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Efficacy and Mechanisms of Biventricular and Left/Right Direct Cardiac Compression in Acute Heart Failure Sheep

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Abstract: Direct cardiac compression (DCC) with implanted heart patches has previously demonstrated efficacy of biventricular (BiV) support in acute heart failure (HF) sheep. We hypothesized that this was primarily due to a left ventricular (LV) effect. This study compared BiV, LV, and right ventricular (RV) assists in terms of hemodynamic and energetic response. Ten sheep underwent instrumentation and device implantation at least 1 week prior to study. HF (50% reduction in cardiac output) was maintained with intravenous esmolol infusion. BiV, LV, and RV assists were activated randomly with intervening stable HF periods. BiV assist was more effective than either LV or RV assist in restoring hemodynamic parameters; however, there was no difference in efficacy of LV and RV support. RV assist preserved left coronary flow patterns and chamber geometry compared to other assist conditions, but increased LV preload. These results suggest that LV and RV support each make a significant contribution to the efficacy of BiV assist, albeit through different mechanisms. **Key Words:** Heart assist devices—Univentricular assistance—Left ventricular function—Myocardial energetics.

Direct cardiac compression (DCC) during emergency cardiopulmonary resuscitation or in the open-chest situation is widely accepted as a means of supporting the failing heart. However, its practicality and efficacy has been less convincing when implemented as dynamic cardiomyoplasty (biologic assist) or as a mechanical heart assist device. The potential of DCC for the treatment of chronic heart failure (HF) remains largely unexplored (1).

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial showed a 48% improvement in 2-year survival in patients with severe HF who received traditional blood-contacting mechanical heart assist (2,3). However, it also demonstrated shortcomings of available devices, in particular, device malfunction, infection, thromboembolism, and hemorrhage (2,3). The lack of blood contact with DCC heart assist confers compelling advantages over the currently available "flow-through" devices.

In previous studies, we have shown that our DCC device can restore circulatory parameters in awake sheep with acute HF (4). This study examined the effect of biventricular (BiV) DCC but did not address the contribution of left ventricular (LV) and right ventricular (RV) DCC independently. We hypothesized that the efficacy of BiV DCC arose primarily due to LV effects. The aim of this study was to compare the efficacy of BiV, LV, and RV assists in terms of LV hemodynamic and energetic response, and to examine the effect of these assist states on cardiac geometry and coronary flow patterns.

MATERIALS AND METHODS

Ten Merino ewes (body weight 52 ± 5 kg) were used in this study, approved by the institutional Animal Care and Ethics Committee. All animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animals Resources, National Research Council, and published by the National Academy Press, revised 1996.

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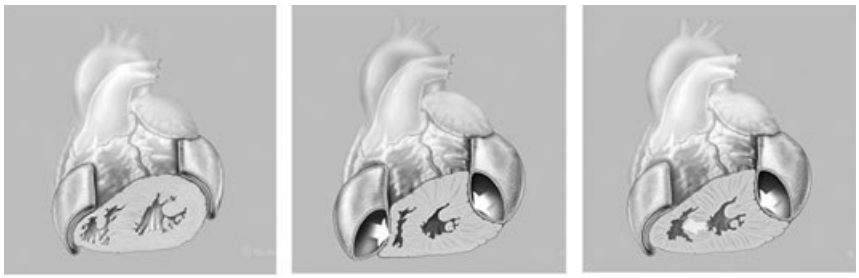

FIG. 1. Illustration of the DCC device applied to the heart in cross-sectional view. During baseline and HF, patches remain collapsed on the ventricular free walls. The device may provide BiV, LV, or RV (not shown) support.

DCC device

The experimental DCC device consists of two inflatable silicone patch elements biointegrated to the LV and RV epicardium by means of a porous silicone material on the visceral patch surface. Each patch has a heart contacting (visceral) membrane that is more distensible than the outer (parietal) wall, with the two enclosing an air chamber. Inflation and deflation of the patches is driven by an extracorporeal pneumatic pump using the electrocardiogram (ECG) R wave to trigger a computer-based control and monitoring system (Amlab Technologies, Sydney, New South Wales, Australia). The epicardial adhesion of the patches also allows the application of negative (suction) pressure to the surface of the heart during diastole. An illustration of the patches on the heart is shown in Fig. 1.

