

ORIGINAL ARTICLE

Extracardiac approach to functional mitral regurgitation: a cost-effective approach to addressing heart failure

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ABSTRACT

Background Heart failure is frequently associated with severely impaired ventricular function and manifests often with functional mitral regurgitation (FMR). This is a complex syndrome that is primarily due to abnormal function of the ventricular muscle in the presence of normal mitral leaflets and annulus. Present surgical treatment options approach the problem through mitral valve annulus and leaflets, rather than ventricular muscle. We developed a concept that provides a ventricular solution to this problem.

Methods After early proof-of-concept studies with polyester mesh, the BACE (Basal Annuloplasty of the Cardia Externally) device was developed along these lines—an adjustable silicone band that is implanted by means of slim polyester belt loops, and secured at the base of the heart. This device can be adjusted remotely under echocardiographic guidance, by inflating the inbuilt balloons that are connected to subcutaneous ports. Initial evaluation in animals showed long-term device safety. Safety and efficacy studies were performed in patients at 4 centres in India. They all underwent coronary artery bypass graft and implantation of the BACE device to correct mitral regurgitation (MR) on a beating heart.

Results The animal evaluation included 2 components—a group of animals with severe FMR induced by rapid ventricular pacing with long-term implants to establish safety and efficacy and a group of normal animals implanted in a GLP laboratory to ensure device safety for regulatory purposes. The patient population included 11 patients, with a mean age of 58. The mean presurgical left ventricular ejection fraction was 31.8%. The mean MR grade (3.3±0.6) improved to 0.6±0.5 post-BACE implantation (p<0.05). The mean number of bypass grafts was 2.5. The effective improvement

in MR was sustained at 6 months in the patients that had completed that duration of the study. All patients were followed up after surgery clinically and echocardiographically. Heart failure symptoms were reduced in all surviving patients with all of them being in NYHA Class I or II at 1-year follow-up.

Conclusions Epicardial application and adjustment of the BACE device can be performed safely on a beating heart with effective reduction in FMR and sustained benefit in preventing heart failure progression. This early clinical trial shows encouraging results with this approach. This is the first epicardial device for treatment of FMR that can be remotely adjusted. This capability suggests that correction of MR under echocardiograph guidance is feasible.

INTRODUCTION

Heart failure is a growing epidemic all over the world, especially as more patients survive myocardial infarctions. A significant number of these patients manifest with functional mitral regurgitation (FMR). Abnormal ventricular mechanics in the presence of normal mitral valve morphology is a feature of FMR. Mitral valve reconstruction in the form of repair with a restrictive annuloplasty and mitral valve replacement surgery are accepted as reasonable therapeutic options for the management of severe mitral regurgitation (MR) in patients with heart failure. The application and indications for this approach are not well defined.^{1–3} There is a reluctance to refer patients for valve repair or replacement with less-than-severe mitral insufficiency primarily due to the surgical risk associated with mitral valve procedures. Mitral valve repair or replacement in the setting of ischaemic heart disease carries a mortality risk of

2–6%.⁴ Surgical revascularisation alone does not consistently improve ischaemic MR.⁵ Current mitral valve procedures for FMR tend to be restrictive mitral ring annuloplasty, which addresses the mitral annulus, or mitral valve replacement, which addresses the mitral leaflets and annulus. However, the problem is predominantly due to dysfunction of the ventricle, not of the annulus or the leaflets.

To address the root cause of FMR, a new device called BACE (Basal Annuloplasty of the Cardia Externally) was developed. This device is applied to the epicardial surface of the heart. This paper describes the evolution of this device as a low cost and less invasive alternative to conventional surgery, which might range from valve replacement to ventricular assist device implants.

METHODS

BACE description

The BACE device is made up of three main components (figure 1):

1. A circular silicone band that is akin to a belt with four built-in inflatable chambers with connecting silicone tubes.
2. Slim polyester belt loops (4–5) around the band through which the BACE device is secured to the heart.
3. Subcutaneous port assembly with tubes that connect to the inflatable chambers. Normal saline is injected through the subcutaneous ports to inflate the built-in chambers of the tension band. The subcutaneous ports allow the addition to or removal of normal saline remotely without opening the chest wall.

