BRADYARRHYTHMIAS AND CONDUCTION DISTURBANCES AFTER HEART TRANSPLANTATION

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CONTENTS

	PAGE
ABSTRACT	15
CHAPTER 1: INTRODUCTION	19
The immediate effects of transplantation on heart rate and rhythm	20
Cold ischaemia	20
Acute autonomic denervation	21
Persistent bradyarrhythmias	22
Sinus node dysfunction after heart transplantation	23
Electrophysiology	23
Assessment of sinus node function	23
Sinus node function after transplantation	26
Sinus node dysfunction after transplantation	28
Bradyarrhythmias	29
Chronotropic incompetence	31
Assessment of chronotropic competence	31
The "normal" chronotropic response after transplantation	32
Chronotropic incompetence after transplantation	34
Aetiology of sinus node function after heart transplantation	34
Atrioventricular conduction after transplantation	37
Electrophysiology	37
Assessment of atrioventricular conduction	37
AV conduction after transplantation	39
Abnormalities of AV conduction after transplantation	40
Bradyarrhythmias	41
Aetiology	42

PAGE

Intraventricular conduction after transplantation 44

Electrocardiography 44

Aetiology 44

The effects of sympathetic denervation 45

Responses to catecholamines in the transplanted heart 45

Beta adrenergic receptors in the transplanted heart 46

Catecholamines and bradyarrhythmias after transplantation 47

Drugs and the electrophysiology of the transplanted heart 49

Amiodarone 49

Pharmacokinetics 50

Electrophysiology 50

Electrophysiology of amiodarone after transplantation 51

Dose, electrophysiological effects, serum and tissue levels 52

Carbamazepine 53

Phenytoin 54

Diltiazem 54

Permanent pacing after transplantation 56

Pacing for early bradyarrhythmias 56

Indications 56

Timing of implantation 57

The need for long term pacing 58

Pacing for late bradyarrhythmias 59

Modes of pacing transplant recipients 59

Atrial, ventricular or dual chamber pacing? 59

PAGE

The need for rate responsive pacing 61

CHAPTER 2:
PERMANENT PACING AFTER CARDIAC TRANSPLANTATION 63

Introduction 63

Methods 64

Retrospective review 64

Prospective study 64

Statistical analysis 65

Results 65

Indications 65

Timing of pacemaker implantation 65

Drug therapy 67

Type and programming of pacemakers 67

Ischaemic time and donor age 67

Complications 67

Follow up 68

Prospective study 68

Discussion 70

Limitations of the study 70

Indications for permanent pacing 71

Timing of pacing and requirement for long term pacing 71

Late pacemaker implantation 72

Conclusions 72

PAGE

CHAPTER 3:
SINUS AND AV NODE FUNCTION AFTER TRANSPLANTATION 73

Introduction 73

Patients 74

Outcome 75

SECTION 1: ELECTROPHYSIOLOGICAL STUDIES 77

METHODS 77

Sinus node function 77

Atrioventricular node function 78

Statistical analysis 78

RESULTS 80

The electrophysiology of the sinus node 80

Sinus node function 80

Sinus node dysfunction 81

Complications and associations 82

Drug effects and sinus node electrophysiology 84

Amiodarone 84

Anticonvulsants 84

Diltiazem 85

Atrioventricular node electrophysiology 85

Effective refractory periods 85

Incremental atrial pacing 86

Complications and associations 87

Drugs and atrioventricular node physiology 89

PAGE

DISCUSSION 90

Sinus node electrophysiology 90

Sinus node function 90

Sinus node dysfunction 92

Late sinus node dysfunction 93

The aetiology of sinus node dysfunction 93

Conclusions 94

Atrioventricular node physiology 94

Atrioventricular node function 94

Atrioventricular node dysfunction 96

Conclusions 97

SECTION 2: EXERCISE TESTING 98

Methods 98

Analysis 99

Statistical methods 99

Results 100

Changes in heart rate during recovery 101

Exercise response in subjects with sinus node dysfunction 102

Correlation with sinus node electrophysiology, rejection, operative ischaemia and age 104

Drug effects 105

Discussion 106

Changes in exercise response and recovery with time after transplantation 106

Chronotropic competence and sinus node dysfunction 107

PAGE

Determinants of the chronotropic response in transplant recipients 108

Conclusions 108

SECTION 3: 24 HOUR AMBULATORY ELECTROCARDIOGRAPHIC MONITORING 109

Methods 109

Pacing policy 109

Analysis 109

Statistical methods 110

Results 111

Minimum and mean heart rates 111

Bradyarrhythmias and pacing requirements 112

Permanent pacing 114

Correlations with electrophysiology results, ischaemic time, donor and recipient ages 114

Drug effects 115

Discussion 116

Heart rates 116

Bradyarrhythmias, sinus node dysfunction and pacing requirements 116

Conclusions 118

Figures 119

CHAPTER 4: REPRODUCIBILITY OF ELECTROPHYSIOLOGICAL MEASUREMENTS IN TRANSPLANT RECIPIENTS 152

Introduction 152

Methods 153

Statistical analysis 153

PAGE

Results 154

Sinus node function 154

Atrioventricular conduction 154

Atrial and ventricular effective refractory periods 156

Discussion 157

Sinus node function 157

Atrioventricular conduction 158

Atrial and ventricular refractory periods 159

Conclusions 159

CHAPTER 5: THE EFFECTS OF PREOPERATIVE AMIODARONE TREATMENT AFTER HEART TRANSPLANTATION 161

Introduction 161

Methods 162

Electrophysiology 162

Amiodarone assays 162

Statistical analysis 163

Results 164

Subject characteristics 164

Sinus node function 164

Atrioventricular node function 165

Atrial and ventricular refractory periods 166

Amiodarone and desethylamiodarone levels in tissue and serum 166

Correlation of preoperative dose and serum and tissue levels 166

Correlation of amiodarone levels and electrophysiological effects 167

PAGE

The effects of amiodarone on the chronotropic response to exercise 169

Discussion 170

The pharmacokinetics of preoperative amiodarone after transplantation 170

Electrophysiological effects 171

Correlation of cardiac drug levels and electrophysiological effects 172

Conclusions 172

Figures 174

CHAPTER 6: SUMMARY OF CONCLUSIONS 193

REVIEW OF TRANSPLANT RECIPIENTS WITH PERMANENT PACEMAKERS 193

SERIAL PROSPECTIVE STUDIES 193

Electrophysiology 193

Ambulatory monitoring 195

Exercise testing 195

Reproducibility of electrophysiological measurements in transplant recipients 196

The pharmacokinetics and effects of preoperative amiodarone after transplantation 197

Clinical implications 198

APPENDIX 199

REFERENCES 225

RELEVANT PUBLICATIONS AND PRESENTATIONS 241

LIST OF FIGURES **PAGE**

1.1 The normal response to atrial premature stimuli in sinus rhythm 24

2.1 Frequency of pacing and time after transplantation (12 lead ECGs) 69

3.1 Changes in sinus node recovery time in subjects with normal sinus node function 119

3.2. Changes in sinus node recovery in subjects with normal sinus node function 120

3.3 Changes in resting cycle length in subjects with normal sinus node function 121

3.4 Changes in resting cycle length in subjects with normal sinus function 122

3.5 Changes in sinoatrial conduction time in subjects with normal sinus node dysfunction 123

3.6 Changes in sinus node recovery time in seven subjects with sinus node dysfunction 124

3.7 Changes in sinoatrial conduction time in subjects with sinus node dysfunction 125

3.8 Changes in resting cycle length in subjects with sinus node dysfunction 126

3.9 Correlation of sinus node recovery time and sinus cycle length early after transplantation 127

3.10 Correlation of sinus node recovery time and sinus cycle length in longer term survivors 128

3.11 Changes in sinus node recovery time in subjects receiving diltiazem 129

3.12 Changes in atrioventricular effective refractory periods with time after transplantation 130

3.13 Changes in Wenckebach cycle length with time after transplantation 131

3.14 Correlation of atrioventricular effective refractory period and Wenckebach cycle length (600 msec drive) 132

3.15 Correlation of atrioventricular effective refractory period and Wenckebach cycle length (400 msec drive) 133

3.16 Changes in exercise duration with time after transplantation 134

3.17 Changes in heart rate at rest and peak exercise with time after transplantation 135

3.18 Changes in heart rate reserve used at peak exercise with time after transplantation 136

3.19 Changes in the chronotropic response with time after transplantation 137

3.20 Heart rate reserve at peak exercise in subjects with an enhanced exercise response 138

3.21 Differences in exercise time in subjects with an enhanced exercise response 139

3.22 Changes in heart rate during recovery and time after transplantation 140

3.23 Changes in heart rate during recovery and time after transplantation (5 subjects with an enhanced exercise response excluded) 141

3.24 Decrease in heart rate during recovery and time after transplantation 142

3.25 Chronotropic response in a subject with late sinus node dysfunction 143

3.26 Chronotropic response in subjects with early sinus node dysfunction 144

3.27 Chronotropic response at six weeks in subjects with previous sinus node dysfunction 145

3.28 Chronotropic response at six months in subjects with previous sinus node dysfunction 146

3.29 Minimum heart rates during ambulatory monitoring and time after transplantation 147

3.30 Mean heart rates during ambulatory monitoring and time after transplantation 148

3.31 Correlation of minimum daytime heart rate during ambulatory monitoring and spontaneous cycle length at electrophysiological study 149

3.32 Correlation of mean heart rate during ambulatory monitoring and corrected maximal sinus node recovery time at electrophysiological study 150

3.33 Mean heart rates during ambulatory monitoring and diltiazem treatment 151

5.1 Changes in resting cycle length and preoperative amiodarone treatment 174

5.2 Minimum heart rate during ambulatory monitoring and preoperative amiodarone treatment 175

5.3 Mean heart rate during ambulatory monitoring and preoperative amiodarone treatment 176

5.4 Changes in sinus node recovery time and preoperative amiodarone treatment 177

5.5 Changes in sinoatrial conduction time and preoperative amiodarone treatment 178

5.6 Changes in Wenckebach cycle length and preoperative amiodarone treatment 179

5.7 Changes in AV effective refractory period and preoperative amiodarone treatment 180

5.8 Changes in atrial effective refractory period and preoperative amiodarone treatment 181

5.9 Changes in ventricular effective refractory period and preoperative amiodarone treatment 182

5.10 Serum amiodarone and desethylamiodarone concentrations and time after transplantation 183

5.11 Concentrations of amiodarone and desethylamiodarone in cardiac tissue and time after transplantation 184

5.12 Individual changes in serum amiodarone concentration and time after transplantation 185

5.13 Individual changes in cardiac amiodarone concentration and time after transplantation 186

5.14 Individual changes in serum desethylamiodarone concentration and time after transplantation 187

5.15 Individual changes in cardiac desethylamiodarone concentration and time after transplantation 188

5.16 Correlation of cardiac amiodarone concentrations and ventricular effective refractory periods 189

5.17 Correlation of cardiac desethylamiodarone concentrations and ventricular effective refractory periods 190

5.18 Rest peak heart rates on exercise and preoperative amiodarone 191

5.19 Heart rate reserve used at peak exercise and preoperative amiodarone 192

LIST OF TABLES **PAGE**

2.1	Details of transplant recipients receiving permanent pacemakers	66
3.1	Details of subjects who died during the study period	76
3.2	Perioperative rhythm and subsequent sinus node function	84
3.3	Proportion of atrial and atrioventricular ERP measured during atrial pacing studies	86
3.4	The chronotropic assessment exercise protocol	98
3.5	Chronotropic response in four subjects with early sinus node dysfunction	103
3.6	Ambulatory monitoring and electrophysiological data in subjects with sinus node dysfunction	113
4.1	Reproducibility of electrophysiological indices of sinus node function	154
4.2	Reproducibility of indices of atrioventricular node function	155
4.3	Reproducibility of atrial and ventricular effective refractory periods	156
5.1	Correlation coefficients between ventricular effective refractory periods and cardiac levels of amiodarone and desethylamiodarone	168

ABSTRACT

In the immediate postoperative period following heart transplantation acute surgical sympathetic denervation and perioperative ischaemia cause bradycardia in all patients. In some bradyarrhythmias of sinus or atrioventricular node origin persist and may necessitate permanent pacing. The natural history of sinus node dysfunction and abnormalities of atrioventricular conduction after transplantation has not previously been adequately described. The practical importance of such information would be to aid optimum prescription of permanent pacing systems and the avoidance of unnecessary pacing. Arrhythmias are common in patients awaiting heart transplantation and the antiarrhythmic agent amiodarone is frequently prescribed. Amiodarone causes bradycardia and increases the refractoriness of conducting tissue. Previous reports suggest that this unusually long acting drug may affect the transplanted heart even when discontinued at the time of surgery. These reports have been limited by crude measurements of the postulated electrophysiological effects and none has measured drug concentrations directly.

A retrospective study of all transplant recipients who underwent permanent pacing at this centre was undertaken followed by a prospective study of current pacemaker use in the same patients. A prospective study of sinus and atrioventricular node function was then performed in 40 transplant recipients using serial electrophysiological measurements and ambulatory monitoring one, two, three and six weeks, three and six months after transplantation. The response of the sinus node to exercise was also tested three and six weeks, three and six months after surgery. The reproducibility of electrophysiological measurements was assessed in six subjects who each underwent five studies in one day. A separate analysis of the effects of preoperative amiodarone treatment was performed. Cardiac and serum levels of amiodarone and its active metabolite desethylamiodarone were measured in six subjects.

Twenty one of 218 (9.6%) transplant recipients had received permanent pacemakers (13 for sinus node dysfunction and eight for atrioventricular block. After reprogramming to a minimum safe rate only five subjects with previous sinus node dysfunction and one with previous atrioventricular block paced during ambulatory monitoring. Serial electrophysiological studies in 40 transplant recipients revealed a 17.5% incidence of sinus node dysfunction. It resolved in all six subjects with early sinus node dysfunction but developed late in one. There was a significant trend toward shorter sinus node recovery times with time after transplantation in those subjects with normal sinus node function defined by standard criteria. Heart rate also increased with time after surgery. Clinical bradyarrhythmias after the first week were invariably associated with electrophysiological evidence of sinus node dysfunction. A corrected maximal sinus node recovery time which returned to normal by three weeks indicated a good prognosis. Abnormalities of atrioventricular node conduction were rare (one of 40 subjects). Serial exercise testing (in 33 of 40 subjects) showed an improvement in the chronotropic response between three and six weeks after transplantation. Thereafter the response was stable except in five subjects who had a markedly enhanced exercise response and rapid fall in heart rate during recovery six months after transplantation. This suggests efferent sympathetic reinnervation which has not been previously described as early as six months after surgery. Exercise testing was not helpful in distinguishing subjects with sinus node dysfunction from others or in defining prognosis. The reproducibility of electrophysiological measurements in transplant recipients was much better than previously reported for other subjects. This probably relates to autonomic denervation. For a period of six weeks after operation serum and cardiac amiodarone concentrations in patients who took preoperative amiodarone were comparable with those reported in patients taking regular oral treatment. The electrophysiological effects were clearly demonstrable but no clinically significant bradyarrhythmias resulted. A direct correlation between cardiac drug levels and ventricular effective refractory periods but not other electrophysiological measurements was found.

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

THE AUTHOR

I graduated from the University of Manchester in July 1984 with the degree MB ChB. My research, the majority of which is the subject of this thesis, was undertaken in the departments of Cardiology and Cardiopulmonary Transplantation Unit at the Freeman Hospital, Newcastle upon Tyne between March 1991 and August 1993

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LIST OF ABBREVIATIONS

AERP	Atrial effective refractory period
AV	Atrioventricular
AVCS	Atrioventricular conducting system
AVERP	Atrioventricular effective refractory period
bpm	Beats per minute
CAEP	Chronotropic assessment exercise protocol
$CSNRT_{max}$	Corrected maximal sinus node recovery time
ECG	Electrocardiogram
ERP	Effective refractory period
FRP	Functional refractory period
MET	Metabolic equivalent
RBBB	Right bundle branch block
SACT	Sinoatrial conduction time
SNRT	Sinus node recovery time
VERP	Ventricular effective refractory period

CHAPTER 1

INTRODUCTION

Heart transplantation has become an accepted method of treatment for end-stage heart disease in carefully selected patients. Over 19,000 such procedures have now been carried out worldwide[Kaye 1992]. The heart for transplantation is usually excised from a donor at a hospital distant from the recipient and transported in cold cardioplegia solution at approximately 4°C. Despite microscopic evidence of damage to the heart this technique is compatible with good graft function with ischaemic times of up to four hours[Billingham 1980]. The standard method[Lower 1961]for implantation of the transplanted heart involves suturing the donor atria to a residual cuff of recipient atria. This leaves the original recipient sinus node intact although electrically isolated from the new heart by the atrial suture line[Leachman 1979, Cannom 1973]. The autonomic nerves supplying the transplanted heart are severed at the time of operation. Although some efferent sympathetic innervation may occur in a proportion of long term survivors[Wilson 1991]the heart is thought to remain autonomically denervated in all recipients for the first year after transplantation and much longer in some[Stinson 1972, Wilson 1991]. The maintenance of normal heart rhythm is therefore entirely dependent on the transplanted sinus node and specialised conducting tissues.

