2 Study Design:
It was a single centered, random, open clinical trial. Informed consent was obtained from all the patients. After recording the baseline
demographic and hemodynamic parameters, the angiographic parameters were also assessed. PCI was performed according to the conventional methods by the interventional cardiologists. An angiographic criteria of <30% residual stenosis was used to determine the end point of PCI. The incidences of no/slow reflow as well as the use of intracoronary vasodilators like adenosine; sodium nitroprusside; trinitroglycerin (NTG) and GPIIb/IIIa receptor antagonists were also recorded. TIMI flow and TMP grade after PCI were assessed. The total time consumed for the PCI as well as the time required for individual steps of the PCI was evaluated.

D.1.3 The Device:
The PercuSurge GuardWire® Plus Temporary Occlusion and Aspiration System (Medtronic AVE, Santa Rosa, CA) comprises of four principal components (Figure D.1) (Huang et al 2003): the GuardWire® Plus Temporary Occlusion Catheter, the MicroSeal® Adaptor, the Export® aspiration Catheter, and the EZ Flator® inflation device.

a) The GuardWire® temporary occlusion catheter (figure D.2a & b) containing a central lumen connected to a low pressure distal occlusion elastomeric balloon incorporated into the tip and with a diameter ranging from 3–6 mm—the low profile of the deflated balloon facilitates lesion crossing providing protection from distal embolization
b) The EZ Flator® (Figure D.2c) controls the inflation of the occlusion balloon

c) The MicroSeal adapter (figure D.2d) controls the opening and closure of a proximal valve in the GuardWire, allowing inflation and deflation of the distal occlusion balloon; and

d) The Export aspiration catheter (figure D.2a &b) that consists of a 5 French monorail catheter connected to an evacuated 20 ml syringe used to remove thrombotic debris—after that, the GuardWire balloon is deflated and the anterograde flow is restored.
Figure D.1:
The PercuSurge GuardWire Plus Temporary Occlusion and Aspiration System

Figure D.2a: The GuardWire® and the Export® catheter

Figure D.2b: Inflated GuardWire balloon and Export aspiration catheter

Figure D.2c: The EZ-Flator™

Figure D.2d: The MicroSeal® Adapter
D.1.4 Procedure Description:
The PCI procedure was done using femoral arterial approach. After a proper guiding catheter was engaged to the target vessel, the GuardWire® (or conventional soft guidewire in the patient group where DPD was not used) was first attempted to cross the culprit lesion. If there was difficulty passing the GuardWire®, a conventional guidewire was passed over which the GuardWire® was crossed using the buddy wire technique. The GuardWire® was advanced till the distal balloon was positioned a few centimeters beyond the target lesion. It was important not to push the GuardWire® too far distal from the lesion because it may leave side branches unprotected. The GuardWire® catheter then served as an adequate guidewire for delivery of dilatation balloons and a multitude of stents. After inflating the GuardWire® distal balloon, PCI was performed according to the conventional methods. The distal balloon was kept inflated during the treatment of the culprit lesion. Before deflating this balloon, the liberated debris (after PTCA balloon inflation and stent implantation) was aspirated through the Export® aspiration catheter.

D.1.5 Angiographic analysis:
Coronary angiograms were reviewed separately by two independent cardiologists unaware of the patient's history and details, to avoid the inter observer bias. The observers were blinded to the device by showing pre and post angioplasty recordings only. The degree of perfusion was evaluated according to Thrombolysis in Myocardial Ischemia (TIMI) criteria. Good collateral flow was defined as grade 2 or 3 (discussed below). Angiographic thrombus was defined as a filling defect seen in multiple projections surrounded by contrast and in the absence of calcification. Angiographic distal embolization was defined as the angiographic cut-off of the distal branch or vessel at any point during the procedure.
D.1.6 Procedural Time:
Time in minutes required for various steps of the PCI procedure were recorded. The time count was started from the first after the guiding catheter was engaged and viewed under fluoroscopy to ensure that the guiding catheter was in place. Rest of all the time frame were calculated considering the guiding catheter time as zero time or start time of the procedure. Various time periods like time for lesion crossing by the wire, time required to achieve PTCA balloon inflations, time to reach stent implantation and time to achieve optimal TIMI flow were recorded separately in addition to the total procedural time. The *total procedural time*, in our study precisely consists of the time period from first cine of guide catheter engagement till last cine of final TIMI flow achieved.

