Work in progress report - Experimental

Ventricular containment in the prophylaxis of experimental dilated cardiomyopathy

Peter Feindt*, Udo Boeken, J. Litmathe, Emmeran Gams

Department of Thoracic and Cardiovascular Surgery, Heinrich-Heine-University Hospital Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany

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Abstract

End-stage heart failure is an increasing clinical problem with only a few satisfactory therapeutic options. Dilated cardiomyopathy (DCM) is associated with a progressive decline in cardiac function. Our hypothesis was to arrest this worsening of cardiac function by mechanical containment of the dilating heart. In 16 pigs (50 ± 7 kg) DCM with congestive heart failure was initiated by rapid ventricular pacing (220 beats/min) for at least 4 weeks. In group I (n = 8) an elastic net was placed around both ventricles before pacing was induced, whereas in group II (n = 8) only the catheters for hemodynamic measurements were implanted. Comparing hemodynamic data the decrease of cardiac output (CO) and dP/dtmax during the period of stimulation was significantly lower in group I than in group II (CO: gr. I: 1.4 l/min; gr. 2: 4.1 l/min/dP/dtmax; gr. II: +288 mmHg/s; gr. 2: −1350 mmHg/s). This observation could also be made concerning the maximal left ventricular pressure (LVPmax: gr. I: +8.6 mmHg; gr. II: −39.4 mmHg). Ventricular containment with an elastic net seems to be a prophylactic option in cardiac insufficiency caused by ventricular dilation. This ‘cardioplasty’ is able to reduce the development of such a dilation with concomitant heart failure.

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1. Introduction

Although the number of patients with chronic failure of the left ventricle has tripled in the western industrial nations within the last 10 years, both, the heart transplantation and the supply with mechanical assist devices show as hopeful therapeutic options a variety of complications and contraindications. Longer waiting lists and hence — times concerning transplantation as well as immense high costs, impaired biological compatibility and a great apparatus effort concerning mechanical support may lead to the conclusion that these therapeutic tools are not able to provide the growing number of patients under all economic, numerical and medical aspects in a sufficient manner.

More than 1000 patients worldwide have been subjected to a cardiomyoplasty operation, however, until now, the method has not been able to gain acceptance in general [1,2]. Chronic remodeling is one of the essential mechanisms in progression of dilated cardiomyopathy. It has already been shown, that the progression of the left ventricular dilatation can be avoided using a cardiomyoplasty, however, a significant effect on the systolic pump function could not be proved, yet. The reasons for such unsatisfactory hemodynamic results of the cardiomyoplasty may be caused by the aspect that the electrical conditioning of the skeleton muscle is subjected to exorbitant morphological and functional changes in the course of time. However, a postoperative decrease of the patients complaints according to at least one to two classes according to NYHA has to be succeeded [2].

The essential contribution to this improvement is provided by the so-called ‘girdling effect’, i.e. in the elastic limitation of the diastolic volume. Kass et al. [3] could show that the improvement in cardiac function after cardiomyoplasty can be explained only in parts by a cardiomyoplasty may be caused by the aspect that the electrical conditioning of the skeleton muscle is subjected to exorbitant morphological and functional changes in the course of time. However, a postoperative decrease of the patients complaints according to at least one to two classes according to NYHA has to be succeeded [2].

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a passive, external device could represent a new direction in the therapy of myocardial insufficiency.

After construction of a special net with elastic and static qualities, we investigated in the current study the question whether it is possible to perform an optimal prophylaxis of myocardial dilation with this developed net.

2. Materials and methods

All animals used in this study received humane care in compliance with the ‘Guide For the Care and Use of Laboratory Animals’ (National Institutes of Health of The United States of America, NIH publication 85-23, revised setting of 1985).

For inducing ventricular dilation and subsequent myocardial insufficiency we chose the method of rapid ventricular pacing. For this method it was shown that a tachycardia-induced progressive heart failure is considered to display many of the clinical features of heart failure in patients. We wanted to investigate, whether the early implementation of the net has a prophylactic influence on the development of a cardiac dilation and pump insufficiency. We formed two groups of eight animals (Munich Mini Pigs) each which are marked as groups I and II in the following.