The immediate effects of transplantation on heart rate and rhythm

After implantation and reperfusion in the recipient the transplanted heart invariably requires chronotropic support[Stinson 1975, Cabrol 1989, DiBiase 1991]. Sinus node dysfunction, manifest as nodal bradycardia, sinus bradycardia and sinus arrest, remains very common during the first few days after transplantation[Miyamoto 1990]. Atrioventricular conduction disturbances also occur but much less frequently[Miyamoto 1990]. The cause of the immediate postoperative depression of the sinus rate has not clearly been elucidated. Surgical trauma to the sinus node and its blood supply, acute autonomic denervation and prolonged cold ischaemic storage are possible aetiological factors.

Cold ischaemia

Although there is no direct evidence that prolonged cold ischaemia causes immediate bradycardia in the transplanted heart it has been suggested that long operative ischaemic times may predispose to its persistence[Heinz 1990,1991, Markewitz 1992].

The effects on the unassisted heart rate of prolonged cold ischaemia without autonomic denervation have not been studied in humans. Kontos and colleagues[1970] used a very similar ischaemic storage temperature (5°C) to that used in current clinical practice during transplantation experiments in dogs. The ischaemic time was however short at around 10 to 15 minutes. Bradyarrhythmias (nodal bradycardia, sinus bradycardia and sinus arrest) were frequently observed in the transplanted heart despite the consistently short ischaemic periods. It therefore seems unlikely that the duration of ischaemia, within the usual range in current clinical practice, will materially effect the frequency and extent of postoperative bradyarrhythmias.

Transient fascicular[O'Connell 1982] and AV block[Ellis 1980] are relatively common after conventional surgery but with the exception of valvular procedures[Smith 1972, Jaeger 1992], the

incidence of persistent bradyarrhythmias is substantially lower than after transplantation[Bahnson 1991]. In contrast with transplant recipients, AV block is more common than sinus dysfunction and preexisting conduction abnormalities are the major determinant of persistent postoperative bradyarrhythmias[Emlein 1992]. Prolonged operative ischaemia does not predispose to persistent postoperative bradyarrhythmias after conventional surgery[Emlein 1992]. However, the duration of ischaemia is more prolonged and the myocardial temperature much lower during the transplant procedure so these situations cannot be regarded as closely analogous.

Acute autonomic denervation

The long term effect of autonomic denervation after heart transplantation is an increase in the resting heart rate[Bexton 1984a, Alexopoulos 1988, Scott 1993]presumably due to loss of the normally dominant vagal tone. However the immediate effects of **acute** surgical denervation have not been systematically studied in man. Dempsey and colleagues[1970] showed that acutely denervated cats have a lower than normal heart rate for the first day after surgery. Willman and colleagues[1963] reported that dogs undergoing autotransplantation invariably required "supportive therapy" whereas sham operated dogs who were exposed to the same cardiopulmonary bypass and hypothermic cardioplegia procedures did not. Unfortunately the exact nature of the "supportive therapy" and the heart rate responses of the animals were not reported.

The mechanisms underlying the initial bradycardia and subsequent development of the tachycardia observed in long term transplant survivors are unclear. The possibilities will be discussed in the forthcoming section on the effects of autonomic denervation.

Persistent bradyarrhythmias

The early bradyarrhythmias described above are almost universal. The majority of transplant recipients will subsequently develop stable sinus rhythm within the first postoperative week[Miyamoto 1990]. However more persistent bradyarrhythmias may occur in between 18% and 48% of patients[Miyamoto 1990,Heinz 1990]. They are most commonly caused by sinus node dysfunction[Miyamoto 1990, Heinz 1990, DiBiase 1991]and less commonly by atrioventricular block[Miyamoto 1990, Janosik 1990, Dodinot 1991, DiBiase 1991]. These persistent rhythm and conduction disturbances may necessitate permanent pacemaker implantation. It is in regard to the mechanism, predictability and management of these arrhythmias that the principal practical applications of this research thesis lie.

Electrophysiology

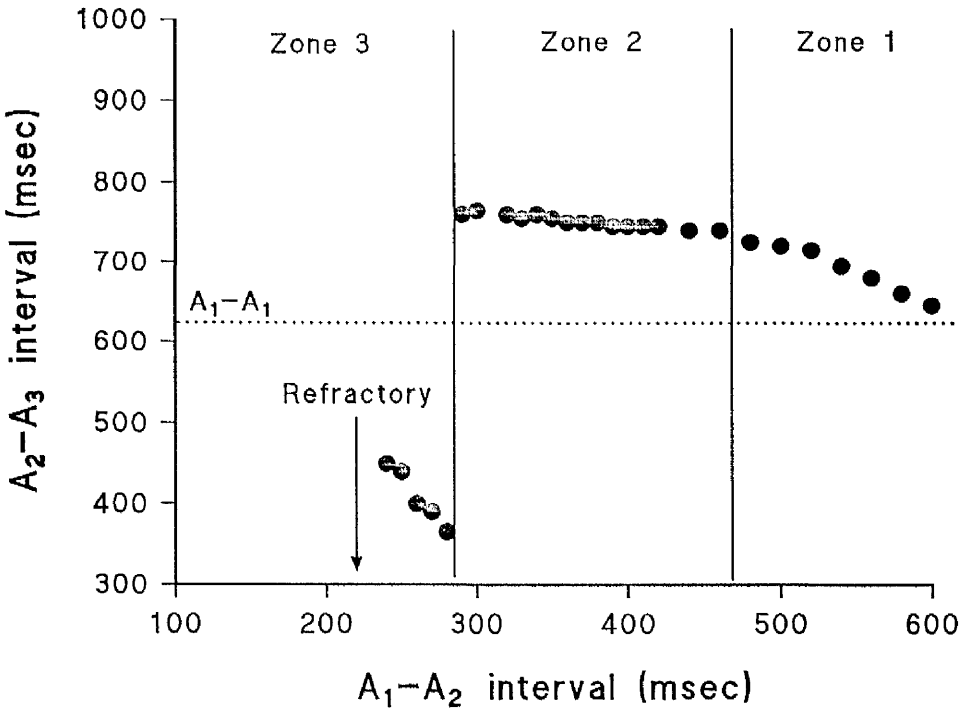
Assessment of sinus node function

The electrophysiological assessment of sinus node function is based primarily on the suppression of its automaticity by overdrive atrial pacing[Mandel 1971]and measurement of sinus node recovery time (SNRT). Mandel and colleagues[1971]showed that the duration of atrial pacing over a range of 15 to 180 seconds makes little difference to the subsequent pause and that it usually maximal after pacing at 400msec cycle length. The most important index of sinus node function is the **corrected maximal** sinus node recovery time ($CSNRT_{max}$) calculated by subtracting the spontaneous sinus cycle length from the maximal sinus pause after termination of atrial pacing at a variety of cycle lengths[Narula 1972]. The accepted upper limit of normal $CSNRT_{max}$ is 525msec[Narula 1972].

After the termination of overdrive pacing during measurement of SNRT the longest cycle is usually the first. Secondary pauses occur when a subsequent cycle is longer than the first and their presence may indicate sinus node dysfunction[Benditt 1976].

The measurement of sinoatrial conduction time (SACT) is also usually undertaken during sinus node studies because abnormalities of sinoatrial conduction are often associated with sinus node dysfunction[Strauss 1976]. There are two accepted methods for measurement of SACT. The method of Strauss[1973] uses progressively more premature atrial extrastimuli during sinus rhythm. The response of the sinus node depends on the degree of prematurity of the extrastimulus and is illustrated in figure 1.1. Initially the extrastimulus does not reset the sinus node and the next cycle is fully compensatory (zone 1 or zone of collision). With increasing prematurity the extrastimulus penetrates and resets the sinus node (zone 2 or zone of reset). The return cycle length then becomes

Figure 1.1: The normal response to atrial premature stimuli in sinus rhythm



Key: A_1= spontaneous sinus beat, A_2= extrastimulus
A_3= following sinus beat

fixed over a range of prematurity of the extrastimulus. The difference between this return cycle length and the spontaneous cycle length reflects the sum of the time taken for the extrastimulus to penetrate the node and the next sinus impulse to conduct to the atrium. Traditionally this interval was divided by two on the assumption that conduction times into and out of the sinus node were equal[Strauss 1973]. However Steinbeck[1977,1978]and colleagues have since shown that conduction out of the node is slower. The SACT is now usually expressed as the total conduction time into and out of the node. The part of zone 2 nearest to zone 1 is used to calculate SACT in order to avoid error due to the increased refractoriness of atrial tissue around the sinus node with increasingly premature extrastimuli. Narula[1978]and colleagues showed that an alternative method produced very similar results. This method[Narula 1978] involves atrial pacing at just less than the spontaneous cycle length for eight cycles and subtracting the length of the first non paced cycle from the spontaneous cycle length.

The reported normal range of total SACT varies considerably from 80-140msec[Steinbeck 1975]to 132-312msec[Strauss 1973]. A widely accepted upper limit of normal is 250msec[Josephson 1979, Mackintosh 1982, Bexton 1984a, Heinz 1990].

The effective refractory period of the sinus node (SNERP) has also been suggested as a useful index of sinus node function[Kerr 1983]. It is measured by the introduction of progressively more premature extrastimuli after atrial "drive" pacing for eight beats. It is defined as the longest interval between the pacing drive and the premature impulse which results in interpolation of the extrastimulus[Kerr 1983]. The interpolation response to atrial extrastimulation (zone 3) occurs when the premature impulse fails to reset the sinus node. The return cycle is therefore shorter than the original sinus cycle. Kerr[1988] studied the effects on SNERP of changing the drive cycle length and of pharmacological autonomic blockade. A decrease in drive cycle length

increased the SNERP, sympathetic blockade increased and parasympathetic blockade decreased the SNERP. These are identical to changes in atrioventricular node refractoriness observed with the same manipulations.

The reported normal range of SNERP is 250-500msec[Kerr 1983]. Kerr and Strauss[1983] found that the SNERP reliably differentiated subjects with and without clinical sinus node dysfunction. However these results have not been reproduced by other investigators and their clinical relevance has not been widely accepted. Also the SNERP cannot be measured in some subjects because atrial refractoriness precedes the zone of interpolation.

The clinical usefulness of electrophysiological sinus node function tests in the normal innervated heart has been questioned[Gupta 1974, Jordan 1978]. Autonomic tone is thought to be a confounding variable[Gupta 1974, Jordan 1978] and pharmacological blockade has been shown to improve the reproducibility of these measurements[Gupta 1974, Desai 1981, Alboni 1983]. It is likely therefore that they are of greater clinical significance in transplant recipients than in other patients[Mason 1980].

Sinus node function after transplantation

Electrophysiological evaluation of sinus node function after transplantation has been undertaken by several groups of investigators both in the immediate postoperative phase[Mackintosh 1982, Heinz 1992a, Jacquet 1990]and in long term survivors[Cannom 1973, Bexton 1984a, Mason 1980].

The accuracy of several of these studies[Mackintosh 1982, Heinz 1992a, Jacquet 1990]was potentially limited by their use of P waves on the surface ECG for measurement of conduction and recovery times. P wave morphology is often abnormal after transplantation[Sandhu 1990] and the exclusion of recipient P waves may be difficult. The most detailed investigations were both performed in long term survivors by Bexton[1984a]

and Mason[1980]and their results were very similar. The spontaneous cycle length in denervated donor atria was significantly less than in both innervated transplant recipient[Bexton 1984a] and control atria[Mason 1980]. This finding is in keeping with studies of pharmacological autonomic blockade[Jose 1966, Jordan 1978, Vallin 1980] and reflects the dominance of parasympathetic tone on the normal innervated sinus node. Bexton and colleagues[1984a] reported a clear correlation between the donor sinus rate and the calculated "intrinsic" heart rate[Jose 1970]in the absence of any evidence of sinus node dysfunction.

Both Bexton[1984a] and Mason[1980] reported that the $CSNRT_{max}$ was within the normal range for innervated hearts in most subjects. Bexton and colleagues[1984a]also found that those with more prolonged $CSNRT_{max}$ all had other abnormalities suggesting sinus node dysfunction such as secondary pauses and abnormal sinoatrial conduction time. The donor sinus node responded more predictably than the recipient sinus node to faster pacing rates. In contrast with innervated hearts[Mandel 1971]Bexton and colleagues[1984a]found that recovery times were significantly longer after 30 seconds of pacing than either shorter or longer periods. Mason[1980] and colleagues also compared their results with those of control subjects and found no significant differences between controls and the innervated transplant recipient atria. The response to increased pacing rates was more predictable in the donor atria and the $CSNRT_{max}$ was achieved at faster rates in most subjects. Bexton[1984a] and colleagues also reported a much stronger correlation between $CSNRT_{max}$ and spontaneous cycle length in the donor ($r=0.93$) than the recipient ($r=0.59$) atria.

Bexton[1984a] and colleagues also measured SACT using both the Strauss[1973]and Narula[1978]methods in donor and recipient atria. The results using the different methods correlated much more closely in donor than recipient atria.

Heinz[1992b] and colleagues attempted to measured the SNERP in 28 subjects early after transplantation. They were able to measure SNERP in only 18 (64%) compared with 87% in studies on innervated non-transplant subjects[Kerr 1983]. Where it could be measured the SNERP was significantly shorter than that reported in innervated hearts. This is in keeping with the dominance of parasympathetic autonomic tone in the innervated heart and suggests that the SNERP could not be measured in more denervated than innervated subjects because it was shorter than the atrial ERP. There was no significant difference in SNERP between those subjects with normal and abnormal sinus node dysfunction (defined by $CSNRT_{max}$ <525msec).

Sinus node dysfunction after transplantation

In the majority of studies[Mackintosh 1982, Bexton 1984a, Jacquet 1990] sinus node dysfunction has been defined using standard criteria ($CSNRT_{max}$ ≥525msec, SACT ≥250msec[Narula 1972]). The reported incidence of early sinus dysfunction is high (approximately 50%)[Mackintosh 1982, Heinz 1992a, Jacquet 1990]. However in all these studies the incidence of clinical bradyarrhythmias was also unusually high at around 50% of all transplant recipients. The relatively low incidence of clinical bradycardia in a much larger series[Miyamoto 1990] suggests that existing electrophysiological studies may have overestimated the frequency of the problem. Only Bexton and colleagues[1984a] have reported the incidence of sinus node dysfunction in long term survivors (4-14 months) at 29%.

The concurrence between abnormalities of the different parameters ($CSNRT_{max}$, SACT, secondary pauses and relatively long spontaneous cycle length) of sinus node function is much more consistent in denervated transplanted hearts compared with innervated hearts[Bexton 1984a].

The discovery of any clinical or electrophysiological variable which could reliably predict the resolution of early sinus node dysfunction would have important benefits. In particular the appropriate timing and prescription of permanent pacing systems could be improved. There has been only one serial electrophysiological study of sinus node function in transplant recipients. This was a small study and was limited to recipients of permanent pacemakers[Heinz 1992c]. Of eight subjects studied, seven had persistently abnormal sinus node recovery times at up to four years after transplantation despite maintaining normal sinus rhythm. A previous study by the same group[Heinz 1992a] relied on ambulatory ECG, rather than electrophysiological criteria (normal defined as continuous sinus rhythm, mean resting heart rate > 80 beats per minute (bpm) and absence of sinus pauses) and had suggested that normalisation of sinus node function was more frequent. In that study the rhythm on the eleventh postoperative day to some extent predicted subsequent sinus function. Although the differences were not statistically significant 68% of subjects with early sinus bradycardia and abnormal CSNRT recovered normal sinus function compared with 62% of those with intermittent nodal rhythm, 45% of those with continuous nodal rhythm and 25% of those with complete asystole.

