Chapter 7:
Development of Acute Ischemic Heart Failure in Sheep

Abstract

The goal of the present study was to develop a large animal model of acute ischemic left ventricular heart failure that can be used to assess the influence of the PUCA pump on the heart and circulatory system under realistic conditions. We tested the hypothesis that mild stenosis of the coronary artery in combination with mild ventricular pacing induces acute heart failure condition.

Mean aortic pressure (AoP), left ventricular end-diastolic pressure (LVEDP), stroke volume (SV) and myocardial systolic shortening (MSS) were compared 30 minutes after a pacemaker-induced tachycardia in anaesthetized sheep (n=3) without and with ±50% stenosis of the proximal LCx. All parameters measured restored to the basic levels when the stenosis was absent. When the LCx was partially occluded, the mild PM-induced tachycardia resulted in decreased AoP ($P=0.045$) as well as in decreased SV ($P=0.048$); the LVEDP remained high ($P=0.002$). Also the recovery of the MSS was impaired when stenosis was present ($P=0.002$). These values indicate that acute heart failure conditions were present.

The technique used proved to be safe and allows fine-tuning of the demand ischemia. The model can be used to study the effect of LV mechanical support during acute heart failure conditions.

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Introduction

Heart failure (HF) is a major public health problem in the western countries. In the United States HF leads to a 6-year mortality rate of 80% in men and 65% in women\(^1\). Treatment and care of these patients cost this country about $8 billion annually\(^2\). Many patients with HF have reversible ventricular dysfunction. This group includes patients in cardiogenic shock after heart surgery or after myocardial infarct. Some of these patients did not respond sufficiently to pharmacological therapy and therefore need mechanical assist to survive.

Mechanical circulatory support systems assist the pump function of the failing ventricle. These devices can generate enough blood flow to guarantee adequate organ perfusion and can help patients to survive severe heart failure. Furthermore, the mechanical assist has proven to be successful for improving the physical condition of HF patients and to bridge them to heart transplantation\(^3\). Recent experience with long-term ventricular assist showed evidence that the myocardium can recover from end-stage heart failure\(^4\).\(^5\). Those results suggest that the mechanical circulatory assist may become an alternative therapy for management of the heart failure.

During the past decade our group has been involved in the biological evaluation of the MEDOS HIA Ventricular Assist Device\(^6\)\(^6\) and in the development and testing of the Pulsatilie Catheter (PUCA) pump\(^9\)\(^\)\(^11\). Most experiments were performed in healthy animals. The goal of the present study was to develop a large animal model of acute left ventricular heart failure (LVHF), which can be used to assess the functioning of the PUCA pump assist during acute heart failure conditions.

We tested the hypothesis that mild (±50%) stenosis of the proximal left circumflex coronary artery (LCx) combined with mild pacemaker-induced tachycardia may develop acute LVHF due to demand ischemia, whereas the separate phenomena themselves do not impair the cardiac function.

Methods

All animal experiments were performed according to the rules of the Ethical Committee on Animal Research at the University of Groningen.

Three clinically healthy sheep with mean body weight 76.3 ± 15.3 kg were premedicated with 0.008 mg/kg i.m. Robinul (Wyeth, Hoofddorp, Holland). Anesthesia was induced with 30 mg/kg i.v. Nesdonal (Rhône-Poulenc Rorer, Amstelveen, Holland). The sheep were intubated and ventilated (Ohmeda 7000 Ventilator, Ohmeda, Madison, WI, USA) with mixture of 100% oxygen and 1.5-2.5% Isoflurane (Abbott, Queenborough, Kent, UK). Perioperative analgesia was
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provided with 2-4 ml i.v. Finadyne (Schering-Plough, Brussels, Belgium). A 7.5 F Swan-Ganz catheter (Baxter-Edwards, Irvine, CA, USA) was positioned into the pulmonary artery via the left jugular vein to monitor cardiac output. A pressure catheter was placed into the aorta via the left carotid artery to monitor aortic pressure. Left thoracotomy was performed in the fifth intercostal space, the pericardium was opened and sewed to the wound edge. Anticoagulation with 2500 IU/hour i.v. Heparin (Leo, Weesp, Holland) was started after the opening of the pericardium. A pressure catheter was inserted into the left ventricle via the left atrium. A screw-type Delrin coronary artery constrictor, designed and manufactured in our department, was positioned above the very proximal part of the LCx. Two pairs of ultrasonic crystals (Triton Technology, San Diego, CA, USA) were implanted in the myocardium to measure LV myocardial segment length: one pair in the region perfused by LCx (ischemic area), and the other pair in the region perfused by the left anterior descending (LAD) coronary artery (control area). A pair of pacing leads was attached to the myocardium and connected to an external pacemaker (PM; Savita G3, Paris, France) to control the heart rate. A prophylactic administration of 100 mg Lidocaine, given as a slow intravenous bolus before the LCx became partially occluded, was used to prevent ventricular arrhythmias.

