Hemodynamic and Metabolic Effects of Paced Linkage Following Heterotopic Cardiac Transplantation

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Background and Purpose  Heterotopic cardiac transplantation is a valuable surgical technique that maximizes the use of donor organs. However, recipient heart function may decline steadily postoperatively with resulting clinical deterioration. Paced linkage has the potential of reducing afterload and enhancing coronary flow of both hearts, thereby improving recipient- and donor-heart function. This may have long-term as well as short-term benefits.

Methods and Results  The study was performed on 11 heterotopic transplant recipients. The two hearts were linked with a pacemaker (paced linkage) to produce recipient heart systole during different periods of donor-heart diastole. The recipient ventricular contraction was timed to occur during early, mid, and late diastole of the donor heart. Hemodynamic baseline measurements were compared with the optimal counterpulsated data. Paced linkage produced significant improvements in total cardiac output, 5.0±0.9 compared with baseline 4.5±0.8 L/min (P=.021); recipient coronary sinus flow, 278±145 versus 186±108 mL/min (P=.022); and aortic systolic pressure, 135±27 versus 123±27 mm Hg (P=.005). There was an overall improvement in systolic ventricular performance in the recipient heart when pace linked, as evidenced by a significant increase in left ventricular systolic pressure of 118±36 compared with the baseline value of 108±33 mm Hg (P=.016), an increase in ejection period from 174±30 versus 203±48 (P=.046), and a decrease in the pre-ejection period of 147±37 when paced versus 181±39 milliseconds (P=.013). The metabolic studies showed a significant decrease in hypoxanthine release from a baseline level of 0.4 μmol/L to a paced value of −0.06 μmol/L (P=.002); these very low values would suggest that there is no evidence of ischemia. Hemodynamic changes in the donor heart included a significant reduction in the left ventricular end-diastolic pressure from 6.8±4.4 versus baseline of 10.5±5.8 mm Hg (P=.029) and in maximum −dP/dT from 3.2±1.7 versus baseline of 2.1±1.1.

Conclusions  Paced linkage after heterotopic cardiac transplant produces significant functional improvements in both hearts. Permanent pacemaker implantation may sustain these acute benefits and prevent the premature deterioration of the recipient heart. (Circulation. 1994;90:2342-2347.)

Key Words  pacing • hemodynamics • transplantation

Heterotopic heart transplantation is a valuable surgical technique for a specific subset of patients. At our institution, this operation accounts for 10% of heart transplants. However, premature deterioration of the recipient heart frequently occurs after heterotopic transplantation. In some patients, the recipient heart may fail to eject, as evidenced by continual aortic valve closure. In extreme cases, there may even be continuous aortic regurgitation.

The mechanism of this deterioration is unknown, although possible factors include the surgical ischemia time, the natural progression of the underlying heart disease, or the competitive contraction of the two hearts.

Afterload might be reduced and coronary flow increased if each ventricular systole were synchronized with the period of least systemic resistance. This situation may be achieved by linking the two hearts, using pacing techniques, to produce alternating ventricular systole. In a study in sheep, Raza et al7 demonstrated that the cardiac index was increased significantly by pacing the hearts sequentially. Kennelly et al8 described the use in humans of a dual atrial triggered pacing system that allowed either heart to dictate the rate, but this study did not include any hemodynamic evaluation. Breedveld et al9 described, in a case study, the use of a dual-chamber device (DDD) to ensure alternating cardiac contractions (paced linkage) with associated clinical and hemodynamic benefits. Although promising, these studies have not demonstrated adequately the hemodynamic influence of paced linkage, nor have they considered the potentially deleterious effects of rapid atrial pacing on the recipient heart.

This study was designed to evaluate the short-term hemodynamic and metabolic effects of paced linkage in heterotopic cardiac transplant patients. The metabolic influence of the increased heart rate was assessed in the recipient heart.

Methods

Patient Population  The study group consisted of nine men and two women, with a mean age of 50.6 years (range, 25 to 61 years). These patients were studied at a mean interval of 14.3 months after hetero-

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topographic heart transplantation. The underlying cause was dilated cardiomyopathy in four patients and ischemic heart disease in six. The indication for heterotopic transplantation was a donor-recipient organ-size mismatch in all patients. Pulmonary vascular resistance exceeding 4 wood units was present in five of these patients (four of which had ischemic heart disease).

The surgical technique has been described previously. This technique was applied to all patients with the inclusion of an anastomosis between the donor pulmonary artery and the recipient right atrium (Fig 1). The donor left heart acted as a left ventricular assist device.

