Reversed remodelling in dilated cardiomyopathy by passive containment surgery is associated with decreased circulating levels of endothelin-1

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Abstract

Objective: To evaluate the influence on circulating levels of endothelin-1 and big endothelin-1 in relation to echocardiographic findings and functional assessment, by passive containment surgery in heart failure patients with dilated cardiomyopathy. Methods: Thirteen patients with dilated cardiomyopathy subjected to cardiac surgery received the Acorn Cardiac Support Device. Patients with ischemic dilated cardiomyopathy (n = 6) underwent coronary artery bypass surgery receiving one to three bypass grafts. In the idiopathic dilated cardiomyopathy group (n = 7), mitral valve plasty was performed in five patients while two patients received the cardiac support device only. Circulating plasma levels of endothelin-1 and big endothelin-1 were measured in all patients before surgery and 12 months after surgery. Concomitantly New York Heart Association functional class and 6-min walk were evaluated and cardiac dimensions measured with echocardiography. Results: Following surgery there was a significant decrease in circulating plasma levels of endothelin-1 (5.9 ± 0.6 pM preoperatively vs 4.3 ± 0.3 pM postoperatively, P < 0.05). New York Heart Association functional class improved (2.8 ± 0.2 preoperatively vs 1.8 ± 0.2 postoperatively, P < 0.05). The 6-min walk increased (384 ± 24 m preoperatively vs 465 ± 33 m postoperatively, P < 0.05). There was also a decrease in left ventricular end diastolic diameter (69 ± 2 mm preoperatively vs 62 ± 2 mm postoperatively, P < 0.05) and left ventricular end systolic diameter (60 ± 2 mm preoperatively vs 54 ± 3 mm postoperatively, P < 0.05). Linear correlation revealed a relationship between decreased left ventricular end diastolic diameter and decreased endothelin-1 levels (R = 0.56; P < 0.05). Conclusions: Following passive containment surgery using the Acorn Cardiac Support Device there is a decrease in circulating levels of endothelin-1 concomitant with a decrease in cardiac dimensions and function improvement.

Keywords: Cardiac support device; Dilated cardiomyopathy; Heart failure; Endothelin

1. Introduction

Heart failure is an increasing problem in the ageing western world population. The prognosis for patients with advanced heart failure and dilatation of the heart is poor despite improvements in pharmacological treatment [1,2]. Since heart transplantation due to several reasons is unavailable to many patients, other surgical procedures have been developed for treatment of drug-resistant heart failure including shape-changing procedures such as the Dor procedure [3] and passive containment surgery [4]. These procedures are based on the finding that the failing heart undergoes numerous structural and functional changes often referred to as ventricular remodelling [5]. These changes often include ventricular dilatation establishing an auto-inductive process with a further deterioration of heart function. The increased wall tension in the failing dilated heart will induce compensatory mechanism including neurohormonal activation in an attempt to restore cardiac function. The endothelins (ET) constitute a family of four closely related peptides (ET-1, ET-2, ET-3 and ET-4) derived from the respective precursor forms big endothelins 1–4 by ET converting enzymes. Heart failure is associated with increased levels of plasma ET-1 and a role for ET-1 has been postulated in structural and functional changes in the failing remodelling heart [6].

We have therefore evaluated the effects of passive containment surgery using the Acorn Cor Cap™ Cardiac Support Device (CSD) in heart failure patients on circulating plasma levels of ET-1 and big ET-1.

2. Material and methods

2.1. Patient selection

Between June 2001 and December 2003, 13 patients (11 males, 2 females) with idiopathic (i.e. unknown cause of disease) or ischemic (i.e. coronary artery disease as likely cause of disease) dilated cardiomyopathy (CM) received the
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. The cardioplegia contained KCl 100 mmol, MgSO4 8 mmol, glucose 28 mmol, THAM 20 mmol and saline 0.9% to a volume of 1000 ml. Overall CPB time was 92 ± 9 min (n = 13) and cross-clamp time was 49 ± 5 min (n = 11). Cross clamp was not used for the two patients receiving the CSD alone. CABG patients received an average of two grafts [1–3] with the LIMA used in all patients and when needed additional saphenous vein was used as graft material. Five 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. All standard American Society of Anaesthesiologists non-invasive monitors and peripheral intravenous and intra-arterial catheters were placed before induction. Anaesthesia was induced using fentanyl (10–20 μg/kg) and midazolam (0.03–0.05 mg/kg). Intubation was facilitated with atracurium. Patients were ventilated to achieve normocapnia (PaCO2 35–45 mmHg). A flow-directed pulmonary artery catheter and transoesopha-
geal echocardiography probe were inserted after induction. Anaesthesia was maintained with intermittent fentanyl and isoflurane or sevoflurane pre-CPB and an infusion of propofol (1–4 mg/(kg h)) during and after CPB. All patients received levosimendan (Simdax \textsuperscript{\textregistered}, Orion Pharma, Esbo, Finland) as an inotrope starting with a loading dose of 12 µg/kg prior to skin incision, followed by a continuous infusion of 0.1 µg/(kg min) during 24 h. The CSD was applied as previously described [7].

