The Effects of Atrial Pacing on the Synergy and Hemodynamics of the Orthotopically Transplanted Canine Heart

By Severi Mattila, M.D., Neil B. Ingels, Jr., Ph.D., George T. Daughters II, M.S., Stephen C. Adler, M.D., Lewis Wexler, M.D., and Eugene Dong, Jr., M.D.

SUMMARY
Instantaneous left ventricular dynamics were measured from cineradiographs utilizing implanted tantalum coils as myocardial site markers in the orthotopically transplanted canine heart. Four parameters of myocardial synergy were obtained: mean shortening, anisotropy of contraction, mean time to half shortening, and asynchrony of contraction. Estimates of end diastolic volume, end systolic volume, stroke volume, ejection fraction, and cardiac output were obtained. Heart rate was altered by pacing the left atrium of the donor heart. Of the nine parameters, only cardiac output was significantly changed by alterations in heart rate. The invariance of stroke volume with rate resulted in a proportional increase in cardiac output with cardioacceleration.

Additional Indexing Words:
Left ventricle  Segmental shortening  Time-to-half shortening
Stroke volume  Cardiac output  Asynchrony  Anisotropy

ATRIAL PACING is commonly used to prevent cardiac arrhythmias in the immediate postoperative period following orthotopic cardiac transplantation. Chartrand, Dong and Shumway\(^1\) have shown that pacing increases cardiac output in dogs for up to 72 hr after transplantation. Little is known, however, about the effects of pacing on the transplanted heart during the ensuing period of recovery.

We have recently developed a technique to measure myocardial synergy and ventricular dynamics in the intact subject following thoracotomy. At surgery small tantalum coils which serve as permanent myocardial site markers for subsequent cineradiographic study are inserted into the mid-wall of the left ventricular myocardium. In this way, measurement can be made of the magnitude and rate of segmental shortening, and the spatial and temporal synergy of myocardial contraction; instantaneous ventricular volumes can also be estimated.

This method was used to evaluate the effects of atrial pacing in dogs for the period of two to 14 days following orthotopic cardiac transplantation.

Materials and Methods
Surgical Techniques. Five mongrel dogs weighing 10-15 kg underwent cardiac transplantation. Pentobarbital (25 mg/kg) was used for anesthesia and a Kay-Cross disc oxygenator for cardiopulmonary bypass. The surgical technique has been previously described.\(^2\) During surgery one pacing wire was inserted at the left atrial appendix of the donor heart to serve as the negative electrode. An additional wire in the neck muscles of the recipient was used as the positive electrode. The ends of both wires were brought to the exterior through the skin in the neck.

Using a modification of the method described by Carlsson and Milne,\(^3\) four tantalum coils measuring 0.8 mm in diameter and 2 mm in length were inserted through the epicardium into the left ventricular midwall of the excised donor heart. Two coils were placed along the left anterior descending coronary artery and two along the major marginal branch of the circumflex coronary artery (fig. 1). These sites lie in a plane nearly parallel to that of the image intensifier when the dog is placed in the left lateral position on the X-ray table.

Postoperative Drug Therapy. Antithymocyte globulin, azathioprine\(^4\) (3 mg/kg) and dipyridamole\(^5\) (50

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\(^1\)Imuran, Burroughs Wellcome.
\(^2\)Persantine, Geigy.
mg) were administered to all dogs on a daily basis after surgery.

Pacing Studies. Studies were performed on awake, intact subjects without premedication. The dogs were trained to lie quietly in the left lateral position on the X-ray table while single plane cineradiographs were obtained at 33 frames per second on Kodak RAR 35 mm film using an Arriflex camera and a Philips 150 KVP, 1000 ma source and the 5 inch mode of a Philips dual mode image intensifier. The system was dimensionally calibrated and fixed geometry was maintained throughout all studies. Figure 2 shows a typical frame from a cineradiograph obtained in this study.