Local ethical committee approval and written informed consent were obtained before commencement of the study.

The inclusion criteria stipulated that both hearts be in sinus rhythm. Patients were excluded from the study if there was any clinical evidence of rejection.

**Catheter Type and Placement**

Patients were in a supine non-sedated postabsorptive state during the studies. Two temporary pacing wires were introduced through the subclavian vein. The first was a 6F bipolar pacing wire that was positioned in the donor right atrium and connected to the atrial input of a temporary DDD pulse generator (Medtronic Inc). The second, a 5.5F bipolar atrial J pacing wire was positioned in the atrial appendage of the recipient right atrium. This was connected to the ventricular input of the pulse generator.

A 7.5F Swan-Ganz catheter was inserted into the right femoral vein and positioned in the pulmonary artery, so that wedge pressure recordings could be obtained on inflation of the balloon. Both the digital and analog signals were displayed on a portable scope (Sirecust 960).

A 7F coronary sinus flow catheter (Webster Laboratories) was introduced through the left subclavian vein into the coronary sinus of the recipient heart. Flow signals were digitally stored on a personal computer (PC), and a hard-copy printout was obtained from the Mingograf 7 (Siemens).

A 7F high-fidelity, dual-pressure transducer catheter (Millar Instruments) was inserted through the right femoral artery. The catheter was positioned alternately across each of the aortic valves, so that the distal transducer lay in the left ventricle and the proximal transducer lay in the ascending aorta. This catheter enabled the simultaneous recording of left ventricular and aortic pressures from each heart in turn. These signals were digitally recorded onto an optical disk on a 33-MHz 386 PC at a sampling frequency of 1000 Hz. Parallel analog signals were recorded on the Mingograf 7 for real-time visual scrutiny and a hard-copy printout.

**Procedure**

After changes in the pacing configuration were made, the patient was maintained in a constant state for at least 5 minutes before any measurement or sampling was undertaken. The order in which the pacing configurations (including the baseline) were examined was randomized.

**Baseline Measurements**

The parameters recorded at baseline were pulmonary artery, pulmonary capillary wedge, and recipient right atrial pressures. Simultaneous left ventricular and aortic pressure traces were recorded with the Millar catheter.

Total cardiac output was determined by thermodilution using the Swan-Ganz catheter. All recordings were made in triplicate, and the mean value was determined. Coronary sinus flow was determined using established techniques as described by Ganz et al.

Paired arterial and coronary sinus blood samples were taken after 5 minutes in each baseline or paced setting for (1) saturations, analyzed on a hemoxymeter OSM2 (Radiometer) and (2) analysis of the purine hypoxanthine.

**Pacing Intervals**

In six patients, recordings were taken with the recipient heart paced at a similar rate to the donor heart but in an asynchronous manner. This was to determine whether any hemodynamic changes were purely secondary to an increase in the recipient heart rate.

Paced linkage was achieved by sensing the donor atrium and pacing the recipient atrium. The interval between sensing in the donor and pacing in the recipient heart, as depicted by the
AV delay of the pulse generator, was varied to produce recipient systole during early, mid, and late diastole of the donor heart. These intervals were chosen (as opposed to fixed AV settings on the pacemaker) because considerable variation was seen in the intrinsic conduction of the recipient heart. The optimal pacing interval was defined as that which maximized the greatest number of variables within a patient.

**Hemodynamic and Metabolic Parameters**

All left heart pressures were digitally recorded, allowing detailed computer analysis (software packages provided by Telectronics Pty Ltd). The signals from both the donor and recipient hearts were averaged over a 10-second period for baseline and for each of the paced intervals.

For each heart, the left ventricular systolic and end-diastolic pressures were recorded. The maximum and minimum values of the first derivative were calculated subsequently. The left ventricular pre-ejection and ejection periods (determined by superimposition of left ventricular over aortic traces timed from the ECG) were measured using an interactive graphics program.

The systemic arterial, pulmonary artery, and recipient right atrial pressures were noted, and the pulmonary and systemic vascular resistances were calculated.

The digitized coronary sinus flow signals were analyzed using a specialized software package. The difference in the arterial and coronary sinus saturations was used in conjunction with the flow rates to determine the myocardial oxygen uptake. Paired arterial and coronary sinus samples were also analyzed for hypoxanthine content as a metabolic marker of ischemia.13

In brief, 0.8 mL of blood was mixed with an equal volume of a 1.3-mol/L solution of perchloric acid for the extraction of soluble metabolites. The resultant supernatant was neutralized and then analyzed for nucleotides and nucleosides using a reverse-phase high-pressure liquid chromatography (HPLC) method12 on a Merck-Hitachi HPLC system (BDH Instruments).