D.1.7 Study Endpoints:
The primary endpoint of this study was to evaluate the presence of distal embolization, which was demonstrated by Thrombolysis in myocardial Infarction (TIMI) flow and Myocardial Blush grade. Secondary endpoints was to evaluate the clinical performance of the GuardWire® system combined with Plain-old balloon angioplasty (POBA) and/or stenting in AMI patients during emergency PCI which included immediate technical device success, angiographic success and procedural success. Patients were followed for two years and Major Adverse Cardiac Events (MACE: Death, ReMI, TLR, TVR, Emergent PCI or CABG) were assessed at the end of one year and two year.

D.1.7.1 Assessment of Blood flow :

**(A) Thrombolysis In Myocardial Infarction (TIMI) flow grades:**
The culprit lesion was determined by its anatomical location, its perfusion characteristics according to Thrombolysis in Myocardial Infarction (TIMI) classification for flow through the infarct related vessel (Sutsch et al 2000):
TIMI flow 0 was assigned if there was no antegrade flow beyond the point of occlusion or there was no visible filling of any collateral channels.

TIMI I flow was designated if there was penetration without perfusion or minor perfusion i.e. contrast material passes beyond area of obstruction, but “hangs up” and fails to opacify entire coronary bed distal to obstruction for duration of cineangiographic filming sequence. There was filling by means of collateral channels of side branches of the vessel but without any dye reaching the epicardial segment of that vessel.

Blood flow was graded as TIMI II when there was partial or mild perfusion. Contrast material passes across obstruction or its rate of clearance from distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by previously occluded vessels. Partial filling occurs via collateral channels of the epicardial segment of the vessel.

TIMI III flow was assigned for complete and good perfusion as visualized by complete filling of the vessel. Antegrade flow into bed distal to obstruction occurs as promptly as antegrade flow into bed proximal to obstruction, and clearance of contrast material from the involved bed is a rapid as clearance from an uninvolved bed in same vessel or opposite artery.

**(B) Myocardial blush grade/ TIMI myocardial perfusion (TMP):**

Perfusion can be defined as tissue blood flow at the capillary level. Perfusion of the myocardium can be categorized using the TIMI myocardial perfusion (TMP) classification described below (Gibson et al 2000):

Myocardial blush was graded as 0 when there was failure of the dye to enter the microvasculature. There was either minimal or no ground-glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion.
TMP grade 1 was assigned when the dye slowly enters but fails to exit the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection.

TMP grade was considered as 2 when there was delayed entry and exit of dye from the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e., dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout).

TMP grade 3 was designated when there was normal entry and exit of dye from the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or only mildly/moderately persistent at the end of washout phase (i.e. dye is gone or mildly/moderately persistent after 3 cardiac cycles of the washout phase and noticeably diminis hes in intensity during the washout phase), similar to that in an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3.

D.1.7.2 Device success:
Device success was defined as successful deployment of the GuardWire® catheter, occlusion of the distal flow and performance of aspiration.

D.1.7.3 Angiographic success:
Angiographic success was defined as residual lumen diameter stenosis < 20% and TIMI flow grade 3 after the intervention.

D.1.7.4 Procedural success:
Procedural success was defined as angiographic success without the occurrence any periprocedural adverse events.
D.1.7.5 Periprocedural adverse events:
Periprocedural adverse events were defined as distal embolization, spasm or no/slow reflow during the procedure, and all causes of death, New ST elevation or non ST elevation AMI, emergent CABG, or repeat percutaneous target vessel Revascularization within 3 days of the index procedure.

D.1.7.6 Slow/No Reflow (NR):
Coronary occlusion leads to cellular necrosis and myocardial damage. During a short period of occlusion, a variable amount of myocytes may become necrotic while the microvascular network is still intact. If coronary occlusion is prolonged, the microvasculature shows loss of its anatomic integrity (Van't hof et al 1998). At the time of coronary reopening, myocardial reperfusion is achieved only in areas with anatomically preserved microvasculature, where as reflow does not occur in myocardium with extensive microvascular damage. The NR phenomenon is therefore associated with relatively more extensive necrosis and, as a consequence, is a predictor of poor regional and global contractile function. Angiographic NR was defined as the cessation of flow into the distal coronary circulation of the treated vessel with a to and fro contrast movement after intervention (TIMI grade 0 or 1 flow in patients with prior TIMI grade 2 or 3, or TMP grade 0 or 1) not attributable to high grade stenosis or spasm of the original target lesion.