Surgical preparation

Anesthesia was induced with sodium thiopentone (20 mg/kg) followed by intubation and mechanical ventilation (Bird model 8, Bird Australia, Chatswood, New South Wales, Australia) with 2 L/min of oxygen, 2 L/min of nitrous oxide, and 1.5–2.0% isoflurane inspired. Hartmann's solution was given intravenous as maintenance fluid.

Following left lateral thoracotomy at fifth rib level with partial removal of the rib and pericardiotomy, size 16 or 20 A and 4 or 6 A Transonic flow probes (Transonic Systems, Inc., Ithaca, NY, USA) were placed around the ascending aorta (for measurement of cardiac output [CO]) and left main coronary artery (for measurement of coronary blood flow [CBF]), respectively. The hemiazygos vein was ligated immediately outside the pericardium to avoid systemic contamination of coronary sinus blood. Six piezoelectric sonomicrometer crystals (Sonometrics Corp., London, Ontario, Canada) were inserted close to the endomyocardium of the LV to measure anterioposterior, septolateral and base-apex dimensions (Fig. 2). Segmental length between the crystals was measured using sonomicrometry "time of flight" principle.

DCC patches were positioned over the LV and RV free walls and were secured to the visceral pericardium by stay sutures (4–0 prolene, J & J Medical, New South Wales, Australia). Driving conduits, ECG, and flow probe cables exited the chest wall through the seventh intercostal space and were tunneled subcutaneously to exit on the sheep's dorsum at the costal margin.

After intercostal nerve blockade with 0.5% bupivacaine (Astra Pharmaceuticals Pty Ltd., New South Wales, Australia), the chest incision was closed in layers following inflation of the lungs. The sheep were recovered from anesthesia followed by postoperative pain management using buprenorphine (0.3 mg/6 h intra-muscular [i.m.]/Reckitt Benchiser Healthcare Ltd., Hull, UK). Ampicillin, 1 g/day i.m. for 3 days, was used perioperatively for prevention of infection.

Cardiac assist studies

Studies were performed at least 1 week after DCC patch implantation, with the animals under anesthe-

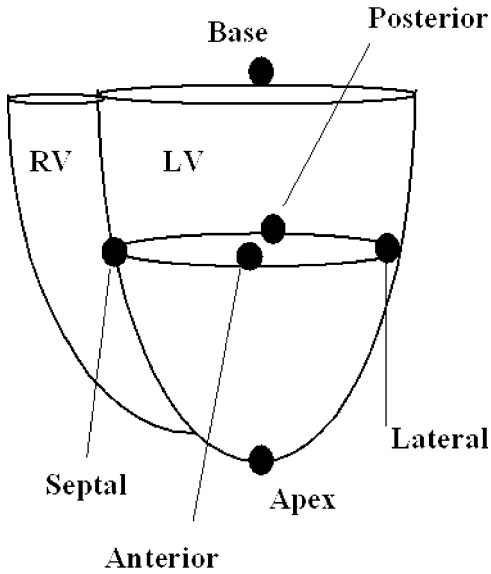

FIG. 2. Position of the sonomicrometer crystals in the left ventricle. Three orthogonal axes were measured; anterior-posterior, septal-lateral, and apical-basal.

TABLE 1. *Hemodynamic parameters during the five study phases*

	Baseline	HF	HF + BiV DCC	HF + LV DCC	HF + RV DCC
CO (L/min)	3.2 ± 0.6	1.4 ± 0.4*,**	2.9 ± 0.7	2.2 ± 0.5*,**	2.2 ± 0.5*,**
HR (beats/min)	103 ± 12**	85 ± 10*	85 ± 10*	84 ± 12*	84 ± 10*
SV (mL)	32 ± 8	16 ± 5*,**	34 ± 8	27 ± 5**	26 ± 6*,**
MABP (mmHg)	65 ± 16	38 ± 7*,**	59 ± 13	46 ± 13*,**	48 ± 13*,**
LVSP (mmHg)	79 ± 15	52 ± 9*,**	82 ± 11	68 ± 12*,**	68 ± 12*,**
LVEDP (mmHg)	21 ± 8	22 ± 7	22 ± 7	22 ± 7	24 ± 8*,**
Max LV dP/dt (mmHg/s)	1196 ± 370**	474 ± 154*,**	1613 ± 349*	1564 ± 287	1438 ± 286
Min LV dP/dt (mmHg/s)	–1160 ± 306**	–521 ± 262*,**	–2894 ± 1637*	–1650 ± 619*,**	–1561 ± 616**
RVSP (mmHg)	27 ± 10	23 ± 6**	37 ± 9	30 ± 5	33 ± 7
RVEDP (mmHg)	15 ± 6	15 ± 4	16 ± 5	16 ± 5	15 ± 4

