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Changes in natriuretic peptides following passive containment surgery in heart failure patients with dilated cardiomyopathy☆

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Abstract

To evaluate the influence on circulating plasma levels of natriuretic peptides following passive containment surgery in heart failure patients with dilated cardiomyopathy, thirteen patients with dilated cardiomyopathy subjected to cardiac surgery received the Acorn Cardiac Support Device. Patients with ischemic cardiomyopathy ($n=7$) underwent coronary artery bypass surgery receiving 2–3 bypass grafts. In the idiopathic cardiomyopathy group ($n=6$), mitral valve plasty was performed in five patients while one patients received the Cardiac Support Device only. Circulating plasma atrial natriuretic peptide, brain natriuretic peptide and C-type natriuretic peptide were measured in all patients before surgery and 12 months postoperatively. Following surgery there was a significant decrease in circulating plasma levels of brain natriuretic peptide (0.14 ± 0.04 ng/ml vs. 0.06 ± 0.03 ng/ml, $P<0.05$). No significant changes were seen in circulating plasma levels of atrial natriuretic peptide or C-type natriuretic peptide. NYHA functional class improved (2.7 ± 0.1 vs. 1.8 ± 0.2, $P<0.001$). The 6-min-walk increased (354 ± 35 m vs. 473 ± 31 m, $P<0.01$). There was a decrease in left ventricular end diastolic diameter (73 ± 2 mm vs. 65 ± 2 mm, $P<0.001$) and left ventricular end systolic diameter (65 ± 2 mm vs. 56 ± 3 mm, $P<0.01$). Following passive containment surgery using the ACORN Cardiac Support Device functional improvement and reversed remodelling is accompanied by decreased BNP levels.

Keywords: Cardiac support device; Dilated cardiomyopathy; Heart failure; Natriuretic peptides

1. Introduction

The failing heart undergoes numerous structural and functional changes referred to as ventricular remodelling [1]. Progressive ventricular dilatation is a frequently occurring component in this process and has also been shown to be an important prognostic factor [2]. Reversal of ventricular dilatation can be achieved by pharmacological treatment and if not sufficient by surgical intervention [3]. The Acorn Cor Cap™ Cardiac Support Device (CSD; Acorn Cardiovascular Inc.; St Paul, MN, USA) is a mesh-like polyester fabric which is positioned around the dilated failing heart in order to reduce wall stress and facilitate a reversed remodelling of the heart, and thereby reshape the heart from a dilated spherical shape to an ellipsoidal shape.

Natriuretic peptides are a family of hormones including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). Plasma levels of natriuretic peptides increase in patients with cardiovascular disorders and heart failure [4].

In this paper we have therefore, evaluated the effects of passive containment surgery using the CSD in heart failure patient on circulating plasma levels of ANP, BNP and CNP.

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2. Materials and methods

2.1. Patient selection

Between April 2004 and October 2006, 13 patients (12 males, 1 female) with idiopathic (i.e. unknown cause of disease; $n=6$) or ischemic (i.e. coronary artery disease as likely cause of disease; $n=7$) cardiomyopathy (CM) received the CSD either in conjunction with other surgical procedures ($n=12$) or as the sole procedure ($n=1$). The study was approved by the Local Ethical Committee at the Karolinska Hospital and written consent was obtained from all patients.

Inclusion criteria which all had to be fulfilled included (i) left ventricular end diastolic diameter (LVEDD) >60 mm or indexed to >30 mm/m^2 body surface area (BSA), (ii) ejection fraction (EF) of 10–45%, (iii) NYHA class III or IV, or when in class II only if a history of at least one previous class III or IV episode, (iv) stable drug therapy, (v) mitral regurgitation (MR) $<2+$ (unless accepted for MR surgery). Exclusion criteria included end stage heart failure requiring inotropic support, hypertrophic CM, cardiac re-operations, myocardial infarction <90 days or systemic disease (pulmonary, renal or hepatic dysfunction). Seven of the patients were accepted for CABG (ischemic CM) and the remaining six were initially accepted for mitral valve surgery (idiopathic CM) although one of these patients received the CSD