D.1.8 Data analysis:
Continuous variables are expressed as mean ± SEM (standard error of mean) and were compared using unpaired Student’s t test. Independent variables included were age, sex, classic coronary risk factors, angiographic lesion characteristics and interventional strategies are expressed as value or percentages and were compared by Chi Square test. A p value <0.05 was considered to be statistically significant.
D.2 SAFETY AND EFFICACY OF THE CORONARY SINUS REDUCER STENT (Neovasc Reducer®) IN REFRACTORY ANGINA

D.2.1 The Device

The Coronary Sinus (CS) Reducer (Neovasc Reducer®, Neovasc Medical Ltd, Israel) is a balloon expanding stainless steel “stent” designed to establish a permanent and controlled narrowing of the CS which is the “final pathway” of the cardiac venous drainage. It increases coronary venous pressure and is intended for treatment of Ischemic heart diseases. The Reducer® is made of surgical grade 316 LWM stainless steel, seamless tubular mesh, laser cut into pre-specific geometric pattern. It is available in one model “one size fits all”. Different sizes diameters will be achieved by using different balloon sizes. The device length is 25.4 mm and diameter of 3.2 mm in its collapsed non-expanded sate. It can be deployed in vessels with diameters range from 7.0 to 15.0 mm. Recommended pressure used for deployment is 2 to 3 atm. The Reducer® has uniform design with no welding points and flexible longitudinal struts. Its smooth internal and external surfaces prevent damage to the vessel wall. The Reducer is implanted using a percutaneous trans-venous approach. It is provided bare (un-mounted) and is hand crimped on the delivery system (delivery system recommended is Cordis-OPTA™ PRO) in the cathlab during the procedures (Figure D.3a & b). It is installed on a delivery catheter with an over the wire (OTW) mechanism, and introduced into the coronary sinus by right heart catheterization through the right internal jugular vein.
Figure D.3a: The Coronary sinus reducer stent (Neovasc Reducer®)

Figure D.3b: Neovasc Reducer® stent mounted on the balloon

Figure D.4: Proposed Theory for the mechanism of action of Reducer® stent

By increasing CS pressure, redistribution of coronary venous flow occur to jeopardized areas of myocardium distal to an arterial occlusion.
D.2.2 Patient Population

The CS Reducer® stent is intended for patients with refractory angina pectoris despite medical treatment, who are either not amenable or are at high risk for revascularization by coronary artery bypass grafting CABG or by PCI.

D.2.2.1 Inclusion Criteria

Patients with CAD proven by angiography with chronic refractory angina despite medical therapy, who are either not amenable or are at high risk for revascularization by CABG or PCI were considered for the study. Patients with CCS angina class III to IV with objective evidence of reversible ischemia of the left ventricle at the territory of the LAD or LCX coronary arteries were included in the study. Reversible ischemia was diagnosed by myocardial perfusion scan, and/or by dobutamine induced stress echocardiography (DSE).

D.2.1.2 Exclusion Criteria

Patients with MI within last 3 months, PCI or CABG within last 7 months; severe arrhythmias, including chronic atrial fibrillation; decompensated heart failure; severe valvular heart disease; pacemaker or any other electrodes in the coronary sinus; mean right atrial pressure > 15 mmHg; who have undergone tricuspid valve replacement or repair; reversible myocardial ischemia only due to right coronary artery disease were excluded from the study.

D.2.3 Study design and follow-up:

It was a first-in-man, prospective, open-label, safety-feasibility study. The Ethics committee of Apollo Hospitals, Ahmedabad, approved the protocol and all the patients gave written informed consent for participation. Ten patients meeting the eligibility criteria (D.2.2) were considered for the CS reducer stent implantation.
D.2.3.1 Pre Implantation Screening tests:

- Treatment with aspirin 100 mg/day and clopidogrel 75 mg/day was started one week prior to Reducer implantation.
- ECG, Treadmill Exercise Test (TMT), radionuclide perfusion study with SPECT technique and/or DSE were done at baseline before implantation of the CS Reducer stent.
- The Seattle angina questionnaire to assess quality of life and CCS angina class was filled at baseline prior to the implantation procedure.
- MSCT angiography was performed prior to implantation for CS diameter measurement. CS diameter, 2-4 cm distal to the ostium of the CS. The diameter measurement was repeated during invasive angiography for verification prior to implantation of Reducer® stent.

D.2.3.2. Reducer® stent Implantation Procedure

Under fluoroscopic guidance a pre-shaped guiding sheath was introduced into the ostium of the coronary sinus through a right internal jugular vein access site. After CS pressure was recorded, angiography of the CS was performed to size the vessel and to locate side branches bifurcation sites. The dimensions of the proximal segment of the coronary sinus were measured using Quantitative Coronary Analysis (QCA). The most suitable site for implantation was chosen according to the vessel diameter and in order to avoid implantation over side branch bifurcation. The Reducer, crimped on a balloon was then inserted over the wire into the coronary sinus, positioned at the desired site, and implanted by balloon inflation. Post-implantation CS angiography was performed to ensure appropriate implantation, patency of the CS, appropriate reduction of the lumen's diameter, and lack of migration of the Reducer, thrombosis within the Reducer or the CS, perforation or dissection of the CS.
D.2.3.3 Post Implantation Follow Up
All the implanted patients were followed up from hospitalization till a period of 1 year.