2.1. Origins of the net

The net was mechanically constructed using a special woven monofilament consisting of polyvinylidenfluoride (PDVF).

2.2. Procedures in group I

In the group I all measuring catheters as well as the net and the pacemaker were placed in the right ventricle during the operation using a lateral thoracotomy. The net was placed circular around the right and left ventricle attached under release of the apex. After 4.1 ± 0.7 days, the pacemaker was activated up to a maximum frequency of 220 beats per minute. Under hemodynamic control these animals then were paced for 28.1 ± 5.1 days, before the final operation was performed with explantation of the heart and following histological examination.

2.3. Procedures in group II

In group II we performed according to group I, however, without application of a net, so that these animals just served as control-group: After 5 ± 0.9 days, the pacemaker was activated up to a maximum frequency of 220 beats per minute. Under hemodynamic control these animals then were paced for 27.1 ± 4.4 days, before the final operation with explantation of the heart and following histological examination was carried out.

Comparing groups I and II the prophylactic use of the net should be examined for the progression of a ventricular dilatation and following myocardial insufficiency.

2.4. Pacemaker protocol

All animals were paced with an external one chamber cardiac pacemaker (type Pace 101 H, company Dr Osypka, Rheinfelden, Germany). The bipolar pacemaker probe (model KY 66 II, Osypka-Company, Rheinfelden, Germany) was fixed transvenously into the right ventricle. After an interval of 2 days after the first operation the stimulation was started in the VVI mode with a frequency of 140 bpm. The frequency was increased daily with 20 beats/minute in order to achieve the maximum frequency of 220 bpm after some days. The animals then were stimulated with this frequency until the final operation under registration of the hemodynamic changes.

2.5. Anesthesia

Premedication with 10 mg ketamine (Ketanest®), 4 mg azaperone (Stresnil®) and 1 ml atropin (Atropinsulfat Braun®) was performed as intramuscular injection. Narcosis was started by 12 mg thiopental sodium (Trapanal®). A continuous inhalation anesthesia consisting of enfurane and an N₂O/O₂ was applied. The relaxation was started with a dose of 2 ml pancuronium bromid (Pancuronium®) and further doses if necessary. For analgesia we used doses of 0.5 mg fentanylhydrogencitrat (Fentanyl® Janssen).

2.6. Operative procedure

A left lateral thoracotomy was performed by a 10–15 cm long incision in the 5th ICS. For prophylaxis of ventricular arrhythmias 5 ml of lidocaine 2% (Lidocain®) was applied intravenously.

Systemic heparinization was performed with 2000 IE heparin intravenously (Liquemin®). At the front wall of the left ventricle a Konigsberg-catheter was implanted for the registration of the left ventricular pressure (LVP) and dp/dt (Konigsberg P4.0X6-S-CK, Konigsberg Instruments, Inc, Pasadena, CA, USA); then a right ventricular pacemaker electrode (KY 66 II, Osypka Company, Rheinfelden, Germany) was placed into the right ventricle using a transmural approach. An ECG-cable, also located, on the LVP-catheter was fixed at the left auriculum. After preparation of the Truncus pulmonalis, a cardiac output flow-probe was positioned around the pulmonary artery (Triton ART2 Flow Probe, TRI-200-307-K/L-Y50CM-CSTY-KB, Firma Konigsberg Instruments, Inc, Pasadena, CA, USA). All catheters were placed subcutaneously through the back of the animals and the pacemaker electrode was connected with the pacemaker aggregate (type Pace 101H, Osypka Company, Rheinfelden, Germany). In group I the net was implanted now. Finally the chest was closed.
in the usual way. After this an animal vest which contained a bag for the external cardiac pacemaker was adapted to the pigs. All animals received antibiotic therapy for 5 days with two times daily 20 mg/kg body weight lincomycine (Albiotic®).