The device is available in 1 cm increments from 21 to 41 cm to accommodate hearts of different sizes.

Evolution of the device: from concept to animal evaluation and human trials

The early concept of external basal support of the heart arose out of animal work we had performed to validate the concept of ventricular containment in

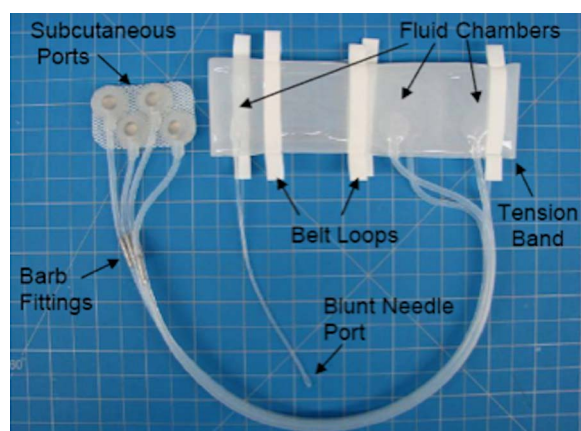


Figure 1 BACE (Basal Annuloplasty of the Cardia Externally) device with subcutaneous ports.

heart failure. We noticed that wrapping the base of the heart with polyester mesh, and tightening the circumferential mesh under echocardiographic guidance provided significant improvement in the degree of MR. Furthermore, this approach also contained the base of the heart, and maintained heart size, thereby controlling heart failure. Early research and development of this device required many iterations. Finally, the device described above was developed and evaluated in extensive animal experiments which included 24 sheep in 3 centres (Michael Reese Hospital, Chicago, Illinois, North Carolina State Veterinary School, Raleigh, North Carolina, St Joseph's Translational Research Institute, Atlanta, Georgia, USA). Thereafter, one group of nine animals with FMR due to dilation of the ventricles from rapid ventricular pacing were tested of which five survived.⁶ Another group of normal animals were studied for FDA GLP studies. The animal studies conclusively showed efficacy and safety of the BACE device at up to 6 months of follow-up, postimplant. There were no instances of coronary sinus thrombosis or coronary artery impingement in the animal studies.

Clinical feasibility study

The study protocol to evaluate BACE in human patients was submitted to the DCGI (Drug Controller General of India) for approval and to the notified bodies of the European Union. The study sites were selected and the study was approved by each site's Ethics Committee (IRB equivalent). All patients signed informed consent for BACE device implantation and the concomitant procedures. From December 2008 to February 2015, 23 patients were enrolled at 7 institutions based on protocol-specified inclusion and exclusion criteria (table 1).

All patients were implanted with the BACE device and after that coronary artery bypass graft (CABG) procedures were performed. At baseline, all patients had impaired ventricular function and greater than moderate degree of MR (table 2). The degree of MR was monitored carefully pre-BACE and post-BACE implantation using transoesophageal echocardiography (TEE). All the procedures were performed with the heart beating.

For purposes of formal separation of protocols, this report deals with the feasibility studies and detailed clinical course of the first 11 patients with the new version the BACE device. These 11 patients were enrolled because they had ischaemic or FMR that was more than moderate in degree. All these patients were being considered for CABG surgery.

The subsequent enrollees are part of an ongoing CE mark study.

