

## Ventricular arrhythmias in long term survivors of orthotopic and heterotopic cardiac transplantation

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**SUMMARY** Fourteen long term survivors with orthotopic (recipient heart replaced by donor heart) and nine with heterotopic cardiac transplants (recipient heart retained) had 24 hour ambulatory electrocardiographic monitoring to detect ventricular arrhythmias. Arrhythmia was uncommon in the patients with orthotopic transplants; none of them had more than one extrasystole per hour. In the patients with heterotopic cardiac transplants the recipient's own heart showed significantly more frequent ventricular arrhythmias than the corresponding donor heart: abnormal complexes (mean/24 h) 4583 *vs* 42.7; extrasystoles 1772 *vs* 17.8; pairs 121 *vs* 0.8. There was no relation between the abnormal ventricular activity of the two hearts in the patients with heterotopic transplants on a beat by beat, hourly, or 24 hour basis. There was no consistent diurnal variation in the frequency of the abnormal ventricular beats after cardiac transplantation. The occurrence of ventricular arrhythmia was unrelated to the interval from operation to the study.

In long term survivors of cardiac transplantation the denervated heart shows a little ventricular ectopic activity even when compared with normal hearts. In patients with heterotopic transplants ventricular arrhythmias commonly occur in the recipient's own heart; these are probably related to the underlying severity of the original disease.

Ventricular arrhythmias during ambulatory monitoring have been reported to be more frequent in patients after conventional orthotopic cardiac transplantation than in normal subjects.<sup>1-3</sup> Most of these arrhythmias occur soon after the operation.<sup>4</sup> Little is known about their occurrence, possible causes, and potential influence on prognosis in late survivors of cardiac transplantation.<sup>5</sup>

The development of two channel electrocardiographic recorders and computerised analysers permits the separate identification of the QRS complexes of the two hearts (donor and recipient) after heterotopic cardiac transplantation and a quantitative simultaneous study of the ventricular arrhythmias of both hearts during Holter monitoring.

The purpose of our study was to (a) find out how common ventricular arrhythmia was in the den-

ervated heart late after transplantation, (b) to assess whether ventricular arrhythmia was more common after heterotopic transplantation than after orthotopic transplantation, and (c) to compare the occurrence of ventricular arrhythmia in the denervated donor and innervated recipient hearts in patients with heterotopic transplants.

### Patients and methods

Fourteen men with orthotopic (mean (SD) age 45 (8) years) and nine patients with heterotopic (eight men and one woman, age 42 (10) years) cardiac transplants were studied by ambulatory 24 hour electrocardiographic monitoring. Donor hearts were obtained from individuals aged 22 (7) years. The surgical techniques are described elsewhere.<sup>6,7</sup> The interval from operation to the study varied from six to 42 months (mean 20) in the orthotopic and from seven to 18 months (mean 11) in the heterotopic transplantation group. Most of the patients were taking a mixture of drugs (cyclosporin, azathioprine, prednisolone, aspirin, dipyridamole, and diuretic) but no patient was on an antiarrhythmic drug. All patients were symptom free, ambulant, and performing their

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Accepted for publication 15 December 1987

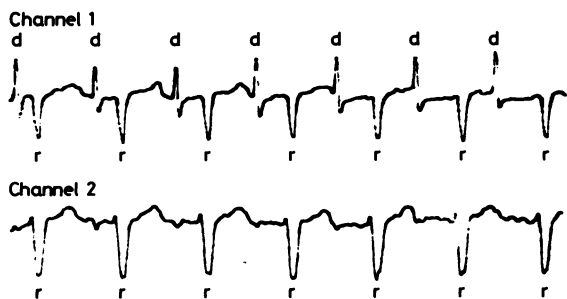


Fig 1 Typical electrocardiographic trace from 24 hour Holter monitoring of a patient with a heterotopic cardiac transplant. Channel 1: donor's (d) and recipient's (r) QRS complexes are clearly distinguishable. Channel 2: recipient's (r) QRS complex is dominant.

usual daily activities. Each patient kept a detailed diary of activity and symptoms. The most recent biopsy specimen was normal in 21 patients but two patients showed evidence of mild rejection.

#### ELECTROCARDIOGRAPHIC RECORDING

Ambulatory 24 hour electrocardiograms were recorded on Oxford Medilog II recorders with two channels. The skin was carefully prepared and electrodes were placed to record modified lead V1 and V4 in patients with orthotopic transplants. In patients with heterotopic transplants a modified V4R lead was recorded instead of V1 to permit better separation of the two QRS complexes. Because the donor heart lay to the right of the recipient heart its QRS complex was clearly delineated in V4R whereas in lead V4 the QRS complex of the recipient's own heart was dominant. Figure 1 shows a typical electrocardiographic trace from a patient with a heterotopic cardiac transplant.