*$P < 0.05$ compared to baseline values, **$P < 0.05$ compared to BiV DCC assist.
$n = 10$ for all groups except MABP ($n = 8$) and RV pressures ($n = 5$).
HR, heart rate; MABP, mean arterial blood pressure; RVSP, RV systolic pressure; RVEDP, RV end-diastolic pressure.

sia as described for patch implantation. Arterial and LV pressure were monitored via a carotid artery cutdown using DTXPLUS (Ohmeda Pty Ltd., Singapore) and Mikro Millar (Millar Instruments Inc., Houston, TX, USA) transducers, respectively. Another Mikro Millar catheter inserted into one of the patches monitored driving pressure. A 6 Fr right judkins catheter was inserted via a jugular cutdown, approximately 2–3 cm into the coronary sinus with contrast guidance.

Acute HF was induced using i.v. esmolol (esmolol hydrochloride, Boots Healthcare Australia Pty Ltd., North Ryde, New South Wales, Australia) 2.5 g diluted in 500 mL normal saline. The drug was infused with an IVAC 591 infusion pump (IVAC Corp., San Diego, CA, USA) to achieve a stable reduction of 50% in CO. DCC assist was timed to commence 2 ms after the ECG R wave, with systolic assist duration 35% of the R-R interval and driving pressure of 190 ± 41 mmHg and diastolic suction of –5 ± 17 mmHg. BiV, LV, and RV DCC assists were activated in random sequence, with no difference in driving pressure. Stability of HF was confirmed between each assist state. Data acquisition in each study phase was performed when hemodynamics had stabilized, and paired aortic and coronary sinus blood samples were collected at this time for blood gas analysis.

Pressure signals were amplified by Triton System 6 pressure amplifiers (Triton Technology, Inc., San Diego, CA, USA), while instantaneous aortic and left coronary artery blood flow velocities were monitored by the Transonic flowmeter (Transonic Systems, Inc.). The integral of the flow curves describes CO and CBF, respectively. Stroke work (SW) was calculated as SW = stroke volume (SV) × (LV systolic pressure [LVSP] – LV end-diastolic pressure [LVEDP]), and myocardial oxygen consumption (MVO_2) was calculated as MVO_2 = CBF × (aortic oxygen content – coronary sinus oxygen content). Segmental shortening was calculated using sonomicrometry as (end-diastolic length – end-systolic length)/end-diastolic length and expressed as a percentage.

Animals were euthanized at the end of the studies with an i.v. overdose of 3 g KCl. The heart was harvested, and the left ventricle was blotted dry and weighed after removing both atria, RV free wall, epicardial fat, and the large blood vessels. Sonomicrometer crystal positions were confirmed.

Data analysis

All data were expressed as mean ± SD. All parameters were compared at the five study phases (baseline, HF, HF + BiV DCC, HF + LV DCC, and HF + RV DCC) using repeated measures analysis of variance (ANOVA) with Bonferroni post hoc comparisons. Friedman repeated measures ANOVA on ranks with Student–Newman–Keuls post hoc comparisons were used for nonnormally distributed data. Statistical analyses were performed using SigmaStat software (SPSS, Chicago, IL, USA).

RESULTS

Hemodynamic effects of bi- and univentricular DCC

Hemodynamic parameters at each condition are displayed in Table 1. Esmolol infusion caused a significant 57 ± 11% reduction in CO ($P < 0.001$), which was achieved through reduction in both heart rate (17 ± 13%, $P < 0.05$) and SV (46 ± 19%, $P < 0.001$). BiV DCC restored CO and SV; however, when LV or RV assist was applied, increases in CO remained below baseline ($P < 0.001$ and $P < 0.001$) and BiV assist ($P < 0.001$ and $P < 0.001$) conditions. Similarly, mean arterial blood pressure and LVSP were reduced following esmolol infusion and restored with BiV DCC, yet remained below baseline and BiV assist