Surgical procedure for BACE implantation and CABG

The pericardium was opened and the heart was inspected (refer to figures 2 and 3). A pericardial

Table 1 Major inclusion and exclusion criteria

Inclusions	Exclusions
▶ Adults of either gender from 22 to 80 years of age, inclusive	▶ NYHA Class IV after optimal medical therapy
▶ Grade 2 or more functional MR per 2D or 3D transthoracic echocardiography	▶ Structural abnormality of the mitral valve
▶ Symptomatic (NYHA Class \geq II) heart failure patient with MR	▶ High pulmonary artery pressures
▶ Participant undergoing concomitant CABG or aortic valve surgery	▶ Severe diastolic dysfunction of the left ventricle on echocardiography
▶ Normal mitral valve leaflets	▶ Transmural MI within 30 days of enrolment; non-ST segment elevation MI within 7 days of enrolment
	▶ Previous mitral valve surgery, CABG or other previous cardiac surgery that would preclude proper placement of the BACE
	▶ Chronic renal failure requiring dialysis

cradle was created to position the heart for better access. Baseline measurement of heart circumference and BACE device size selection typically were made before placing the patient on bypass, if cardiopulmonary bypass was used. The circumference of the heart at the base was measured with a piece of intravenous tubing that could be slipped around the heart at the atrioventricular groove and the measurement was repeated at least once for confirmation. After the first seven implants, we measured the circumference of the heart about an inch below the atrioventricular groove. Once the measurement was verified, a BACE device that was 1 cm larger than the measured size was selected. Attempts were made to ensure that the measurement was carried out with the patient at resting filling conditions, that is, before any cardiac manipulation for off-pump surgery or before connecting the patient to cardiopulmonary bypass. After selection of appropriate size, the BACE device was slipped around the heart and positioned at the atrioventricular groove, in such a way that a significant portion of the band subtended the subannular myocardium. Typically, the heart was lifted up and 'positioned' by Medtronic Starfish stabiliser applied close to or on the apex of the heart to facilitate this manoeuvre.

Table 2 Participant baseline characteristic summary

Age—year	55.7
Gender	10 males; 1 female
Left ventricular ejection fraction (%)	31.72 \pm 6.99
MR grade	3.32 \pm 0.46
NYHA class	III to IV

The belt loops were then secured on the atrial and ventricular side of the mitral annulus by placing one suture on each side of each belt loop with 4/0 polypropylene. The belt loops on the posterior aspect of the heart were secured before CABG, taking care to avoid any coronary arteries or veins. The inflatable balloon chambers are built into the tension band in such a way that they subtend the mitral component of the base of the heart. The tension band can be moved around to some extent, within the belt loops in a manner similar to a belt to optimise this positioning. As part of the design, the anterior part of the tension band is fitted with a much smaller chamber with a separate tube that can be filled with a blunt needle (blunt needle port—figure 1). If needed, this chamber can be inflated to lift the tension band off the pulmonary trunk and right ventricular outflow tract like a bridge. This chamber was not been inflated in any of the enrolled patients, but was necessary in the experimental animals.

The tubing from the BACE device was threaded through to the subcutaneous ports, while ensuring that the tubing was lying flat and that the tubes were not crossed. The tubes were cut to length, if required. Each BACE device tube was attached to the barb fitting of the corresponding subcutaneous port and secured with 2/0 silk ties. Subcutaneous ports were placed in the required location (typically in a small subcutaneous pocket is the left subcostal quadrant of the anterior abdominal wall). Using a 22 G Huber or standard sharp needle for each port, BACE device chambers were filled with saline. TEE was used to assess the reduction in MR dynamically. Tension on the BACE device was checked to ensure even distribution over the entire circumference. We made sure that the BACE device maintained contact with the ventricular walls throughout the cardiac cycle, with no evidence of haemodynamic compromise.

After BACE device positioning and securing the posterior belt loops, coronary artery grafting was completed. If the patients did not haemodynamically tolerate lifting of the heart, they were connected to cardiopulmonary bypass. Implantation of the BACE device was completed after conclusion of the bypass surgery, with securing of the anterior belt loops and inflation of the chambers. If there were any haemodynamic issues or arrhythmias, the chambers were not inflated acutely but were filled later through the subcutaneous ports once the patient was stable or the arrhythmias were controlled. In 4 of the 11 patients, anteroapical scars were plicated (n=2) or reconstructed (n=2). All of these were performed on a beating heart, four of whom had support with cardiopulmonary bypass.

