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Passive ventricular constraint amends the course of heart failure: a study in an ovine model of dilated cardiomyopathy

J.M. Power[a,*], J. Raman[b], A. Dornom[a], S.J. Farish[c], L.M. Burrell[a], A.M. Tonkin[a], B. Buxton[b], C.A. Alferness[d]

[a]*Department of Medicine, University of Melbourne (Austin and Repatriation Medical Centre Campus), Melbourne, Australia*
[b]*Department of Cardiothoracic Surgery, University of Melbourne (Austin and Repatriation Medical Centre Campus), Melbourne, Australia*
[c]*Department of Public Health and Community Medicine, University of Melbourne (Parkville Campus), Melbourne, Australia*
[d]*Acorn Cardiovascular Inc., St. Paul, MN, USA*

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Abstract

Objective: Dilated cardiomyopathy (DCM) is associated with a progressive deterioration in cardiac function. We hypothesised that some of the deleterious effects of DCM could be reduced by mechanically limiting the degree of cardiac dilatation. **Methods:** A Transonic 20A cardiac output (CO) flow-probe was implanted in the pulmonary artery of 12 adult (52±4 kg) sheep. Early heart failure was created by rapid right ventricular (RV) pacing for 21 days at a rate which resulted in an initial 10% decrease in CO (to a maximum of 190 bpm). A custom polyester jacket (Acorn Cardiovascular, St Paul, MN) was then placed, via a partial lower sternotomy, on the ventricular epicardium of all sheep. Animals were randomised either to jacket retention (wrap) or removal (sham). Pacing was recommenced at a higher rate (that initiated a further 10% decrease in CO) for 28 days. Haemodynamic and echocardiographic parameters were determined at baseline, implant and at termination. **Results:** At termination, the left ventricular fractional shortening was significantly higher ($p=0.03$), the degree of mitral valve regurgitation lower (scaled 0–3) ($p=0.03$) and the left ventricular long axis area smaller ($p=0.02$) in the wrap animals compared with sham. **Conclusions:** In this model of heart failure, ventricular constraint with a polyester jacket diminished the deterioration in cardiac function associated with progressive dilated cardiomyopathy. These results suggest that maintainance of a more normal cardiac size and shape may be beneficial in patients with dilated cardiomyopathy.

Keywords: Heart failure; Cardiomyopathy; Ventricular function; Remodelling

This article is referred to in the Editorial by S. Goldstein (pages 468–469) in this issue.

1. Introduction

Despite advances in pharmacological therapy, heart failure (HF) remains an unresolved problem in a large patient population. It has been suggested that preventing further ventricular dilatation may impede the progressive deterioration in cardiac function associated with heart failure [1]. Initial interest in this hypothesis emanated from investigations of the mechanisms of the apparent improvement in functional status observed in HF patients who have undergone dynamic cardiomyoplasty [2]. Some results have assigned a dominant role for this outcome to the augmentation of the contractile function of the heart by the paced muscle wrap [3,4], while others have suggested that it is the constraining effect of the wrap on the dilating ventricles that is important [5,6]. The latter hypothesis has been examined in several studies in animal models of heart failure and all have found, in varying degrees and formats, that passive ventricular constraint alone improves outcome in comparison to control [1,7,8]. In one, using a canine

*Corresponding author. Tel.: +61-3-9496-4090; fax: +61-3-9496-4099.
E-mail address: jmp@austin.unimelb.edu.au (J.M. Power)

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model of rapid pacing induced heart failure, a functionally static cardiomyoplasty wrap procedure performed on failed hearts prevented the further remodelling that would normally be expected with continued rapid pacing [1]. This finding complemented other studies in which cardiomyoplasty was performed prospectively in normal hearts, later paced into failure. In the other two studies the heart was wrapped prior to induction of heart failure [7,8].

If indeed passive ventricular constraint can significantly slow or stabilise the usual remodelling process associated with HF, then a synthetic wrap will considerably simplify the procedure in comparison with the major surgical procedure of cardiomyoplasty. Two recent studies have looked at this proposal. In both, the ventricles of normal animal hearts were bound with synthetic membranes and heart failure was induced. In one study, failure was induced by rapid pacing [8] and in the other, by intracoronary artery doxorubicin [7]. In both studies, passive ventricular constraint prevented most of the subsequent ventricular dilatation and preserved much of the left ventricular function compared with nonwrapped animals.