Bradyarrhythmias

The diagnosis of bradyarrhythmias after heart transplantation from the surface ECG can be problematic because of the presence of P waves originating from the electrically isolated recipient atrium[Leachman 1969]. In this way donor sinus arrest with nodal escape rhythm may be mistaken for atrioventricular block[Marchena 1989]. The limitations of oesophageal electrocardiography in transplant recipients have been previously described[Ellenbogen 1987]. Pacing the donor atrium will usually make the correct diagnosis clear and is easily performed through epicardial pacing wires which are placed at the

time of operation at most centres[Dibiase 1991].

As previously discussed a degree of suppression of sinus node automaticity is usual in the first few days after transplantation. Significant sinus node dysfunction is usually manifest by persistent relative sinus bradycardia or sinus arrest with nodal escape rhythm after the fourth or fifth postoperative day[Heinz 1990, Miyamoto 1990, Jacquet 1990]. In some patients asystole may result from failure of automaticity of the distal conducting system[Heinz 1992a]. There are no reports of 24 hour ECG monitoring in early sinus node dysfunction, although the impression of sustained rather than paroxysmal bradyarrhythmias is gained from published series. The reported frequency of significant bradyarrhythmias due to sinus dysfunction varies between 18%[Miyamoto 1990] and 48%[Heinz 1990]. Between 55% and 92% of these resolve within the following 21 days[Miyamoto 1990, Jacquet 1990, Heinz 1992a]. Those with persistent bradyarrhythmias after this time will generally require permanent pacing.

A few recipients develop bradyarrhythmias suggestive of sinus node dysfunction more than a month (late) after transplantation [Dibiase 1991, Miyamoto 1990, Adonizio 1990, Berke 1973, Mackintosh 1982]. Although some of these patients have had previous early bradyarrhythmias[DiBiase 1991]in others they arise de novo. In contrast with early bradyarrhythmias they may be paroxysmal[Bexton 1983a, Mackintosh 1982]. In most instances these patients have been treated with permanent pacemakers. In one report a patient with a history of episodic sinoatrial block subsequently died during a period of ambulatory monitoring[Mackintosh 1982]. It is of note, however that the terminal rhythm was progressive atrioventricular block rather than sinus arrest and moderate rejection was found at post mortem.

The only study comparing directly electrophysiological sinus node function tests with ambulatory monitoring was published by Bexton and colleagues[1983a]. Fourteen

recipients between four and 14 months after transplantation were studied. Three had "relative bradycardia", all of whom had an abnormal donor CSNRT. One subject had paroxysmal bradyarrhythmias, two had sustained bradycardia.

Chronotropic incompetence

Assessment of chronotropic competence

The normal heart rate response to exercise can be modelled as a linear function involving exercise intensity, age, resting heart rate and maximal functional capacity and is independent of the exercise protocol used[Wilkoff 1989]. Wilkoff[1989] and colleagues define heart rate reserve as maximum age predicted heart rate minus resting heart rate and the metabolic reserve as the peak exercise minus resting workload measured in metabolic equivalents (METS[1]). At any stage of exercise the percentage heart rate reserve and percentage metabolic reserve should be equal.

Although this model is not dependent on any particular exercise protocol the most physiological assessment of the chronotropic response is probably best achieved by the use of a protocol specifically designed for chronotropic assessment which is structured to collect heart rate data at less than maximal as well as maximal exercise intensity: the chronotropic assessment exercise protocol (CAEP)[Wilkoff 1989].

There is no widespread agreement as to the definition of chronotropic incompetence. The most accurate definition is probably that proposed by Wiens and colleagues[1984]: a peak heart rate less than 2 standard deviations from a population mean at a given peak workload. This is approximately 85 bpm for 4 METS, 100 bpm for 6 METS and 120 bpm for 8 METS peak workload[Wiens 1984]. Most authors have, however

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[1] 1 Metabolic equivalent[Chaitman 1992](MET) = 3.5 ml Oxygen consumption/minute/kg body weight= the approximate Oxygen consumption while standing at rest.

used a simple peak heart rate definition of chronotropic incompetence varying between 110 bpm and 135 bpm [Holden 1978, Vallin 1980(a), Simonsen 1987, Johnston 1987, Kallryd 1989].

The reported incidence of chronotropic incompetence in patients with conventional sinoatrial disease varies between 28% and 57% when defined by a heart rate of less than 120 bpm at peak exercise[Rosenquist 1990]. Simonsen[1987] reported that 17%, 40% and 60% of subjects had peak heart rates of less than 110, 125 and 136 bpm respectively.

No definition of chronotropic incompetence has been proposed for transplant recipients. The mean resting heart rate of approximately 100 $\pm$ 10 bpm in long term survivors[Alexopoulos 1988, Scott 1993] probably makes the application of criteria derived from patients with innervated hearts invalid. Exercise studies after pharmacological autonomic blockade[Areskog 1985] have shown similar resting heart rates of 100 $\pm$ 10 bpm and peak heart rates at peak oxygen consumption of 140 $\pm$ 10 bpm in untrained individuals. However these studies are not directly comparable with the denervated heart as the actions of circulating catecholamines will also be blocked.

The assessment of chronotropic competence in transplant recipients may be particularly important when making decisions about the need for rate responsiveness in a permanent pacing system.

The "normal" chronotropic response after transplantation

The chronotropic response to both static and dynamic exercise is abnormal in all transplant recipients[Shaver 1969, Stinson 1972, Clark 1973, Pope 1980, Savin 1980, Savin 1984]. The absence of autonomic innervation results in a much slower initial increase in heart rate compared with normal subjects. In the early stages cardiac output is primarily augmented by the Frank-Starling mechanism and increased stroke volume[Pope 1980]. There is also a modest

early increase in heart rate which is not abolished by beta-blockade[Shaver 1969, Bexton 1983b] and is probably mediated by the direct chronotropic effect of increased venous return[Blinks 1956]. Later the heart rate and contractility increase under the influence of circulating catecholamines[McLaughlin 1978] but the peak heart rate is subnormal compared with innervated controls[Savin 1980]. The importance of autonomic innervation is demonstrated by the finding of partial normalisation of the chronotropic response in a proportion of long term survivors with evidence of efferent sympathetic reinnervation[Johnson 1991].

There have been no serial studies of the chronotropic response to exercise in the early post transplant period. Two cross-sectional studies have been published[Quigg 1989, Rudas 1991]. Quigg and colleagues[1989] exercised 23 recipients, 11 within three months of transplantation and 12 later. The resting and peak exercise heart rates were lower and the increase in heart rate less in those exercised early. Only the increase in heart rate with exercise was significantly different. Exercise tolerance was probably a confounding variable. The maximum workload and oxygen consumption were also lower in those exercised early, the workload significantly so. Rudas and colleagues[1991] exercised 52 transplant recipients grouped according to time after operation. They reported that the medium (mean 16 months) and long term (mean 42 months) survivors had a brisker immediate response to exercise, a higher peak heart rate and more rapid decrease in heart rate after exercise. These findings were attributed by the authors to "functional reinnervation". Wilson and colleagues[1991] subsequently demonstrated convincing evidence of structural sympathetic reinnervation and it is likely that some of Rudas' subjects had efferent sympathetic reinnervation. The range of responses within the groups was not well described and the frequency of reinnervation is therefore unclear.

Chronotropic incompetence after transplantation

There have been no previous studies which have systematically assessed chronotropic competence in transplant recipients with sinus node dysfunction. Some authors have advocated implanting various types of rate responsive pacemakers[Loria 1988, Osterholzer 1988, Miyamoto 1990, Kacet 1991]but the assumption that the chronotropic response to exercise is inadequate does not appear to have been formally tested. Midei and colleagues[1990] exercised three patients with rate responsive pacemakers who required pacing at rest and reported a good native chronotropic response which overrode the pacemaker in each case.

Aetiology of sinus node dysfunction after transplantation

The precise aetiology of sinus node dysfunction after heart transplantation is unknown. It is likely that early (less than one month after transplantation) and late sinus dysfunction have differing aetiologies.

Late sinus dysfunction is less common, the timing of onset is unpredictable and it is not reliably associated with a history of bradycardia in the immediate postoperative period[Miyamoto 1990, DiBiase 1991]. Little is known about the aetiology although several reports have linked it to the development of occlusive coronary disease[Berke 1973, DiBiase 1991, Grinstead 1991].

Early sinus dysfunction is more common, its timing is consistent and recovery is common[Miyamoto 1990]. Suggested causes include prolonged operative ischaemic time, allograft rejection, advanced donor age, direct surgical trauma to the sinus node and disruption of its blood supply[Mackintosh 1982, Bexton 1984a, DiBiase 1991]. There is no evidence to support a role for donor age or rejection in the pathogenesis of this problem.

Two studies from the same centre have linked bradycardia attributable to sinus node dysfunction with prolonged operative ischaemic time[Miyamoto 1990, Jacquet 1990]. Heinz and colleagues[1990, 1991] have previously reported that a prolonged ischaemic time was associated with transient but not with persistent sinus node dysfunction. This is not however, restated in a more recent report[Heinz 1992a]. Mackintosh[1982] reported no difference in ischaemic times between subjects with and without sinus node dysfunction and DiBiase and colleagues[1991]found no difference between those patients requiring and those not requiring permanent pacemakers.

The evidence for the role of direct surgical trauma and disruption of blood supply to the sinus node area is much more convincing. Stovin and Hewitt[1986] found evidence of surgical sinus node damage in approximately 50% of donor hearts excised at retransplantation. An alternative operative technique involving total atrial excision and separate great vein anastomoses may virtually eliminate the risk of sinus dysfunction[Couetil 1991]. DiBiase and colleagues[1991] reported a much higher incidence of abnormalities of the sinus node artery in patients requiring pacemakers for sinus node dysfunction. In addition there are close resemblances between the natural history of sinus node dysfunction after transplantation and animal models of the sick sinus syndrome which involve surgical excision of the sinus node[Moran 1981, Sterba 1984]. It is of particular interest that denervation of the heart after excision of the sinus node delays the development of stable subsidiary atrial pacemakers in these models[Sterba 1984]. Chronotropic incompetence on exercise is also documented in such models[Ardell 1991]but long term follow up studies have not been reported.

It has been suggested that adenosine may be an important mediator of early sinus node dysfunction after transplantation[Ellenbogen 1988, Heinz 1993]. This suggestion is based on several observations. The condition responds to theophyllines which are adenosine

antagonists. The transplanted heart is known to be supersensitive to adenosine[Ellenbogen 1990]. Adenosine is released from ischaemic myocardium[Fox 1974] and there is a link between perioperative ischaemic time and sinus node dysfunction in some reports[Heinz 1990,1991]. Adenosine may be an important mediator of sinus node dysfunction[Watt 1985]in other patients.

However the relevance of these observations is open to question. Theophyllines also cause catecholamine release[Vestal 1983] and the acute time course of adenosine release from ischaemic myocardium[Fox 1974]is incompatible with the clinical profile of early sinus node dysfunction. Given the very short half life of circulating adenosine (less than one minute) one would have to postulate continued adenosine release from the transplanted heart over a period of days or weeks after the perioperative ischaemic period and there is no evidence that this occurs. The sustained pattern of early sinus node dysfunction after transplantation and the frequency of its resolution contrast with the intermittent but persistent nature of sinus node dysfunction in other patients. A common mechanism therefore seems unlikely.

Electrophysiology

Assessment of atrioventricular conduction

The functional assessment of atrioventricular (AV) conduction is usually undertaken by measurement of conduction times and by assessment of its responses to atrial extrastimuli[Damato 1969(a), Wit 1970, Dhingra 1973] and rapid incremental atrial pacing[Damato 1969(b), Rosen 1972].

The conduction time across the AV node is assessed by measuring the interval between atrial and His potentials in the His bundle electrogram (AH interval)[Scherlag 1969]. The reported normal ranges of the AH interval vary between 45-100msec[Peuch 1971] and 85-150msec[Schuilenberg 1972]. Infranodal (infra-Hisian) conduction is measured by the interval between the His bundle potential and the earliest sign of ventricular activation (HV interval). The normal range for innervated hearts is 25-55msec[Narula 1970, Castellanos 1971, Peuch 1971].

The refractory periods of the parts or all of the atrioventricular conducting system (AVCS) are measured using progressive premature atrial extrastimuli. The standard technique involves the introduction of an extrastimulus both during sinus rhythm and following an eight to 10 cycle pacing "drive" at various cycle lengths[Cagin 1973, Denes 1974]. The **effective** refractory period (ERP) is defined as the maximum interval between a sinus or "drive" beat and a premature stimulus that fails to propagate through that tissue[Wit 1970]. It is therefore measured proximal to the tissue in question. For example the ERP of the AV node is the longest interval between the drive stimulus and extrastimulus which results in failure of the extrastimulus to propagate through the AV node. The **functional** refractory period (FRP) is the minimum interval between

successive impulses conducted through the tissue and is therefore measured distally[Wit 1970](eg AV node FRP is the shortest interval between successive His bundle electrograms). Standardisation of the cycle length of the pacing drives is important as an increase in drive rate increases the ERP and decreases the FRP of the AV node[Denes 1974]. The voltage of the extrastimulus also affects the refractory periods (decrease with increasing energy) and is usually standardised at twice the diastolic threshold[Josephson 1979]. The most accurate assessment of AV node refractory periods requires the recording of His bundle and ventricular electrograms to assess the refractoriness of the more distal parts of the AVCS[Akhtar 1975]. However during antegrade stimulation the atrium or AV node are the sites of maximum refractoriness in the great majority of subjects[Akhtar 1975]. The reported normal ranges of AV node ERP are from 230-365msec to 280-430msec[Denes 1974, Akhtar 1975, Schuilenburg 1972].

The response to incremental atrial pacing is most commonly assessed by determination of the Wenckebach point[Bissett 1975, Josephson 1979]. This is the cycle length during incremental pacing at which Wenckebach conduction first occurs. Bissett and colleagues[1975] showed that there is good correlation between the Wenckebach point and the ERP of the AVCS. The Wenckebach point usually lies between 350 and 500msec in normal subjects but can vary considerably from this in the absence of disease[Josephson 1979].

There is substantial inter-subject variation in indices of AV node function but the intra-subject variation over time is not so pronounced. The variation between measurements of the AH interval, AV node ERP and wenckebach point, in both short[Reddy 1975, Cinca 1986] and long term[Bergfeldt 1991] studies of their reproducibility is less than 10%. The Wenckebach point is more consistent than the refractory periods[Bergfeldt 1991]. It has been suggested that differences in autonomic tone may be responsible for both inter and intra-subject variation[Josephson 1979].

If autonomic tone is responsible then denervation of the heart may improve the consistency and clinical usefulness of these measurements. Studies using pharmacological autonomic blockade[Tonkin 1980, Vallin 1980(b)] have shown changes in AH interval, refractory periods and Wenckebach points of similar magnitude to the observed intra-subject variation but not to the very large inter-subject variation. The consistency of different measurements of AV conduction is also improved with a clear correlation between the AH interval and ERPs after autonomic blockade and not before[Vallin 1980].

AV conduction after transplantation

The functional properties of the AV node in transplant recipients have been investigated in several studies[Cannom 1973, Goodman 1976, Bexton 1984b, Heinz 1992d] and the results are similar.

The resting AH interval is within the normal range for innervated hearts. It lengthens with increasing rates of atrial pacing[Cannom 1973, Bexton 1984b] indicating that decremental conduction is an intrinsic property of the AV node independent of autonomic innervation. These findings are in keeping with the balanced effects of autonomic blockade observed in pharmacological studies[Tonkin 1980].

The refractory periods of the denervated AV node are also within normal limits[Bexton 1984b, Goodman 1976]. However the wide intersubject variation in these small studies may be obscuring refractory periods which are significantly shorter than in innervated hearts. Pharmacological autonomic blockade studies support this contention. The ERP and FRP are reduced suggesting a dominant vagal influence on refractory periods[Tonkin 1980, Prystowsky 1981] and the determination of AV node ERP is more often limited by atrial refractoriness after autonomic blockade than before[Prystowsky 1981].

The effect on refractory periods of an increase in pacing rate is unclear. Goodman[1976] and colleagues found no change whereas Bexton[1984b] and colleagues reported an increase in ERP and decrease in FRP as is observed in normal innervated hearts[Denes 1974].

Bexton and colleagues[1984b] reported a normal broad range of Wenckebach points between 270 and 590msec in 14 long term survivors and similar results were obtained by Heinz and colleagues[1992c]in the immediate postoperative period. These results are in keeping with a balanced autonomic effect on the Wenckebach point in pharmacological studies[Tonkin 1980]. Bexton[1984b] also reported a good correlation between AV node ERP and the Wenckebach point as previously reported in innervated hearts[Bissett 1975].