Assessment of MR

In each centre, MR was assessed using intraoperative TEE performed by a trained cardiologist. MR was

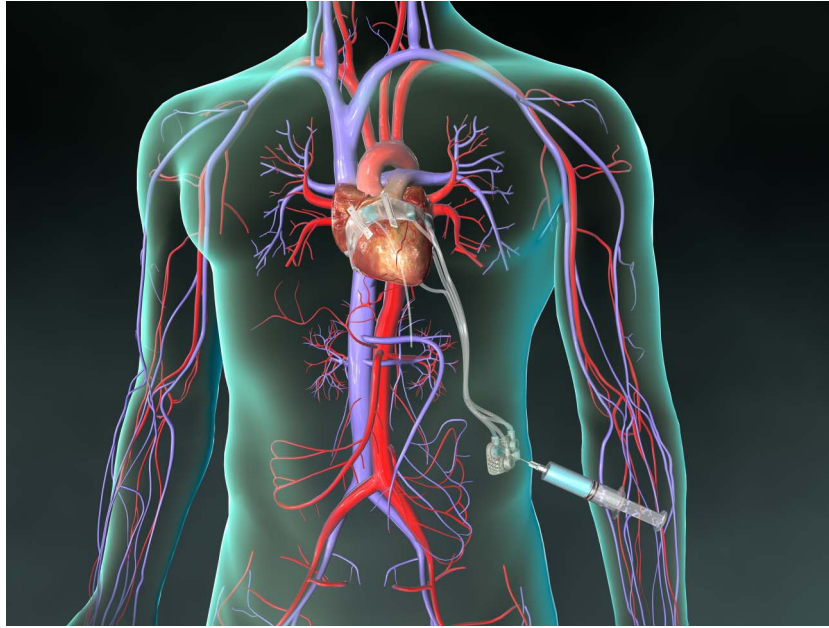


Figure 2 Schematic diagram of the deployed BACE (Basal Annuloplasty of the Cardia Externally) device and subcutaneous ports.

assessed and quantified visually with a combination of PISA, jet velocity and vena contracta. Evaluation of MR was performed at the end of the procedure, using TEE and the mean blood pressure was raised to pre-operative levels. To test the durability of MR reduction, the mean blood pressure was raised to 90–100 mm Hg for a few minutes, with a combination of vasopressors, volume or both. This assessment was performed immediately after completion of the procedure, either during or after chest closure. MR was graded on a 5-point scale from 0 to 4. While this may not be state-of-the-art, this grading system was considered the most reliable method of assessment by the advisory board at the time the protocol was drafted in 2007.

All patients are being followed clinically and by echocardiograms at 1, 3, 6 and 12 months post-BACE

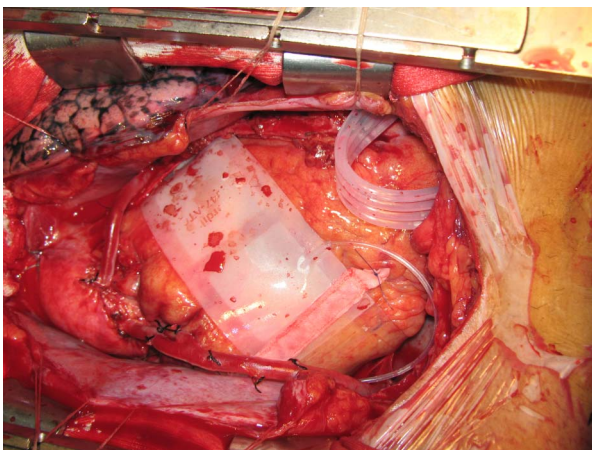


Figure 3 Intraoperative photograph of the BACE (Basal Annuloplasty of the Cardia Externally) device implant and coronary artery grafts.

implantation surgery. In the perioperative period, patients were monitored and managed haemodynamically according to the existing standards of care for CABG surgery.