#### ARRHYTHMIA ANALYSIS

We used a computerised template system (J Johnston, Oxford), based on a QRS pattern recognition that could classify QRS complexes into different families, to analyse the ventricular arrhythmias. The system consisted of a Z80A pre-processor and a DEC LSI-11 master. The normal QRS complex was defined by the operator and recognised by the system thereafter. Any unrecognised QRS complex was screened carefully by the operator and if its shape indicated a ventricular origin or abnormal ventricular conduction it was classified and subsequently recognised as an "abnormal complex". We used the following definitions: extrasystole, an abnormal complex with a coupling interval less than 80% of the previous RR interval; pair, two consecutive abnormal complexes; run, three or more abnormal com-

plexes with a rate less than 120 per minute; ventricular tachycardia, three or more ventricular extrasystoles with a rate greater than 120 per minute. Figure 2 shows an example of ventricular extrasystoles from the donor and the recipient heart of a patient with a heterotopic transplant.

Every electrocardiographic tape from the group with heterotopic transplants was analysed twice and the dominant QRS complex on each channel was identified separately. In the heterotopic transplant group we attempted to correlate the frequency of the abnormal complexes and ventricular extrasystoles in the two hearts during the whole 24 hour period and also on an hourly basis. In addition, we attempted to study the possible temporal relation between individual extrasystoles in the two hearts.

The times of waking up and sleeping were noted and the mean rates of abnormal complexes and extrasystoles during sleep and wakefulness were calculated in both groups.

Finally, in both groups we examined the severity of arrhythmia and the interval since operation to see whether there was a correlation.

#### STATISTICAL ANALYSIS

All data are expressed as mean values (1 SD). We used the paired or unpaired Student's *t* test and the non-parametric Wilcoxon test as appropriate.

#### Results

##### CLINICAL CHARACTERISTICS

Not surprisingly, the donor hearts were obtained from individuals who were younger than the recipients ( $p < 0.001$ ). The ages of the donors and

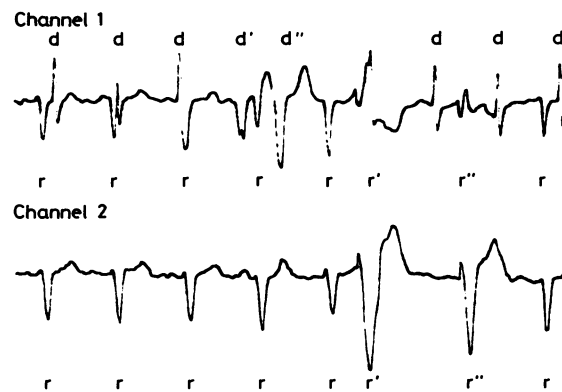


Fig 2 Electrocardiographic trace of a patient with heterotopic cardiac transplantation with extrasystoles from both hearts. Channel 1: donor's (d) QRS complex is dominant. Channel 2: recipient's (r) QRS complex is dominant. *d'* and *d''*, extrasystoles from donor's heart. *r'* and *r''*, extrasystoles from recipient's heart.

the recipients in the orthotopic and heterotopic transplant groups were not significantly different. The mean interval from operation to the study was longer in the orthotopic group than the heterotopic transplantation group ( $p < 0.02$ ).

No symptoms were reported by patients during the 24 hour study period.

#### ARRHYTHMIAS

Tables 1 and 2 shows the number of the "abnormal complexes", extrasystoles, pairs, and runs in the two groups of patients. Ventricular tachycardia was not seen in any patient. Nine (39%) out of the 23 denervated hearts had no abnormal ventricular activity at all and in rest such activity was infrequent. This low occurrence of ventricular arrhythmia was similar in the donor hearts of both groups. We saw many abnormal complexes and extrasystoles in the recipient hearts of those patients with heterotopic transplants.

Analysis of the arrhythmia frequency in those with heterotopic transplants on a 24 hour or hourly basis showed no relation between the two hearts. The occurrence of an extrasystole in the one heart did not correlate with the presence of an extrasystole in the other heart.

Table 3 shows the frequency of abnormal complexes per hour during sleep and waking. Abnormal complexes were less common during sleep in four donor and two recipient hearts in the nine patients with heterotopic transplants. In the orthotopic group three of the eight patients with abnormal ventricular activity showed a decline in the frequency during sleep. The occurrence of extrasystoles during the 24 hour period was also reduced during sleep.

Finally, the occurrence of abnormal complexes or ventricular extrasystoles was unrelated to the time since operation in both the orthotopic and heterotopic groups.