2.7. Data collection and statistical analysis

The signals of the measuring catheters were transmitted to the Triton system and digitalized there. The values of the variables were stored digitally for the subsequent analysis on a laptop computer. In both groups seven times of measuring were performed:

- operation day (OP);
- pacemaker starting (Pacer ON);
- achieving the maximum stimulation frequency (Pacer MAX);
- after 25% of time with maximum stimulation (T 25%);
- after 50% of time with maximum stimulation (T 50%);
- after 75% of time with maximum stimulation (T 75%);
- end of observation.

The following parameters were measured continuously at all measuring times over a period of at least 2 min:

- heart rate (HR);
- cardiac output (CO);
- maximal left ventricular pressure (LVP max);
- maximal left-ventricular pressure rise time (dp/dt max).

All data are demonstrated as mean value with standard error of the mean. The statistical analysis was performed with the software of SYSTAT®. All parameters were compared between groups 1 and 2. Employing the variance analysis, at first the baseline values were compared between both groups in order to recognize significant preoperative differences. Subsequently the difference of the measured or calculated values between the OP day and the day of the final operation was calculated. This difference was then analyzed using a one way variance analysis to compare the influence of the net implantation on the changes of the hemodynamic parameters between the groups. A P-value of < 0.05 was considered to be statistically significant.

3. Results

3.1. Comparison of baseline values

After implantation of all catheters, we measured the baseline values and compared these between groups I and II. Variance analysis was used as statistical method. No significant differences were found for HR and stroke volume, whereas for CO (P = 0.012), maximal left ventricular pressure (LVP max, P = 0.048), and maximal left-ventricular pressure rise time (dp/dt max, P = 0.005) significant higher values could be detected in group II (Figs. 1–3: OP day).

3.2. Heart rate (HR)

Regarding the baseline values no significant differences between groups I and II became evident. There was also no significant difference in the change of HR during the period of pacemaker-stimulation between the groups (Table 1).

3.3. Cardiac output (CO)

Regarding the baseline values before the first operation, a significant difference between the animals of groups I and II was measured (P = 0.012). It was shown, that the animals without net implantation (group I: 10.6 ± 0.6 l/min versus group II: 13.0 ± 0.4 l/min) had higher values before starting the study. Fig. 1 shows the course of cardiac output in the two groups. It is obvious that the CO was higher in group I at the end of experiments than in group II, although these animals had started with a higher baseline value. In comparison of the difference during the period of study time a significantly lower decrease of CO in group I (P = 0.0001) was evident (Table 1).

3.4. Maximal left ventricular pressure (LVP max)

The comparison of the baseline values before the first operation shows slightly a significant difference between the animals of groups I and II (P = 0.048) (group I: 87.9 ± 6.0 mmHg versus group II: 109.8 ± 7.3 mmHg). Fig. 2 shows the course of the maximal left ventricular pressure in the two groups. It is obvious that the LVP max was higher in group I at the end of experiments than in group II.
although the animals of group II had started with a higher baseline value. Comparing the decrease of the maximal left ventricular pressure between both groups during the period of study time a significantly lower decrease in group I ($P = 0.0001$) was evident.

3.5. Maximal left-ventricular pressure rise time ($dp/dt_{max}$)

Regarding the baseline values before the first operation a significant difference between the animals of groups I and II ($P = 0.012$) could be observed. Before starting the protocol, the animals of group II showed significantly higher values also for this parameter, so that the contractile state of the left ventricle in these animals without a net was better than in group I at this time (group I: $1762.5 \pm 188.7$ mmHg/s versus group II: $2625.0 \pm 148.7$ mmHg/s). Fig. 3 shows the course of the maximal left-ventricular pressure rise time ($dp/dt_{max}$) in the two groups. At the end of the study, $dp/dt_{max}$ was higher in group I than in group II. For this parameter the final value was even higher than the baseline value in group I, whereas a significant decrease could be shown in group II (group I: $2050 \pm 146.8$ mmHg/s versus group II: $1275.0 \pm 93.1$ mmHg/s). Comparing the differences between first and last measuring of both groups, a significant difference ($P = 0.0001$) was evident (Table 1).