TABLE 2. *CBF pattern parameters during the five study phases*

	Baseline	HF	HF + BiV DCC	HF + LV DCC	HF + RV DCC
Mean CBF (mL/min)	145 ± 32**	63 ± 20*,**	91 ± 40*	76 ± 35*	82 ± 34*
Maximum CBF (mL/min)	466 ± 103**	304 ± 69**	965 ± 291*	740 ± 255*,**	534 ± 218**
Minimum CBF (mL/min)	–153 ± 84**	–144 ± 76**	–515 ± 303*	–439 ± 211*	–286 ± 142**
Systolic CBF (%)	22 ± 11**	25 ± 33**	–68 ± 65*	–47 ± 83*	–1 ± 25**
Diastolic CBF (%)	78 ± 11**	75 ± 33**	168 ± 65*	147 ± 83*	101 ± 25**

*$P < 0.05$ compared to baseline values, **$P < 0.05$ compared to BiV DCC assist.
$n = 9$ for all groups.
CBF is through the left main coronary artery.

when LV or RV DCC was applied. LVEDP was unchanged in all conditions, except RV assist, when it was significantly elevated compared with baseline ($P < 0.05$) and BiV assist ($P < 0.05$). BiV, LV, and RV assists significantly improved maximum and minimum LV dP/dt, and in the case of BiV assist, this was beyond baseline values ($P = 0.027$ and $P < 0.05$). No significant effect on RV systolic pressure (RVSP) and end-diastolic pressure was observed, except during esmolol-induced HF, when RVSP was significantly less than with BiV assist ($P = 0.003$).

Effects of bi- and univentricular DCC on coronary flow patterns

The effects of BiV, LV, and RV assists on CBF (through left main coronary artery) are displayed in Table 2. Total coronary flow was reduced with esmolol infusion (most likely due to reduced oxygen demand) and remained below baseline for all three assist conditions. BiV assist caused peak forward and retrograde CBF to increase significantly compared to all other study phases (except LV assist for peak retrograde CBF). BiV and LV assists also caused significant alterations to the phasicity of CBF; systolic CBF was completely retrograde with BiV and LV DCC, and this was significantly different from baseline ($P < 0.001$), HF ($P < 0.001$), and RV DCC ($P = 0.014$).

Energetic effects of bi- and univentricular DCC

SW, MVO_2, and resulting LV efficiency are displayed in Fig. 3. SW and MVO_2 were significantly reduced with esmolol infusion ($P < 0.05$ and $P < 0.05$), but LV efficiency (SW/MVO_2) remained unchanged. The reduction in MVO_2, like coronary flow, was probably due to a reduction in oxygen demand as oxygen extraction was unchanged across the study phases, $P = 0.253$ (data not shown). BiV, LV, and RV assists all restored SW to baseline level, while MVO_2 remained unchanged from HF alone. While no significant difference in SW between BiV, LV, and RV assists could be demonstrated, LV efficiency was significantly improved with BiV DCC compared with LV or RV assists alone ($P = 0.002$ and $P = 0.004$, respectively).

Effects of bi- and univentricular DCC on cardiac geometry

The effect of BiV, LV, and RV assists on cardiac shape was assessed using sonomicrometry of three orthogonal LV dimensions (Fig. 4). End-diastolic dimensions were unchanged throughout the study period. Anterior-posterior end-systolic length was increased with both BiV and LV DCC assists compared to baseline ($P = 0.002$ and $P = 0.001$, respectively), which resulted in reduced shortening of this axis during these phases ($P < 0.001$ and $P < 0.001$).

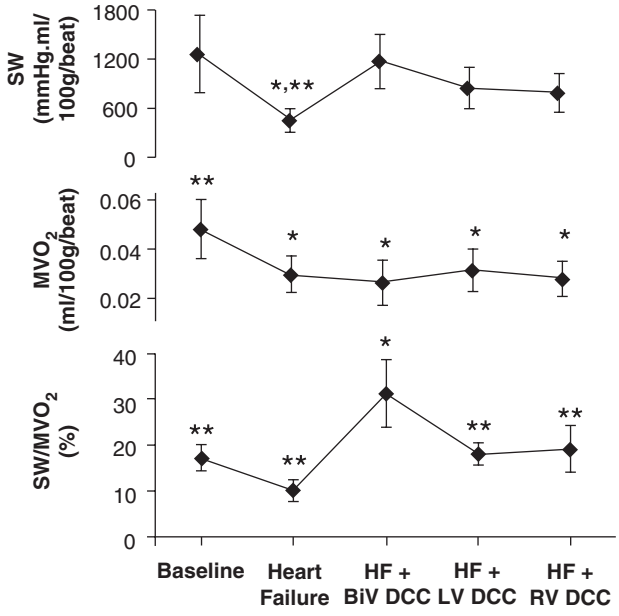

FIG. 3. SW and MVO_2 in the five study phases. SW/MVO2 (%) is an indication of LV efficiency; when DCC device is active, this represents the combined efficiency of native heart and DCC. *$P < 0.05$ compared to baseline values; **$P < 0.05$ compared to BiV DCC assist. $n = 10$ in each group.