Table 1
Preoperative characteristics of patients and surgical procedures

Patient no.	Age (years)	Sex	Ethiology	Surgery in addition to CSD
1	61	M	Ischemic	LIMA-LAD; SVG-M
2	78	M	Idiopathic	–
3	72	M	Ischemic	LIMA-LAD; SVG-M, RPD
4	72	M	Ischemic	LIMA-LAD; SVG-M, RPD
5	32	M	Idiopathic	C-E Physioring 28 mm
6	56	F	Idiopathic	C-E Physioring 26 mm
7	51	M	Ischemic	LIMA-LAD; SVG-M, RPD
8	58	M	Idiopathic	C-E Physioring 30 mm
9	66	M	Idiopathic	C-E Physioring 30 mm
10	59	M	Idiopathic	C-E Physioring 30 mm
11	70	M	Ischemic	LIMA-LAD; SVG-RPD
12	63	M	Ischemic	LIMA-LAD; SVG-D, RPD
13	65	M	Ischemic	LIMA-D; SVG-M, RPD

C-E, Carpentier-Edwards; LIMA, left internal mammary artery; D, diagonal branch of the LAD; SVG, saphenous vein graft; M, marginal branch of the circumflex artery; RPD, right posterior descending artery.

alone due to MR $\leq 1+$ at the time of surgery. The patient characteristics are presented in Table 1.

2.2. Medications

Prior to surgery all patients were on beta-blockade, diuretics, ACE-inhibitor ($n=12$) or AII blocker ($n=1$). This was maintained unchanged postoperatively.

2.3. Device implant

All patients were operated on through a midline sternotomy using cardiopulmonary bypass (CPB) with a centrifugal pump (BP 80, Biomedicus Biomed; Houston, TX, USA) and a membrane oxygenator (Affinity, Medtronic Inc., Minneapolis, MN, USA) primed with Ringers solution. During CPB the temperature was allowed to drift to 34 °C.

Cardiac arrest was achieved with a cardioplegia solution mixed 1:4 with blood and delivered at a temperature of 4 °C. Cross-clamp was not used for the patient receiving the CSD alone. CABG patients received an average of three grafts [2, 3] with the LIMA used in all patients and saphenous vein was used as additional graft material. Six patients in the idiopathic group underwent mitral valve surgery with a Carpentier–Edwards Physioring (see Table 1).

All patients received their routine daily cardiac medications on the morning of surgery. Anesthesia was performed and the CSD was applied as previously described [5].

2.4. Natriuretic peptide analysis

Plasma for analysis of BNP was obtained from a peripheral vein before surgery and at patient follow-up 12 months postoperatively. The samples were collected into EDTA vacuum tubes from non-fasting patients in the afternoon, kept in ice slush and centrifuged. The plasma was then frozen at −70 °C and stored until analysis. The content of ANP, BNP and CNP was determined using commercially available peptide immunoassay for ANP, BNP and CNP, respectively (Peninsula Laboratories LLC, San Carlos, CA, USA). The range for the assays was 0–25 ng/ml, intra-assay variation $<5\%$ and inter-assay variation $<14\%$.

2.5. Echocardiographic examinations

Prior to surgery and 12 months postoperatively all patients were evaluated by transthoracic echocardiography (System 5, GE Vingmed, Hortem, Norway). All examinations were performed with the subjects in left lateral decubitus position by the same physician.

2.6. Statistical evaluation

Data are presented as mean$\pm$standard error of mean (S.E.M.). ANP, BNP and CNP, New York Heart Association (NYHA) functional class, the 6-min-walk and cardiac dimensions were compared by Wilcoxon's signed ranked test. $P<0.05$ was considered significant.

3. Results

All patients survived the surgical procedure and could leave the hospital. Average ICU stay was 5 ± 2 days and hospital length of stay was 17 ± 3 days. Follow-up was complete at 12 months postoperatively.

Following surgery there was an improvement in NYHA functional class (from 2.7 ± 0.1 to 1.8 ± 0.2, $P<0.001$) and an increase in the 6-min walk (from 354 ± 35 to 473 ± 31 m; $P<0.01$; Fig. 1a,b).

3.1. Echocardiographic findings

There was a significant, gradual and sustained reduction in cardiac dimensions measured as LVEDD and LVESD which