Electrophysiological assessment of infranodal conduction in transplant recipients has been undertaken by several investigators[Cannom 1973, Goodman 1976, Bexton 1983]. In the majority of cases[Cannom 1973, Goodman 1976, Bexton 1983] the HV interval was within the normal range. This suggests that autonomic tone has little or no influence on the resting HV interval and is in keeping with the lack of an effect of pharmacological autonomic blockade in innervated hearts[Tonkin 1980].

Abnormalities of AV conduction after transplantation

The only systematic study of AV conduction disturbances in the early stages after transplantation was undertaken by Buja and colleagues[1992]. They reported complete AV dissociation in 14% (21/146) of all recipients. It developed on the first or second postoperative day in 20 subjects and on day six in one. In 18 of 21 subjects with complete AV dissociation the block was nodal, the remaining three had infra-Hisian block. One to one conduction returned within 16 days in all subjects with nodal block but in none of those with infra-Hisian block. Subsequent electrophysiological study

revealed that seven of the patients with nodal block had prolonged HV intervals. Although Buja and colleagues[1992] state that AV node refractory periods were measured in their study they do not report these results.

Amongst long term survivors Bexton and colleagues[1983]found two of 14 with prolonged HV intervals. The clinical significance of such an abnormality in an asymptomatic subject is questionable. Even in subjects with established bundle branch block a prolonged HV interval has only been clearly associated with an adverse prognosis in those with symptoms[Dhingra 1976, Scheinman 1977]. Bexton[1983] and colleagues also found evidence of dual AV nodal conduction pathways in 29% of subjects but this may be no greater than the normal population frequency[Casta 1980, McComb 1992].

Bradyarrhythmias

In comparison with bradyarrhythmias due to sinus node dysfunction there are few reports concerning the frequency and natural history of bradyarrhythmias due to AV block after transplantation.

Miyamoto and colleagues[1990] reported a very slow ventricular response to atrial fibrillation in 1% of recipients early after transplantation but it is not clear whether permanent pacing was subsequently required. In the series by DiBiase and colleagues[1991] 4 of 556 recipients required pacemakers for complete or high degree AV block. The timing of permanent pacing in these patients was not stated. Two groups of authors[Dodinot 1991, Buja 1992] report a significantly higher incidence of AV block: 7% and 14% respectively. In the series by Buja and colleagues[1992] it resolved in 85% of cases, whereas Dodinot and colleagues[1991] reported that 64% required permanent pacing for persistent AV block. Buja and colleagues[1992] also implanted pacemakers in seven patients with prolonged HV intervals at a subsequent electrophysiological study but the

pacemakers were not used during a mean of 12 months of follow up. Two patients with transient nodal AV block and normal AH and HV intervals at electrophysiological study subsequently required permanent pacemakers for late AV block. One of these had bifascicular block after restoration of 1:1 conduction.

There are no published data concerning the frequency of lesser degrees of AV block in transplant recipients. In a large electrocardiographic study Sandhu and colleagues[1990]did not discuss first degree AV block although it is not clear whether the PR interval was measured.

There are two reports in the literature of sudden death during ambulatory monitoring[Mackintosh 1982, Grinstead 1991] in transplant recipients. Although at least one of these authors linked the event to sinus node dysfunction[Mackintosh 1982]the mechanism appeared to have involved AV dissociation in each case.

Aetiology

As with sinus node dysfunction the differences between early and late AV block after transplantation suggest differing aetiologies neither of which is clearly established. Of those authors reporting a high incidence of AV block[Dodinot 1991, Buja 1992] only Dodinot and colleagues[1991] offer any theory as to aetiology. They attribute the problem to various unspecified "myocardial protection problems". Late AV block may result from occlusive graft coronary disease[Grinstead 1991].

Allograft rejection has also been suggested as a cause of AV block[Dodinot 1991, Janosik 1990]. Pathological changes in the conducting system during acute rejection have been demonstrated in animal models[Bieber 1969]but their relationship with AV conduction disturbances has not been established.

Transient AV block is common after conventional coronary surgery using hypothermic bypass and may be related to the high concentration of potassium in cardioplegia solutions[Ellis 1980]. However the principal determinant of **persistent** high degree AV block after conventional surgery is pre-existing intraventricular conduction system disease[Emlein 1992]suggesting that the block is intraventricular rather than intranodal in this group.

INTRAVENTRICULAR CONDUCTION AFTER TRANSPLANTATION

Electrocardiography

Right bundle branch block (RBBB) and RSR' QRS morphology with normal QRS duration are very common ECG findings after heart transplantation. Sandhu[1991] and colleagues have published the only systematic ECG study of intraventricular conduction abnormalities in transplant recipients. They found RBBB in 10% of recipients and RSR' in 35%. Left posterior hemiblock was also present in 60% of subjects with RBBB. These abnormalities were usually evident on the first postoperative day and their frequency remained constant over three years of follow up in 46 subjects.

No patient in this study[Sandhu 1991] developed clinically important bradyarrhythmias or required permanent pacing and progression of intraventricular conduction disturbances has not been reported elsewhere.

Aetiology

The aetiology of intraventricular conduction disturbances after transplantation is unclear. Sandhu[1991]and colleagues found no relationship between allograft rejection, operative ischaemic time, donor age or preoperative pulmonary vascular resistance and conduction abnormalities. They did however, demonstrate an association with posterior rotation of the long axis of the heart as assessed by radionuclide techniques and postulated that mechanical torsion of the heart during surgery may be responsible.

As previously discussed transient fascicular block is common after conventional surgery[O'Connell 1982, Rippe 1984]and may relate to long cross clamp time or potassium cardioplegia. However the evolution of more persistent intraventricular conduction disturbances is more unusual and certainly much less frequent than after transplantation[Sandhu 1991].

THE EFFECTS OF SYMPATHETIC DENERVATION

As already discussed, sympathetic denervation, particularly acute denervation, may cause early bradycardia in transplant recipients. However, there have been no previous studies designed to evaluate this hypothesis or to explore the role of catecholamines or beta receptors in the subsequent emergence of resting tachycardia in the majority of patients or the persistent bradyarrhythmias observed in some.

Myocardial catecholamine concentrations fall dramatically within the first few weeks after transplantation[Cooper 1962, Willman 1963, Kontos 1970]. In animal experiments no direct correlation was found between the degree of myocardial catecholamine depletion and cardiac performance[Peiss 1966] but the report by Wilman and colleagues[1963] strongly suggests that it is responsible for the observed depression of inotropic and chronotropic function in the immediate postoperative period. Chester and colleagues[1992a]have shown that changes in ß receptor density in the donor heart before implantation correlate with subsequent cardiac performance.

Changes in the level of adrenergic stimulation are known to lead to changes in tissue responsiveness[Lefkowitz 1982]. For example patients with chronic heart failure have persistently high levels of adrenergic stimulation which results in decreased sensitivity to catecholamines and beta-receptor down regulation[Bristow 1982].

Responses to catecholamines in the transplanted heart

Changes in catecholamine sensitivity and beta receptors in the denervated transplanted heart have been investigated by several groups of authors with conflicting results. In early animal experiments increased sensitivity of the transplanted dog heart to exogenous noradrenaline was reported by several groups of authors[Willman 1963, Cooper 1964,

Donald 1965). Lurie and colleagues(1983) also demonstrated this phenomenon in rabbit hearts following heterotopic transplantation and in addition found an increase in beta-receptor density suggesting a postsynaptic mechanism of supersensitivity.

In human heterotopic transplant recipients Yusuf and colleagues(1987) reported increased sensitivity to isoprenaline infusion in the transplanted heart as compared with both the innervated recipient heart and normal controls. However in this study potential changes in parasympathetic tone in controls and recipient hearts were ignored. It has been shown that increased vagal tone can attenuate the heart rate response to isoprenaline infusion in normal subjects(Arnold 1986). Quigg and colleagues(1989) confirmed this observation in orthotopic transplant recipients but found no difference in isoprenaline sensitivity when controls were pretreated with atropine. Similar results were reported by Gilbert and colleagues(1989) but in addition they demonstrated increased sensitivity of the transplanted heart to adrenaline as compared with the innervated atrial remnant. They concluded that the transplanted heart exhibited supersensitivity of **pre-synaptic** origin due absence of sympathetic nerve terminals and failure of adrenaline re-uptake(Trendelenburg 1963) (Isoprenaline is not taken up by sympathetic nerve terminals).

Beta-adrenergic receptors in the transplanted heart

Several studies have measured directly beta-receptor density in human heart tissue procured by endomyocardial biopsy from transplant recipients and controls. The results have been conflicting. Gilbert and colleagues(1989) reported significantly reduced beta receptor density compared with controls, two studies(Denniss 1989, Brodde 1991) found no significant difference while Chester and colleagues(1992) report increased receptor density in transplanted hearts. The variance in absolute ß-receptor densities (expressed as fmol/g protein) between each of these studies was up to 300% and the time after transplantation

and the methods of obtaining control tissue also differed. Differences in ß-receptor subtypes were analysed in two of these studies[Brodde 1991, Chester 1992b] and again the results are conflicting. Chester and colleagues[1992b] reported that the observed absolute increase in receptor density was due to an increase in $ß_1$ receptors with no significant change in $ß_2$ receptors whereas Brodde and colleagues[1991] reported an increase in the ratio of $ß_2$:$ß_1$ receptors.

Catecholamines and bradyarrhythmias after transplantation

When considering the hypothesis that early bradycardia and subsequent tachycardia in transplant recipients are due to changes in catecholamines and ß-receptor function, serial measurements of each would be of considerable importance.

To date all studies of catecholamine responses have been cross sectional. Quigg and colleagues[1989] showed that plasma noradrenaline both at rest and peak exercise was elevated in transplant recipients. Noradrenaline levels were also found to be higher in longer term recipients (more than three months after operation) compared with recent recipients. Plasma adrenaline was also elevated at rest and peak exercise but intersubject variation was large and the difference was not statistically significant.

Of the studies examining ß-receptor density, two assessed differences between recent transplant recipients and long term survivors[Brodde 1991, Chester 1992b]. Chester and colleagues[1992b] studied 43 recipients but serial measurements were only undertaken in eight and the exact frequency and timing were not detailed. They reported a distinct peak in ß-receptor density during the fourth postoperative month in the study group as a whole but this was not statistically significant in the subgroup who underwent serial measurements. Brodde and colleagues[1991] studied eight recipients at weekly and then monthly intervals for six to 18 months. Although there was no change in overall ß-

receptor density at any time there was a progressive increase in the ratio of $ß_2$ to $ß_1$ receptors from 80:20 in the first nine weeks to 65:35 after 25 weeks.

The findings reported by Brodde and colleagues[1991] are theoretically more attractive in explaining the observed changes in heart rate after transplantation and are more in keeping with other studies[Denniss 1989, Gilbert 1989, Quigg 1989]. Immediately after transplantation local noradrenaline release from sympathetic nerve terminals in the sinoatrial node will cease. Circulating catecholamines then become the major influence on heart rate. The presence of and importance of sinoatrial node $ß_2$ adrenoceptors in the chronotropic response of normal hearts has been convincingly demonstrated[Hall 1989]. Noradrenaline does not act at $ß_2$-receptors thus a relative increase in cardiac $ß_2$ receptors would increase the importance of circulating adrenalin as compared with local and circulating noradrenaline in the regulation of heart rate. The evolution of this change over time may explain the observed heart rate changes.

Serial studies of sensitivity to adrenaline and noradrenaline infusion in the immediate postoperative period and some months after transplantation would be needed to confirm or refute this hypothesis.

DRUGS AND THE ELECTROPHYSIOLOGY OF THE TRANSPLANTED HEART

After transplantation, tachyarrhythmias requiring specific treatment with antiarrhythmic drugs are uncommon[Scott 1992]. However transplant recipients may have been taking amiodarone pre-operatively and because of the high incidence of epileptic seizures in the first few weeks[Baulac 1989] anticonvulsant drugs with cardiac electrophysiological effects such as phenytoin and carbamazepine may be prescribed. Diltiazem is also used in some transplant recipients as an antihypertensive particularly in those intolerant of nifedipine. It may also be useful in the prevention of graft coronary disease[Schroeder 1993].

Amiodarone

Amiodarone is a highly effective anti-arrhythmic agent[Heger 1981, Neri 1987] and is unique amongst such drugs because it has little or no negative inotropic action[Cleland 1987, Hamer 1989]. It is often therefore prescribed for patients with end stage heart disease awaiting cardiac transplantation[Cameron 1988, MacDonald 1991].

Unlike other anti-arrhythmic agents amiodarone has a very long half life and it has been reported that preoperative amiodarone affects the transplanted heart[Cameron 1988, Macdonald 1991, Chelimsky-Fallick 1992, Heinz 1992a]. All of these authors have reported that preoperative amiodarone causes early bradycardia but does not change the incidence of persistent bradyarrhythmias or increase the need for pacemaker implantation. These studies were limited to intermittent measurements of heart rate and observation of the duration of atrial pacing. None included detailed electrophysiological assessment.

Pharmacokinetics

Amiodarone is highly lipid soluble and its pharmacokinetics are complex, probably best fitting a four compartment model[Holt 1983]. The volume of distribution is huge with considerable stores of the drug in adipose tissue during chronic administration[Latini 1984, Barbieri 1986]. The elimination half life in patients taking long term amiodarone ranges from 13 to 120 days[Somani 1989] and the situation is further complicated by the significant electrophysiological actions of the main metabolite desethylamiodarone. Knowledge of the metabolism of desethylamiodarone is limited but its volume of distribution is even larger and its elimination half life longer than that of the parent compound[Bandyopadhyay 1987]. In contrast with subjects maintained on amiodarone therapy the blood levels of desethylamiodarone are higher than those of the parent compound in subjects who have discontinued the drug[Bandyopadhyay 1987] and the relative clinical importance of the metabolite is probably greater.

The pharmacokinetic situation after transplantation is unique. In the absence of further drug administration the primary target organ is free of amiodarone and its metabolites whereas there will be substantial amounts in adipose and other tissues . None of the existing studies of the effects of amiodarone after transplantation[Macdonald 1991, Cameron 1992, Chelimsky-Fallick 1992] has attempted to measure the drug or its metabolite in serum or myocardium.

Electrophysiology

The electrophysiological effects of oral amiodarone in conventional doses were extensively studied by Mitchell and colleagues[1989]. Changes in sinus node function indices were maximal and stable within two weeks of the start of treatment. The spontaneous cycle length and corrected sinus node recovery times (CSNRT) increased

by approximately 15% and 30% respectively[Mitchell 1989]. Similar but less consistent changes were reported by another group of investigators immediately after adminstration of intravenous amiodarone[Touboul 1979]. It is of note that the interindividual variation in these responses was considerable in both reports. The sinoatrial conduction time (SACT) was also measured by Touboul and colleagues [1979] but no consistent change was reported. The results of animal experiments do suggest that sinoatrial conduction is depressed by amiodarone[Castillo-Fenoy 1978]. Mitchell and colleagues[1989] also reported increases in atrial and ventricular ERPs, AV node ERP and Wenckebach cycle length after oral amiodarone. The time course of these changes was similar to that of changes in sinus node function described above (one to two weeks). In contrast Wellens and colleagues[1984] reported that only the AV node ERP changed acutely after administration of intravenous amiodarone.

The clinical antiarrhythmic efficacy, changes in QT duration and ventricular functional refractory periods develop over a much longer time course of 10 to 20 weeks[Mitchell 1989]. Changes in ventricular ERPs occurred over an intermediate time course. This is probably due to the dominant role of the metabolite desethylamiodarone in these effects[Talajic 1987, Stark 1991].

The electrophysiology of amiodarone after transplantation

In addition to unique pharmacokinetics, the situation may be further complicated by the denervated state of the transplanted heart. Amiodarone has significant anti-adrenergic activity in the innervated heart[Polster 1976]and its actions may be different in the absence of autonomic innervation. The anti-adrenergic effects of amiodarone are probably at intracellular rather than beta receptor level[Polster 1976]and the effects of changes in adrenergic stimulation after transplantation are unknown.

There have been no previous electrophysiological studies of the effects amiodarone on the transplanted heart. Charlier and colleagues[1970] studied the actions of amiodarone in dogs following pharmacological autonomic blockade. Acute administration of intravenous amiodarone reduced the heart rate and this response was not abolished by pretreatment with propranolol. As previously noted this pharmacological model of autonomic denervation is of limited accuracy as regards the transplanted heart because the effects of circulating catecholamines are also antagonised.