**Statistical Analysis**

Data were expressed as mean±SD values. Statistical analysis was performed with t tests for paired data. For each parameter studied, the baseline value was compared with the optimal paced value. All results are expressed as two-tailed probability. The limit of significance was taken to be $P<.05$.

**Results**

**Unlinked, Rate-Matched, Cardiac Output Measurements**

There was no significant change in cardiac output when the baseline values were compared with the rate-matched but unlinked paced values (4.5±0.8 versus 4.55±0.9 L/min when paced).

**Combined Hemodynamic Data**

Table 1 summarizes the combined hemodynamic data.

The optimal pacing interval corresponded with the early setting in five patients, the late setting in five, and the mid setting in two. The mean AV delay values were 7 milliseconds (early), 100 milliseconds (mid), and 220 milliseconds (late).

Cardiac output was significantly increased by counterpulsation from a mean value of 4.5±0.8 to 5.0±0.9 L/min. Despite a large interpatient variability, there was a significant increase in coronary sinus flow from 186±108 to 278±145 mL/min. Significant increases were also seen in the systolic aortic pressure from a mean of 123±27 to 135±27 mm Hg. Systemic and pulmonary vascular resistances were unaltered by counterpulsation.

**Recipient-Heart Hemodynamic Data**

There was a significant increase in left ventricular systolic pressure from the baseline value of 108±33 mm Hg to the optimal paced value of 118±36 mm Hg. In addition, there was an increase in the ejection period and a decrease in the pre-ejection period from 174±30 to 203±48 milliseconds and from 181±39 to 147±37 milliseconds, respectively. The maximum $-dP/dT$ showed a significant increase with a positive trend in $+dP/dT$. These changes (outlined in Table 2) were not secondary to any alteration in filling pressures because there was no change in the left ventricular end-diastolic pressure.

**Donor-Heart Hemodynamic Data**

These results are presented in Table 3.

There was a small but statistically significant reduction in the left ventricular end-diaostolic pressure of the donor heart, from 10.5±5.8 to 6.8±4.4 mm Hg ($P=.029$), and a significant increase in the maximum $-dP/dT$ from 2.1±1.1 to 3.2±1.7 mm Hg/ms ($P=.04$). The measured indices of systolic performance showed a trend to improvement, although none reached significance. The mean peak left ventricular pressure was increased from 127±26 to 140±34 mm Hg, while maximum $+dP/dT$ increased from 1.7±0.6 to 2.2±1.0 mm Hg/ms. There was a reduction in the pre-ejection period and an increase in the ejection period.

**Metabolic Studies**

These results are presented in Fig 3.

The amount of hypoxanthine released into the blood was used as a metabolic index of ischemia.13 From the paired coronary sinus and femoral artery blood samples, the difference of arterial − venous hypoxanthine

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**Table 1. Combined Hemodynamic Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CO, mm Hg</th>
<th>CS Flow, mL/min</th>
<th>Ao Sys, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.4±6.6</td>
<td>180±320</td>
<td>179±195</td>
</tr>
<tr>
<td>2</td>
<td>4.4±4.8</td>
<td>140±185</td>
<td>145±148</td>
</tr>
<tr>
<td>3</td>
<td>4.8±4.9</td>
<td>195±210</td>
<td>118±134</td>
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<td>4</td>
<td>5.0±6.7</td>
<td>130±180</td>
<td>125±140</td>
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<tr>
<td>5</td>
<td>3.8±4.1</td>
<td>230±290</td>
<td>126±160</td>
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<tr>
<td>6</td>
<td>4.7±5.1</td>
<td>130±180</td>
<td>152±141</td>
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<td>3.0±4.0</td>
<td>75±480</td>
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<td>4.6±5.0</td>
<td>230±180</td>
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<tr>
<td>9</td>
<td>6.1±5.6</td>
<td>450±577</td>
<td>112±121</td>
</tr>
<tr>
<td>10</td>
<td>3.7±3.7</td>
<td>35±103</td>
<td>92±104</td>
</tr>
<tr>
<td>11</td>
<td>4.2±4.5</td>
<td>245±360</td>
<td>122±129</td>
</tr>
</tbody>
</table>

Baseline: $P=.021$, Optimal CP*: $P=.022$, Baseline*: $P=.005$

CO indicates cardiac output; CS, coronary sinus; Ao Sys, aortic systolic pressure; and CP, counterpulsation.