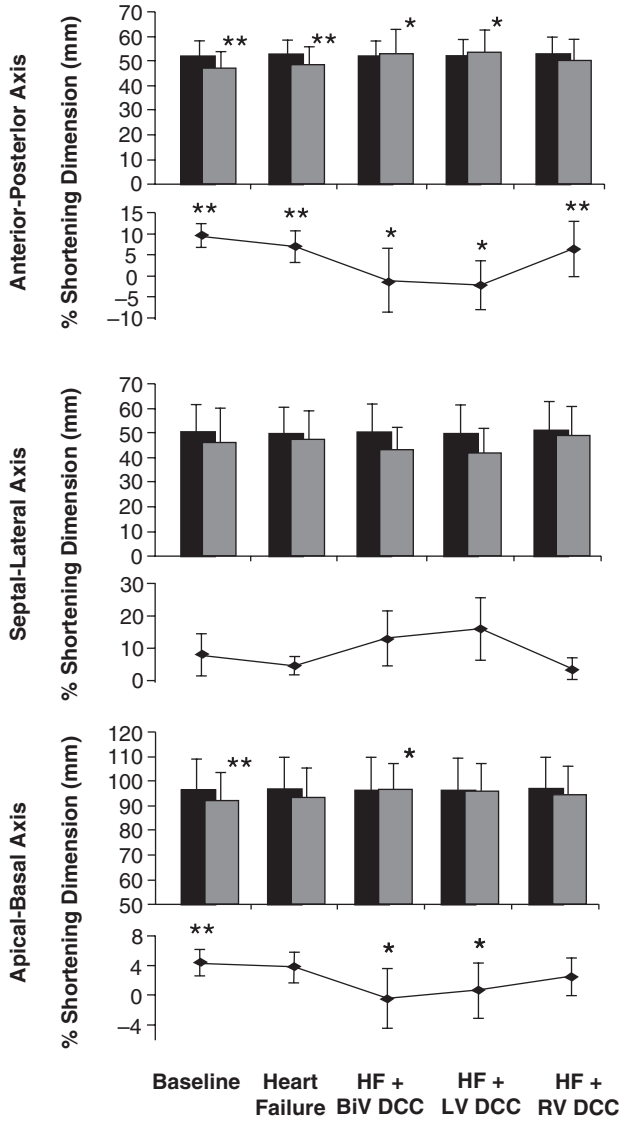

FIG. 4. LV dimensions of three orthogonal axes measured by sonomicrometry. Dark columns indicate end-diastolic values; light columns indicate end-systolic values. *$P < 0.05$ compared to baseline values; **$P < 0.05$ compared to BiV DCC assist. $n = 5$ for anterior-posterior axis; $n = 4$ for septal-lateral axis; and $n = 3$ for apical-basal axis.

DCC assist demonstrated the opposite response in septal-lateral dimensions and shortening (as patches are placed on lateral free walls). Septal-lateral shortening was greatest, and end-systolic dimension was shortest with BiV and LV assists; however, these failed to reach significance ($P = 0.137$ and $P = 0.091$, respectively). Similar to the anterior-posterior axis, apex-base shortening was reduced with BiV and LV DCC compared to baseline ($P < 0.05$ and $P < 0.05$). Taken together, these results demonstrate that BiV and LV assists result in the greatest shortening of the septal-lateral axis, at the expense of anterior-posterior and apex-base shortening. That is, BiV and LV assists cause the greatest deviation from normal cardiac geometry during systole.

DISCUSSION

The results of this study demonstrate that BiV DCC assist in stable, acute, esmolol-induced HF restores circulatory parameters to baseline values. While LV or RV DCC confers some hemodynamic benefit, it is inferior to that of BiV assist. Interestingly, LV and RV assists are equally effective in terms of hemodynamic and energetic response; however, their mechanisms of action appear to differ. RV assist resulted in less alteration to coronary flow patterns and cardiac geometry, presumably due to the fact it was not directly compressing on the LV. In spite of this, however, LVSP and CO were just as high with RV DCC as with LV assist. One likely contribution is increased preload with RV assist, demonstrated by elevated LVEDP.