3.6. Summary of the comparisons between group I versus II

In Table 1 the comparisons of differences during the period of study time are summarized for groups I and II, regarding their statistical relevance.

4. Discussion

In former years the main concept has been to develop a net which contains both dynamic and static qualities. At first it was the group around Konertz [4], who dealt with the cardiac support device (CSD) in animal experiments as well as in clinical application. The CSD is a preformed-knitted woven polyester device with relatively elastic qualities, tight-fitting placed around both ventricles. The CSD was examined in two different models of experimental cardiac insufficiency. In a rabbit model, Sabbah [5] induced an insufficiency by means of coronary microembolisms. He found decreased left ventricular filling volumes in CSD treated animals and an improved cardiac function in the 3 and 6 months follow-up. Power and colleagues [6] could prove similar results in experiments with sheep’s using a model of rapid ventricular pacing. It can be noticed, that in these animal studies the systolic ventricular function was not improved considerably by the implantation of the CSD-net. After these animal experiments the CSD-net was then used under clinical conditions. Konertz and Kleber [7] report on experiences in 27 patients. The CSD was used isolated without another surgical intervention in 11 of these 27 patients, simultaneously additional operative procedures as mitral valve reconstructions, mitral valve replacement, and coronary bypass surgery were applied to the other 16 patients. All 27 patients were at the time of operation at least in NYHA class III. The 11 patients which only received the CSD, showed a dilatative cardiomyopathy as cause of cardiac insufficiency. A significant decrease of the left ventricular end diastolic diameter was found after 3 and 6
months. An insignificant increase of the left ventricular ejection fraction was accompanied by clinical improvement which was expressed in a lower NYHA class. In conclusion of the CSD-net results it can be noticed that a significant improvement in the diastolic function could be reached, however, without clear results for the systolic function.

The influence of the net used in our current setup on the course of a cardiac insufficiency caused by a dilation should be examined in the actual study. We have therefore taken the net into its position in group I in the context of the first operation – before ventricular dilation was produced by rapid ventricular pacing to study a more prophylactic effect of cardioplasty. The heart rate was the only parameter which was influenced by means of pacemaker stimulation. Since all animals were stimulated after a standardized protocol, no significant difference between the groups became evident during the whole time span of observation. After beginning of pacemaker stimulation we noticed a rapid deterioration of the systolic function in animals of group II without net. These results agree with the findings of Takagaki [8]. He proved, that the systolic left ventricular function was deteriorated significantly after 4 weeks of rapid ventricular pacing. In his study significant decreases were found as in our animals concerning the cardiac output, the maximal left ventricular pressure and the maximal left-ventricular pressure rising time.

In group I animals which had primarily got the net implantation, a significantly lower aggravation of the systolic function let itself be seen during the period of pacemaker stimulation in comparison with the control group II. These results are in conflict with the findings of Vaynblat [9] who attached a PTFE net around the ventricles before induction of a cardiac insufficiency. He could state a significantly lower aggravation of the systolic function of the heart in comparison with the control group without net. Since these animals could build up higher maximal pressures at the end of the test period and the contractility of these hearts was considerably better than in control animals, we think that a certain dynamic component also could be reached by the material qualities of our. The elasticity of the net seems to have made a significant systolic pump support possible due to the available reaction force after a diastolic dilation. The great significance of the physical qualities of the material used was also point out in earlier studies [5,9–12]. A second important role for the elasticity have the degree of tissue adhesion with other structures and in that the degree of fibrosis [6]. We have found only low adhesions in our animals with the surrounding tissue mostly so that this fact also could justify our good results regarding the systolic function.