Table 1 Complexes with abnormal QRS shape and ventricular arrhythmias detected during 24 hour monitoring in patients with orthotopic cardiac transplants

No	Abnormal complexes	Extrasystoles	Pairs	Runs
1	0	0	0	0
2	5	2	0	0
3	0	0	0	0
4	21	19	1	0
5	9	9	0	0
6	0	0	0	0
7	9	9	0	0
8	0	0	0	0
9	3	2	0	0
10	1	1	0	0
11	1	3	0	0
12	0	0	0	0
13	0	0	0	0
14	29	6	2	1
Mean	5.9	3.6	0.3	0.1

#### Discussion

We are unaware of any previous reports of Holter monitoring of ventricular arrhythmias in patients with heterotopic cardiac transplants. This is perhaps because patients with this type of cardiac transplantation (where the original heart is retained) are rare and it is difficult to separate the QRS complexes of the two hearts during ambulatory monitoring. We found that the occurrence of ventricular arrhythmias was similar in the donor hearts of patients with orthotopic and heterotopic transplantation, so differences in surgical technique and haemodynamic function do not seem to influence significantly the occurrence of ventricular arrhythmia. In contrast, the recipient hearts of the heterotopic transplantation group showed substantially greater ventricular arrhythmia, probably because of contributory factors such as the presence of severe coronary or myocardial disease, possible dysfunction of the autonomic regulatory pathways,<sup>8-10</sup> and surgical trauma.

Table 2 Complexes with abnormal QRS shape and ventricular arrhythmias detected during 24 hour monitoring in patients with heterotopic cardiac transplants

No	Donor heart				Recipient heart			
	Abnormal complexes	Extrasystoles	Pairs	Runs	Abnormal beats	Extrasystoles	Pairs	Runs
1	20	20	4	0	14608	3421	410	241
2	0	0	0	0	2337	860	23	0
3	4	4	0	0	41	35	6	0
4	8	8	0	0	18	18	2	2
5	0	0	0	0	19	17	0	0
6	0	0	0	0	222	200	0	0
7	11	11	3	0	2658	7599	90	91
8	4	2	0	0	25	13	0	0
9	337	115	0	0	11317	3788	563	318
Mean	42.7	17.8	0.8		4583†	1772†	121*	

Compared with the donor heart: \* $p < 0.05$ . † $p < 0.01$ .

Table 3 Number of abnormal complexes per hour while patients were awake and asleep

Heterotopic					Orthotopic		
No of patient	Donor		Recipient		No of patient	Donor	
	Awake	Asleep	Awake	Asleep		Awake	Asleep
1	1.3	0.1	256	1302	2	0.1	0.4
2	0	0	115	69	4	1.1	0.6
3	0.1	0.5	1.9	1.7	5	0.2	0.8
4	0.4	0	0.4	1.7	7	0.3	0.3
5	0	0	0.9	0.9	9	0.1	0
6	0	0	7.2	12.8	10	0	0.1
7	0.6	0.2	328	845	11	0.3	0
8	0.3	0	1.2	1	14	1.7	0.7
9	7.2	27	687	40			

Ventricular arrhythmias were uncommon in the denervated transplanted heart; they were no more common than in normal individuals.<sup>11-13</sup> Only one denervated heart in this series showed more than a hundred extrasystoles in 24 hours; again this is probably within normal limits. The infrequent occurrence of ventricular arrhythmias during continuous ambulatory electrocardiographic monitoring in patients after orthotopic cardiac transplantation accords with previous studies,<sup>14</sup> although in these patients arrhythmias were less vigorously measured.

Several factors may be implicated in the arrhythmogenesis after cardiac transplantation. Supersensitivity to circulating catecholamines,<sup>15</sup> rejection episodes, and accelerated atherosclerosis<sup>16</sup> could favour the production of arrhythmia in the donor heart. But the low frequency of extrasystoles implies that such factors have a limited role. In the innervated hearts of the heterotopic group severe underlying disease (coronary artery disease, congestive cardiomyopathy) is the most likely cause for the increased numbers of arrhythmias. The lack of correlation between the arrhythmia in the donor and recipient heart underscores the importance of the different aetiological factors causing extrasystoles. In addition, the absence of simultaneous occurrence of arrhythmia indicates either lack of effect of the stimuli common for both hearts, such as hormonal factors and physical activity, or different bases for these stimuli in each heart.

Unlike normal subjects<sup>17</sup> we found no overall reduction in extrasystoles during sleep. Denervation of the donors' hearts and autonomic dysfunction<sup>12-14</sup> of the severely diseased recipient's own hearts might be responsible for the absence of a diurnal variation. It was interesting that some of the denervated donor hearts did show a reduction in extrasystoles during sleep; this probably reflects the lowered plasma catecholamines seen during sleep, with perhaps some added amplification caused by denervation supersensitivity.

Despite the frequent occurrence of extrasystoles in the recipient heart our patients did not report dizziness or palpitations. This presumably reflected the relatively small contribution of the recipient heart to total cardiac output.

Our study is limited by the short duration (24 hours) of electrocardiographic monitoring, since there is a significant day to day variability in the frequency of extrasystoles in patients with innervated hearts<sup>18</sup>; there is no information on such variability after cardiac denervation. The generally low occurrence of arrhythmia suggests that there will be less day to day variation in counts.

In conclusion, ventricular arrhythmias were no more common in donor hearts than in normal individuals. In contrast, the very high occurrence of ventricular extrasystoles in recipient hearts was probably related to their underlying severe disease. There was no evidence of simultaneous arrhythmia in both recipient and donor hearts.

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