Surgical left ventricular radius enlargement by patch insertion on the beating heart: a new experimental aneurysm model

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Abstract

We presented a novel experimental aneurysm model for studies in left ventricular (LV) reconstruction techniques and assessed LV function. In eight pigs, the LV radius and geometry were enlarged surgically on the beating heart by inserting an aortic allograft construct. Haemodynamics and LV dimensions were assessed by echocardiography at baseline and under dobutamine stress. Surgery was successfully performed without lethal blood loss or arrhythmias. LV end-diastolic and end-systolic short-axis areas increased from 13.0 ± 1.7 to 17.0 ± 4.3 cm² (P = 0.001) and from 4.0 ± 0.9 to 13.0 ± 2.6 cm² (P = 0.001), respectively. Stroke volume decreased from 56 ± 11 to 33 ± 16 ml (P = 0.001). Incremental dobutamine infusion concurred with a biphasic response on fractional area shortening. Mitral valve insufficiency ranging from grades 2 to 4 was observed. In the pig, a novel, reproducible aneurysm model for acute cardiac dysfunction was created on the beating heart. Innovative (surgical) strategies for (staged) reconfiguration of the ventricle, e.g. adjustable Dor procedures and stepwise volume restraining cardiac support devices, can be tested for efficacy using this acute model.

Keywords: Left ventricular aneurysm • Animal models • Myocardial remodelling • Heart failure

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome and a major public health problem (in the USA overall incidence, >550,000 per year; prevalence, 5 million) [1]. The leading causes of HF are hypertension and ischaemic heart diseases [2, 3]. Recently, Dor’s original approach for surgical reshaping of the dilated left ventricle (LV) gained renewed interest as therapeutic option after maximum medical therapy [4, 5]. However, in the clinical setting, the outcome of the Dor operation is uncertain and related to the right time point of intervention and optimal LV volume reduction not leading to excessively increased end-diastolic pressure, according to Klautz and co-workers [5]. Currently, ventricular reshaping is performed in one invasive surgical session, while stage-wise titrated volume reduction may facilitate more optimal adaptation of the myocardium subjected to a smaller radius.

Current animal models may mimic radius enlargement, but lack adjustability, stability and predictability of end-diastolic volume. The developed animal model holds promise for adjustability.

The objectives of this study were (i) to assess the effect of an acute LV radius enlargement by patch insertion (iatrogenic aneurysm, AnLV) on cardiac performance and (ii) to study the effect of dobutamine stress conditions.

MATERIALS AND METHODS

Animals

Eight pigs weighing 79 ± 5 kg received humane care in compliance with the Animal Experimentation Committee of University of Utrecht and the ‘Guide for the Care and Use of Laboratory Animals’, published by the National Institutes of Health (National Institutes of Health publication 85-23, revised 1985).

Anaesthesia and euthanasia

Animals were kept anaesthetized in the supine position and mechanically ventilated as described before [6]. Preoperatively, 160 mg of acetylic salicylic acid and a bolus of 75 mg of clopidogrel were administered. Animals were anticoagulated with heparin (ACT >250 s) and were euthanized with pentobarbitalnatrium (200 mg/kg) intravenously.

Surgical procedure

After median sternotomy, the heart was suspended in the pericardial cradle. A bidirectional ultrasound flow probe was placed
around the aorta (Transonic Systems Inc., Ithaca, NY, USA). The heart was displaced vertically using the Starfish Cardiac Positioner (Medtronic Inc., Minneapolis, MN, USA) for exposure of the LV lateral/posterior aspect. An LV was performed without a cardiopulmonary bypass. With the epicardial echo probe, the future course of the cut in the LV was identified (in the posterior wall in between the papillary muscles, from the apex close to the circumflex artery) for entire surgical procedure, see Fig. 1 and Supplementary Video 1).

**Step 1**: attachment of a pouch (freshly harvested aortic allograft) to the outer surface of the LV to be in place before the ventriculotomy. The graft consisted of an aortic arch, a common innominate artery, a left subclavian artery and a 6–7 cm descending aorta. The graft was cut open in length. With a suture, the preferred line of stitching the graft was marked left and right along the course of the preferred cut in the LV muscle. The patch was sutured in an everting way with a polypropylene suture 2-0 running to the epicardium/myocardium, including supportive strips of Teflon felt and pericardium for haemostasis. First, the tapered distal portion of the graft was sutured close to the circumflex artery whereafter the sides of the patch towards the apex were attached. The stitches were placed deeply in the myocardium, taking care that bites were not overriding into the area where the ventriculotomy was intended to be made. The proximal arch was fashioned around the apex. Thereafter, the wall in between the innominate artery and subclavian artery was divided to allow introduction of the blister scissor under inflow restriction and head-up body positioning (one scissor leg inside the LV across the apex and one leg in the space between the epicardium and patch). Under inflow restriction, ventriculotomy was made (middle panel). The access to the pouch is closed after de-airing, and the heart is subsequently preloaded (right panel). Full procedure, see supplementary video. RV: right ventricle; R: radius; PPM: posterior papillary muscle; APM: anterior papillary muscle.