2.4. Endothelin analysis

Plasma for analysis of ET-1 and big ET-1 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 $-70^\circ$ C and stored until analysis. The content of ET-1 and big ET-1 like immunoreactivity was determined by radioimmunoassay using commercially available antisera (6901 and 6912, respectively, for ET-1 and big ET-1; Peninsula, Belmont, CA, USA). Human ET-1 or big ET-1 labelled with iodine-125 was used as a tracer and synthetic ET-1 or big ET-1 (Neosystems, Strasbourg, France) as standard. The assay samples were incubated at 4$^\circ$ C in 0.1 mol/l phosphate buffer, pH 7.4 containing 0.1% bovine serum albumin and 0.1% Triton X. The detection limit of the ET-1 assay was 1.0 fmol/tube and for the big ET-1 assay 0.2 fmol/tube.

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 ± standard error of mean (SEM). ET-1 and big ET-1, New York Heart Association (NYHA) functional class, the 6-min walk and cardiac dimensions were compared by Wilcoxon’s signed ranked test. The association between ET-1 levels and cardiac dimensions was evaluated by Pearson’s correlation test. $P < 0.05$ was considered significant.

3. Results

All patients survived the surgical procedure and could leave the hospital. Average ICU stay was 3 ± 1 days and hospital length of stay was 16 ± 3 days. Follow-up was 12 months postoperatively.

Following surgery there was an improvement in NYHA functional class (from 2.8 ± 0.2 to 1.8 ± 0.2; $P < 0.05$) and an increase in the 6-min walk (from 384 ± 24 m to 465 ± 33 m; $P < 0.05$) (Fig. 1A and B; Table 3).

3.1. Echocardiographic findings

There was a significant, gradual and sustained reduction in cardiac dimensions measured as LVEDD and LVESD. LVEDD and LVESD decreased from 69 ± 2 mm and 60 ± 2 mm to 62 ± 2 mm and 54 ± 3 mm, respectively, 12 months postoperatively ($P < 0.05$; Fig. 2A and B). No statistically significant change in ejection fraction (EF) was detected at follow-up 12 months postoperatively.

<table>
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<tr>
<th>Patient no.</th>
<th>Preoperative NYHA</th>
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<td>1</td>
<td>3</td>
<td>2</td>
<td>LIMA-LAD</td>
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<td>LIMA-LAD; SVG-RPD</td>
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3.2. ET-1 and big ET-1

Basal plasma levels of ET-1 and big ET-1 were 5.9 ± 0.6 pM and 0.52 ± 0.08 pM, respectively. Following surgery there was a significant decrease in circulating plasma levels of ET-1 at follow-up 12 months postoperatively (4.3 ± 0.3 pM, P < 0.05) (Table 4) but no statistically significant changes were observed in circulating plasma levels of big ET-1 (0.50 ± 0.1 pM). There was a direct correlation between the decrease in circulating plasma levels of ET-1 and the reduction in LVEDD (R = 0.56; P < 0.05).

4. Discussion

In this study we have evaluated the effects of passive containment surgery, using the Acorn CSD, on circulating plasma ET levels in relation to cardiac dimensions in patients with dilated CM. At follow-up 12 months postoperatively there was a significant reduction in plasma levels of ET-1 combined with a significant reduction of left ventricular dilatation.

