

ELECTRICALLY STIMULATED BIOLOGICAL NEO-VENTRICLE FOR AORTIC COUNTERPULSATION: AN ANIMAL EXPERIMENT IN SHEEP

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SUMMARY

14 adult sheep were used for acute experiments: an aorto-pericardial pouch of a donor sheep was created. This biological conduit was anastomized in parallel to the descending aorta of a recipient sheep, using the aortic root as an inflow valve to the conduit. ECG-triggered nervous FES was applied during cardiac diastole to simulate aortic counterpulsation. Stimulation was performed during various hemodynamic conditions.

During 6 experiments a standardized surgical procedure suitable for long term studies was established. A neoventricle with 70 to 80ml filling volume was found to be optimal in size. In another 8 experiments hemodynamic measurements were performed. Under stable hemodynamic conditions the stimulation of the biological skeletal muscle ventricle induced a significant increase in mean diastolic pressure of 58.8% ($p < 0.0004$). During pharmacologically induced periods of cardiac failure the stimulation of the APPC increased the mean diastolic pressure significantly by 60.5% ($p < 0.002$). Supra-systolic pressures were obtained during all 8 experiments.

STATE OF THE ART

The chronic shortage of donor organs for cardiac transplantation and the high costs for mechanical assist devices demand the development of alternative cardiac assist devices for the treatment of severe chronic heart failure. Therefore, cardiac assistance by stimulated skeletal muscles is currently investigated as a possible alternative. The goal of the presented study was to evaluate the hemodynamic efficacy of a newly designed biological skeletal muscle ventricle in an acute sheep model. The biological pump was used as an aortic counterpulsation device.

MATERIAL AND METHODS

14 sheep weighing 57.5 +/- 6.2 kg were used. The animals were put under general anesthesia and intubated. Anesthesia was maintained with halothan and nitrous oxide. At the end of experiment the animals were sacrificed.

Surgical procedure:

The pericardium and the entire thoracic aorta including the aortic valve were excised from fresh sheep cadavers prior to the operation. These excised homografts were cryopreserved according to clinically approved techniques and defrosted at the time of the experiment. Surgery was started by two teams, one preparing the recipient animal and the other constructing the neo-ventricle from the aortic homograft.

Construction of the biological neo-ventricle:

The aortic homograft was incised longitudinally twice in its middle section and enlarged by two strips of pericardium to create an aorto-pericardial pouch conduit (APPC).

Preparation of the recipient sheep:

The left latissimus dorsi muscle (LDM) was detached from the thoracic wall under careful preservation of its insertion to the humeral bone and the supplying neurovascular pedicle. LDM was divided longitudinally into two branches with respect to the intramuscular neurovascular supply. A segment of the third rib was removed and LDM was placed in the left hemithorax. To continue the procedure the fifth and sixth rib were resected.

Connection of the APPC to the circulation and positioning of LDM:

The APPC was connected in parallel with the descending aorta of the recipient sheep. The proximal part was anastomosed with the recipient aorta distal to the common brachiocephalic trunk, using the aortic root as an inflow valve to the conduit. The distal end of the APPC was cut back to the appropriate length and connected with the descending aorta above the diaphragm. The two branches of LDM were wrapped around the APPC in counterrotating fashion and fixed to each other and to the remaining parts of the fifth and sixth rib.

Activation of the biological skeletal muscle ventricle (SMV) by FES:

Device:

Four stimulation electrodes were applied to the epineurium of the thoracodorsal nerve and the electrode leads were led out percutaneously. Three ECG-sensing electrodes were fixed to muscles of wall and both, pacing and sensing leads were connected with an external stimulation device.

Stimulation parameters:

Rectangular pulses with 0.6 msec duration at a frequency of 28 Hz were used for burst stimulation. Current was adjusted to achieve maximum tetanic contraction of LDM. R-wave triggered stimulation at a rate of 1:2 or 1:3 with the native heart rate was applied during diastole to simulate counterpulsation.

Hemodynamic Measurements:

A flow-directed pulmonary artery catheter was introduced from the left jugular vein. A aortic catheter was introduced into the left ventricle from the left carotid artery. Saline-filled plastic catheters were placed either directly into the left carotid artery close to the brachiocephalic trunk and introduced into the abdominal aorta from the left femoral artery. These hydraulic pressure catheters were connected to Van-den-Burg disposable pressure transducers. For flow measurements three Flow Probes were placed around the proximal and distal part of the homograft and around the descending aorta between the proximal and distal anastomosis. All hemodynamic variables were recorded simultaneously by a computerized registration unit. This unit includes an analog to digital converter and systems for data analysis

Experimental sequence (N=8):

Short periods of stimulation, consisting of 10 to 20 contractions were performed repetitively to avoid fatigue of the unconditioned, fast fatigable LDM. Heart failure was induced by rapid intravenous infusion of a betablocker (Breviblock®) and stimulation was repeated.