RESULTS

All patients completed 6-month and 12-month follow-up. The first patient completed 84-month follow-up recently. [Table 3](#) outlines the demographic and preoperative characteristics of the patients.

Surgical outcomes

There were no clinically significant problems related to the implantation procedure with the BACE device. All patients underwent CABG using a left internal mammary artery and saphenous vein grafts (range 1–4 grafts). Four patients had perioperative placement of an intra-aortic balloon pump (IABP) for haemodynamic support. The indication for IABP use was in accordance with customary practice and CABG surgical protocol at each institution. There were no postoperative infarcts as assessed by a combination of cardiac enzymes (CK-MB and Troponin) and ECG changes.

Two patients had significant perioperative complications that were not related to the BACE device or procedure. One patient had a coagulopathy and had to be re-explored 8 hours postsurgery for bleeding that seemed to be coming from the back of the heart where the myocardium had been explored for a graft to a small circumflex marginal artery. The heart had to be lifted up to inspect the area. For better visualisation, the BACE device was cut through the silicone tension band and removed without incident. The patient recovered well. This patient had a dramatic reduction in the degree of MR after the BACE device

Table 3 Demographic summary

Participant ID	1-01	1-02	1-03	1-04	1-05	1-06	1-07	2-01	2-02	3-01	4-01
Age (years)*	50	51	67	54	50	68	52	55	45	68	53
Gender	M	M	M	M	F	M	M	M	M	M	M
Diagnosis	IMR	IMR	IMR	IMR	IMR	IMR	IMR	IMR	IMR	IMR	IMR
Other cardiac pathology											
MI	X ²	X		X				X		X	X ³
CAD	X	X	X	X	X	X	X	X	X	X	X
LV dysfunction	X	X	X		X	X		X		X	X
Cardiomyopathy	X							X			X
Angina	X		X		X	X	X		X		X
Other pathology											
Type 2 diabetes	X							X		X	
Hypertension	X	X	X		X	X	X				X
Hypercholesterolaemia	X	X	X	X	X	X	X				
DVT			X								
CKD										X	

*On date of implant.

CAD, coronary artery disease; CKD, chronic kidney disease; DVT, deep vein thrombosis; IMR, ischaemic MR; MI, myocardial infarction.

implantation and CABG. After removal of the device, however, the degree of MR recurred after discharge to the preoperative level at follow-up echocardiography 3 months later. The other patient developed profound leg ischaemia related to balloon pump insertion, ~12 hours postsurgery. When the balloon pump was removed, the patient suffered a significant reperfusion injury with severe lactic acidemia and peripheral vascular collapse, which ended in a fatal arrhythmia.

The mean number of bypass grafts was 2.55 ± 0.68 . The risk scores (Logistic Euroscore and STS morbidity and mortality) were assessed for all patients. The mean Logistic Euroscore risk score for mortality was 16.78% and the combined predictor for morbidity and mortality by the STS risk model was 26.14%. The mean intensive care unit length of stay was 4.67 days. **Table 4** provides the risk score for each patient, using Euroscore and STS risk models.

MR grade

Preoperatively, after implantation of the BACE device and dynamic adjustment under echocardiographic guidance, we were able to reduce the grade of MR to trivial or trace in all patients. Intraoperative echocardiography showed that MR had been reduced from a mean of 3.3 ± 0.4 preoperatively (**table 2**) to 0.6 ± 0.5 postoperatively ($p < 0.05$; **figure 4**). The effective improvement in MR was sustained in the ongoing assessments in the nine patients who have the device in place.

NYHA functional status

Preoperatively, the mean NYHA functional status in these patients was 3.14, and with all patients were either in Class 3 or 4. The functional class had improved significantly at 3 and 6 months postoperatively, to I or II in all surviving patients.