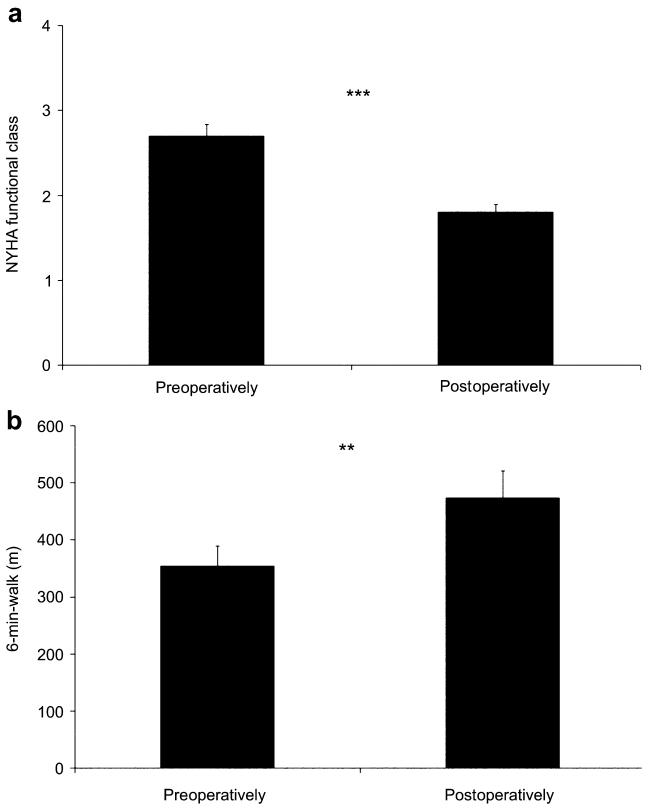

Fig. 1. (a,b) NYHA functional class and 6-min-walk results preoperatively and at follow-up 12 months postoperatively. Results are given as mean$\pm$S.E.M. [$P<0.001$ (***) respectively, $P<0.01$(**)].

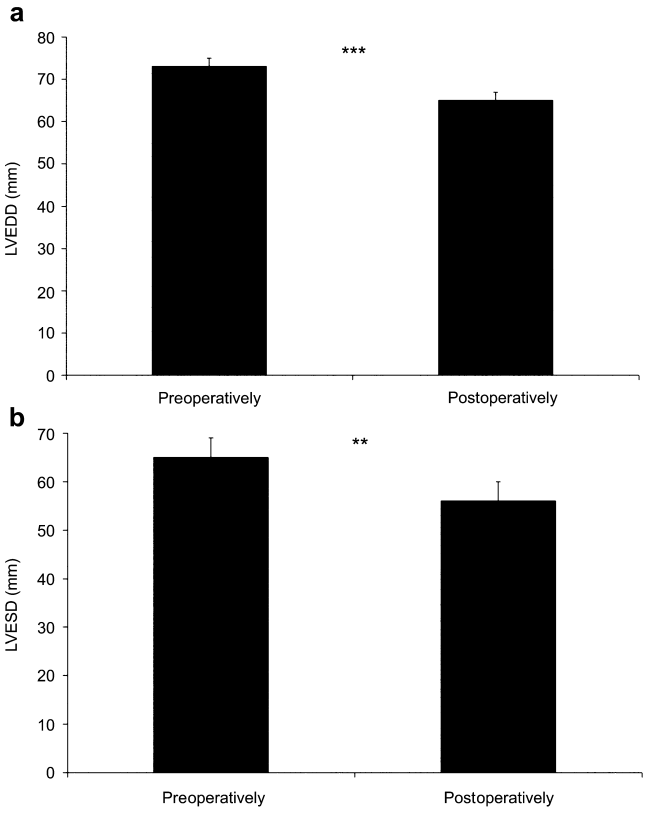

Fig. 2. (a,b) Echocardiographic findings preoperatively and at follow-up 12 months postoperatively. Left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD). Results are given as mean ±S.E.M. [$P<0.001$ (***) respectively, $P<0.01$ (**)].

decreased from 73±2 mm and 65±2 mm to 65±2 mm ($P<0.001$) and 56±3 mm ($P<0.01$), respectively, 12 months postoperatively (Fig. 2a,b). There were no statistically significant changes in left ventricular EF at follow-up (preoperatively 22±2%; postoperatively 25±3%).

3.2. Natriuretic peptide levels

Preoperative plasma levels of ANP, BNP and CNP were 0.17±0.03, 0.14±0.04 and 0.049±0.004 ng/ml, respectively. At 12 month follow-up the plasma levels of BNP had decreased significantly to 0.06±0.03 ng/ml ($P<0.05$). The circulating plasma levels of ANP and CNP remained unchanged at follow-up (Fig. 3).

4. Discussion

The failing heart undergoes numerous structural and functional changes referred to as ventricular remodelling [1]. Progressive ventricular dilatation is a frequently occurring component in this process and has also been shown to be an important prognostic factor [2].