The electrocardiographic signal and cine frame marker were recorded on an Electronics for Medicine Physiological Recording Oscillograph with a paper speed of 100 mm/sec. A metal tipped solenoid, activated by the electrocardiographic R wave, was used to mark this event on the cineradiograph. Recordings were first obtained without pacing, then with atrial pacing up to 180 beats/min. Pacing pulses were provided by a Medtronic 5800 pacemaker.

Data Reduction. The six instantaneous distances between the myocardial markers were obtained from a frame-by-frame analysis of the cineradiographs as previously described.

For each beat, end diastolic length (EDL) was defined for each segment as the maximum length attained during the QR interval of the electrocardiogram and end systolic length (ESL) was defined as the minimum length attained during that contraction. Percentage shortening for each segment was calculated as:

\[ S = \frac{EDL - ESL}{EDL} \times 100, \]

and the time in msec required to accomplish half of this shortening (T50) was also determined for each segment.

Mean shortening (\( \bar{S} \)) was calculated as the average of the shortening values for the four principally circumferential segments (1–2, 1–3, 2–4, 3–4) and mean time to half shortening (\( T50 \)) was calculated from the segmental T50 values in the same fashion.

Anisotropy (AI) was defined as the standard deviation of the shortening values for the four segments, and asynchrony (AS) as the standard deviation of the T50 values for these four segments.

The rationale behind the use of these parameters (\( \bar{S}, \) AI, T50, and AS) to quantitate myocardial synergy has been previously described. Briefly, they are justified as follows:

1. Mean Shortening (\( \bar{S} \)): an efficient ventricle must shorten by a sufficient amount to eject adequate stroke volume against the load.
2. Anisotropy (AI): an efficient ventricle will contract uniformly in all regions (i.e., isotropically). Dyskinesis will be reflected by increases in the value of AI.

**Figure 1**

The canine heart, showing placement of tantalum coils. Coils 1 and 4 are placed along the left interventricular coronary artery, and coils 2 and 3 along a marginal branch of the circumflex coronary artery.

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**Figure 2**

A typical frame from a cineradiogram obtained in these studies. Images of the radiopaque markers (1–4) are labeled in accordance with figure 1. RM indicates the solenoid-activated R wave marker, and PW the pacing wire in the left atrium of the donor heart.
### Table 1

**Summary of Experimental Results**

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<th>Dog no.</th>
<th>Wt (kg)</th>
<th>No. days postop</th>
<th>Heart rate*</th>
<th>% EDL</th>
<th>% EDL</th>
<th>T50 msec</th>
<th>AS msec</th>
<th>EDV ml</th>
<th>ESV ml</th>
<th>SV ml/kg</th>
<th>% EDV</th>
<th>CO ml/kg/min</th>
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Abbreviations: $\overline{S}$ = Mean shortening; $\overline{AI}$ = Anisotropy; $T_{50}$ = Mean time to half shortening; $AS$ = Asynchrony; $EDV$ = End diastolic volume; $ESV$ = End systolic volume; $SV$ = Stroke volume (normalized to body weight); $EF$ = Ejection fraction; $CO$ = Cardiac output (normalized to body weight).
3. Mean time to half shortening (T50): an efficient ventricle will shorten quickly after contraction. This parameter expresses the average speed of myocardiocellular contraction, and is related to systolic time intervals.

4. Asynchrony (AS): an efficient ventricle will have nearly identical T50's for each segment. If segments are contracting at different rates or at different times after excitation, ventricular function will be impaired and AS values will increase.

An estimate of left ventricular volume was obtained based on an ellipsoidal ventricular model whose minor axis was the segmental length 3-4 and whose semimajor axis was the length 2-3. End diastolic and end systolic volumes were calculated using end diastolic and end systolic values of these segmental lengths. Stroke volumes and ejection fractions were obtained from these volumes on a beat-to-beat basis, and cardiac output was calculated as the product of the mean stroke volume and the mean heart rate for the sequence.