Heart failure is an increasing medical problem mainly due to an ageing population and advances in the treatment of other cardiac diseases. When pharmacological treatment in advanced heart failure is insufficient, surgical procedures may be considered for patients with severe failure. Heart transplantation is one surgical treatment for patients with severe heart failure, which however is susceptible for a limited amount of patients due primarily to lack of organ donors as well as contraindications to the procedure. Therefore, other surgical procedures such as partial left ventriculectomy, the Dor procedure and passive containment surgery using the Acorn CSD are being evaluated for treatment of heart failure and ventricular dilatation [4,8,9].

Initial studies with the CSD have demonstrated beneficial effects including decreased cardiac dimensions and functional improvement [4,7] and although the long-term effects on mortality and morbidity are yet to be established, the CSD represents a novel and promising tool in preventing and reversing ventricular dilatation in patients with severe heart failure. Currently, clinical studies are under way worldwide. The results of these studies will be of great importance to evaluate the long-term effects of the CSD and to improve the selection of patients suitable for the CSD [10,11]. In spite of no clear-cut effects on EF, SV or CO observed at rest among our patients, the increase in 6-min walk and decreased NYHA functional class suggest beneficial effects for patient status by the CSD application. The mechanisms for the improved patient status is unclear but may be related to decreased mechanical wall stress associated with the volume overload which causes numerous maladaptive compensatory mechanisms [4]. It is well known that neurohormonal activation may stimulate cardiac remodelling in heart failure and indeed treatment with drugs like ACE-inhibitors and β-blockers have the potential for promoting reversed remodelling [12,13]. This seems to occur in subsets of patients only, thus emphasizing the importance of alternative treatment options in pharmacologically resistant advanced heart failure. In accord, all of our patients were on long-standing medication with ACE-/AII-inhibitors, β-blockade and spironolactone, yet they all had severe ventricular dilatation combined with advanced heart failure suggesting that for these patients pharmacological treatment was insufficient.

The potent vasoconstrictor and mitogenic peptide ET is well known to be activated in heart failure [6]. Numerous clinical and experimental studies have demonstrated increased tissue and plasma levels of ET, alterations in ET receptor subtype expression with down-regulation of myocardial ETB receptors,
changes in clearance of ET from the circulation as well as variability in functional effects of ET in heart failure. The down-regulation of ET$_B$ receptors affects circulating levels of ET-1 as the ET$_B$ receptor has an important role in the clearance of ET-1 [14–16]. Increased plasma ET-1 levels also correlates with increased NYHA class [17] and elevated levels of ET-1 in patients with heart failure is a predictor of cardiac death [17,18]. Furthermore, in dilated CM, ET-converting enzyme (ECE) activity remains unchanged suggesting that the increased levels of ET observed are caused by reduced clearance rather that increased production of ET-1 [15]. In accord, ET-1, but not the precursor form Big ET-1 decreased following surgery among our patients indicating a normalization of ET-1 clearance among the patients postoperatively.

Clinical studies with endothelin receptor blockade in patients suffering from pulmonary arterial hypertension have showed improved exercise capacity and improved haemodynamics. The endothelin receptor blocker bosentan has therefore been approved for treatment of patients with pulmonary arterial hypertension [16]. Based on the fact that the endothelin system is activated in heart failure several clinical studies with endothelin receptor antagonists have been performed similarly. At present no conclusive data exists on possible clinical improvement with endothelin receptor antagonism in patients with heart failure [19]. Another suggested possible approach to achieve a reduction in the activation in the endothelin system is by inhibiting ECE, since most ECE blockers also inhibit neutral endopeptidase. This combined inhibition results in decreased endothelin levels via ECE inhibition and increased levels of endogenous vasodilators via neutral endopeptidase inhibition [15].

4.1. Study limitations

The major limitation with this study is the lack of a control group. 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. The observed improvement in circulating ET-levels coincides with, and may be attributed to, the surgical improvement of the ventricular dilatation. Importantly, most patients also underwent additional surgical interventions (i.e. coronary bypass grafting or mitral valve annuloplasty) which have been demonstrated to evoke reversed remodelling [20,21] and the impact of the different surgical procedures on ET-levels cannot be determined. We can therefore not exclude the possibility that the decrease in ET-levels has been generated by the combined surgical strategy. However, the common surgical denominator for all patients was application of the CSD and the direct correlation between the LVEDD and ET suggests that improvement of LV anatomy has beneficial effects on ET plasma levels.

In conclusion, reduction of left ventricular dimensions by passive containment surgery in heart failure patients correlates with improvement in functional status, reduced cardiac dimensions and decreased plasma levels of ET-1.

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References