- ECG: 12 lead ECG was done at hospital discharge visit, end of 1 month, 3 months and at 6 months.
- TMT, SPECT test and DSE were repeated at 6 months post implantation and compared with baseline tests.
- CT angiography was repeated at 1-3 days and 6 months after CS Reducer implantation.
- The Seattle Angina Questionnaire was filled at end of 3 months and 6 months of Reducer Implantation and CCS angina class was assessed at the end of 6 months.

D.2.3.4 Screening & Follow Up Tests Procedures

(A) CCS Classification for Angina:
CCS angina class reflects the clinical status/improvement of the patient. It is graded as per clinical symptoms of the patients as follows:

- CCS 0 Asymptomatic
- CCS I Ordinary physical activity such as walking or climbing stairs does not cause angina. Angina with strenuous, rapid or prolonged exertion at work or recreation.
- CCS II Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in a cold, or in wind, or under emotional stress, or during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
- CCS III Marked limitation of ordinary physical activity. Walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.
- CCS IV Inability to carry out any physical activity without discomfort — anginal syndrome may be present at rest.
(B) Treadmill Exercise Test (TMT):
TMT was done on MAC 5000, GE machine using Standard Bruce Protocol. The treadmill protocol is consistent with the patient's physical capacity and the purpose of the test. The Bruce multistage maximal treadmill protocol has 3-minute periods to allow achievement of a steady state before workload is increased. In older individuals or those whose exercise capacity is limited by cardiac disease, the protocol can be modified by two 3-minute warm-up stages at 1.7 mph and 0 percent grade and 1.7 mph and 5 percent grade. This is called modified bruce protocol. We have used standard bruce protocol for all evaluations.

METABOLIC EQUIVALENT: The term metabolic equivalent (MET) refers to a unit of oxygen uptake in a sitting, resting person; 1 MET is equivalent to 3.5 ml \( \text{O}_2/\text{min/kg body weight} \). Work activities (like in TMT) are calculated in multiples of METs; this measurement derived from TMT was used to determine exercise prescriptions, assess disability, and standardize the reporting of submaximal and peak exercise workloads. An exercise workload of 3 to 5 METs is consistent with activities such as raking leaves, light carpentry, golf, and walking at 3 to 4 mph. Workloads of 5 to 7 METs are consistent with exterior carpentry, singles tennis, and light backpacking. Workloads in excess of 9 METs are compatible with heavy labor, handball, squash, and running at 6 to 7 mph.

(C) Myocardial Perfusion imaging by SPECT technique:
The most commonly performed imaging procedure in nuclear cardiology is single-photon emission computed tomography (SPECT) imaging of myocardial perfusion. Following injection of the chosen radiotracer, the isotope is extracted from the blood by viable myocytes and retained within the myocyte for some period of time. Photons are emitted from the myocardium in proportion to the magnitude of tracer uptake, in turn related to perfusion. The standard camera used in
nuclear cardiology studies, a gamma camera, captures the gamma ray photons and converts the information into digital data representing the magnitude of uptake and the location of the emission. Tc 99m Tetrofosmin was used as a radiotracer and a dual head millennium VG, GE USA gamma camera was used for the image acquisition and processing. A one-day stress-rest protocol was followed. 10 mci of Tc-99m Tetrofosmin was injected at rest, followed by rest imaging done 45-60 minute later. 3hrs after rest injection, the patient was subjected to stress on treadmill and than given 30 mci of Tc-99m Tetrofosmin. Stress imaging is done after 45 minute of stress injection. If the patient cannot be subjected to physical exercise, pharmacological stress was given with Adenosine. ECG gated SPECT Imaging was done both stress as well as rest studies. During an ECG-gated image acquisition, the patient's ECG was monitored simultaneously with the image (Germano et al 1999). As the peak of an R wave is detected, the "gate" opens and a set number of milliseconds of imaging information is stored in a "frame." For a typical gated SPECT acquisition, each R-R interval is divided into eight frames. After the first 125 milliseconds of imaging data have been recorded in frame 1, the gate closes and then instantly reopens, allowing the second 125 milliseconds of information to be recorded in frame 2. This sequence continues through the prespecified number of frames throughout the cardiac cycle. When the R wave of the next beat is detected by the ECG-gated system, the sequence is repeated for each beat that occurs throughout the image acquisition. The number of counts recorded during any individual cardiac cycle is insufficient to create an interpretable image. When several hundred beats have been recorded, an average cardiac cycle representing all the recorded beats can be reconstructed by redisplaying the frames sequentially in a cine or movie format.