The purpose of this study was to examine the concept of passive ventricular constraint as a treatment for HF in animals that were already in HF at the time of implantation.

We utilised an ovine model of tachycardia-induced progressive heart failure and a purpose designed biocompatible fabric jacket and compared cardiovascular function and structural remodelling in sham operated animals with animals that had undergone a wrap procedure.

2. Methods

The protocol for this study was approved by the Animal Ethics Committee of the Austin Hospital under the guidelines published by the National Health and Medical Research Council of Australia and conforms with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.1. Initial surgical preparation

Twelve adult merino sheep (mean weight 52±4 kg) were anaesthetised with propofol 2 mg/kg and ventilated with halothane and oxygen. A single 3-cm incision was made in a left intercostal space and a Transonic (Transonic Systems, Ithaca, NY) 20A cardiac output flow-probe was positioned around the pulmonary artery. Permanent indwelling polyethylene catheters were implanted in a carotid artery and a jugular vein. The flow-probe leads and catheters were tunnelled subcutaneously to the dorsum of the animals. A steroid-tipped bipolar ventricular pacing lead (Capsure® SP, Model 4024, Medtronic, MN) was placed transvenously in the apex of the right ventricle. The proximal lead end was connected to a modified 'data block', which allowed the right ventricle to be paced from wires exiting at the animals dorsum with modified external pacemakers (Medtronic model 5880A).

Antibiotics (1 g ampicillin and 80 mg gentamicin sulphate, both i.v.) were given prophylactically immediately after surgery and for 3 days following. Flunixin meglumine, 50 mg i.m., was given prior to surgery and post-operatively once daily for two days as an analgesic and anti-inflammatory agent.

2.2. Data collection

2.2.1. Echocardiography

Images of the left ventricle (LV) and the left atria (LA) were obtained by right-sided trans-thoracic echocardiography under intravenous anaesthesia (propofol 0.1 mg/kg/min+ketamine 0.2 mg/kg/min) using a 3-MHz probe and a Sonos 1000 unit (Hewlett-Packard). The planimetered LA and LV cross-sectional areas were obtained from a uniform long axis view in diastole and were calculated automatically from a scrolled endocardial outline. Left ventricular fractional shortening was determined in M mode from a short axis view of the LV just below the insertion of the papillary muscles. The degree of mitral valve regurgitation was assessed by colour Doppler and scored, (0–3), in degrees of increasing severity. The images were measured independently by two experienced observers and the mean determined.

2.2.2. Haemodynamic parameters

The animals were anaesthetised (propofol 0.1 mg/kg/min+ketamine 0.2/kg/min) and ventilated with room air supplemented with oxygen. A catheter introducer sheath was placed in a carotid artery and a 5F micro manometer-tipped catheter (Millar Instruments) was introduced into the LV. Haemodynamic signals from these catheters and from the cardiac output (CO) flow-probe together with an ECG recording were processed, digitised and recorded using a MacLab system (MacLab 8, ADI Instruments) and a Macintosh computer. Derived parameters were computed online using this system.

2.2.3. The model of dilated cardiomyopathy and heart failure

The rapid ventricular paced animal model of HF has been widely used and is considered to display many of the features of HF in patients [9]. In our derivative of this model we, as have others [10], utilised the relationship between the rate and duration of pacing initially to create a model of early HF and later to intensify the severity of cardiac dysfunction. In previous pilot studies we found that the response of individual animals to rapid ventricular pacing varies i.e. the relationship between the level of tachycardia induced HF and the pacing rate differs particularly when the desired outcome is not severe endstage

HF. In order to standardise the degree amongst the animals at each stage of the study, we utilised the values from the continuous CO measurement to modify the pacing rates according to the individuals acute response to rapid pacing.

The initial pacing rate was determined as follows. After a post surgical 10–14 day recovery period the CO in normal sinus rhythm (NSR) over a period of 2 min was measured on a minimum of ten different occasions and the mean determined. Pacing was commenced (at twice pacing threshold, range 2–6 ma) and the rate increased, to a maximum value of 190 bpm, until the mean paced CO was 90% of the mean CO in NSR (Rate A). After 21 days of pacing at Rate A there were significant changes in cardiovascular function (see below) indicative of moderate or early heart failure.