Dose, electrophysiological effects, serum and tissue levels

Despite considerable variation in bioavailability in some studies[Pourbaix 1985], in practice serum levels of amiodarone usually correlate with current dosage[Somani 1989, Malling 1989]. In contrast, correlations between serum levels and electrophysiological or therapeutic effects are weak and inconsistent[Rotmensch 1984, Mitchell 1989, Somani 1989, Malling 1989]. This is probably due to the very considerable inter-subject variation in the relationship between plasma and tissue levels of amiodarone[Giardina 1990]. Giardina and colleagues[1990] directly measured amiodarone concentrations in humans and reported tissue to plasma ratios of between 7:1 and 51:1 for myocardium and 83:1 to 699:1 for adipose tissue. Clinical efficacy, functional ventricular refractory periods and QT duration are better correlated with serum desethylamiodarone than amiodarone levels[Mitchell 1989].

The relationship between duration of treatment and tissue levels has also been examined but existing studies[Barbieri 1986, Giardina 1990]have been limited by small subject numbers and infrequent sampling. Barbieri and colleagues[1986] confirmed that tissue accumulation of amiodarone and desethylamiodarone occurs over approximately one month of oral treatment. In subjects treated for at least 88 days Giardina and colleagues[1990] found that tissue concentrations were independent of cumulative dose.

There are as yet no published studies which have sought to correlate electrophysiological effects with tissue concentrations directly.

Carbamazepine

Carbamazepine is widely used for the treatment of epilepsy and neurogenic pain. Cardiac electrophysiological effects were first noted in animals[Steiner 1970]. A series of reports of adverse reactions in humans including extreme sinus bradycardia[Herzberg 1978], nodal bradycardia[Beerman 1978, Byrne 1979] and atrioventricular block[Hamilton 1978] then followed. Preexisting conduction system disease was a predisposing factor in many cases[Beerman 1975].

The only systematic electrophysiological study in humans was undertaken by Kennebäck and colleagues[1991]. Ten patients were studied, six of whom had ECG abnormalities before treatment with carbamazepine (fascicular and bundle branch blocks and first degree AV block in one of these). Seven subjects were evaluated during "steady state" treatment with confirmed therapeutic drug levels. Spontaneous cycle length and sinus node recovery times showed highly variable change during carbamazepine therapy, increasing in some subjects and decreasing in others with an overall mean increase of 10%. Similarly variable changes were noted in Wenckebach cycle length but atrial and AV nodal refractory periods did not change significantly. No attempt was made to control for changes in autonomic tone during these studies which may have reduced their reliability[Gupta 1974, Jordan 1978].

There are, as yet, no reports of the actions of carbamazepine on the denervated transplanted heart.

Phenytoin

The important cardiac electrophysiological actions of this anticonvulsant have been recognised for many years. It is a clinically useful antiarrhythmic agent, particularly for ventricular arrhythmias in the setting of digitalis toxicity[Bigger 1968, Wit 1975].

Phenytoin has very variable effects on sinus rate and other indices of sinus node function[Caracta 1973, Dhatt 1979, Tsuchioka 1986]. It has been suggested that these differences may relate to differences in autonomic tone[Rosati 1967] and to the presence or absence of preexisting sinus node disease[Wit 1975, Tsuchioka 1986]. The lack of any direct action on isolated animal atria preparations also supports the importance of these other factors[Strauss 1968] in determining the response to phenytoin. The effects on atrial and AV nodal refractory periods are similarly variable increasing in some subjects and decreasing in others[Caracta 1973].

There are no published reports concerning the actions of phenytoin on the denervated heart or any using pharmacological blockade to control for changes in autonomic tone.

Diltiazem

The electrophysiological effects of diltiazem have been studied by several groups. Talajic and colleagues[1992]studied the effects of intravenous administration of various doses of diltiazem. The drug plasma concentrations achieved were similar to therapeutic levels during chronic administration[Henry 1980]. There were significant effects on electrophysiological indices of atrioventricular node function. The Wenckebach cycle length increased consistently in a dose dependent pattern. The change in atrioventricular ERP was highly dependent on atrial rate. At faster drives the increase was substantial but was much less prominent with a slower drive. In contrast to the AV node, there was

no significant change in any index of sinus node function or in atrial ERP. Corrected maximal sinus node recovery time and sinoatrial conduction time were unchanged. At the highest dose there was a small increase in resting cycle length. In contrast, Legrand and colleagues[1984] reported no change in resting heart rate after administration of similar doses of intravenous diltiazem. Legrand and colleagues also reported no change in the chronotropic response to exercise after diltiazem treatment.

Kumar and colleagues[1991]reported no change in sinus or AV node function parameters after five to seven days treatment with oral diltiazem at a dose of 60mg three times daily. Given the low bioavailability of oral diltiazem[Henry 1980]the plasma concentrations achieved were probably substantially less than in the studies described above but this dose is commonly used.

In animal experiments intact autonomic reflexes reduced the effects of diltiazem[Nayebpour 1990]. There have been no previous reports of the electrophysiological effects of diltiazem in the transplanted heart or of studies involving pharmacological autonomic blockade in humans.

Pacing for early bradyarrhythmias

Indications

The indications for permanent pacing in transplant patients with bradyarrhythmias are poorly defined[DiBiase 1991] and implantation rates vary widely from as low as 4%[Miyamoto 1990] to as high as 29%[Loria 1988].

Accepted indications for permanent pacing in the general population include persistent or intermittent symptomatic bradyarrhythmias and bradyarrhythmias likely to reduce life expectancy[Frye, ACC/AHA Task Force 1984]. Concern about sudden death in transplant recipients with sinus node dysfunction[Mackintosh 1982] has led some authors to advocate considerable widening of the criteria for permanent pacing in transplant recipients[DiBiase 1991, Grinstead 1991]. In the series reported by DiBiase and colleagues[1991] 61% of pacemaker implantations were in asymptomatic patients, some with sinus bradycardia. Mackintosh and colleagues[1982] postulated that subsidiary pacemakers were less reliable in the denervated heart. Although this is in keeping with clinical observations in the immediate postoperative period[Stinson 1975, Cabrol 1989, DiBiase 1991] there is neither good evidence that it is a persistent problem nor to suggest that asymptomatic subjects with apparently reliable subsidiary pacemaker function are at risk of lethal bradyarrhythmias. The two monitored bradyarrhythmic deaths reported in the literature were associated with other potentially fatal complications: severe graft coronary disease in one instance[Grinstead 1991] and acute rejection in the other[Mackintosh 1982]. It is by no means clear that permanent pacing would have prevented these deaths. Sudden death of transplant patients with pacemakers and no evidence of pacing system failure has been reported on several occasions[Markewitz 1987, DiBiase 1991].

In the first few days after heart transplantation ventricular compliance is reduced[Davies 1987, Young 1987] and the ability of the heart to increase cardiac output by increased stroke volume is therefore limited. A relative bradycardia of 80 bpm or less[DiBiase 1991] may be haemodynamically deleterious in this situation and may necessitate temporary pacing. There is however, no evidence that the high resting heart rate seen in long term survivors[Alexopoulos 1988, Scott 1993] is advantageous or that permanent pacing for persistent relative bradycardia is beneficial.

Timing of implantation

The optimum timing of permanent pacemaker insertion for early bradyarrhythmias after transplantation is contentious with some centres advocating pacing at seven to 10 days[Payne 1991] and others recommending a delay of at least two or three weeks[Loria 1988, Miyamoto 1990, Smilovitch 1991]. This largely reflects the different experiences of the respective centres as regards the frequency and timing of recovery of sinus dysfunction (this is discussed further in the next section). A policy of early permanent pacemaker implantation may enable earlier discharge from hospital in some instances. It will however, result in unnecessary procedures particularly in those patients with sinus dysfunction which often resolves within the first three weeks[Miyamoto 1990, Heinz 1990]. Although sinus dysfunction will subsequently resolve in some patients the three week timing adopted by most centres represents the best compromise between the risk of an unnecessary invasive procedure in an immunocompromised subject and the limitations of continued temporary pacing.

Some authors have advocated pharmacological treatment of persistent sinus dysfunction with agents such as terbutaline[Cook 1989] or theophylline[Redmond 1993]. Redmond and colleagues[1993] demonstrated that their use of permanent pacemakers was markedly

reduced by this strategy. However they selected subjects for theophylline therapy simply on the basis of rhythm and heart rate thus the frequency of sinus node dysfunction was not established by standard criteria. All the patients who received theophylline required no further treatment for bradyarrhythmias after three months. This contrasts with a persistent requirement for permanent pacing in a variable proportion of subjects in most other series[DiBiase 1991, Payne 1991, Heinz 1990]. The pharmacological approach might be more generally applicable if a group of recipients with sinus node dysfunction could be reliably identified who were known to have a very good prognosis for recovery.

The need for long term pacing

There are large differences in the reported frequency of long term pacing requirements in transplant recipients who receive permanent pacemakers. This may in part be due to differences in diagnostic criteria and pacemaker programming. DiBiase and colleagues[1991]reported persistent bradycardia (60 to 90 bpm) in 84%, 75% and 57% of pacemaker recipients at three, six and 12 months respectively. The method of assessment, the frequency of symptomatic bradycardia and the pacemaker programming parameters are not stated in this report[DiBiase 1991]. Payne and colleagues[1991]used 24 hour ambulatory monitoring and demonstrated that the majority of (86%, six of seven) patients remained pacemaker dependent at between six months and three years with underlying symptomatic bradycardia.

In contrast Miyamoto[1990] and Heinz[1990]respectively reported that only 29% (five of 17) and 22% (two of nine) of pacemaker recipients required long term pacing. Ambulatory monitoring was not undertaken routinely in either of these studies. Neither of the two recipients described by Loria and colleagues[1988] required long term pacing and this was confirmed by ambulatory monitoring in each case.

These studies all relate to patients paced for sinus node dysfunction. There are no data in the literature concerning long term pacing for atrioventricular block.

Pacing for late bradyarrhythmias

Late bradyarrhythmias (more than one month after transplantation) requiring permanent pacing have been reported by several authors[Berke 1973, Addonizio 1990, Miyamoto 1990, DiBiase 1991] but they are infrequent in comparison with those occurring in the early postoperative period[DiBiase 1991].

The indications for late pacemaker implantation are less contentious with only one group of authors advocating substantially different criteria from those accepted for the general population. Grinstead[1991] and colleagues proposed prophylactic permanent pacing for patients with occlusive graft coronary disease following the death of one such transplant recipient during ambulatory monitoring. However it seems unlikely that such a strategy would improve survival as this is determined by the extent of the ischaemia, rather than resulting conduction disturbances, in other patients with acute cardiac ischaemia[Col 1972, Ginks 1977].

Modes of pacing in transplant recipients

Atrial, ventricular or dual chamber pacing?

The optimum mode of pacing in transplant recipients is controversial. Physiological (atrial or dual chamber) pacing is advocated by several authors[Markewitz 1987, Loria 1988, Osterholzer 1988, Payne 1991]. The advantages in non-transplant patients have been clearly established[Perrins 1983, Ebagosti 1988, Fisher 1988]. The haemodynamic benefits in transplant recipients have been confirmed despite the abnormal atrial morphology which results from the standard operative technique[Midei 1990, Parry 1992]. Parry and colleagues[1992]also found that

synchronous recipient and donor atrial pacing increased the cardiac output in some subjects although it made no significant difference in their patient group overall. McClurken and colleagues[1993]demonstrated a more reliable haemodynamic improvement with synchronised pacing but their study involved smaller patient numbers and was restricted to the first postoperative week. The clinical importance of these findings in medium and long term recipients remains to be established.

Two groups of authors from large transplant centres[Miyamoto 1990, DiBiase 1991]advocate the routine use of ventricular pacemakers for several reasons. Their concerns about the risk of later development of atrioventricular block are shared by other authors who implant physiological systems but insert ventricular leads in all recipients[Markewitz 1987, Osterholzer 1988]. There is however no evidence to support this concern. Markewitz and colleagues[1992] recently reported that none of 21 pacemaker recipients developed AV block during a mean follow up period of 16 months (three to 53 months). In contrast with sinus node disease in non transplant patients, Heinz and colleagues[1992c]also report consistently normal AV conduction in a group of transplant recipients with sinus node dysfunction. Although Buja and colleagues[1992] reported the development of late AV block in two patients, both had a history of early AV block and neither had sinus node dysfunction. The infrequent requirement for long term pacing is also cited as a reason for choosing a simple ventricular device[Miyamoto 1990]. If the requirement for long term pacing were predictable then this might be a reasonable approach but as previously discussed a substantial minority of patients will pace long term and would probably benefit from physiological pacing. Miyamoto[1990] and colleagues also state that ventricular pacing avoids the need for electrophysiological assessment of AV node function. This is not a valid argument as AV node function is easily assessed during atrial pacemaker implantation.

The need for rate responsive pacing

Some authors routinely implant rate responsive pacing systems[Loria 1988] while others implant them in some patients[DiBiase 1991, Miyamoto 1990] but do not state the criteria on which this decision is made. Activity sensing systems have been most commonly employed.

As previously discussed the heart rate response to exercise is abnormal in all transplant recipients [Pope 1980, Savin 1980] and there is no generally agreed definition of chronotropic incompetence in this group. In normal subjects rate responsive pacemakers can closely mimic the normal sinus node response[Noura 1987] but their function in transplant recipients has never been systematically evaluated. It may be that the exercise response of all transplant recipients including those without bradyarrhythmias could be improved by rate responsive pacing. If true then this would be a powerful argument for routinely implanting rate responsive pacemakers in those who needed a permanent pacemaker anyway.

Permanetter and colleagues[1992]have shown that elevated pulmonary capillary wedge pressures during exercise in transplant recipients can be reduced to physiological levels by atrial pacing. However they also showed that circulating catecholamines were reduced by atrial pacing. The useful peripheral actions of catecholamines during exercise may therefore be attenuated by pacing. Significant clinical benefit from routine rate adaptive pacing has not been demonstrated. It is unlikely that the normal (innervated pattern) exercise response could be reproduced in view of the high resting heart rate[Scott 1993] and consequent reduced heart rate reserve. Accurate programming to achieve a good exercise response in this situation may be also be problematic.

A recipient atrium sensing system which restores a more physiological heart rate response to exercise has been described both in animals[Chartrand 1987] and in humans[Osterholzer

1988, Kacet 1991). Although this is theoretically attractive the technique may be limited by a high incidence of recipient sinus node dysfunction(Bexton 1984). There is as yet no evidence that such "artificial reinnervation" would be of significant clinical benefit. Sigmund and colleagues(1992) report no significant benefit from atrial pacing synchronised with recipient atrial P waves during exercise studies involving 13 transplant recipients.

CHAPTER 2

PERMANENT PACING AFTER CARDIAC TRANSPLANTATION

A retrospective review of permanent pacing in 218 adult transplant recipients and a prospective study of current pacemaker use

Introduction

The exact indications for permanent pacing in transplant recipients are controversial with widely varying rates of implantation at different centres[Miyamoto 1990, Loria 1988].

The permanent pacing policy has changed over the course of the transplant programme at this centre. Initially VVI pacemakers were implanted between eight and 21 days after transplantation, many on a prophylactic basis, when the resting heart rate was below 70 beats per minute. Many of these recipients appeared not to require long term pacing and subsequently pacemakers were only implanted for symptomatic bradyarrhythmias which persisted after the third postoperative week. Increased use was also made of physiological and rate responsive systems as it was thought these would improve exercise tolerance. Pacemaker programming was largely empiric with rates chosen to mimic those of other transplant patients without sinus or AV node dysfunction.

This study was undertaken to examine the exact indications for permanent pacing in our patients and to identify any characteristics which may predispose to bradyarrhythmias requiring permanent pacing. We sought to determine the need for long term pacing in transplant recipients who received permanent pacemakers and in particular to identify any factors which could predict a requirement for long term pacing.

Methods

Between May 1985 and March 1992, 218 adults underwent orthotopic heart transplantation at this centre. The standard operative procedure as described by Lower and colleagues[1961]was used in each case. Temporary epicardial atrial and ventricular pacing wires were placed at the time of operation in each patient and were removed on or around the 21st postoperative day.

Retrospective review

The clinical records of all patients with permanent pacemakers were examined. The interval between transplantation and pacing, the indication, pacemaker type and programming were noted. Therapy with cardioactive drugs, including preoperative amiodarone, was recorded. Pacemaker related complications were noted. Resting 12 lead ECGs taken at three monthly intervals during routine follow up were examined.