Ongoing beta-blocker therapy is discontinued 48 hours prior to the test. 

*DOUBLE PRODUCT* (DP) was evaluated as one of the measures of exercise capacity of the patient along with METs. It is the product of

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maximum heart rate with maximum systolic blood pressure achieved and reflects exercise tolerance. Left ventricular ejection fraction (%) and the severity of ischemia was evaluated using SPECT test.

**(D) Dobutamine induced stress echocardiography (DSE)**

Dobutamine was used as the agent for pharmacological stress. 2D-Echocardiography evaluation of heart was performed using GE VIVID 4 machine. The method involves incremental infusion protocol of 10, 20, 30, and 40 µg/kg/min, augmented by atropine to obtain an adequate HR response when necessary. Images were obtained at each stage of dobutamine infusion. Regional wall motion abnormalities and severity of ischemia was evaluated. Severity of Ischemia was graded (as 0=no ischemia 1=mild ischemia 2=severe ischemia) and compared at baseline and 6 months.

**(E) Cardiac Multislice Computed Tomography (MSCT) Angiography**

It is an x-ray-based technique. An x-ray source that rotates on a circular path around the patient emits a fan-shaped beam of x-rays that passes through the body. Collimators are used to confine the x-ray beam to the slice that shall be imaged; its thickness can vary from less than one to several millimeters. Opposite to the x-ray source, extremely sensitive detectors record the intensity of x-rays that have passed through the body. Based on the x-ray attenuations obtained from a multitude of angles, a cross-sectional image of the body is calculated. Scanning was done using Brilliance 40 MSCT scanner (Phillips Medical System) during a breath hold with retrospective electrocardiographic gating. The Brilliance 40 is a 40 * 0.625 mm collimation scanner with gantry rotation speed of 0.42 s per rotation, minimal slice thickness 0.67 mm and temporal resolution < 210 ms. A volume of 60 to 110 ml of contrast media is injected intravenously at a rate of 4 to 5 ml/s. Scanning was performed at 120 Kv, 600 to 800 mAs depending on patient size. Reconstruction of the images was
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done using a window centered at 75% of the R-R interval to coincide with the left ventricular diastasis. Reconstructed images is viewed in multiple formats: original axial slices, curved multiplanar reformats along with axis of the vessel of interest, and cross sectional images perpendicular to the vessel's center line. Preimplantation CS diameter was evaluated using MSCT. The exact location and patency of the CS reducer stents were also studied.

D.2.4 Safety Endpoints of the Study:
Following events were recorded as the safety endpoints of the study

1. Major Adverse Cardiac Events (MACE), defined as death; MI; perforation of the CS; occlusion of the CS; need for urgent dilatation of the Reducer during 6 months post implantation of the device.
2. Successful delivery and deployment of the Neovasc Reducer® stent in the CS per procedure as assessed by angiogram immediately post implantation.
3. Patency of the lumen, correct location and absence of migration of the Device from the site of implantation as evaluated by MSCT 1-3 days and 6 months post implantation

D.2.5 Efficacy Endpoints of the Study:

Improvement in the Ischemia: Improvement in the magnitude of Ischemia in the Seattle Questionnaire, CSS angina class improvement, improvement in ST segment changes in ECG, Improvement in reversible ischemia and myocardial perfusion by SPECT test and DSE test at 6 months follow up compared to baseline was recorded to find out effectiveness of the device.

D.2.6 Data Analysis:
Baseline Demographic details were expressed as Mean±SEM or as percentage of patients. Data related to improvement parameters in SPECT, echocardiography & TMT results are analyzed using Student's t test. The p value < 0.05 is considered to be statistically significant.
D.3 SAFETY AND FUNCTIONALITY OF AN IMPLANTABLE DEVICE (REMON ImPressure®) FOR NON INVASIVE MONITORING OF PULMONARY ARTERY PRESSURE CHRONIC HEART FAILURE

D.3.1 The Device
The Remon CHF system (ImPressure®, Remon Medical Technologies, Israel), a pressure monitoring system has two main components: the implant (Figure D.5a) and the Remon desktop system (Figure D.5b). The implant size is less than 3x3x16mm and it is made of titanium case that encapsulates the implant’s internal parts. A self-expandable nitinol anchor for positioning of the implant in the desired location within the pulmonary arterial vasculature is attached to the titanium case. The anchor design allows adaptation to a range of vessel sizes (15-25 mm in diameter). The implant is designed and calibrated to function in a pressure range of -10 to 100mmHg. The main parts of the implant are the energy exchanger, control chip, pressure sensor and energy reservoir. The Remon desktop system is an acoustic based system that transmits and receives signals from the Remon implant via a transducer that is in contact with the body. The desktop system also manages and stores the received signals and presents the pressure values measured by the Remon implant. When interrogated by the desktop system through a handheld transducer, the implant is activated and subsequently measures the pressure and transmits the data acoustically to the desktop system.