In order to intensify the degree of HF a second rate (Rate B) was determined immediately prior to the wrap or sham procedure in the same manner as Rate A was previously determined. Twenty four hours after, the surgery pacing was recommenced at Rate B and continued for 28 days.

2.2.4. Surgical procedure in early heart failure (wrap or sham procedure)

In this procedure a biocompatible polyester mesh fabric jacket (Acorn Cardiovascular, St Paul MN), shaped to cup the ventricular apex and with a longitudinal opening for size adjustment, was placed around both ventricles from the apex to the atrio-ventricular junction. The jacket was retained in six (wrap) animals and removed in the other six (sham) animals.

The animals were induced with intravenous propofol (2 mg/kg), intubated and ventilated with 100% oxygen. General anaesthesia was maintained with intravenous propofol (6 mg/kg/h) plus ketamine (3 mg/kg/h). The animals were placed in dorsal recumbency. A lower partial sternotomy was performed, which extended from the xiphoid process to approximately two-thirds of the way to the thoracic inlet. The pericardium was incised longitudinally and a pericardial cradle was formed (Fig. 1). The myocardial jacket was guided over the heart and fixed posteriorly with large titanium ligature clips (Ligaclips® Ethicon) to the parietal pericardium at the level of the atrioventricular groove. The anterior surface of the jacket was sutured to the pericardium, also above the atrioventricular groove with 5/0 sutures (Prolene® Ethicon). The jacket was then wrapped firmly around the heart and the cut edge sutured (2/0 Prolene® Ethicon) and trimmed of excess material. At this stage, the jacket was removed from the sham animals. The pericardium was closed in all animals with 5/0 sutures (Vicryl® Davis and Geck). The sternotomy was closed in layers: initially with stainless

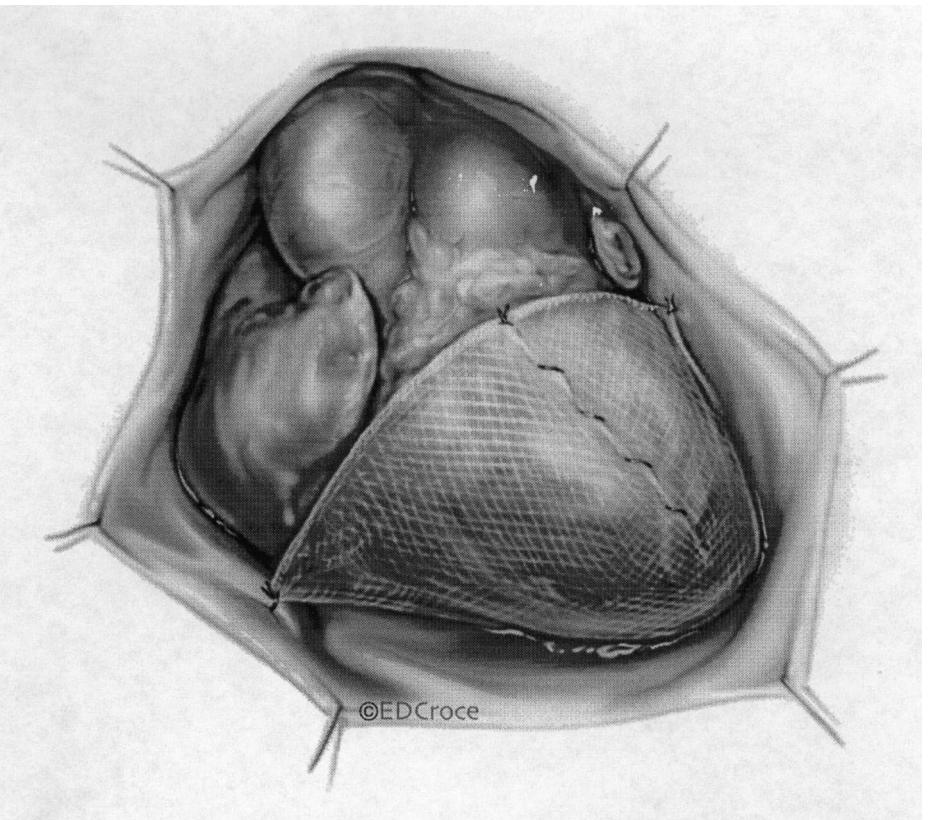

Fig. 1. Position and attachment of the jacket on the epicardial surface of the two ventricles. The Ligaclips® are on the undersurface of the heart and therefore not visible.