In conclusion, the method of static-dynamic cardioplasty must be regarded furthermore as an experimental procedure. If the therapeutical profit should be confirmed also under clinical circumstances, improvements in the implantation technique will attain a greater importance. A less invasive implantation method with avoidance of a complete sternotomy should be possible. Furthermore, procedures must be developed which make a standardization of the net tension possible at time of implantation. The continuous online registration of pressure volume loops has primarily to be mentioned here during adapting the net. We have used this procedure with some animals in the meantime and think that it is so possible to find out the point of the optimal net tension. The static-dynamic cardioplasty is an interesting surgical procedure with low effort and costs for the therapy of dilated cardiomyopathy and all forms of the cardiac insufficiency accompanied by a dilation of the heart as we could demonstrated in this animal model.

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### References

[5] Sábbah HN, Chaudry PA, Mishima T, Sharov VG, Maltsev VA, Undrovinas AL, Kleber FX, Konertz W. Passive constraint of

### Table 1
Comparison of difference $\Delta$ (OPday/final day) between groups I and II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\Delta$ (OPday/final day) I versus II</th>
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<tr>
<td>HR</td>
<td>n.s.</td>
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<td>CO</td>
<td>$P = 0.0001$</td>
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<td>LVP$_{\text{max}}$</td>
<td>$P = 0.0001$</td>
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<tr>
<td>$\frac{\text{d}p}{\text{d}t_{\text{max}}}$</td>
<td>$P = 0.0001$</td>
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Appendix A. Conference discussion

Dr C. Yankah (Berlin, Germany): I would like to ask a question on your experimental design. First the age and weight of your minipigs?

Dr Feindt: The pigs were 6 months. Well, the mini-pigs were in weight of between 40 and 50 kg.

Dr Yankah: We experienced in our cardiomyopathy minipig model that as the pigs grow, they have an increase in body weight and size by 40% within 6–8 weeks, the heart size increased by 20%. Can you comment on this?

Dr Feindt: Not more at this time point.

Dr Yankah: How long did you keep your pace maker induced cardiomyopathy animals?

Dr Feindt: Experiment time, depends, between 6 and 8 weeks.

Dr Yankah: Eight weeks? That means a significant increase in the heart size and the ventricular wall thickness and structural changes with pacing. How did you define your cardiomyopathy with respect to function and the heart size as compared to the control group? The definition might differentiate heart size and function by normal growth from heart size and the ventricular function by experimentally induced cardiomyopathy at a given time period.

Dr Feindt: First, in the experiments, we resected the pericardium and we don’t see a growth of the hearts in this 2 months. We make echocardiographs and we don’t see any growth of the animals themselves. We only see a deterioration in cardiac function, which we only measured in this experiment with the contractility. If this was reduced by more than 40%, we say this pig is now insufficient.

Dr K. Athanassiadi (Athens, Greece): I would like you to comment a little bit more on cardiomyoplasty and your method comparatively. As you stated in your objectives your synthetic polyester net compresses less the ventricles of the heart than a muscle. Could you please explain that?

Dr Feindt: I don’t understand your question. I don’t make some difference in our net and other nets, for example. Sure, there is a difference to the cardiomyoplasty. I only say that the results of cardiomyoplasty, when the contractility of this muscle is reserved, then you can compare some results, but it was only anecdotal.

Dr J. Vaage (Stockholm, Sweden): You have shown that if you put the net on very early when you start pacing, it has a prophylactic effect, then also it has a therapeutic effect. But actually one control group I am missing. That is when you have induced the heart failure, instead of putting on the net, then you should have had a group where you just observe the natural development. When you put on the delayed net, how do you really know that the observed effect was not the natural development of the disease?

Dr Feindt: I think you can see in the group 2, after the first operation, was beginning the ventricular pacing. We have done this in some animals for 6 weeks. You know from the literature that when you make it for 3 months, it’s relatively stable, and you have the same results as after 2 weeks of pacing. And in our group 2, up to the cut of the second operation, we have the controls what happened in the normal way.