Table 4 Patient risk profile at baseline

	EuroScore (logistic)	STS risk model (morbidity and mortality)
Patient 1	29.59	22.6
Patient 2	3.67	18.2
Patient 3	18.86	20.1
Patient 4	2.27	17.6
Patient 5	5.4	17.3
Patient 6	20.86	28.7
Patient 7	3.94	19.6
Patient 8	28.5	42.7
Patient 9	2.27	13.2
Patient 10	13.8	31.6
Patient 11	55.43	55.9
Mean	16.78	26.14
SD	16.47	12.92

DISCUSSION

Mitral valve repair or replacement requires an intracavitary cardiac surgical procedure. These major cardiac procedures, performed with the aid of cardiopulmonary bypass and cardioplegic arrest, are associated with significant complications and risks. Consequently, mitral valve repair is primarily reserved for patients with severe MR. As moderate MR appears likely to progress and is associated with adverse outcomes, particularly in the context of ischaemic heart disease,^{7–10} a means of addressing the mitral valve with a favourable risk-to-benefit ratio for moderate MR is needed.

We reported our earlier experience with the original concept for BACE device using a polyester surgical mesh in patients with functional MR that were undergoing complex cardiac surgery and showed that the BACE approach is effective, durable and safe.¹¹

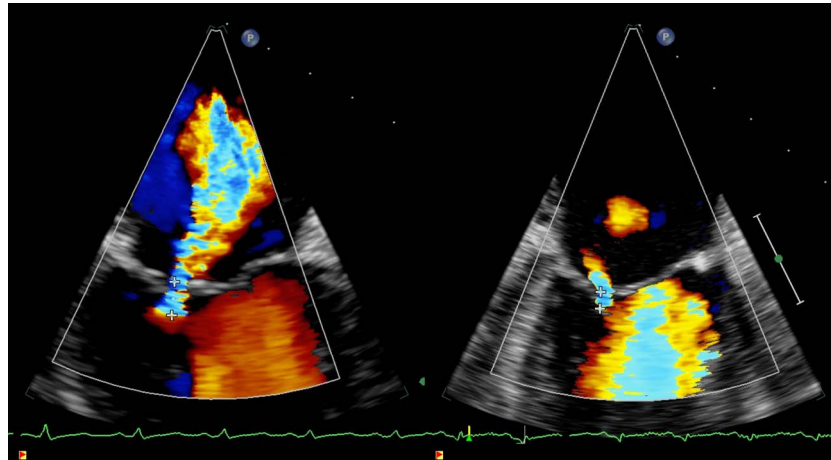


Figure 4 PISA measurement on transoesophageal echocardiography, preimplant and postimplant.

Though this demonstrated proof of concept, polyester surgical mesh is not easily adjustable after implantation. Fibrous tissue reaction and adhesions to the mesh make it extremely difficult to remove the device later, if indicated. The current BACE device is designed using dimethylsilicone for the tension band, which limits tissue adhesion. The silicone allows building the inflatable chambers for customised application of pressure on the mitral valve annulus and subannular muscle, which helps correct MR by impacting on different areas of the muscular annulus and subannulus. The thin polyester belt loops around the tension band allow anchoring of the device to the surface of the heart. In addition to all this, the notion of remote adjustability with a syringe and a needle under echocardiographic guidance is very attractive and convenient.

In an elegant set of experiments, Levine showed that the mechanism behind ischaemic MR was unlikely to be corrected by restrictive annuloplasty alone.¹² Failure of ring annuloplasty in ischaemic MR has been shown to be due to persistent tethering of the posterior leaflet,¹³ though it must be remembered that the ‘tethering’ is an echocardiographic finding rather than a pathological fibrous tethering.

When one considers the long-term data from the Acorn CorCap trial in heart failure patients, survivals were similar between the treatment and control groups, demonstrating no late adverse effect on mortality. The treatment group had significant reductions in left ventricular end-diastolic volume ($p=0.029$). In a subgroup of patients with intermediate left ventricular end-diastolic dimensions, there was a significant reduction in the Kaplan-Meier estimate of the freedom from the composite end point of death and major cardiac procedures ($p=0.04$).¹⁴ This was seen in the first group of patients undergoing BACE device implants also.