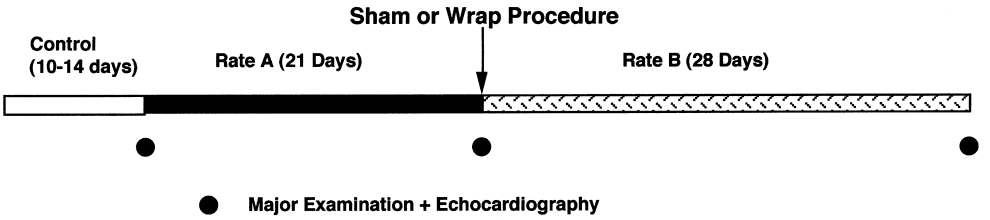

Fig. 2. Schematic representation of the experimental protocol showing periods of pacing at Rate A and Rate B and the data collection points.

steel wire sutures, 2/0 Dexon® (Davis and Geck) in the sternal tissue pad and 1 Ethilon® (Ethicon) skin sutures. Antibiotics (1g ampicillin and 80 mg gentamicin sulphate, both intravenously) were given prophylactically immediately after surgery and for 3 days following. Flunixin meglumine, 50 mg i.m., was given prior to surgery and post-operatively once daily for two days as an analgesic and anti-inflammatory agent.

2.3. Experimental protocol

A schema of the experimental design is shown in Fig. 2. Detailed descriptions of the procedures are given above. After the animals had recovered from an initial surgical preparation they were rapid paced for 21 days to induce early heart failure. A wrap or sham procedure was then performed and pacing continued for an additional 28 days at a higher pacing rate. Animals were then euthanased. A haemodynamic and echocardiographic examination was performed at the end of the baseline period (approximately 14 days after the initial surgical preparation), after 21 days of pacing at rate (A) (immediately prior to the wrap or sham procedure) and after 28 days of pacing at rate (B) (termination).

3. Statistical analysis

Data was analysed using a computerised statistical package (SAS Inst, Gary NC). The two groups (sham and wrap) were compared at baseline, wrap or sham procedure and at termination, using the Wilcoxon rank-sum test. Differences within the wrap and sham treatment groups from control to wrap/sham procedure and from wrap/sham procedure to termination were compared using paired Student's *t*-test. Results are expressed as mean±SD and a p value of <0.05 was considered significant.

4. Results

The hearts from the wrap animals were examined at post mortem at the end of the study. In all animals, the position of the jacket remained unchanged from implantation and both ventricles were entirely enclosed. Mean data from animals at baseline and after 21 days of pacing of pacing at Rate (A) and after a further 28 days of pacing at Rate (B) are shown in Table 1. There was no significant differences *between* the wrap and sham groups at baseline. Similarly, after 21 days of pacing at Rate A the parameters from both groups were not significantly different except for $-dP/dt_{max}$. There were, however, significant differences *within* groups with significant changes in cardiac function and structure (Table 2). Left ventricular contractility, expressed as LV fractional shortening (LVFS) decreased by approximately one third in both groups while the LV long axis area more than doubled.

After 28 days of pacing at Rate B there were significant changes *both* between and within the groups (Table 1). Over this pacing period cardiac function deteriorated

Table 1
Between group comparisons of haemodynamic and echo cardiographic parameters

Parameter	Baseline			Paced 21 days at Rate A			Paced 28 days at Rate B		
	Pros. sham	Pros. wrap	*p*	Pre-sham	Pre-wrap	*p*	Sham	Wrap	*p*
RV pacing rate (bpm)	N/A	N/A		188±4	190±0	NS	206±5	213±4	NS
Normal sinus rhythm (bpm)	75±18	87±18	NS	77±15	93±20	NS	104±24	101±22	NS
Arterial pressure (mm Hg)	94±8	85±14	NS	95±9	87±20	NS	88±6	89±18	NS
Mitral valve regurgitation (0–3)	0	0		0.33±0.05	0	NS	2.7±0.52	0.7±0.82	0.03
$+dP/dt_{max}$ (mm Hg/s)	1060±265	1102±487	NS	677±160	863±181	0.02	595±115	676±276	NS
$-dP/dt_{max}$ (mm Hg/s)	−1226±239	−1604±432	NS	−839±73	−1297±336	NS	−997±296	−915±197	NS
Cardiac output (l/min)	6±1.3	6±1.2	NS	4.2±0.78	4.1±1.2	NS	3.53±1.3	3.33±0.81	NS
Stroke volume (ml)	75±14	65±5	NS	55±16	46±14	NS	36±15	34±10	NS
Minimum LV pressure (mm Hg)	3±2.48	2±3.48	NS	9±2.93	6±4.62	NS	16±5.53	9±3.69	0.027
SVR[a] (dynes/s/cm^{-5})	1437±346	1256±285	NS	1827±364	1853±881	NS	2167±810	2232±657	NS

[a] SVR=Systemic vascular resistance.