The ischaemic time, donor age and episodes of rejection were recorded for all transplant recipients.

Prospective study

Twenty four hour ambulatory electrocardiography was performed in 18 of 19 surviving patients with pacemakers. In 16 patients a recording was made with the pacemaker parameters programmed as at the time of implantation. In those patients in whom pacemaker activity was detected during the initial recording the pacemaker was reprogrammed to 50 beats per minute with the rate sensor inactivated if present. The 24 hour ambulatory ECG was then repeated. Two patients had their pacemaker reprogrammed in this way to minimise its use before the initial recording.

Statistical analysis

Statistical analyses were performed using the Student's t test or Mann-Whitney U test as appropriate. Results are expressed as mean $\pm$ 1 standard deviation.

Results

The results are summarised in table 2.1. Of 218 adult heart transplant recipients, 21 (9.6%) received permanent pacemakers.

Indications

The indication for pacing was sinus node dysfunction in 13 patients representing 62% of those receiving a pacemaker and 5.9% of all transplant recipients. This was manifest as sinus bradycardia in 10 patients with rates of 30 to 60 beats per minute and by sinus arrest with nodal escape rhythm in three. Eight patients (38% of those paced, 3.7% of all recipients) had pacemakers because of atrioventricular block, six of these had second or third degree block and two had atrial flutter with variable block.

Timing of pacemaker implantation

The mean interval between transplantation and permanent pacing was 19.4 days (range eight to 90 days). Only one pacemaker was implanted after the first postoperative month. This patient had no early bradyarrhythmias but subsequently had evidence of bradycardia-tachycardia syndrome on 24 hour ambulatory monitoring. This patient died four months after transplantation from infection and renal failure and was not therefore included in the prospective part of the study.

TABLE 2.1: Details of transplant recipients receiving permanent pacemakers

Patient Number	Post-op day implanted	Mode	Indication	ECG (months post-op) 3	6	9	12	24	36	Tape 1	Tape 2	Comments
1	18	VVI	SND	-	-	-	-	-	-	-	-	Paces only at night tape 2
2	14	VVI	SND	-	-	-	-	-	-	+	+	
3	8	VVI	AVB	-	-	-	-	-	-	-		
4	9	VVI	SND	+	-	-	-	-	-			Not in prospective study
5	15	VVI	AVB	-	-	-	-	-	-	-		
6	19	DDD	SND	+	+	+	+	+	+	+	+	Upgraded form VVI because of pacemaker syndrome.
7	9	VVI	AVB	+	-							Died at 7 months.
8	17	VVI	SND	-	-	-	-	-	-	-		
9	16	VVIR	SND	-	+	-	-	-	-	-		
10	9	VVIR	AVB	+	-	-	-	-	-	+	-	
11	15	VVIR	AVB	-	-	-	-	-	-	+	-	
12	20	VVIR	SND	+	-	+	+	+		+	+	Unable to tolerate VVI pacing (chronotropic incompetence)
13	10	DDDR	SND	+	+	+	+	-		+	-	
14	90	VVIR	SND									Late sinus dysfunction, died renal failure/infection.
15	12	VVIR	AVB	-	-	-	-	-		+	-	
16	14	VVIR	SND	-	-	-	-			-		
17	15	VVIR	AVB	-	-	-	-			+	-	
18	26	AAIR	SND	-	+	+	-			+	+	
19	25	AAIR	SND	-	-	-				+	-	Pacemaker induced AVNRT
20	21	DDDR	AVB	+	+	+				+	+	
21	25	AAIR	SND	+	-					+	-	

KEY: SND= Sinus node dysfunction, AVB= Atrioventricular block, AVNRT= AV node reentrant tachycardia, + pacing, - not pacing, Tape 1= 1st ambulatory electrocardiogram, Tape 2= 2nd ambulatory electrocardiogram after reprogramming.

Drug therapy

Four of 21 patients (19%) had taken amiodarone before transplantation, each at a dose of 200mg daily for between one and 36 months. Isoprenaline was used in all subjects but only in the immediate postoperative period (less than one week). No other cardioactive drugs were prescribed.

Type and programming of pacemakers

Ventricular pacemakers were implanted in 15 patients (eight rate responsive), atrial pacemakers in three (all rate responsive) and dual chamber in three (two rate responsive). VVI pacemakers were programmed to 70 bpm, DDD to 90 bpm. Rate responsive pacemakers were all activity sensing units and were programmed to a minimum rate of 80 bpm and a maximum rate of 130 bpm.

Ischaemic time and donor age

There was no difference between the operative ischaemic time in those patients who subsequently required permanent pacemakers and those who did not (169 ± 40 minutes *v* 169 ± 46 minutes) ($p=0.99$) or between the donor ages (31.9 ± 9.5 years *v* 29.6 ± 9.3 years) ($p=0.34$). The patients with pacemakers had a mean of 0.41 episodes of rejection (of at least "moderate" grade[Billingham 1981]) in the first postoperative month compared with 0.32 episodes for other transplant recipients. This difference was not statistically significant ($p=0.18$).

Complications

There were two episodes of lead displacement during 350 endomyocardial biopsy procedures with a permanent transvenous ventricular lead in place. On both occasions

the pacemaker had been implanted within the preceding 14 days. Both leads were repositioned without incident. No atrial leads were displaced during 73 procedures with atrial leads in situ. There were no pacemaker related infective episodes.

Follow up

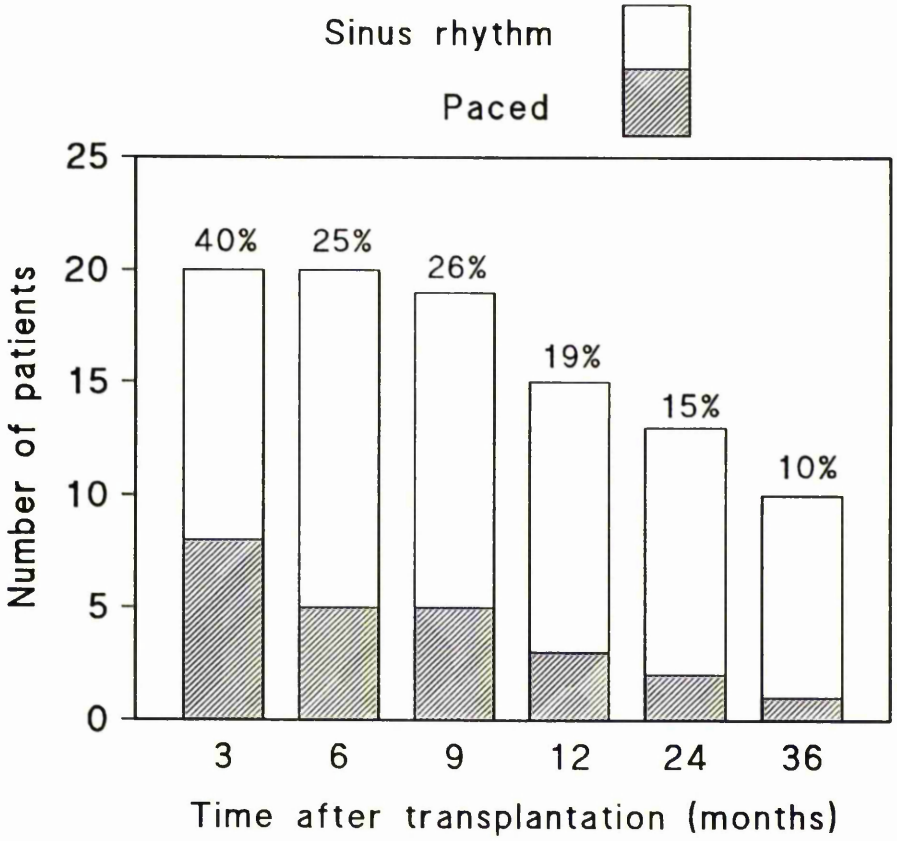
The frequency of pacing on resting 12 lead ECGs declined progressively with time after transplantation from eight of 20 (40%) at three months to 1/10 (10%) at 36 months (Figure 2.1).

Prospective study

During the single 24 hour ambulatory ECG recording prior to reprogramming, 12 of 18 patients paced intermittently. The remainder did not pace at any time. The presence of pacing was clearly related to the type and programming of the pacemaker implanted. Only one of five patients with a simple VVI device paced whereas 10 of 13 rate responsive pacemakers were used, often at rates of greater than 100 beats per minute.

Following reprogramming only five patients continued to pace during a further 24 hour ambulatory ECG recording. Two of these paced only at night. One of the patients with a rate responsive pacemaker who paced intermittently on the initial recording did not tolerate inactivation of the rate sensor. The original indication in this patient was sinus node dysfunction and the underlying rhythm was sinus at 60 bpm. Informal exercise testing produced no increase in heart rate and the patient experienced extreme fatigue and presyncope. The pacemaker was therefore programmed to 50-130 bpm VVIR. Ambulatory monitoring showed continued intermittent pacing. No other patient reported any adverse effects from reprogramming.

Figure 2.1: Frequency of pacing and time after transplantation (12 lead ECGs)



Following reprogramming to minimise pacemaker use only one of seven (14%) subjects paced for atrioventricular block was pacing compared with four of 11 (36%) initially paced for sinus node dysfunction.

No patient who received a permanent pacemaker before the 15th postoperative day was pacing on the final ambulatory ECG. There was no difference in operative ischaemic time between those patients who paced long term (160±36 minutes) and those who did not (160±45 minutes).

Discussion

Limitations of the study

The patients included in this study were identified retrospectively by having had a permanent pacemaker implanted. Other patients with sinus node dysfunction or atrioventricular block may therefore, have been excluded. Although 12 lead ECGs were available for all patients at three monthly intervals, the ambulatory recordings were performed at variable times between three and 65 months. Single 24 hour ambulatory electrocardiograms may be insufficient to be certain that the pacemakers are no longer required. However Miyamoto and colleagues[1990] removed an infected pacemaker in one of their patients on the evidence of 24 hours of ambulatory monitoring without adverse effect. Our follow up ECG data and the differences in the reported incidence of sinus node dysfunction between early[Mackintosh 1982, Heinz 1992a] and late electrophysiological studies[Bexton 1984a]do suggest that it resolves with time. Exercise tolerance was not formally assessed. We cannot therefore from these data alone exclude some benefit from pacing during exercise in patients without an absolute requirement at rest.

Indications for permanent pacing

The proportion of patients paced because of AV block in this study (38%) is substantially higher than in most other published series where between 0%[Payne 1991, Heinz 1992a] and 10%[DiBiase 1991] of implantations have been for AV block. However in several smaller studies the frequency of AV block requiring a permanent pacemaker has been higher[Janosik 1990, Buja 1992, Dodinot 1991]. The reasons for this discrepancy are unknown. There were no major differences in operative technique or post operative management or in such variables as ischaemic time, donor and recipient ages.

Our implantation rate for sinus node dysfunction of 5.9% compares with rates of between 4%[Miyamoto 1990] and 22%[Heinz 1992a] reported by other centres.

The differences in implantation rates between these two studies primarily reflect the incidence of bradyarrhythmias rather than implantation criteria. Heinz and colleagues have consistently reported[1990, 1992a] a very high incidence of sinus node dysfunction (approx 50%). In contrast Miyamoto and colleagues[1990] observed significant bradyarrhythmias in fewer patients. Our implantation rate is similar to the large series reported by DiBiase and colleagues[1991] (7.4%).

Timing of pacing and requirement for long term pacing

Although to some extent fortuitous, our finding that no patient who received a pacemaker before the third week required long term pacing emphasises the benefits of delaying the decision to implant a pacemaker.

Of the patients studied by ambulatory monitoring in our series 28% (5 of 18) required long term pacing. This is closely comparable with results from two other series[Miyamoto 1990, Heinz 1990]. The reasons for a much higher frequency of long term pacing (between 57% and 86%) in other reports[DiBiase 1991, Payne 1991] are unknown.

Unnecessary pacemaker implantation could be avoided if prognostic indicators of the need for long term pacing could be identified. This study is the first to show that the likelihood of long term pacing depends to some extent on the original indication. Only 14% subjects studied who were paced for AV block required long term pacing in contrast with 36% of those paced for sinus node dysfunction.

Late pacemaker implantation

One of 21 pacemakers in our series was implanted 90 days after transplantation. This is in keeping with previous reports which have described occasional patients developing late bradyarrhythmias[Berke 1973, Miyamoto 1990, DiBiase 1991] but these have been substantially less common than in the immediate postoperative period.

Conclusions

A requirement for long term pacing in transplant recipients receiving pacemakers soon after transplantation is unusual. It is more frequent in those with sinus node dysfunction than in those paced for atrioventricular block.

However there are, at present, no clear prognostic indicators of subsequent pacing requirements in those with persistent bradyarrhythmias after the third week. A pacing system suitable for long term use should therefore be selected. We recommend that implantation is delayed until at least 21 days after transplantation and until the patient is otherwise ready for discharge from hospital in order to reduce the frequency of unnecessary implantations.

CHAPTER 3

SINUS AND ATRIOVENTRICULAR NODE FUNCTION AFTER CARDIAC TRANSPLANTATION

A prospective serial study in 40 transplant recipients using electrophysiological testing, exercise testing and 24 hour ambulatory ECG monitoring.

Introduction

A significant minority of transplant recipients develop postoperative sinus and or atrioventricular (AV) node dysfunction. Some of these receive permanent pacing systems. In many cases sinus and AV node function improve but their natural history has not been clearly established because serial studies on the same recipients in the immediate postoperative period and during longer term follow up have not been performed.

This study aims to determine the natural history of these conditions during the first six months after transplantation. Various potential aetiological factors will be examined and any variables which may be able to predict persistence of sinus or atrioventricular node dysfunction will be identified. Better assessment of long term pacing requirements and more appropriate pacemaker prescription for transplant recipients should result.

Patients

Forty transplant recipients were recruited for the study. All 44 adult recipients transplanted between October 1991 and January 1993 were considered for the study. Three patients were excluded, two did not survive the first postoperative week, one required prolonged intensive care and it was considered inappropriate to request participation in a research project. One patient refused consent.

All underwent orthotopic transplantation using the standard atrial anastomosis technique described by Lower and colleagues[1961]. The donor heart was perfused and topically cooled with St Thomas's cardioplegia solution at a temperature of 4°C. Temporary epicardial pacing wires were inserted at the time of surgery and routinely removed three weeks after operation. Two pairs were attached to the donor atrium and one pair to the ventricle. The spontaneous cardiac rhythm was recorded immediately after defibrillation, after weaning from cardiopulmonary bypass and on return to the intensive care unit. All patients were initially treated with an isoprenaline infusion which was discontinued between one and six days after transplantation.

Surveillance endomyocardial biopsies were performed at weekly intervals for six weeks, two weekly until 12 weeks, monthly until six months and three monthly thereafter. Further biopsies were performed if there was clinical suspicion of rejection. Biopsies were histologically graded using the Billingham classification[Billingham 1981].

Temporary cardiac pacing was used in the immediate postoperative period in all subjects. This was continued for between one and 21 days in order to maintain a minimum heart rate of 50 bpm. Those subjects who continued to require pacing three weeks after transplantation had a permanent pacemaker implanted. A requirement for pacing was defined by the occurrence of symptomatic bradyarrhythmias during normal activity or symptomatic chronotropic incompetence on exercise testing after withdrawal

of temporary pacing.

Immunosuppression was achieved with Cyclosporin, Azathioprine and Prednisolone. After transplantation additional cardioactive drugs were prescribed for non cardiac indications in six subjects. Anticonvulsants were required in four subjects: carbamazepine in one, phenytoin in two and both were used at different times in a further subject. Diltiazem was prescribed for hypertension in five subjects. The details of dose and timing of therapy for additional drugs are recorded in appendix 6.0.

Preoperative amiodarone had been prescribed in 11 subjects at doses of between 200mg and 800mg daily for between four and 60 months. No subject received postoperative treatment with amiodarone.

Thirty six subjects (90%) were male. The indication for transplantation was ischaemic heart disease in 20, dilated cardiomyopathy in 17, congenital heart disease in two and valvular disease in one. The mean ($\pm$standard deviation) recipient and donor ages were 46.6$\pm$11.8 years and 35.3$\pm$10.5 years respectively.

All subjects gave fully informed written consent and all investigations were approved by the joint ethical committee of the University of Newcastle upon Tyne and Newcastle District Health Authority.