**Supplementary Video 1**: On the beating heart, an iatrogenic aneurysm was created by enlarging the LV radius with an aortic allograft. First, the graft was sutured as a pouch onto the exposed circumflex territory where after the ventriculotomy was made with a blister scissor under inflow restriction. LV was filled and de-aired while the entry to the pouch was oversutured.

**Figure 1**: Essential steps in iatrogenic radius enlargement on the beating heart. Upper, left to right: cross-section normal heart, pouch sutured to the epicardium before ventriculotomy, dilated heart with graft covering the LV defect, respectively. Lower left: displaced heart exposing latero-posterior heart surface. Middle panel: an aortic allograft (including aortic arch, common innominate artery and left subclavian artery with 6–7 cm descending aorta) was cut open in length. The patch was sutured to the outer surface of the LV (circumflex territory). The innominate artery and the subclavian artery were fashioned, allowing introduction of the blister scissor under inflow occlusion and head-up body positioning (one scissor leg inside the LV across the apex and one leg in the space between the epicardium and patch). Under inflow restriction, ventriculotomy was made (middle panel). The access to the pouch is closed after de-airing, and the heart is subsequently preloaded (right panel). Full procedure, see supplementary video. RV: right ventricle; R: radius; PPM: posterior papillary muscle; APM: anterior papillary muscle.
was extended 6–7 cm in total length between the papillary muscles and up to about 1.5 cm away from the circumflex artery. Cardiomyotomy was monitored using epicardial echocardiography. With a finger in the heart, the extent of ventriculotomy and the gross integrity of internal structures were checked.

Step 4: Subsequently, after de-airing, a vessel clamp was placed across the stump of the innominate and subclavian arteries, which were subsequently closed with a running suture. Inflow to the heart was gradually restored by releasing the caval snare and by moving the animal back into the horizontal position. In some cases, a couple of pledge-supported sutures had to be placed at the patch-ventricular junction to control major bleeding when LV pressure was elevated.

**Experimental protocol**

Data were collected before (control stage) and after ventriculotomy (after stabilization of haemodynamics, at dilated stage, at baseline and, to determine the ventricular inotropic response, during dobutamine infusion at 5 and 10 μg/kg/min).

**Echocardiography**

Chamber dimensions were obtained from epicardial ultrasound images (Prosound SSD-5000, 5 MHz probe UST-5280-5, Aloka Holding Europe AG, Zug, Switzerland) in the short-axis view at the midpapillary level. The LV internal diameter (LVID) was measured in longitudinal length, and the LV internal area (LVIA) was obtained without including the papillary muscles. Both were recorded in end-systole and end-diastole. The fractional area shortening (FAS) was calculated as \( \frac{[\text{LVIA}_{\text{ED}} - \text{LVIA}_{\text{ES}}]}{\text{LVIA}_{\text{ED}}} \times 100 \% \).

**Post-mortem examination**

In resected hearts, the patch was removed, the length of the incision in the LV was measured, the mitral valve apparatus was inspected and the LV was checked for clots.

**Statistical analysis**

Linear mixed-effects analysis of variance model accounted for repeated measurements on each animal. Animals were included as random effects, and stages (control and dilated), conditions (baseline, dobutamine 5 μg/kg/min and dobutamine 10 μg/kg/min) and their interaction as fixed effects. To assess statistical significance, appropriate contrasts were selected. Data are presented as mean ± SD. A probability value of less than 0.05 was considered statistically significant.

**RESULTS**

**Animals**

Ventriculoplasty was successfully performed on the beating heart in all animals with a blood loss of 378 ± 222 ml over the entire test protocol of 6 h. Fluid balance was corrected with i.v. plasma expanders, physiological saline solution and Hartmann’s solution before taking measurements. In three cases, additional, multiple haemostatic sutures were necessary. Four animals needed defibrillation whereafter a stabilization period was allowed.

**Haemodynamics and cardiac dimensions**

The increased end-systolic and end-diastolic dimensions indicate a significant acute enlargement associated with a significant decrease in FAS (Table 1). In addition, mitral valve insufficiency, ranging from grades 2 to 4, was observed in all cases (data not shown). AnLV resulted in an immediate decrease in pump function indicated by a decreased stroke volume (SV) and cardiac output (CO), which concurred with a decrease in mean arterial pressure (MAP).