Passive containment surgery using the CSD has experimentally been demonstrated to reduce adaptive mechanisms associated with increased wall stress and to attenuate further ventricular dilatation and improve cardiac function. Initial experimental studies in different heart failure models and with various species suggested that application of

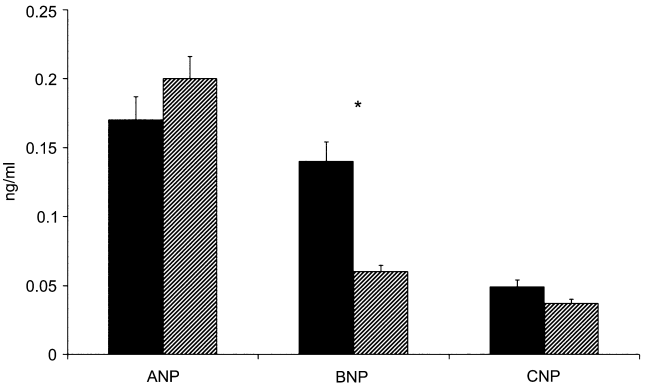

Fig. 3. Circulating plasma levels of natriuretic peptides preoperatively (filled bars) and at follow-up 12 months postoperatively (hatched bars) in thirteen patients with dilated cardiomyopathy subjected to passive containment surgery. Results are given as mean±S.E.M. [$P<0.05$ (*)].

the CSD diminished the deterioration in LV function and improved reversed LV remodelling [6]. Numerous additional experimental studies have given results indicating reversed remodelling; reversal of chronic molecular and cellular abnormalities after CSD application in heart failure models [7, 8]. Further experimental studies using pressure–volume relationships have shown no increase in chamber stiffness or diastolic filling pressures [10]. Our own and others short-term results with the CSD in heart failure patients have indicated amelioration of symptoms and improved cardiac function [5, 9].

In heart failure patients with dilated cardiomyopathy subjected to passive containment surgery using the CSD, a significant reduction in cardiac dimensions measured as left ventricular end diastolic diameter and left ventricular end systolic diameter, improved functional capacity (measured as NYHA class and 6-min-walk) and improved quality of life (measured by the Uniscale score) have been demonstrated [11].

ANP and BNP are synthesized and secreted from myocytes in response to myocardial stretch and overload. BNP and the inactive N-terminal fragment of the pro hormone pro-BNP (NT-pro BNP) have been shown to have diagnostic and prognostic value in various settings of acute as well as chronic heart failure [12].

Following coronary artery bypass grafting in patients with decreased EF BNP levels have been found to decrease significantly 10 months postoperatively [13]. In addition, changes in NT-pro BNP following mitral valve repair have been correlated with changes in heart failure symptoms and LV dimensions [14].

Earlier studies of BNP levels following heart failure surgery using left ventricular reconstruction have shown decreased levels of BNP at postoperative follow-up . These finding are coherent with our findings in the present study with significantly reduced plasma levels of BNP, reduced cardiac dimensions and improved functional capacity at 12 months follow-up after passive containment surgery using the CSD. In contrast, the circulating plasma levels of ANP and CNP did not change significantly during the study period. Earlier findings have demonstrated BNP and NT-pro BNP to have diagnostic and prognostic implications in heart failure

patients (see [4]). There was no direct correlation between reduction of circulating plasma levels of BNP and reduction of cardiac dimensions (measured as LVEDD and LVESD) or functional improvement (measured as NYHA functional class and 6-min-walk). Due to the small number of patients included in this study and the limited follow-up time, further larger studies exploring the potential long-term correlation between changes in BNP levels and other functional and/or prognostic parameters would be of great interest. To what extent BNP measurements may replace or add further information to other means of postoperative evaluation following heart failure surgery remains to be established.

4.1. Study limitations

The major limitations with this study are the lack of a control group and the small number of patients included. This is due to the fact that the number of patients meeting the inclusion criteria is limited at our institution and we have, therefore, chosen to include all eligible patients in the study. Most patients also underwent additional surgical interventions (i.e. coronary bypass grafting or mitral valve annuloplasty which have been demonstrated to evoke reversed remodelling) and the impact of the different surgical procedures on BNP levels cannot be determined. We can therefore, not exclude the possibility that the decrease in BNP levels has been generated by the combined surgical strategy. However, the common surgical denominator for all patients was application of the CSD and the reduced BNP levels clearly imply positive effects in heart failure patients postoperatively.

Acknowledgments

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