Table 2
Within group comparisons of haemodynamic and echo cardiographic parameters[a]

Parameter	A	B	A	B
LVFS (%)	$p=0.03$	$p=0.03$	$p=0.02$	NS
LV Area (cm^2)	$p=0.02$	$p=0.008$	$p=0.02$	NS
RV pacing rate (bpm)	N/A	$p=0.004$	N/A	$p=0.001$
Normal sinus rhythm (bpm)	NS	NS	NS	NS
Arterial pressure (mm Hg)	NS	NS	NS	NS
Mitral valve regurgitation (0–3)	N/A	$p=0.02$	N/A	NS
$+dP/dt_{max}$ (mm Hg/s)	$p=0.01$	NS	NS	NS
$-dP/dt_{max}$ (mm Hg/s)	$p=0.007$	NS	$p=0.04$	NS
Cardiac output (l/min)	NS	NS	NS	NS
Stroke volume (ml)	$p=0.03$	$p=0.002$	$p=0.02$	NS
Minimum LV pressure (mm Hg)	$p=0.03$	$p=0.03$	$p=0.04$	NS
Systemic vas. resist. (dynes/s/cm^{-5})	NS	NS	NS	NS

[a] Columns A are the results of a comparison within the respective groups between values for baseline and after 21 days of pacing at Rate (A). Columns B are the results of a comparison within the respective groups between values after 21 days of pacing at Rate (A) and after 28 days of pacing at Rate (B).

significantly in the sham group compared with the wrap group. At termination LVFS was halved (Fig. 3) and LV long axis area increased by one third in the sham animals (Fig. 4). A significant degree of mitral regurgitation developed in these animals and minimum LV pressure was higher. In contrast, in those animals who underwent the wrap procedure, no significant differences in measured parameters occurred during this second pacing period and very little mitral regurgitation was evident. Overall, there were no significant differences in CO between the two groups.

The two RV pacing rates (Rates A and B) were similar for both groups, however, Rate (B) was significantly higher than Rate (A) in both. Therefore, the effects of a similar mechanism for the intensification of the level of HF produced very different results, which was dependent on the presence of passive ventricular constraint from the fabric wrap.

5. Discussion

Progressive ventricular remodelling, especially dilatation of the left or both ventricles, is a fundamental finding in heart failure and many of the mechanisms of terminal failure are directly related to ventricular enlargement. For the ultimate therapeutic goal of reversing remodelling to occur, cardiac enlargement must first be halted. There are two broad ways this can occur: either indirectly by reversing the remodelling pattern, or directly by surgical reduction. The surgical options currently in use for the treatment of heart failure are based on one or both of these pathways. Direct intervention by surgical reduction of the left ventricle has produced inconclusive results with a decline in cardiac function and resumption of left ventricular dilatation following initial post surgical improvement [11,12]. There are a number of procedures which are based on indirect intervention in the remodelling process. Mitral

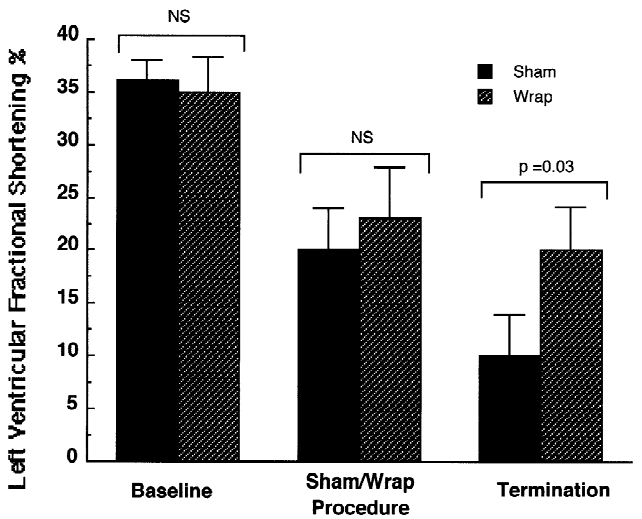

Fig. 3. Mean (±SD) left ventricular fractional shortening at baseline, after 21 days pf pacing at Rate A and following an additional 28 days of pacing at Rate B.