**Effects of dobutamine**

Before AnLV (control stage), dobutamine infusion reduced chamber dimensions, leading to an increase in FAS.

**Table 1: Effect of radius enlargement and dobutamine infusion and its interaction on cardiac chamber dimensions and haemodynamics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control stage (n = 8)</th>
<th>Dilated stage (n = 8)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>5 μg/kg/min</td>
<td>10 μg/kg/min</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>63 ± 10</td>
<td>67 ± 12</td>
<td>85 ± 16</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>56 ± 11</td>
<td>65 ± 12</td>
<td>67 ± 30</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.5 ± 0.9</td>
<td>4.4 ± 1.5</td>
<td>5.9 ± 3.6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>88 ± 14</td>
<td>100 ± 16</td>
<td>120 ± 18</td>
</tr>
<tr>
<td>LVID (cm)</td>
<td>4.0 ± 0.3</td>
<td>3.9 ± 0.4</td>
<td>3.7 ± 0.7</td>
</tr>
<tr>
<td>LVIDES (cm)</td>
<td>2.1 ± 0.4</td>
<td>1.7 ± 0.3</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>LVIAES (cm²)</td>
<td>13 ± 1.7</td>
<td>12 ± 1.9</td>
<td>12 ± 3.6</td>
</tr>
<tr>
<td>LVIAES (cm²)</td>
<td>4.0 ± 0.9</td>
<td>3.4 ± 0.7</td>
<td>3.2 ± 0.9</td>
</tr>
<tr>
<td>FAS (%)</td>
<td>68 ± 7</td>
<td>70 ± 8</td>
<td>72 ± 4</td>
</tr>
</tbody>
</table>

CO: cardiac output; FAS: fractional area shortening; HR: heart rate; LVIAES: left ventricular internal area end-diastolic; LVIAED: left ventricular internal area end-systolic; LVIDES: left ventricular internal diameter (=2 × r) end-diastolic; LVIDED: left ventricular internal diameter (=2 × r) end-systolic; MAP: mean arterial pressure; SV: stroke volume (n = 8 for both stages).
After AnLV, LV dimensions decreased minimally at low-dose stimulation (5 μg/kg/min), and the effect of higher stimulation (10 μg/kg/min) did not further decrease chamber dimensions. The FAS showed a biphasic response to dobutamine stress. Low-dose dobutamine marginally increased global systolic function as expressed by an increase in the MAP, SV and CO. At high-dose dobutamine, systolic function did not improve further.

Post-mortem examination

Inspection showed an average length of cardiotomy of 6 cm, minimal cutting damage to the lateral side of the papillary muscle, no damage to the chordae tendineae or mitral valve leaflets with minimal fibrin clots in the ventricular cavity.

DISCUSSION

We demonstrated that (i) acute presetted LV radius enlargement by dilating patch surgery can be successfully performed without cardiopulmonary bypass and major blood loss on the beating heart; (ii) AnLV resulted in a significant acute decrease in systolic function and overall cardiac performance and (iii) dobutamine stress tended to show a decreased inotropic response after radius enlargement.

AnLV resulted in a significant decrease in global cardiac function. As an advantage, by using a fixed size allograft pouch, relatively standardized reductions in cardiac performance may be induced. The observed reduced function is not important due to loss of contractile mass since, by using the sparing suturing technique as depicted in Fig. 1, only a small rim of ~0.5 cm may become ischaemic and thus dysfunctional. Our recent study with adjustable patch sizes showed the feasibility of inducing a predefined decline in cardiac function in acute animals [9].

Limitations

Since the effect of true controls (only patch without ventriculotomy) was not evaluated, we cannot exclude possible influence of the suture line on global cardiac performance. Furthermore, this acute model is iatrogenic in the sense that loss of pump function was induced by radius enlargement and change in LV geometry only (mimicking chronic HF) because this condition was not established by loss of myocardium, heart valve disease, hypertension or arrhythmias as seen in patients with chronic HF. The premature acute results cannot be extrapolated yet to the chronic condition ‘aneurysm’, and therefore a survival model is warranted in which gradual adaptation of the heart muscle and its function can be studied.

CONCLUSION

In pigs, non-ischaemic patch insertion on the beating heart led to an iatrogenic aneurysm with a decline in cardiac function, which marginally improved on dobutamine stimulation. Innovative (surgical) strategies for reconfiguration of the ventricle, e.g. adjustable Dor procedure and stepwise volume restraining cardiac support device, can be tested for efficacy.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

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Conflict of interest: none declared.

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