The implant is implanted in the right pulmonary artery (RPA) via a catheterization procedure using a percutaneous catheter-based delivery system. The fundamental of the delivery system is based on a commercial 10 French introducer and a pusher. The implant, which is pre-placed in a loading tube, is pushed using the pusher, through the introducer to the desired deployment site at the pulmonary artery of the patient.
D.3.2 Patient Population

The Implantable device was intended for patients with Chronic Heart Failure (CHF), graded as NYHA functional class III to IV.

D.3.2.1 Inclusion Criteria

CHF patients with NYHA class III/IV who had the ability to visit the clinic frequently during the six months following the implantation were considered for the study.

D.3.2.2 Exclusion Criteria:

Patients with known atrial or ventricular septal defects, with a Ventricular Assist Device (VAD) implanted, who were candidates for heart transplantation if it is deemed that they have a possibility of receiving a heart within the next 6 months, with any type of lead at the heart right side, with any terminal illness, or with a life expectancy of less than 1 year, post pneumonectomy, in atrial fibrillation, with abnormal coagulation profile, with severe chronic renal failure, with severe chronic obstructive pulmonary disease, with active myocarditis, whose RPA diameter is less than 15mm or more than 25mm (according to the CT angiography done before the initiation of the study) were excluded from the study.
D.3.3 Study Design and Follow Up

It was a first-in-man, prospective open clinical safety and functionality study. Ethics committee of SAL Hospital, Ahmedabad approved the study protocol and all the patients gave written informed consent for participation. Ten patients meeting the eligibility criteria (D.3.2) were enrolled for the monitoring device implantation in the RPA.

D.3.3.1 Pre Implantation Procedures:

- RPA was measured using three different techniques including CT angiography, echocardiography and invasive angiography for cross verification. Baseline demographic details, medical history, Left Ventricular Ejection Fraction by echocardiography, NYHA functional Class were recorded for all the patients.
- Baseline hemodynamic assessment was also obtained prior to implantation by Right Heart Catheterization. A control pressure measurement was also performed using a Millar Catheter which was considered as gold standard for comparison of the ImPressure® Device efficacy measurement.

D.3.3.2 Implantation Procedure:

The device was percutaneously implanted, using delivery system (Remon delivery system) at the desired implantation site in the RPA. The procedure was done via the internal jugular vein and utilized the 10 Fr Introducer sheath of the delivery system. The process was performed under fluoroscopic guidance. During and following the implantation, Fluoroscopy images of the introducer and implant in the pulmonary artery were collected to track the location of the implant.

3.3.3 Post Implantation Device Follow up:

- Immediately following successful implantation, pressure measurement was performed using the Remon desktop system. Simultaneous pressure measurements were done with the Millar...
catheter, which was used as the gold standard for evaluating the implant pressure measurement accuracy.

- All the implanted patients were followed every week for the 1st month followed by every month for 6 months post implantation for measurement of PAP to assess the functionality of the device.
- Right heart catheterization and measurement with Millar catheter was repeated at 6 months to verify the functionality and accuracy of the device.
- Clinical follow up of the patients was done till one year post implantation.

D.3.4 Safety Assessments
Safety data was collected acutely, at time of implantation and at long term during the one year follow up. Any serious adverse events or implant related complications till one year of follow-ups were recorded as safety endpoints of the study. CT angiography evaluation for visualization and patency of the device was done within six months.

D.3.5 Functionality & Accuracy Assessments
Functionality: Successful communication between implant and external system in 80% of the patients throughout the study follow up demonstrated the functionality of the device.
Accuracy: Comparison of measurements from implant with Millar catheter was done to find out the accuracy of the device. The implant should measure PA diastolic pressure with a total error of up to 10 mmHg as compared to the Millar control article.

D.3.6 Data Analysis
Baseline data was expressed as Mean±SEM and continuous variable as % patients or no. of patients. Regression analysis was derived to find out correlation between variables. A p<0.05 was considered to be statistically significant.
**Bland-Altman analysis:** The statistical analysis method that was used for evaluating the accuracy of the Remon CHF system is the Bland-Altman analysis for assessing the agreement between two measurement methods (Bland et al 1986). The pressure waveform was sampled simultaneously from the test (ImPressure® device) and control article (Millar Catheter). The pressure value of the test and control article was compared for the same time.