*Values expressed as mean±SD.
was calculated. There was a reduction in hypoxanthine release from 0.14 to -0.06 μmol/L (P = .002).

**Discussion**

This study has demonstrated that the hemodynamic status of the heterotopic transplant patient may be significantly improved by paced linkage. This improvement occurs predominantly by enhancement of recipient-heart function and is not associated with any detrimental metabolic effects.

**TABLE 2. Recipient Heart Hemodynamic Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>LV Sys, mm Hg</th>
<th>EP, ms</th>
<th>PEP, ms</th>
<th>-dP/dT, mm Hg/ms</th>
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<tbody>
<tr>
<td>1</td>
<td>166-190</td>
<td>0-200</td>
<td>0-120</td>
<td>0.6-0.9</td>
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<tr>
<td>2</td>
<td>99-116</td>
<td>201-280</td>
<td>132-120</td>
<td>0.7-0.8</td>
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<tr>
<td>3</td>
<td>140-166</td>
<td>178-235</td>
<td>187-96</td>
<td>1.1-1.8</td>
</tr>
<tr>
<td>4</td>
<td>122-121</td>
<td>152-146</td>
<td>184-156</td>
<td>4.8-6.4</td>
</tr>
<tr>
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<td>133-135</td>
<td>205-200</td>
<td>130-120</td>
<td>1.2-1.3</td>
</tr>
<tr>
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<td>160-220</td>
<td>230-190</td>
<td>0.8-0.6</td>
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<tr>
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<td>206-235</td>
<td>180-125</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td>10</td>
<td>109-112</td>
<td>120-150</td>
<td>240-200</td>
<td>0.8-0.8</td>
</tr>
<tr>
<td>11</td>
<td>113-108</td>
<td>170-160</td>
<td>170-210</td>
<td>0.7-0.7</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD.

**TABLE 3. Donor Heart Hemodynamic Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>LV Sys, mm Hg</th>
<th>LV EDP, mm Hg</th>
<th>+dP/dT, mm Hg/ms</th>
<th>-dP/dT, mm Hg/ms</th>
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</thead>
<tbody>
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<td>1</td>
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<td>16-4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
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<td>145-151</td>
<td>14-6</td>
<td>1.3-2.2</td>
<td>1.3-1.5</td>
</tr>
<tr>
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<td>145-211</td>
<td>20-16</td>
<td>2.1-3.1</td>
<td>1.4-1.8</td>
</tr>
<tr>
<td>4</td>
<td>126-134</td>
<td>12-8</td>
<td>3.2-4.7</td>
<td>5.4-6.1</td>
</tr>
<tr>
<td>5</td>
<td>108-141</td>
<td>5-4</td>
<td>1.2-1.6</td>
<td>1.4-5.5</td>
</tr>
<tr>
<td>6</td>
<td>157-158</td>
<td>8-9</td>
<td>2.0-2.3</td>
<td>2.8-2.9</td>
</tr>
<tr>
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<td>1.6-2.1</td>
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<tr>
<td>8</td>
<td>112-102</td>
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<td>1.8-1.2</td>
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</tr>
<tr>
<td>9</td>
<td>108-113</td>
<td>6-2</td>
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<td>2.3-2.6</td>
</tr>
<tr>
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<td>115-119</td>
<td>16-10</td>
<td>2.3-2.4</td>
<td>2.1-2.4</td>
</tr>
<tr>
<td>11</td>
<td>107-117</td>
<td>8-10</td>
<td>1.6-2.0</td>
<td>1.9-2.1</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD.

**Fig 3.** Bar graph showing hypoxanthine release from the recipient heart during baseline and pacing in early, mid, and late diastole of the donor heart.

Theoretically, heterotopic transplantation should result in two hearts acting in parallel, each contributing to antegrade flow. In practice, the recipient heart often fails to contribute to cardiac output, with infrequent opening of the aortic valve. The worst scenario reveals retrograde flow caused by almost continuous aortic and mitral regurgitation. This asynchrony and competitive contraction may well contribute to a progressive deterioration of recipient-heart function in this group of patients, as has been reported by our group and others.3,4

Ten of the 11 patients studied in this series showed a significant improvement in total cardiac output when counterpulsation was compared with baseline values. During the baseline recordings, the recipient aortic valve failed to open with every beat. This was particularly the case when the systolic periods of the two hearts coincided. Using sequential pacing, we were able to time the systolic intervals of the two hearts so that the recipient aortic valve opened with every beat. This could account for the observed increase in cardiac output (Fig 4) but does not explain the mechanism.