Outcome

One subject withdrew consent for the study for unspecified reasons after the third week. There were five deaths during the study period (Table 3.1). None was related to study investigations. None was attributable to arrhythmias.

Significant allograft rejection (of at least moderate severity[Billingham 1981] occurred on 10 occasions in 10 subjects.

Table 3.1: Details of subjects who died during the study period.

Patient number	Age	Sex	Cause of death	Time after transplantation
2	39	Male	Spinal haemorrhage	5 months
11	33	Male	Pancreatitis	3 weeks
19	31	Female	Severe rejection	11 days
21	53	Male	Intrathoracic sepsis	4 weeks
25	52	Male	Cytomegalovirus colitis	5 months

SECTION 1.
ELECTROPHYSIOLOGICAL STUDIES

METHODS

Electrophysiological studies were performed on six occasions in each subject one, two, three and six weeks, three and six months after transplantation. All subjects were studied in the supine position after resting for at least 30 minutes. Temporary cardiac pacing was discontinued for at least ten minutes prior to each study.

The surface ECG was recorded throughout the study using standard lead I and chest lead V1. The first three studies were performed using temporary epicardial pacing wires. The remaining studies were carried out at the time of surveillance endomyocardial biopsies. An atrial "J" configuration quadripolar electrode catheter (Bard electrophysiology) was inserted through the right internal jugular vein and placed in the donor atrium. Its position within the donor atrium was confirmed by fluoroscopy and by simultaneous monitoring of the surface ECG and atrial electrograms.

All studies were performed with a programmed stimulator delivering a constant square voltage wave form of two msec duration at twice diastolic threshold. Intracardiac electrograms and surface ECG signals were recorded with a Gould electrostatic recorder at a paper speed of 100 mm per second. Measurements were subsequently made to an accuracy of five msec.

Sinus node function

The spontaneous cycle length was calculated from an average of ten cardiac cycles before any pacing intervention. Sinus node recovery time (SNRT) was assessed by overdrive pacing of the donor atrium for 30 seconds at varying cycle lengths and

measuring the interval between the last paced and the first spontaneous sinus beats. Decremental cycle lengths at 100 msec intervals were employed starting from just below the spontaneous sinus rate to a minimum of 400 msec. At least one minute elapsed between each pacing sequence. The corrected sinus node recovery time (CSNRT) was calculated by subtracting the spontaneous cycle length from the SNRT. Sinoatrial conduction time was measured by the method of Strauss[1973] (single atrial extrastimuli in sinus rhythm).

Atrioventricular node function

Incremental atrial pacing (minimum cycle length: 300 msec) was performed and the cycle length at which Wenckebach AV conduction first occurred was recorded. The effective refractory period of the atrioventricular conduction system (AVERP) was also measured by single atrial extrastimuli in sinus rhythm and with eight beat drives at two different cycle lengths. Cycle lengths of 600 msec and 400 msec were used in preference but Wenckebach conduction during the drive or a high resting heart rate necessitated the use of 700 msec and 500 msec in some instances. Measurements of AVERP were made from atrial electrograms and conduction confirmed from the surface ECG recordings. When the effective refractory period of the atrium (AERP) exceeded AVERP the AERP was recorded.

Statistical analysis

Statistical analyses were performed using an IBM compatible computer and Minitab (version 7.0, 1989, Minitab Inc, Statten Island, New York, USA) and Statgraphics (version 2.6, STSC Inc, Rockville, Maryland, USA) statistical software.

The changes in sinus node function parameters over time were analysed by two way analysis of variance on subjects and times. Subjects with more than 50% of intended observations missing were excluded. Isolated missing data were estimated using the Minitab Generalised Linear Model command function. Changes in atrioventricular node function indices with time were analysed by one way analysis of variance in view of the larger numbers of unobtainable measurements. Paired t tests were used to compare sinus and AV node function indices at specific time points and to compare atrioventricular refractory periods at different drive cycle lengths. Linear correlation was used to interrelate simultaneous measurements of sinus and AV node function parameters. Fisher's exact and Chi squared tests were used to examine the relationship between sinus node dysfunction and rejection, perioperative rhythm and subsequent mortality. Unpaired t tests were used to compare operative ischaemic times, donor and recipient ages and sinus node function.

RESULTS

The electrophysiology of the sinus node

Sinus node function

In 33 of 40 subjects (82.5%) sinus node function remained within normal parameters (corrected maximal sinus node recovery time less than 525 msec and sinoatrial conduction time less than 250 msec) for the duration of the study. The analyses in this section are restricted to these 33 subjects.

Corrected maximal sinus node recovery time ($CSNRT_{max}$) decreased significantly with time after transplantation ($p < 0.0001$). Figure 3.1 illustrates the changes in overall mean $CSNRT_{max}$. The individual changes varied considerably. In general those subjects with initially short sinus node recovery times (less than 200 msec) exhibited no change or had small increases whereas the remainder had significant decreases. Figure 3.2 illustrates the individual changes in corrected maximal sinus node recovery time between one week and six months. Both these measurements were available for 28 of 33 subjects $CSNRT_{max}$ decreased in 20 (71%) and increased in eight (29%).

Parallel decreases in mean resting cycle length were observed with time after transplantation (figure 3.3). Decreases in mean resting cycle length continued throughout the six month study period. The individual changes in resting cycle length between one week and six months are illustrated in figure 3.4. Cycle length decreased in 23 of 28 subjects (82%) and increased in five (18%). The initial resting cycle length was less than 700 msec in all five subjects in whom it subsequently increased. The overall mean cycle length at six months was 695 msec.

The sinoatrial conduction time was within normal limits in all studies in all 33 subjects with consistently normal corrected sinus node recovery times. There was a significant change with time after transplantation ($p=0.02$, figure 3.5). Unlike the other

indices of sinus node function where a smooth progression over time is observed the change occurred abruptly between three and six weeks. The mean sinoatrial conduction time during the first three weeks was 153±38 msec compared with 138±40 msec during later measurements ($p=0.017$, paired t test). The difference in mean sinoatrial conduction time of 15 msec represents a difference of approximately 10% between sinoatrial conduction time measured by epicardial and by endocardial electrodes.

Sinus node dysfunction

Sinus node function was abnormal by standard criteria (corrected maximal sinus node recovery time >525msec) on at least one occasion in seven of 40 subjects (17.5%). Two subjects were in nodal rhythm one week after operation. Figure 3.6 illustrates the changes in corrected maximal sinus node recovery time ($CSNRT_{max}$) in these seven subjects with time after transplantation. Six of seven subjects had an abnormally prolonged $CSNRT_{max}$ at week one and it returned to normal in all six by the sixth postoperative week. No increase in sinus node recovery time was observed in these six after the second week. One subject had normal sinus node function by standard criteria until three months after operation. However prolonged secondary pauses accompanied measurements of recovery time in this subject from week one. Secondary pauses were not recorded in any other subject with normal sinus node recovery times.

Sinoatrial conduction times (SACT) were abnormal by standard criteria (>250 msec) on ten occasions in five subjects. All five subjects also had an abnormally prolonged $CSNRT_{max}$ on at least one occasion. In five studies in three subjects an abnormal SACT was associated with a normal $CSNRT_{max}$. Figure 3.7 illustrates the variation in SACT over time in the subjects with abnormal sinus node recovery times. Two subjects with abnormal sinus node recovery times had normal SACT throughout the

study period. One subject exhibited reciprocal change with an abnormal sinus node recovery time and normal SACT in the first six weeks and normal sinus node recovery times with abnormal SACT (271 and 269 msec) thereafter. Another subject had abnormal sinoatrial conduction which recovered by three weeks and this recurred in the setting of normal sinus node recovery times six months after transplantation. An unusually short SACT of four msec was recorded in one subject six weeks after transplantation.

Changes in resting sinus cycle length in the seven subjects with sinus node dysfunction are illustrated in figure 3.8. The trend to shorter sinus cycle length with increasing time after transplantation parallels shorter sinus node recovery times in most subjects.

However, resting sinus cycle length is not a reliable predictor of sinus node recovery time in the study group as a whole, particularly in the first three weeks. For example the range of $CSNRT_{max}$ for a resting cycle length of 700-800msec was between 140 and 1430msec. The relationship between these variables in the first three weeks is illustrated in figure 3.9. The correlation tends to be stronger later (six weeks to six months) after transplantation (figure 3.10). The open data points in figures 3.9 and 3.10 have been excluded from the regression analysis as outliers.

Complications and associations

Two subjects with sinus node dysfunction received permanent pacemakers 22 and 24 days after transplantation. Sinus node function remained abnormal at 21 days in each, one experienced presyncope during normal daily activity, the other had severe exercise limiting chronotropic incompetence.

Rate responsive pacing systems were used in both subjects: one received a dual chamber pacemaker because of impaired atrioventricular conduction, the other an atrial system. They represent 5% of the study group overall and 29% of those with sinus node dysfunction. These two subjects were paced via temporary epicardial wires until implantation of a permanent pacemaker. At three months sinus node function was normal by standard criteria in both patients who received permanent pacemakers. The results of 24 hour ambulatory monitoring in these subjects are described later.

Two of seven subjects with sinus node dysfunction died during the study period compared with three of 33 others. This difference was not statistically significant ($p=0.2$) and none of the deaths was attributable to arrhythmias.

Allograft rejection was not associated with sinus node dysfunction. Two of seven subjects with sinus node dysfunction had significant rejection (moderate) compared with eight of 33 with normal sinus node function ($p=0.57$).

There was no association between operative ischaemic time and subsequent sinus node function. The ischaemic time was 182 ± 51 minutes in those recipients with sinus node dysfunction compared with 179 ± 52 minutes in the remainder ($p=0.91$). There were no relationships between donor or recipient ages and subsequent sinus node dysfunction. The donor and recipient ages were respectively 31 ± 7 and 47 ± 13 years in those subjects with sinus node dysfunction and 36 ± 11 and 46 ± 12 years in the remainder ($p=0.2$ and $p=0.88$).

The spontaneous cardiac rhythms recorded in the immediate postoperative period and their relationship to subsequent sinus node dysfunction are summarised in table 3. The rhythm after weaning from cardiopulmonary bypass appears to be predictive of subsequent sinus node function. However both the positive and negative predictive accuracy of this observation at 71% and 76% respectively are poor.

Table 3.2: Perioperative rhythm and subsequent sinus node dysfunction

Stage	Normal sinus node function (33 subjects)		Subsequent sinus node dysfunction (7 subjects)		Significance
	Sinus	Other	Sinus	Other	
Defibrillation	16(48%)	17(52%)	4(57%)	3(43%)	p=0.50
Off bypass	25(76%)	8(24%)	2(29%)	5(71%)	p=0.03
ITU	28(85%)	5(15%)	4(57%)	3(43%)	p=0.13

Key: Defibrillation - immediately after implantation and defibrillation of the transplanted heart.
Off bypass - after weaning from cardiopulmonary bypass.
ITU - after return to the intensive care unit.

Drug effects and sinus node electrophysiology

Amiodarone

The effects of preoperative amiodarone treatment are detailed in chapter 5. The exclusion of the 11 subjects who received preoperative amiodarone from the analyses of sinus node function presented above did not significantly influence any of the results, quantitatively or qualitatively.

Anticonvulsants

The four subjects who were treated with anticonvulsants had normal sinus node function by standard criteria on each occasion. There was no clear or consistent change in any electrophysiological index of sinus node function. The corrected maximal sinus node recovery time ranged from 120 to 390 msec during treatment with carbamazepine, from 155 to 460 msec with phenytoin and from 135 to 675 msec prior to anticonvulsant treatment in these four subjects.

Diltiazem

Five subjects received diltiazem during the study period. Figure 3.11 illustrates the changes in sinus node recovery time in these five. Two had abnormal sinus node function early after transplantation but this had returned to normal by the start of diltiazem treatment in each case. There were insufficient data for statistical analysis but no clear trend was evident. A very similar pattern was observed in resting cycle length changes. Unlike sinus node recovery times and resting cycle length there was no change in mean sinoatrial conduction time over the study period. Thus comparisons of sinoatrial conduction times before and after diltiazem treatment in the same patients are valid. In the three subjects with normal sinus function there was no difference in the mean sinoatrial conduction time prior to (140 ± 14 msec) and following (145 ± 18 msec) diltiazem treatment ($p=0.51$, paired t test).

Atrioventricular node electrophysiology

In view of the recognised effects of diltiazem on atrioventricular nodal function[Talajic 1992], studies performed during diltiazem treatment were excluded from the following general analysis. No subject received diltiazem throughout the study period.

Effective refractory periods

Measurement of AVERP was frequently limited AERP during these studies. The AERP exceeded the AVERP in a total of 70% of studies with a 600 msec drive and 53% with a 400 msec drive. The proportion of studies with AERP exceeding AVERP did not show any clear trend with increasing time after transplantation (table 3.3).

Table 3.3: Proportion of atrial and atrioventricular ERP measured during atrial pacing studies

Time	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
600 AERP > AVERP	76%	74%	66%	71%	73%	59%
AVERP > AERP	24%	26%	34%	29%	27%	41%
400 AERP > AVERP	58%	53%	47%	73%	46%	48%
AVERP > AERP	42%	47%	53%	27%	54%	52%

The AVERP was measurable on at least one occasion in 23 subjects (58%) with a 600 msec drive and in 34 subjects (85%) with 400 msec drive. It ranged from 220 to 500 msec and from 200 to 420 msec with 600 and 400 msec drives respectively. The AVERP was abnormal compared with standard criteria for AV nodal ERP (>450 msec at 600 drive[Denes 1974, Akhtar 1975, Schuilenberg 1972]) on four occasions in two subjects.

The analysis of changes in AVERP with time and drive cycle length was complicated by the frequent but inconsistent limitation of AERP exceeding AVERP. Of 23 subjects in whom AVERP was measurable with a 600 msec drive, AERP exceeded AVERP in 19 during at least one study. As a consequence the mean AVERP with a 600 msec drive exceeds that with a 400 msec drive in the group as a whole but the reverse is true when the analysis is restricted to paired data from the 38 studies in 22 subjects where AVERP was measurable at both cycle lengths. In these subjects the mean AVERP was 321 ± 51 msec with a 400 msec drive compared with 302 ± 47 msec with at 600 msec. This trend almost achieved statistical significance ($p=0.054$).

The changes in AVERP with time after transplantation are illustrated in figure 3.12. There was no significant change at either drive cycle length ($p=0.7$).

Incremental atrial pacing

The longest cycle length resulting in Wenckebach AV conduction was measurable on at least one occasion in all subjects. The Wenckebach cycle length was less than 300

msec on one occasion in four subjects and on more than one occasion in two. The maximum Wenckebach cycle length recorded in any subject was 700 msec, this was not associated with any clinical evidence of AV node dysfunction, the PR interval on the surface ECG remained within the normal range.

The changes in mean Wenckebach cycle length with time after transplantation are illustrated in figure 3.13. There was a trend toward longer Wenckebach cycle length in the first few weeks after transplantation (416 msec at one week, 392 msec at three months) but the difference was not statistically significant ($p=0.85$).

There was a strong correlation between AVERP and Wenckebach cycle lengths measured at the same study (figures 3.14 and 3.15). The relationship was particularly consistent with AVERP measured with a 600 msec drive from the third week after transplantation. The correlation with a 400 msec drive was somewhat less consistent.

Complications and associations

No subject experienced symptomatic bradyarrhythmia due to AV block or required temporary ventricular pacing after the immediate perioperative period (first six hours). The AVERP was normal in all subjects throughout the first two weeks. It was abnormal by standard criteria for AV nodal ERP (>450 msec with a 600 msec drive) three weeks after transplantation in one subject and between three weeks and three months in another. The longest AVERP recorded was 500 msec three weeks after transplantation in the subject with a single abnormal AVERP, this was associated with a prolonged PR interval on the surface ECG of 240 msec. No subject exhibited a higher degree of AV block at any time.

The subject with abnormal AVERP on three occasions between three weeks and three months after transplantation required a permanent pacemaker because of sinus node

dysfunction and profound chronotropic incompetence on exercise. At the time of implantation the AVERP (600 msec drive) was 460 msec, the Wenckebach cycle length 550 msec and the PR interval 190 msec. In view of these findings a DDDR system was implanted with the AV delay set to 175 msec. The sinus node dysfunction had resolved by the sixth week. The results of subsequent ambulatory monitoring are detailed later.