The following parameters were monitored and recorded with a PC (LabView 4.1, National Instruments, Austin, TX, USA): heart rate (HR), mean aortic pressure (AoP), left ventricular end-diastolic pressure (LVEDP), systolic and diastolic myocardial segment length (LAD and LCx-supply area), and cardiac output. To calculate the stroke volume, the cardiac output was divided to the heart rate.

The following criteria were set to define heart failure: a decrease of the mean aortic pressure by ≥ 25% from the basic value, combined with an increase of the LVEDP ≥ 75% and a decreased stroke volume ≥ 25%.

Experimental Protocol

After the instrumentation was completed, the heart was allowed to stabilize for 45 minutes. The experimental protocol consisted of two consecutive parts: PM-induced tachycardia and PM-induced tachycardia in the presence of a mild LCx stenosis. During the first part the heart rate was stepwise increased by a PM: every 5 minutes the frequency was increased by 10 bpm (starting from 120 bpm) until a heart rate of 180 bpm was reached. At the end of every 5-minute interval all mentioned parameters were recorded. After the final record (HR=180 beats/min) the PM was stopped. All parameters were recorded again 30 minutes after the PM has been switched off.
A mild (±50%) LCx stenosis was then applied with the coronary constrictor. The stenosis was calculated as a percent from the external arterial diameter and was controlled by myocardial systolic shortening measurements. After a resting period of 45 minutes the same pacing procedure was repeated. All parameters were again recorded 30 minutes after the PM was stopped.

Data Analysis

Myocardial systolic shortening (MSS) of the segment length (percent) was calculated as:

\[
\text{MSS} = \frac{\text{EDL} - \text{ESL}}{\text{EDL}} \times 100\%
\]

MSS = myocardial systolic shortening (percent)
EDL = end-diastolic myocardial segment length (mm)
ESL = end-systolic myocardial segment length (mm)

The results were compared with paired Student’s \( t \)-test. Differences were considered significant at \( P < 0.05 \). All data presented in the text are mean values.

Results

PM-induced tachycardia

The PM-induced tachycardia resulted in gradual change of all measured parameters. The mean aortic pressure decreased from 108.7 to 94.0 mm Hg (Fig. 1). The LVEDP increased from 17.9 to 34.0 mm Hg (Fig. 2). The stroke volume decreased from 55.8 to 30.6 ml (Fig. 3). The myocardial systolic shortening decreased from 19.6% to 14.7% in the LAD supply area, and from 20.4% to 14.6% in the LCx supply area.

The results of the measurements obtained 30 minutes after the PM was switched off have been presented in Table 1 and Figures 1-3.

The heart rate was 9% higher than the basic value (\( P = 0.399 \)). The mean aortic pressure almost restored to the basic value (-2%, \( P = 0.113 \), basic values versus the values measured 30 minutes after pacing). The LV end-diastolic pressure decreased with 17% below the basic value (\( P = 0.163 \)). The stroke volume increased with 6% above the basic value (\( P = 0.425 \)). MSS in the LAD-supply area almost restored to the basic value (-5%, \( P = 0.110 \)), as well as the MSS in the LCx-supply area (-2%, \( P = 0.211 \)).
Fig. 1. Mean aortic pressure during PM-induced tachycardia (solid) and during PM + LCx stenosis (dash).

Fig. 2. LV end-diastolic pressure during PM-induced tachycardia (solid) and during PM + LCx stenosis (dash).
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Fig. 3. Stroke volume during PM-induced tachycardia (solid) and during PM + LCx stenosis (dash).