RESULTS

Surgical procedure:

During six experiments a standardized surgical procedure, suitable for long term studies was developed. Two pericardial patches, each sized 8 x 4 cm, created a neo-ventricle of 70 to 80ml filling volume, which turned out to be optimal in size and therefore was used in all further experiments. Macroscopically the division of the LDM did not cause marked cyanosis of parts of the muscle or denervation of parts of the LDM in any case (n = 14). At the end of each

experiment an investigation of the inner surface of the APPC was performed (n = 14). Visual inspection did not reveal any aggregates or thrombotic formations.

Hemodynamic measurements:

During eight experiments the hemodynamic efficiency of the neo-ventricle was evaluated. Stimulation was performed under stable conditions and did affect left ventricular peak pressure (*LVP-max*), mean arterial pressure (*p-mean*) and mean diastolic pressure (*p-dia*), which increased to supra-systolic values in all experiments. Right ventricular (*RVP*) and pulmonary artery (*PAP*) blood pressure did not reveal alterations due to stimulation.

Measurements during normal heart function:

Stimulation of the SMV caused a significant increase of *pT-max* by 19% ($p < 0,04$) and *pA-max* by 27% ($p < 0,02$), while *LVP-max* decreased not significantly by 5% ($p < 0,1$). *pT-min*, *pA-min* and *LVPmin* showed a tendency to decrease, but were not altered significantly by FES. *pT-mean* and *pA-mean* increased significantly by 14% ($p < 0,02$) and 17% ($p < 0,02$) and *pT-dia* showed a significant increment of 26% ($p < 0,01$). *pA-mean* was not applicable, because the pressure curve derived from the abdominal aorta did not allow differentiation between diastole and systole.

Measurements during induced heart failure:

Under this condition the stimulation of the SMV caused a significant increase of *pT-max* by 13% ($p < 0,04$) and *pA-max* by 28% ($p < 0,01$), while *LVP-max* decreased significantly by 8% ($p < 0,04$). *pT-min*, *pA-min* and *LVPmin* were not altered significantly by FES. *pT-mean* and *pA-mean* increased significantly by 13% ($p < 0,002$) and 11% ($p < 0,002$). *pT-dia* showed a significant increment of 19% ($p < 0,01$). Again *pA-mean* was not applicable, due to the reasons mentioned above.

Flow measurements during normal and induced heart failure:

Flow measurements under stable hemodynamic conditions and also under induced periods of cardiac failure revealed that the proximal as well as the distal part of SMV was filled from the aorta during the systole. During the stimulation of the SMV under both hemodynamic conditions blood was ejected from the proximal and distal part of the homograft and led to an inversed cranial flow in the aorta (Mean: Q-graft prox suff: -7,1l/min, Q-graft dist suff: 3,5l/min, Q-aort suff:

-0,5l/min; Q-graft prox insuff: -6,4l/min, Q-graft dist insuff: 3,2l/min, Q-aort insuff: -0,1l/min). Despite the existence of the aortic valve this flow phenomenon was observed in each acute experiment .

DISCUSSION:

Various approaches have been investigated to achieve chronic cardiac assistance using skeletal muscles in the past, but only dynamic cardiomyolasty and recently dynamic aortomyoplasty have found their way into clinical practice. Both configurations are characterized by the presence of an uninterrupted endothelium and a direct coupling of the skeletal muscle contraction to the circulation. In our experimental setup we wanted to combine some basic aspects of cardio- and aortomyoplasty, with new ideas concerning the positioning of the LDM.

The presented APPC is made of hemocompatible biological materials only. Although an endothelium is not present at the time of operation, the preserved basal lamina will provide reendothelialisation of the aortic homograft and the pericardial patches according to the used preservation technique. The activation of the SMV by its muscular envelopment means direct coupling of the skeletal muscle contraction to the circulation, thus fulfilling another basic requirement for efficient cardiac assist with skeletal muscles.

As a result a new type of skeletal muscle ventricle, different from already presented configurations was realized in sheep and a standardised surgical procedure, suitable for long term experiments was established. Activation of the APPC led to reduction of left ventricular

peak pressure and induced marked increases of mean arterial and mean diastolic blood pressure. Referring to criterias for aortic counterpulsation the configuration did produce some of the required hemodynamic changes. In fact counterpulsation-efficacy was not to be expected in this series of acute experiments, in which an unconditioned LDM was used.

According to our flow data we found aortic valves with different states of insufficiency in the proximal part of the homograft in all animals. Taking into account that the highest increase of mean diastolic pressure was produced in case of a completely insufficient aortic valve of the SMV, no further use of this valve should be considered for the next experiments

Summarizing our experimental studies, it is too early for direct comparison with Stephenson's pericardium lined SMV, which worked in circulation up to 589 days or aortomyoplasty, which already has been performed clinically. However, the achieved results encourage us to continue the investigation of our newly designed fully biological SMV. The presented data clearly demonstrate the hemodynamic efficacy of this configuration as an aortic counterpulsation device. Chronic animal experiments using a conditioned LDM will be performed in order to investigate the long-term behaviour and reliability of the configuration and its overall influence to the circulation.

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