The difference between the estimations is plotted against the mean of the two estimations in the Bland-Altman plot (Magalski et al 2002). The estimation of pulmonary diastolic pressure from the two data sets as measured by the two systems (test device and Millar control article) was performed by a cardiologist.
D.4 MEASUREMENT OF DIURNAL VARIATION IN PULMONARY ARTERY PRESSURE NON INVASIVELY USING IMPLANTED DEVICE (REMON ImPressure®) IN CHRONIC HEART FAILURE

D.4.1 Patient Population
Ten Patients implanted with the device (Remon ImPressure®) for non-invasive monitoring of PAP were included in the study.

D.4.2 Measurement of diurnal variation in PAP
Post Implantation of the device, all the ten patients were given conventional CHF drug regime including digoxin, ACEi, diuretics, aspirin, etc) except any beta-blockers.

Following the implantation, all the patients were monitored ambulatoiy for the changes in PAP and other related hemodynamic parameters over a 24 hour cycle every week during the first month. PA systolic and diastolic pressure was monitored non-invasively using the implant every 2 hours during day time and every 3 hours during night. All patients received 1mg/2mg Lorazepam (Ativan®) at bedtime along with the conventional CHF therapies. Period from 8:00 Hrs to 20:00 Hrs comprised the daytime and 22:00 hrs to 6:00 hrs comprised nighttime for analysis.

D.4.3 Parameters Assessed
Systolic and diastolic PAP and other hemodynamic parameters like systemic BP, HR and O₂ saturation (SpO₂) was recorded during each observation. The mean of pressures from all four diurnal cycles was taken for analysis.

4.4 Data Analysis
Data for diurnal variation is expressed at Mean±SEM of the pressures. Paired Student’s t test was used for the comparison of daytime pressure with nighttime pressure. P value of <0.05 was considered to be statistically significant.

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D.5 EVALUATION OF EXERCISE CAPACITY AND VARIATION IN PULMONARY ARTERY PRESSURE FOLLOWING EXERCISE IN CHRONIC HEART FAILURE BY NON-INVASIVE MONITORING USING THE IMPLANTED DEVICE (Remon ImPressure®)

D.5.1 Patient Population
Ten Patients implanted with the device (Remon ImPressure®) for non-invasive monitoring of PAP were included in the study.

D.5.2 Study Procedures
Post implantation of the device, all the patients were on standard Drug Regime for CHF except beta-blockers. At the end of one month of implantation, after completion of the diurnal variation measurements, all the patients underwent TMT. PAP was measured using the implanted device before and after the TMT. Variation in PAP due to exercise and other TMT parameters were recorded.

D.5.3 Parameters Assessed
Systolic and Diastolic PAP and systemic blood pressure were recorded before and after TMT. The total exercise time, METS, and percentage of Target Heart rate (%THR) achieved and systemic BP were recorded.

D.5.4 Data Analysis
Data is expressed as Mean±SEM. Paired Student's t test was used to compare the data before and after TMT. A P<0.05 was considered of statistical significance.
D.6 EFFECT OF METOPROLOL XL (MXL) UPTITRATION ON PULMONARY ARTERY PRESSURE IN CHRONIC HEART FAILURE MONITORED NON INVASIVELY USING THE IMPLANTED DEVICE (Remon ImPressure®)

D.6.1 Patient Population
Ten Patients implanted with the device (Remon ImPressure®) for non-invasive monitoring of PAP were included in the study.

D.6.2 Study Procedures
Post implantation of the device, all the patients were given all conventional CHF therapies except beta-blockers. At the end of one month of implantation, after diurnal variation and TMT measurements were completed, all the patients were loaded with metoprolol XL (MXL) 25mg/d. MXL dose was uptitrated to 50mg/d, 100 mg/day till a target dose of 200mg/d every two weekly according to the MERIT HF criteria (MERIT-HF Study Group 1999). Pulmonary artery pressure was measured before every uptitration to evaluate the effect of MXL in these patients. The dose and duration of other conventional CHF therapy remain unaltered for the study period.

D.6.3 Parameters assessed
Systolic and diastolic PAP, systemic BP, HR and Oxygen saturation was measured before each uptitration. Uptitration of MXL at each visit was performed by the physician depending on the clinical and hemodynamic condition of the patient.