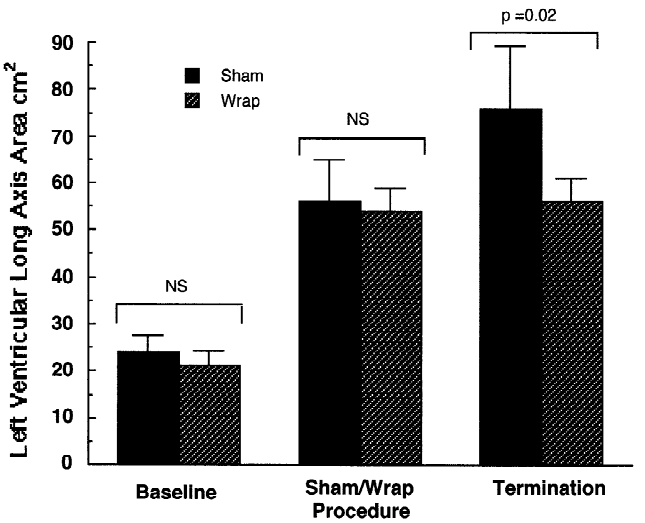

Fig. 4. Mean (±SD) left ventricular long axis area at baseline, after 21 days of pacing at Rate A and following an additional 28 days of pacing at Rate B.

valve regurgitation is a common finding and is associated with a poor prognosis in advanced heart failure. Radical mitral valve annuloplasty has been shown to stabilise cardiac function in some of patients [13]. A broader hypothesis is that if some of the workload of a compromised heart could be relieved, this would allow for reverse remodelling to occur. There is evidence that the chronic implantation of ventricular assist devices may initiate reverse remodelling, although the technology is complex and restricted to relatively few centres [14]. A number of techniques have been devised to co-opt the contractile forces of paced skeletal muscle to enhance circulatory function, however only dynamic cardiomyoplasty has progressed to clinical use. The hypothesis of dynamic cardiomyoplasty was that the failing contractile function of the heart would be augmented by the paced contractions of an electrically transformed latissimus dorsi muscle wrap. Although difficult to quantify, there is evidence that this treatment does improve the condition of many HF patients and that it is associated with demonstrable reverse remodelling [2]. The mechanism behind this improvement, augmented contractility or the constraining effect of the muscle wrap, is subject to debate [15]. A recently published animal study provides evidence that ventricular constraint may play a major role, however in the same report doubt is expressed whether a synthetic wrap would have the structural characteristics necessary to duplicate the protective function of the muscle girdle [1]. Two recent studies [7,8] have looked at this question in two different animal models of heart failure. In both, the normal heart was wrapped prior to the evolution of HF. This has little clinical relevance but they were able to show that this procedure is feasible, stopped much of the increase in LV volume and some of the decrease in function which was exhibited in control animals.

In our study, which utilised an animal model of progressive heart failure, we have shown that passive ventricular constraint with a purposely designed synthetic wrap is feasible and halts the decline in cardiac function and the increase in LV dimensions observed in the parallel sham operated controls.

The work of Sabbah et al. [16–19] provides a partial explanation for the decline in cardiac function that is associated with the assumption of a global profile in dilated cardiomyopathy. They have shown that the severe mitral regurgitation associated with the rounded profile is significantly related to the change in the angle of the mitral valve chordae, resulting in a breakdown of normal mitral valve leaflet coaptation. We believe that this was the mechanism responsible for the dramatic differences in the incidence of mitral valve regurgitation between the two treatment groups.

Further investigation is needed. If the positive outcomes in this study are sustained then passive ventricular constraint with a synthetic wrap may offer a relatively simple and minimally invasive surgical option for the treatment of dilated cardiomyopathy and heart failure. The specific advantages of this technique, no invasion of the circulatory space and minimal surgical trauma, may result in a degree of general acceptance that has alluded other surgical treatments for heart failure.

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