The mechanism behind a broad belt-like support at the level of the atrioventricular groove is threefold:

1. External tightening of the mitral annulus and possibly the tricuspid annulus,
2. Support to the subannular myocardium below the mitral and tricuspid valves,
3. Inward pressure on the akinetic or dyskinetic myocardium in the inferobasal ventricular wall, allowing better coaptation of the mitral valve leaflets.

The current BACE device can positively and selectively deform the areas of the mitral annulus and subannular myocardium (septolateral myocardium or inferobasal ventricular wall). This has an additional effect in reduction in the posterior leaflet ‘tethering’ and promoting a better coaptation of mitral leaflets.

In this prospective cohort study with the current BACE device, external stabilisation of the cardiac base along with support of the subannular myocardium with the BACE device in addition to the remote adjustability is associated with significant improvement in mitral valve function in patients with moderately severe to severe FMR. Sustained improvement in MR grade in patients who had BACE device implantation was seen in the postoperative period and later on clinical and echocardiographic follow-up.

Another important feature of this device is that the adjustment and titration is performed dynamically under echocardiographic guidance. If further adjustment is required at a later date, that can be achieved through the subcutaneous ports. In extremely high-risk patients where there is concern about rapid correction of MR during surgery, it is possible to slowly inflate the device chambers with saline through subcutaneous ports over a few days.

No safety issues related to the BACE device or procedure emerged in this study, which enrolled high-risk patients with triple-vessel coronary artery disease, congestive heart failure and MR. In patients with significant coagulopathy requiring re-exploration of the chest, the BACE device was easily and safely removed without incident, allowing the surgeon to inspect the back of the heart clearly. Though this patients had reduction in MR with BACE device in place, on

device removal, the MR recurred as evidenced by the echocardiogram follow-up at 3 months. If we can apply the analogy of Koch's postulates of cause and effect for infectious disease, this is a good example of a treatment effect with the BACE device that was lost on removal of the device.

The results of this study should be interpreted in the context of a few limitations; small sample size, inadequate assessment of potential confounding variables (for instance, role of myocardial revascularisation after CABG in functional improvement of patient), lack of direct comparison with the current practice of open-heart mitral valve reconstruction or replacement since BACE device implantation is a closed-heart procedure without the requirement for cardiopulmonary bypass. These shortcomings notwithstanding, the findings in this study provide encouragement in terms of safety, which allowed us to pursue a larger study to define efficacy and long-term effectiveness of this approach.

Price differences

The BACE device costs about \$400 to manufacture in small batches and is likely to be sold for around \$1000. A mitral valve prosthetic ring to enable mitral repair costs about \$1500, while a prosthetic valve costs about \$5000. A biventricular pacing device for cardiac resynchronisation therapy is typically sold for around \$15 000. A long-term, durable ventricular assist device costs about \$85 000. No meaningful comparison can be made between the various treatment options here because the numbers of implants with the BACE device are small.

The main advantages of the BACE device are:

1. The less invasive nature of the device, which might help avoid some complications associated with intracavitary approaches (eg, coagulopathy, endocarditis, stroke);
2. The opportunity for dynamic assessment of the mitral and tricuspid valves while adjusting the BACE device around the heart;
3. Support of the ventricular myocardium below the mitral annulus; and
4. The possibility of implanting the device off-pump or on a beating heart.
5. Potentially lower cost compared with conventional mitral valve repair or mitral valve replacement in terms of treatment of MR.
6. Significant cost savings, if compared with VAD implants for the purpose of heart failure management.

Contributors JR and KT worked on the concept of the publication and wrote most of it. CP and RJ contributed to patient recruitment, procedure development and writing up the details of the technical issues.

Competing interests JR is a cofounder of Phoenix Cardiac Devices with founders' equity stake. KT is the Chief Research Officer for Phoenix Cardiac Devices.

Patient consent Obtained.

Ethics approval India—approved by DCGI and each of the following states—Tamil Nadu, Delhi, Karnataka, Andhra Pradesh.

Provenance and peer review Not commissioned; externally peer reviewed.

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