In the normal heart, RV function is largely reliant on contribution from the LV. Li and Santamore (5) demonstrated this in isolated rabbit hearts by inducing selective dysfunction to the LV free wall, RV free wall, or interventricular septum (IVS). While dysfunction of the LV free wall or IVS resulted in reduction of LV and RV developed pressures, RV free wall dysfunction had little effect, even on RV pressure.

In the present study, LV and RV DCC actuators were applied with equal pressure; thus, the left side of the heart was expected to retain its predominant functional role. As most of the parameters measured were left heart or systemic parameters, it was predicted that LV DCC would contribute more than RV DCC to hemodynamic and energetic improvements.

LV and RV DCC, however, demonstrated equal efficacy for almost all circulatory parameters recorded. This is at least partly due to the hemodynamic interaction of the ventricles, with the output of one ventricle becoming the input of the other. In the case of RV DCC, some of the benefits to LV function presumably arose due to increased LV preload, evidenced by elevated LVEDP. This relationship between the ventricles is favorable in this study because sheep do not suffer from cardiovascular disease or chronic LV failure; thus, the Frank-Starling law applies. Caution would be required in sheep with chronic HF, however, where LVEDP is already too high and pulmonary congestion may occur. In this situation, LV DCC alone may be more beneficial, with the introduction of RV assist only if RV failure

ensues. It is recognized that a shortcoming of the present study is that results observed in normal hearts with acute, esmolol-induced failure may differ from those with chronic, ischemic failure.

While other DCC devices are in experimental (6–11) and clinical (12,13) use, these devices are not capable of both univentricular and BiV assists, making the results of the present study difficult to compare with others. From the present study, however, it can be concluded that BiV DCC is superior to that of LV or RV DCC alone, and that LV and RV assists contribute equally to the efficacy of BiV support.

REFERENCES

1. Stevenson LW, Kormos RL, Bourge RC, et al. Mechanical cardiac support 2000: current applications and future trial design. June 15–16, 2000 Bethesda, Maryland. *J Am Coll Cardiol* 2001;37:340–70.
2. Jessup M. Mechanical cardiac-support devices—dreams and devilish details. *New Engl J Med* 2001;345:1490–3.
3. Rose EA, Gelijns AC, Moskowitz AJ, et al. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure Study G. Long-term mechanical left ventricular assistance for end-stage heart failure. *New Engl J Med* 2001;345:1435–43.
4. Huang Y, Gallagher G, Plekhanov S, Morita S, Brady PW, Hunyor SN. HeartPatch implanted direct cardiac compression: effect on coronary flow and flow patterns in acute heart failure sheep. *ASAIO J* 2003;49:309–13.
5. Li KS, Santamore WP. Contribution of each wall to biventricular function. *Cardiovasc Res* 1993;27:792–800.
6. Anstadt MP, Anstadt GL, Lowe JE. Direct mechanical ventricular actuation: a review. *Resuscitation* 1991;21:7–23.
7. Hotei H, Koura Y, Orihashi K, Sueda T, Fukunaga S, Matsuura Y. Development of a direct mechanical left ventricular assist device for left ventricular failure. *Artif Organs* 1997;21:1026–34.
8. Kavarana MN, Helman DN, Williams MR, et al. Circulatory support with a direct cardiac compression device: a less invasive approach with the AbioBooster device. *J Thorac Cardiov Sur* 2001;122:786–7.
9. Kawaguchi O, Goto Y, Ohgoshi Y, Yaku H, Murase M, Suga H. Dynamic cardiac compression improves contractile efficiency of the heart. *J Thorac Cardiov Sur* 1997;113:923–31.
10. Wang Q, Yambe T, Shiraishi Y, et al. An artificial myocardium assist system: electrohydraulic ventricular actuation improves myocardial tissue perfusion in goats. *Artif Organs* 2004;28:853–7.
11. Kaczmarek I, Feindt P, Boeken U, Guerler S, Gams E. Effects of direct mechanical ventricular assistance on regional myocardial function in an animal model of acute heart failure. *Artif Organs* 2003;27:261–6.
12. Anstadt MP, Bartlett RL, Malone JP, et al. Direct mechanical ventricular actuation for cardiac arrest in humans. A clinical feasibility trial. *Chest* 1991;100:86–92.
13. Lowe JE, Anstadt MP, Van Trigt P, et al. First successful bridge to cardiac transplantation using direct mechanical ventricular actuation. *Ann Thorac Surg* 1991;52:1237–43.