THE HAEMODYNAMIC FUNCTION OF INTRATHORACIC SKELETAL MUSCLE VENTRICLES AFTER RECOVERY FROM SURGERY IN PIGS

Massimo Capoccia, Hazel Sutherland, Stanley Salmons, Jonathan C. Jarvis

Department of Human Anatomy and Cell Biology, The University of Liverpool, U.K.

SUMMARY AND STATE OF THE ART

The shortage of donor organs for heart transplantation and the high cost of mechanical assist devices highlight the need for alternatives for the treatment of end-stage heart failure. A promising experimental approach is the use of skeletal muscle ventricles (SMVs), which can be connected to the circulation in various ways to provide both left and right ventricular assistance (1-5). A subcutaneous SMV has pumped in the circulation of the dog as an aortic diastolic counterpulsator for more than 4 years (5). Here we present a new recovery model in pigs. The aim of the study was to form an intrathoracic pumping chamber from the latissimus dorsi muscle (LDM) and to connect it to the descending thoracic aorta in a single surgical procedure without compromising the host circulation.

MATERIALS AND METHODS

Female domestic pigs were used according to the Animals (Scientific Procedures) Act 1986, which governs animal experimentation in the United Kingdom.
Animals were premedicated with azaperone (Stresnil) 2-4 mg/kg i.m., 30-45 minutes prior to transfer to the anaesthetic room. Antibiotic prophylaxis was provided with lincomycin 4.5-11 mg/kg. Induction was achieved with the administration of an i.v. bolus of propofol (Diprivan) 1-2 mg/kg followed by endotracheal intubation. Respiratory assistance was provided to maintain oxygen saturation above 95%. General anaesthesia was maintained by a continuous i.v. infusion of propofol 8-12 mg/kg. Analgesia and respiratory depression were provided by the administration of alfentanil 0.5-1.5 micrograms/kg/hr or diamorphine 0.062-0.09 mg/kg/hr.

Conditioning
The anterior border of the left latissimus dorsi muscle was exposed through a limited flank incision with minimal disturbance of its blood supply. The muscle was partially dissected free from subcutaneous tissue and the chest wall. An epimysial monopolar electrode was placed between the muscle and the costal surface and secured with non-absorbable suture. The pulse generator (Itrel, Medtronic, Inc.) was placed beneath the left rectus sheath muscle. During the operation one unit of blood was harvested and stored under controlled temperature for transfusion purposes in the next, more major surgical procedure. After one week, the stimulator was programmed to deliver stimulation to the LDM at a frequency of 1 Hz with a pulse duration of 190 msec and an amplitude of 5V. Four weeks of prestimulation was used to transform the muscle to a fatigue-resistant type.

Construction of SMVs
The animals were anaesthetized according to the same protocol. The stimulator was removed from the abdominal pocket and a further unit of blood was harvested and stored. The left latissimus dorsi muscle was dissected free from subcutaneous tissue

and the chest wall, leaving its humeral insertion and the neurovascular bundle intact. In order to make the SMV blood-tight during this procedure, the muscle was fashioned into a pumping chamber around a pre-formed lining. The lining was a composite homograft constructed from the pulmonary artery with a complete ring of right ventricular muscle and part of the descending thoracic aorta of a donor pig. Two new electrodes (Model 6500; Medtronic, Inc.) were secured in place, one on the deep and one on the superficial surface of the proximal insertion of the LDM. The SMV was transposed into the left hemithorax through a window in the chest wall, created by partial resection of the anterior portion of the third rib.

Connection to the circulation

The chest was entered through the fifth intercostal space and the pericardium was opened. Two epicardial unipolar pacing leads were placed on the surface of the left ventricle. The muscular and epicardial leads were tunnelled to the original subcutaneous abdominal pocket and connected to an R-wave synchronous pulse train stimulator (LD Pace II, CCC Uruguay). The stimulator was programmed to deliver a burst of impulses at 33 Hz every third left ventricular diastole (1:3 assist ratio).
The SMV conduit was connected to the descending aorta by an end-to-side anastomosis. Blood was then allowed to flow in the SMV, which had previously been filled with heparinised normal saline. Haemostasis was ensured and two chest drains were placed. The wounds were closed in layers and the animal transferred to a recovery area, where two members of the team monitored it over night.

Haemodynamic data collection and analysis

Haemodynamic data were recorded at the time of connection of the SMV. A more complete analysis of SMV function was made at an elective terminal procedure after one week. The previous left thoracotomy was opened and the SMV assessed visually. The heart was then approached through a midline sternotomy. Transducers were placed to measure left ventricular pressure and volume, SMV pressure and volume, SMV and aortic arch pressure, and flow in the aortic root and in the conduit connecting the SMV to the host aorta. The transducers were secured in place with non-absorbable purse-string sutures. Data, including pressure-volume loops, were collected with the SMV off and with the SMV activated at a range of delays and durations in relation to the cardiac cycle.

RESULTS

Three animals were recovered successfully. In two, the SMV was still pumping but the aortic homograft was kinked, resulting in thrombus formation within the SMV. Haemodynamic measurements were made from one of these SMVs after the removal of thrombus and reconfiguration of the conduit. In the third the problem of kinking was avoided by constructing the SMV closer to the aortic arch with a shorter conduit. The SMV was contractile and free from thrombus after pumping in circulation for one week. Activation of the SMV from the end of systole for 80% of diastole increased mean diastolic blood pressure above control levels (obtained with the SMV off) by 11.2±1.6% in one animal and by 15.8±0.3% in the other. Peak diastolic aortic pressure was increased by 16.9±1.4 % and 20.1±1.2%. The left ventricular stroke work in the post-assisted beat was decreased by 8.7±5.8% and 10.1±2.2% and the overall stroke work by 7.4±1.2% and 9.4±0.8%.