**PM-induced tachycardia & LCx stenosis**

The changes in the mean aortic pressure, LVEDP, and stroke volume during pacing in the partial occluded animals were comparable with the changes found during pacing in the non-occluded animals. The mean aortic pressure decreased gradually from 97.7 to 80 mm Hg (Fig. 1). LV end-diastolic pressure increased from 13.7 to 29.9 mm Hg (Fig. 2). The stroke volume decreased from 57.5 to 30.0 ml (Fig. 3). The MSS decreased from 19.4% to 14.2% in the LAD-supply area, and from 18.1% to 11.4% in the LCx-supply area.

The results obtained 30 minutes after the PM was switched off are presented in Table 2 and Figures 1-3. The mean aortic pressure decreased further to 69.7 mm Hg ($P = 0.047$, basic values versus the values measured 30 minutes after pacing). The LV end-diastolic pressure was 27.1 mm Hg ($P = 0.002$). The stroke volume did not restore to the basic values and was 43.4 ($P = 0.044$). The MSS in the LAD-supply area increased to 15.6% ($P = 0.091$). MSS in the LCx-supply area increased as well to 13.5% ($P = 0.002$). The heart rate was 105.3 beats/minute ($P = 0.054$).

All experiments were completed without complications like ventricular fibrillation or severe arrhythmia.
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<table>
<thead>
<tr>
<th>Variable</th>
<th>Basic values</th>
<th>30 min. after PM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>104.7 ± 13.6</td>
<td>114.0 ± 43.2</td>
<td>0.399</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>108.7 ± 10.3</td>
<td>106.7 ± 9.9</td>
<td>0.113</td>
</tr>
<tr>
<td>LV EDP (mm Hg)</td>
<td>17.9 ± 6.1</td>
<td>14.8 ± 1.9</td>
<td>0.163</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>55.8 ± 6.6</td>
<td>59.2 ± 32.9</td>
<td>0.425</td>
</tr>
<tr>
<td>MSS LAD-supply area (%)</td>
<td>19.6 ± 6.0</td>
<td>18.7 ± 6.4</td>
<td>0.110</td>
</tr>
<tr>
<td>MSS LCx-supply area (%)</td>
<td>20.4 ± 7.7</td>
<td>20.1 ± 7.2</td>
<td>0.211</td>
</tr>
</tbody>
</table>

Table 1. Hemodynamic variables\(^b\), presented as mean ± standard deviation) before and 30 minutes after pacing (MAP = mean arterial pressure; LV EDP = left ventricular end-diastolic pressure; MSS = Myocardial Systolic Shortening; LAD = Left Anterior Descending coronary artery; LCx = Left Circumflex coronary artery; P-value: paired Student’s t-test, n = 3)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basic values</th>
<th>30 min. after PM &amp; LCx Stenosis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>96.3 ± 18.0</td>
<td>105.3 ± 23.0</td>
<td>0.054</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>97.7 ± 3.1</td>
<td>69.7 ± 18.0</td>
<td>0.045</td>
</tr>
<tr>
<td>LV EDP (mm Hg)</td>
<td>13.7 ± 2.1</td>
<td>27.1 ± 3.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>57.5 ± 6.1</td>
<td>43.4 ± 12.4</td>
<td>0.044</td>
</tr>
<tr>
<td>MSS LAD-supply area (%)</td>
<td>19.4 ± 6.8</td>
<td>15.6 ± 3.8</td>
<td>0.091</td>
</tr>
<tr>
<td>MSS LCx-supply area (%)</td>
<td>18.1 ± 6.9</td>
<td>13.5 ± 6.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 2. Hemodynamic variables\(^b\) before and 30 minutes after pacing in the presence of ± 50% LCx stenosis (MAP = mean arterial pressure; LV EDP = left ventricular end-diastolic pressure; MSS = Myocardial Systolic Shortening; LAD = Left Anterior Descending coronary artery; LCx = Left Circumflex coronary artery; P-value: paired Student’s t-test, n = 3)

Discussion

There is a considerable need for animal models of acute heart failure to investigate the hemodynamic effects of newly developed circulatory assist devices. The ideal model should be safe, simple, reproducible, and should mimic clinical heart failure conditions. The severity of heart failure in man is assessed most often by measuring exercise performance rather than by measuring of any other parameters\(^12\). In our model exercise is mimicked by the pacemaker-induced tachycardia.
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Heart failure can be induced experimentally by different techniques such as: pressure overload, volume overload, rapid ventricular pacing, myocardial ischemia (coronary stenosis, coronary ligation, injection of microspheres), etc. Pressure overload models are most useful to study the pathogenesis of myocardial hypertrophy, cellular derangements, as well as vascular changes. Volume overload heart failure models are used to study the pathogenesis of hormone and electrolyte disturbances. Inducement of myocardial ischemia is the most suitable technique for development of acute heart failure models and for assessing circulatory assist devices.