There are several potential explanations. The first may be purely a rate phenomenon. To assess this, the baseline cardiac-output measurements were compared with values obtained from pacing the recipient heart at a similar rate to the donor heart but without counterpulsating the two. There was a slight but nonsignificant difference. This implies that the higher recipient heart rate is not the sole cause of the increased cardiac output.

Alternatively, there may be modification of the preload or afterload. The lack of change in the ventricular end-diastolic pressure, mean pulmonary capillary wedge pressure, or mean central venous pressure suggests that there is no alteration in preload. However, we were unable to quantify the differential flow from the common left atrium to the donor and recipient left ventricles, which would be determined by the compliance of the ventricles.

Paced linkage produced a significant increase in systolic aortic pressure, although systemic vascular resistance was unchanged. However, the afterload to which the recipient heart is subjected was reduced at
the time of recipient-heart systole. The arterial pressure immediately before valve opening was lower during counterpulsation than the baseline arterial pressure when the valve failed to open. The reduced afterload would also, in part, account for the decrease in the pre-ejection period. An improvement in coronary flow might well be another factor.

Despite increasing the recipient heart rate, there was no increase in myocardial oxygen consumption from the baseline value of 21±13.3 compared with 24±15 mL/min. This was probably due to a decrease in cardiac work related to the diminished afterload. This suggests that the increase in the coronary sinus flow is secondary to the improved coronary perfusion pressure (created by timing recipient-heart diastole with the period of maximal aortic pressure) rather than an example of autoregulation in response to myocardial demand.

The increased myocardial perfusion may contribute to the improved myocardial performance (evidenced by increased positive and negative dP/dT). Furthermore, the increased cardiac output with no change in oxygen consumption suggests that the ventricle is more efficient.

If we assume aortic valve opening implies ejection, then the period of greatest wall stress (the isovolumetric contraction) is reduced compared with an isovolumetric contraction throughout systole, when the valve fails to open. This may be important for long-term maintenance of left ventricular function. We instituted pacing for short periods, which may be inadequate to evaluate fully the effect of off-loading on either the systolic or diastolic function of the ventricle.

Concern that pacing the recipient heart at a faster rate would increase the metabolic burden and possibly render the heart ischemic proved to be unfounded. Purines are produced because of an imbalance of energy stores, resulting in a breakdown of ATP and in turn an increase in ADP and AMP. The end products of this cascade system are adenosine, inosine, and hypoxanthine. We used hypoxanthine production as a marker of metabolic and/or myocardial injury because it has been shown to be more sensitive than lactate.14 We saw no evidence of altered hypoxanthine release. Additionally, the data presented here show that there was no clinical or ECG evidence of ischemia.
The significant reduction in end-diastolic pressure in the donor heart may be explained by a change in the pattern of ventricular filling. We can speculate that a similar mechanism to that operating in the recipient heart could cause an increase in coronary sinus flow in the donor heart. These changes in coronary perfusion and perhaps, even more importantly, an increase in coronary pressure (increase in arterial pressure for a given combined left atrial pressure) may produce improvement of subendocardial perfusion and ventricular function, as described by Griggs et al.\textsuperscript{15} and Hoffman.\textsuperscript{16} Kitakaze and Marban\textsuperscript{17} have demonstrated in animal work that an increase in coronary perfusion (either pressure or flow) modulated intracellular calcium and consequently contractile force. Although we have shown an improvement in donor-heart hemodynamics, it may be that these changes are less profound in the presence of higher pressures generated by the donor heart.

The study design limited investigation to resting, supine patients who were generally healthy. The physiological influences of paced linkage during postural change and exercise were not assessed, nor was there any evaluation of the potential improvement in cardiac reserve. Enhancement of maximal cardiac performance by paced linkage would be of great importance during situations of maximal stress (ie, exercise or donor-heart rejection). The inability to measure the relative contribution of each heart is a limitation of this study. As a result, the evidence that paced linkage improves cardiac output by supporting the native heart is only indirect. The temporary nature of the study does not allow assessment of the potential influence of paced linkage on the preservation of native heart function.

This study has shown acute hemodynamic changes in the ventricular performance of both the donor and recipient hearts during paced linkage. This suggests that, when paced, the reduction in afterload has a significant effect on both hearts, as evidenced by the improved hemodynamic status. A chronic state of paced linkage could maximize the hemodynamic performance of the heterotopic transplant recipient and translate into clinical improvements. More importantly, this may prevent the observed deterioration in recipient-heart function. Further studies with implantation of permanent pacemakers are required to examine this aspect.

Acknowledgments

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