DISCUSSION

Permanent cardiac assistance from skeletal muscle is an attractive prospect. So far only dynamic cardiomyoplasty and dynamic aortomyoplasty have been introduced into clinical practice. Although the protocol widely used for cardiomyoplasty is far from ideal (6, 7), follow-up studies show that 80% of the patients experience symptomatic improvement. It has, however, been difficult to demonstrate any consistent haemodynamic change (8). The benefit probably derives from a reduction of wall stress, which interrupts the progressive cycle of dilatation and overload. Under these conditions, the muscle is heavily loaded and operates far from the peak of its power curve (9). The active assistance available from skeletal muscle can be optimized by configuring it as a separate auxiliary pump, or skeletal muscle ventricle. The effectiveness of this approach has been clearly demonstrated by work in Detroit, where subcutaneous skeletal muscle ventricles (SMVs) have pumped as diastolic counterpulsators in dogs for up to 4 years (5), longer than any other cardiac assist device, mechanical or biological, in man or animal. The surgical technique for constructing SMVs and evaluating them in circulation has undergone progressive refinement and problems such as thromboembolism and rupture have been largely overcome (10, 11). However, some issues need to be addressed. Subcutaneous placement of the SMV is clearly not feasible in man. The current two-stage surgical procedure is unacceptable for patients in end-stage heart failure. The ligation of the descending thoracic aorta would not be accepted by the majority of surgeons.

We chose the pig as our animal model because it has been agreed that the SMV approach must be shown to work in species other than the dog before clinical application could be considered. Pigs are more sedentary animals than dogs and their muscular and cardiovascular physiology is more similar to that in the human. Our objective was to place an SMV intrathoracically in a single-stage surgical procedure without compromisisng the host circulation. Only one end-to-side anastomosis was required to connect the SMV in circulation. Our preliminary results have shown that these targets have been achieved. The SMV was able to reduce the workload of the heart at the same time as increasing the mean diastolic pressure, and therefore the pressure available to drive coronary flow. The benefits of stimulating the LDM prior to raising it as a graft have been discussed previously (12-14). The main drawback of this approach is the need for a preliminary invasive procedure under general anaesthesia, but this problem could be overcome by the use of non-invasive or minimally invasive techniques of electrode and device placement or stimulation. The use of the composite homograft was the key to forming and connecting the SMV in a single procedure. It has the further beneficial effect of reducing the effective preload for the SMV, and thus decreases the risk of ischaemia of the inner wall. The functional role of the homograft lining could be taken on in clinical practice by a synthetic composite or by a tissue lining produced in culture.

REFERENCES

1. Hooper TL, Stephenson LW. Using skeletal muscle to assist the heart. Br Heart J 1991;66:261-3.
2. Niinami H, Hooper TL, Hammond RL, Ruggiero R, Lu H, Spanta AD, Pochettino A, Colson M, Stephenson LW. Skeletal muscle ventricles in the pulmonary circulation: up to 16 weeks' experience. Ann Thorac Surg 1992;53:750-7.
3. Lu H, Fietsam R Jr, Hammond RL, Nakajima H, Mocek FW, Thomas GA, Ruggiero R, Nakajima H, Colson M, Stephenson LW. Skeletal muscle ventricles: left ventricular apex to aorta configuration. Ann Thorac Surg 1993;55:78-85.
4. Hooper TL, Niinami H, Hammond RL, Lu H, Ruggiero R, Pochettino A, Stephenson LW. Skeletal muscle ventricles as left atrial-aortic pumps: short-term studies. Ann Thorac Surg 1992;54:316-22.
5. Thomas GA, Hammond RL, Greer K, Lu H, Jarvis JC, Shortland AP, Pullan DM, Salmons S, Stephenson LW. Functional assessment of skeletal muscle ventricles after pumping for up to four years in circulation. Ann Thorac Surg 2000;70:1281-90.
6. Gealow KK. Latissimus dorsi stimulation in dynamic cardiomyoplasty: how should we proceed ? Basic Appl Myol 1998;8:41-50.
7. Salmons S. Permanent cardiac assistance from skeletal muscle: a prospect for the new millennium. Artif Organs. 1999 May;23(5):380-7
8. El Oakley RM, Jarvis JC. Cardiomyoplasty: a critical review of experimental and clinical results. Circulation 1994;90:2085-90.
9. Salmons S, Jarvis JC. Cardiomyoplasty: the basic issues. Card Chron 1990;4:1-7.
10. Thomas GA, Lu H, Isoda S, Hammond RL, Nakajima H, Nakajima HO, Colson M, Stephenson LW. Pericardium-lined skeletal muscle ventricles in circulation up to 589 days. Ann Thorac Surg 1994;58:978-88.
11. Thomas GA, Lu H, Isoda S, Hammond RL, Nakajima H, Nakajima HO, Stephenson LW. Skeletal muscle ventricles in circulation: decreased incidence of rupture. Ann Thorac Surg 1996;61:430-6.
12. Mannion JD, Velchik M, Hammond R, Alavi A, Mackler T, Duckett S, Staum M, Hurwitz S, Brown W, Stephenson LW. Effects of collateral blood vessels ligation and electrical conditioning on blood flow in dog latissimus dorsi muscle. J Surg Res 1989;47:332-40.
13. Jones J, Emmanuel J, Sutherland H, Jackson MJ, Jarvis JC, Salmons S. Stimulation-induced skeletal muscle damage: cytoprotective effect of prestimulation. Basic Appl Myol 1997;7:39-44.
14. Tang ATM, Jarvis JC, Hooper TL, Salmons S. Cardiomyoplasty: the benefits of electrical prestimulation of the latissimus dorsi muscle in situ. Ann Thorac Surg 1999;68:46-51.

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