Myocardial ischemia develops when coronary blood flow is not sufficient to meet the metabolic demands of myocardial cells. The easiest way to decrease the coronary flow below the critical level seems to be a coronary occlusion by ligature or injection of microspheres. However, it is extremely difficult to obtain stable heart failure model after acute coronary occlusion, because either cardiogenic shock or compensatory changes occur; an intermediate situation is difficult to achieve. Ventricular arrhythmias followed rapidly by ventricular fibrillation are usual findings after ligation of coronary arteries and lead frequently to death of the experimental animal. Because of this, we tried to develop an acute heart failure with a coronary stenosis instead of an occlusion. The advantage of the stenosis is that it could be decreased or even released, saving the experimental animal in case of severe ventricular arrhythmias.

From previous experiments we learned that it is hard to control the degree of the coronary stenosis when a tourniquet is placed around the coronary artery. Therefore we developed a Delrin screw-type constrictor. The constrictor was fixed above the LCx, so it was not necessary to dissect the coronary artery (a procedure followed always by a coronary spasm). The induced stenosis did not lead to ventricular fibrillation or severe arrhythmia, which proved that the technique used is safe. Furthermore the stenosis did not lead to significant changes in the monitored parameters in rest, which suggested that the myocardial perfusion was not impaired by the constrictor. The latest is in line with the results of mild coronary occlusion reported by others.

The mean aortic pressure, stroke volume, and myocardial systolic shortening in both LCx and LAD-supply areas decreased during pacing without partial occlusion of the LCx; the LVEDP increased. All parameters restored 30 minutes after the PM was stopped. Significant changes were not found between the basic values and the values obtained 30 minutes after the PM was switched off (Table 1). As known, the coronary arteries normally supply blood flow sufficient to meet the oxygen demand of the myocardium during varying workloads. If the oxygen demand
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exceeds the supply, the healthy coronary arteries are able to dilate increasing the blood flow and hence the oxygen supply, a phenomenon known as a coronary autoregulation. The measurement 30 minutes after the PM had been switched off can be compared with a period of 30 minutes rest of a healthy person after severe exercise.

Different results were found during the resting period after the combination of coronary stenosis and PM-induced tachycardia (Table 2). The mean aortic pressure remained significantly lower than the basic values (-29%, \( P = 0.045 \)). The LVEDP remained significantly high (+98%, \( P = 0.002 \)), a common symptom of heart failure. The values of the stroke volume were significantly different as well (-25%, \( P = 0.044 \)). The recovery of the myocardial systolic shortening was significantly impaired in the ischemic area (\( P = 0.002 \)). According to Brashers et al, a narrowing of a major coronary artery by 50% or more impairs blood flow sufficiently to hamper myocardial cellular metabolism under conditions of increased oxygen demand\(^2\), in this case developed by PM-induced tachycardia. Because the myocardium has little tolerance to hypoxia, the myocardial cells become ischemic within seconds. After several minutes the cells lose the ability to contract, hampering the pump function of the heart. The elevation of LVEDP reduced further the sub-endocardial perfusion\(^2\). Although the oxygen demand decreased when the PM was stopped, the hemodynamic parameters did not restore, a post-ischemic myocardial dysfunction described by others as well\(^2\). We concluded that acute heart failure, characterized by moderate depression of the hemodynamic and myocardial function, had developed due to the demand ischemia.

The number of animals used is rather small, but the calculated \( P \)-values showed that the differences between the basic values and the values obtained 30 minutes after the combination of PM-induced tachycardia and partial LCx occlusion became significant after the third experiment. The use of more animals would certainly have increased the statistical power of the study, but on the other hand it would lead to similar results and an unnecessary dead of more experimental animals.

The present study emphasized that a mild ventricular pacing alone is not sufficient to develop an acute heart failure. The combination between mild coronary stenosis and mild PM-induced tachycardia developed acute heart failure in sheep due to demand-induced ischemia. This model is clinically realistic since many patients with coronary artery disease show ischemic symptoms during exercise\(^1\). Because the PUCA pump is mean to be used during acute heart failure, the developed model will be used in further experiments to assess the influence of the device on the heart and circulatory system during these pathological conditions.
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References