D.6.4 Data Analysis
Data is presented as Mean±SEM. Paired Student’s t test was performed to evaluate the efficacy of MXL treatment. A P<0.05 was considered to be statistically significant.
D.7 EFFECT OF METOPROLOL XL ON DIURNAL VARIATION, EXERCISE INDUCED VARIATION IN PULMONARY ARTERY PRESSURE AND EXERCISE CAPACITY IN CHRONIC HEART FAILURE MONITORED NON INVASIVELY USING THE IMPLANTED DEVICE (Remon ImPressure®)

D.7.1 Patient Population
All ten patients implanted with the device (ImPressure®) for monitoring PAP and who were loaded with MXL (section D.6.2) were included in this study.

D.7.2 Study Procedures
As per section D.5.2, all the patients were uptitrated with MXL according to merit-HF criteria.

D.7.2.1 Measurement of MXL effect on Diurnal variation in PAP:
Diurnal measurement cycle (as per section 4.2) was repeated after all the patients reached 100mg/d of MXL Dose. The PAP were compared with the baseline Diurnal variation (without MXL) to evaluate the effect of MXL on diurnal variation in PAP.

D.7.2.2 Measurement of MXL effect on exercise induced variation in PAP and exercise capacity:
TMT was done prior to each uptitration of MXL dose. Exercise duration, METS and PAP before and after exercises were evaluated at each uptitration and compared with the baseline.

D.7.3 Parameters Assessed
Systolic and diastolic PAP were measured non invasively using the implanted device for the diurnal cycle. Systemic BP, HR and SPO₂ were also recorded. PAP was also recorded before and after each TMT along with exercise time, METS, systemic BP and % THR.

D.7.4 Data Analysis
The data was expressed as Mean±SEM. Paired and Unpaired Student’s t-test was used to analyze the results. A p<0.05 is considered to be statistically significant.
D.8 ONE YEAR CLINICAL FOLLOW UP OF CHRONIC HEART FAILURE PATIENTS IMPLANTED WITH THE PULMONARY ARTERY PRESSURE MONITORING DEVICE (Remon ImPressure®)

D.8.1 Patient Population
All ten patients implanted with the device (ImPressure®) for monitoring PAP and who were loaded with MXL (section D.6.2) and monitored for various physiological changes (Diurnal variation and exercise) were included in this study.

D.8.2 Study Procedures
All the patients were followed at the end of one year. Clinical evaluation and echocardiography was done.

D.8.3 Parameters Assessed
LVEF was recorded and compared with baseline data. All patients were evaluated for occurrence of any clinical adverse events.

D.8.4 Data Analysis
The data was expressed as Mean±SEM. Paired Student’s t-test was used to analyze the improvement in ejection fraction. A p value <0.05 was considered to be statistically significant.
D.9 STATISTICAL ANALYSIS

All the statistical tests were conducted using biostatistical softwares like SPSS 12.0.1, Chicago, Illinois; and Primer of Biostatistics. Mean, standard deviations, S.E.M etc were estimated for the demographic data.

D.9.1 Linear Regression and Correlation Coefficient

It finds the equation of a straight line which best fits the data points in a scatter plot. The least-squares method is used to determine the parameters of this simple linear equation. When only two variables are selected, best-fit line is drawn over a scatter plot of the two variables. Correlation coefficients are provided for each equation to find out the correlation between the two variables.

D.9.2 Student's t-test

This is a procedure that tests the difference between the means of two populations for statistical significance (p<0.05). For two-sample, independent group tests, the groups can have equal or unequal sample sizes. A paired group t-test is available when two groups are matched or correlated. An unpaired t-test was performed at the end of study to find the differences between the two treatments on the parameters influenced by the treatments. The value of probability less than 5% (p<0.05) was considered as statistically significant.

D.9.3 Chi-square test

The Chi-square tests for contingency tables (eg. 2x2 tables) are categorized as non-parametric tests. It can be applied to nominal or categorical data. The Chi Square statistic compares the tallies or counts of categorical responses between two (or more) independent groups. The value of probability less than 5% (p<0.05) was considered as statistically significant.
D.9.4 Bland Altman Analysis

It is a statistical method designed for assessing agreement between two methods of clinical measurements (Bland et al 1986). Correlation coefficients are often inappropriate in comparison of clinical measurement of a new measurement technique with an established one. In this graphical method the differences (or alternatively the ratios) between the two techniques are plotted against the averages of the two techniques. The graph displays a scatter diagram of the differences plotted against the averages of the two measurements. Horizontal lines are drawn at the mean difference, and at the mean difference ±1.96 times the standard deviation of the differences. The plot describes agreement between two quantitative measurements. There's no p-value available to describe this agreement but rather a "quality control" concept. It is recommended that 95% of the data points should lie within ±1.96SD of the mean difference. The Bland and Altman plot may also be used to assess the repeatability of a method by comparing repeated measurements using one single method on a series of subjects.