Stroke volumes and cardiac outputs calculated according to this model have been shown to correlate with simultaneously performed dye dilution measurements (unpublished data). The regression equations are: 

\[ SV_{\text{end}} = 98 SV_{\text{dye}} \pm 26 \text{ ml/kg} \]  

and 

\[ CO_{\text{dye}} = 1.02 CO_{\text{dye}} \pm 23.6 \text{ ml/kg-min} \]  

A sequence of seven to ten beats was analyzed at each heart rate and the means and standard deviations calculated for all parameters.

Results

The experimental results are shown in table 1. Of particular interest are the findings that in the group as a whole: 1. mean time to half shortening T50 (which is proportional to the duration of systole) is not reduced as heart rate is increased, and 2. stroke volume is unchanged by heart rate (fig. 3), which results in a proportional increase in cardiac output with increasing rate (fig. 4). Linear regression analysis (summarized in table 2) shows that of the nine parameters studied, only cardiac output is significantly \( P < .01 \) affected by heart rate.

Discussion

The common finding in pacing studies of normal resting canine or human subjects is an invariant cardiac output with increasing rate, due to a significant reduction in stroke volume with cardio-acceleration.\(^6\) \(^7\) \(^8\) This reduction in stroke volume has been attributed to abbreviated diastolic filling periods or mistimed atrial systole at the higher rates.\(^9\) \(^10\)

In a previous study\(^5\) it was shown that these mechanisms alone are inadequate to explain this reduction. The awake resting dog was seen to experience the expected reduction in stroke volume when atrially paced to higher rates. In spite of equivalently altered systolic duration, diastolic filling period, and timing of atrial systole, this reduction in stroke volume with rate was abolished by halothane anesthesia. It was suggested that halothane reduced stroke volumes to a level which decreased demand on the venous reservoir, allowing adequate ventricular filling over the full range of rates studied.
In the present study the duration of systole was unchanged with rate, with the result that the diastolic filling periods in the transplanted heart were reduced even more rapidly at higher rates than in the normal heart. Stroke volume was invariant with rate and mean stroke volume was below normal.11

Dong et al. have shown a persistent increase in blood volume following cardiac transplantation12 possibly due to a loss of the Bainbridge reflex in the denervated heart.13 Thus the potentially increased venous supply together with the reduced ventricular demand (low stroke volumes) could insure adequate filling over the range of rates studied with the result that cardiac output is significantly increased at higher rates.

In one dog (1993), studies were made on the second and thirteenth postoperative days. On the second postoperative day stroke volumes were low, invariant with rate, and cardiac output was significantly \((P < 0.01)\) increased by pacing. On the thirteenth postoperative day, stroke volume had increased and was reduced significantly \((P < 0.01)\) at the higher rate. In this dog the increased stroke volume may well have exceeded the capability of the venous reservoir at the elevated rates with the result that cardiac output did not change with rate.

An unexpected finding was that mean time-to-half shortening (\(T_{50}\)) did not change when the heart was paced to faster rates. This parameter has been shown to be directly proportional to the duration of systole.5 Previous studies in intact dogs and humans have consistently demonstrated a reduction in \(T_{50}\) and the duration of systole with increasing rate.5,14,15 The mechanism underlying the invariance of \(T_{50}\) with rate is presently unclear, but is likely to involve the denervated state of the transplanted heart.

### Acknowledgments

The authors gratefully acknowledge the continued assistance of Louise Shreve and the staff of the data analysis group at the Stanford Linear Accelerator Center, and the valuable technical assistance of Kathleen Haugse and Kathy Shockley.

### References

5. Ingels NB, Daughters GT, Wexler L, Smith NT: The effect of right atrial pacing on left ventricular synergy and hemodynamics in the awake and halothane anesthetized canine subject (Submitted for publication)

---

**Table 2**

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*Units are as shown in table 1, except slope, which is given in (units/beats per min).*

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