Despite the strong relationship between Wenckebach cycle length and AVERP described above it is of note that two subjects with normal AVERP had Wenckebach cycle lengths longer than those recorded with abnormal AVERP. The AVERP varied from 300 to 420 msec with Wenckebach cycle lengths between 580 and 700 msec. Both these subjects had taken preoperative amiodarone, the effects of which will be examined in more detail in chapter 5.

There were no associations between Wenckebach cycle length or AVERP at any time after transplantation and operative ischaemic time, donor or recipient ages. There was no relationship between perioperative rhythms and subsequent abnormal AVERP. The proportions of subjects with AV dissociation were respectively: 33%, 18% and 13%, after defibrillation, after weaning from cardiopulmonary bypass and on return to the intensive care unit. One subject with subsequently abnormal AVERP had AV dissociation throughout the perioperative period but four other subjects with subsequently normal AVERP had the same rhythms.

There was no relationship identifiable between cardiac rejection and any index of AV conduction. The mean Wenckebach cycle length during the ten episodes of moderate rejection was 436 ± 84 msec compared with 405 ± 81 msec in the same subjects when there was no histological evidence of rejection ($p=0.73$). Measurement of AVERP during episodes of moderate rejection was frequently limited by AERP. With a 600 msec drive during episodes of moderate rejection atrial AERP exceeded AVERP on six of 10

(60%) occasions. The mean AERP was 270±24 msec compared with 252±48 msec in the same subjects when there was no evidence of rejection but this difference was not statistically significant (p=0.41). With a 400 msec drive AERP exceeded AVERP during only three of 10 episodes of moderate rejection. The mean AVERP during moderate rejection was 307±40 msec compared with 313±60 msec in the same subjects when there was no evidence of rejection (p=0.87).

Drugs and atrioventricular node electrophysiology

The effects of preoperative amiodarone therapy are described in chapter 5. The relative consistency of measurements of AV conduction over time allows direct comparison of these parameters before and after the start of therapy with other potentially cardioactive drugs.

There were no consistent changes in AV node function parameters due to treatment with carbamazepine and phenytoin. The Wenckebach cycle length varied between 380 and 390 msec during phenytoin treatment, between 320 and 380 msec with carbamazepine and between 330 and 420 msec in these subjects prior to anticonvulsant treatment. The AVERP ranged from 250 to 320 msec during carbamazepine treatment, from 310 and 360 msec with phenytoin and from 260 to 340 msec in these subjects prior to treatment.

There were no significant differences in AV node function parameters before and after treatment with diltiazem five subjects. The mean Wenckebach cycle lengths were 377±33 msec and 383±42 msec respectively (p=0.66). There was a trend toward longer AVERP (400 msec drive) after treatment than before: 321±26 msec and 299±38 msec respectively (p=0.16).

DISCUSSION

Sinus node electrophysiology

Sinus node function

This study demonstrates that amongst those subjects with normal sinus node function by standard criteria (corrected maximal sinus node recovery time less than 525 msec[Narula 1972]) there is a significant shortening of mean sinus node recovery time with increasing time after transplantation. This observation has not been previously reported. There is a parallel decrease in resting sinus cycle length. No subject with normal sinus node function by standard criteria experienced clinically significant bradyarrhythmias thus the clinical significance of this finding is unknown. However it does illustrate that there is relative impairment of sinus node automaticity in some subjects in the immediate postoperative period.

It is well recognised that relative bradycardia is usual in transplant recipients immediately after operation[Stinson 1975, Cabrol 1989]and that tachycardia is usual in long term survivors[Alexopoulos 1988, Scott 1993]. This study is the first to describe the time course of the changes in resting heart rate over the first six months.

The most likely explanation for these changes is the effect of acute sympathetic denervation at the time of transplantation and subsequent adjustment of beta receptor responsiveness. As discussed in chapter 1, further investigation of this hypothesis would require serial testing of heart rate responsiveness to infusions of sympathomimetic drugs in the immediate postoperative phase and in long term survivors.

The change in sinoatrial conduction time between the early (one to three weeks) and subsequent measurements coincided with the change in measurement technique from epicardial wires to endocardial recordings. This is not a surprising result. Of all the indices of sinus node function the sinoatrial conduction time would be expected to be the

most sensitive to the distance between the recording and stimulating electrodes and the sinus node. There have been no previous studies comparing these techniques. From the results of this study epicardial pacing and recording produces sinoatrial conduction times approximately 10% longer than using endocardial electrodes.

The intersubject concordance between normal and abnormal sinoatrial conduction time and sinus node recovery time in this study was good. With all subjects undergoing multiple electrophysiological studies 71% of subjects with abnormal sinus node recovery times had abnormal sinoatrial conduction on at least one occasion. Bexton and colleagues[1984a] undertook only single electrophysiological studies and only 25% of subjects with sinus node dysfunction had abnormally long sinoatrial conduction time. The findings of the present study suggest a common aetiology for abnormalities of sinus node recovery and of sinoatrial conduction but differing factors controlling recovery.

An unusually short sinoatrial conduction time such as that observed on one occasion in this study (4 msec) was reported previously by Bexton and colleagues[1986]. They suggested various potential causes for this phenomenon including pacemaker shift and sinus node reentry. Whatever mechanism is involved, it would appear to have been transient as the phenomenon did not recur during subsequent studies in our subject.

In standard therapeutic doses potentially cardioactive drugs commonly used in transplant recipients (carbamazepine, phenytoin and diltiazem) did not affect significantly sinus node function. This is in keeping with previous studies of the electrophysiological actions of these agents[Caracta 1973, Kennebäck 1991, Talajic 1992] which have reported no consistent changes in the indices of sinus node function. The effect of preoperative amiodarone therapy will be discussed in chapter 5.

Sinus node dysfunction

The 17.5% frequency of early sinus node dysfunction defined by electrophysiological criteria in this study is substantially lower than previous studies which have reported incidences of 44%[Heinz 1992a], 47%[Jacquet 1990]and 50%[Mackintosh 1982]. Two of these studies from large centres have involved substantially smaller numbers of subjects[Mackintosh 1982, Jacquet 1990]. Heinz and colleagues[1992a]have studied more transplant recipients but they have also consistently reported very high rates of symptomatic bradyarrhythmias and subsequent pacemaker implantation compared with other large transplant centres[Miyamoto 1990, DiBiase 1991]. Immunosuppression and organ preservation protocols are similar, it therefore seems likely that local differences in surgical technique may be responsible for an unusually high incidence of sinus node dysfunction reported by this group[Heinz 1992a].

This is the first study to undertake systematic serial electrophysiological measurements of sinus node function from the early post-transplant period through to six months. Early sinus node dysfunction resolved within six weeks in all subjects for whom serial measurements were available. This observation is in keeping with previous reports concerning transplant recipients paced for sinus node dysfunction[Miyamoto 1990, Heinz 1990]. These authors reported that up to 75% of subjects who received permanent pacemakers do not require long term pacing. Similar findings are also recorded in the retrospective study detailed in chapter 2.

The resting sinus cycle length in the subjects with sinus node dysfunction in general decreased as sinus node dysfunction resolved in this study. However resting sinus cycle length is not an accurate enough index of sinus node function to be used as a substitute for sinus node recovery time in the early post-transplant period. The reliability improves after six weeks but care must be taken in the interpretation of this

correlation as it effectively involves the correlation of a variable y with x-y, which will artificially increase the correlation coefficient. This observation is in keeping with the study by Heinz and colleagues[1992c]who reported that resting heart rate was a poor predictor of sinus node recovery time in transplant recipients with permanent pacemakers eight to 36 months after transplantation.

Late sinus node dysfunction

The low observed frequency of late sinus node dysfunction (2.5%) in this study contrasts with a much higher frequency (29%, 4/14 subjects) in the small study reported by Bexton and colleagues[1984a]. Bexton and colleagues did not assess sinus node function in the immediate postoperative period so the high incidence may, in part, reflect persistence of early sinus node dysfunction in some subjects. The frequency of late bradyarrhythmias requiring permanent pacing in other large series[Miyamoto 1990, DiBiase 1991]has been low but sinus node dysfunction in the absence of clinical symptoms was not assessed and may have been more frequent.

Despite normal corrected maximal sinus node recovery times between one and six weeks after transplantation the subject in this study with late sinus node dysfunction consistently exhibited prolonged secondary pauses during electrophysiological tests from one week. Sinus node function was probably abnormal early after transplantation but the pattern was qualitatively different from the other six subjects.

The aetiology of sinus node dysfunction

This study did not identify any aetiological factors for sinus node dysfunction after transplantation. Specifically donor or recipients ages, operative ischaemic time and allograft rejection were not related to sinus dysfunction. The most likely explanation

remains direct surgical trauma[Couetil 1991] and or associated disruption of blood supply to the sinus node[DiBiase 1991].

Conclusions

Serial measurements of corrected sinus node recovery time may be useful in transplant recipients with bradyarrhythmias due to sinus node dysfunction in the first three weeks after transplantation. A falling sinus node recovery time during the second and third weeks probably indicates a good prognosis for the recovery of normal sinus node function. The resting sinus cycle length is not a reliable substitute indicator. Abnormalities of sinoatrial conduction often coexist with abnormalities of sinus node automaticity but their natural history and possibly the aetiology may be different. No specific aetiological factors involved in the pathogenesis of early sinus node dysfunction were identified. Late sinus node dysfunction is much less common and has a different clinical profile suggesting a different aetiology.

Atrioventricular node electrophysiology

Atrioventricular node function

The accurate measurement of AV nodal ERP as opposed to AVERP in this study was limited by the lack of His bundle recordings. AV nodal ERP could not therefore be separated from the ERP of the more distal parts of the AV conducting system. This is unlikely to have led to significant errors however, as His bundle ERP rarely exceeds nodal ERP in normals[Ahktar 1975]and there are no reports of this in transplant recipients.

The range of AVERP recorded in this study is comparable with previously reported AV node ERP[Bexton 1984b, Goodman 1975]. The effect of decreasing the drive cycle length was to increase AVERP. Although this just failed to achieve statistical

significance (p=0.054), the phenomenon was also reported by Bexton and colleagues[1984b] and is likely to be an intrinsic property of the AV node.

The Wenckebach cycle lengths recorded in the current study are on average longer than have been previously reported by Bexton and colleagues[1984b] in a small study of transplant recipients between four and 14 months after operation. They are closer to the broad range of Wenckebach cycle lengths in normal subjects[Jospehson 1979]. Wenckebach cycle lengths of up to 700 msec were recorded with no clinical evidence of AV node dysfunction. Bexton and colleagues[1984b] reported a maximum anterograde Wenckebach cycle length of 410 msec. This compares with a mean of 393 ± 67 msec (range <300 to 570 msec) at six months in the current study. Heinz and colleagues[1992d] reported that ten of 87 subjects (11%) had Wenckebach cycle lengths of more than 430 msec. The reasons for these differences are unclear. The effects of preoperative amiodarone treatment are detailed in chapter 5 but can probably be discounted six months after transplantation. The current study is the largest yet reported.

The strong correlation between AV node ERP and Wenckebach cycle length previously reported in both transplant recipients[Bexton 1984b] and normal subjects[Bisset 1975] has been confirmed in this study. Furthermore, subgroup analysis shows that the relationship is stronger after the third week and with a AVERP drive cycle length of 600 msec. The observation of longer Wenckebach cycle lengths in two subjects with normal AVERP than another with an abnormal AVERP may have important practical implications. The assessment of AV node conduction by incremental pacing alone may be misleading in the first three weeks after transplantation when decisions as to permanent pacemaker prescription may be necessary.

No associations were found between any parameter of atrioventricular node function and operative ischaemic time, perioperative rhythm, and donor or recipient. It

has been previously reported that cardiac rejection causes pathological changes in the conducting system in animals[Bieber 1969]and may lengthen atrial and AV node refractory periods in humans[Wojnar 1992]. There is no evidence from the current study to support the latter contention.

The absence of any consistent effect of diltiazem treatment on the parameters of AV node conduction was surprising in view of previous reports in normals[Talajic 1992]. This may be due to the relatively low mean daily dose (238±68mg). The lack of consistent changes due to anticonvulsant treatment is in keeping with previous reports[Kennebäck 1991, Caracta 1973].

Atrioventricular node dysfunction

Two subjects in this study had abnormal AVERP by standard criteria for AV node ERP (> 450 msec with a 600 msec drive). This has not previously been reported in heart transplant recipients. In this study no clinically significant arrhythmias resulted. The first occurrence of these abnormalities three weeks after transplantation is unexplained. It is however, compatible with the observation that no perioperative factors such as ischaemic time and perioperative heart rhythms were related to its occurrence.

The low incidence of AV node conduction abnormalities is in keeping with several large series[Miyamoto 1990, DiBiase 1991]which have reported a very low incidence of significant abnormalities of AV conduction (around 1%). Buja and colleagues[1992]reported electrophysiological findings in 21 subjects with complete AV dissociation. The frequency of such profound AV conduction disturbances in their series (14%) is unique within the transplant literature and the reasons for this are unclear. The relevance of this series[Buja 1992]to the transplant population as a whole must therefore be open to question.

This is the first study to assess AV conduction by serial electrophysiological measurements. There was no evidence of the development of AV node function abnormalities with time after transplantation in any subject with or without sinus node dysfunction. Thus there is no evidence to support the assertion that a ventricular lead is required for "safety purposes"[Markewitz 1987, Osterholzer 1988, Miyamoto 1990, DiBiase 1991] in subjects receiving permanent pacemakers for sinus node dysfunction.

Conclusions

Electrophysiological abnormalities of AV node function are uncommon in transplant recipients compared with abnormalities of sinus node function. In this study they were not clinically significant and resolved spontaneously within the six month study period. There were no other changes in any index of AV node function related to increasing time after transplantation. The function of the transplanted AV node was not affected by duration of perioperative ischaemia, donor age or the occurrence of rejection. The assessment of AV node function in the first three weeks after transplantation should include measurement of AV node ERP. Wenckebach cycle lengths of up to 700 msec were associated with normal AV node ERP and with no clinical evidence of AV node dysfunction in subjects who had received preoperative amiodarone treatment.

SECTION 2
EXERCISE TESTING

METHODS

The heart rate response to exercise was tested on four occasions in each subject three and six weeks, three and six months after transplantation. A symptom limited treadmill test was performed on each occasion using the chronotropic assessment exercise protocol[Wilkoff 1989]. The time, treadmill speed, gradient and estimated workloads of this protocol are tabulated below.

Table 3.4: The Chronotropic Assessment Exercise Protocol

Stage	Speed(mph)	Gradient(%)	Workload(METS)
1	1.0	2	2.0
2	1.5	3	2.8
3	2.0	4	3.6
4	2.5	5	4.6
5	3.0	6	5.8
6	3.5	8	7.5
7	4.0	10	9.6
8	5.0	10	12.1
9	6.0	10	14.3
10	7.0	10	16.5
11	7.0	15	19.0

Each test was preceded by a 10 minute rest period. The heart rate was recorded with a six lead rhythm strip every minute during exercise and for five minutes during recovery. Exercise tests were omitted whenever the general condition of the patient or specific complications made it difficult for the subject to use the treadmill. No subject was excluded from the analysis of exercise response on the basis of additional drug therapy.

Analysis

The results were analysed both in terms of absolute changes in heart rate and also in terms of the heart rate reserve[Wilkoff 1989]. This is defined as maximum age predicted heart rate (220 - recipient age) minus the resting heart rate. The estimated workload was similarly measured in absolute terms and by calculation of the metabolic reserve, defined as estimated oxygen consumption (METS) at peak exercise less that at rest[Wilkoff 1989]. The expected response of a normal innervated heart would be to achieve of 100% of the calculated heart rate reserve at peak exercise.

Statistical methods

Changes in the chronotropic response, fall in heart rate during recovery and exercise duration with time after transplantation were assessed by one way analysis of variance. Mann-Whitney U tests were used to analyse differences in the chronotropic response and exercise capacity due to acute rejection. Any association between operative ischaemic time, donor or recipient ages and subsequent chronotropic response was sought by linear correlation analysis.

RESULTS

Of 40 subjects recruited into the study as a whole, 31 were available for exercise studies. The five subjects who died during the study did not exercise at any stage; three died early and other complications prevented early exercise tests in the remaining two. Three subjects were unable to walk on the treadmill because of arthritis affecting the hips and or back. One subject withdrew from the study before the first exercise test.

The duration of exercise achieved increased significantly with time after transplantation ($p<0.001$, figure 3.16) as would be expected with improving general fitness after major surgery.

Heart rates at rest and peak exercise both increased significantly with time after transplantation ($p<0.001$). These changes are illustrated in figure 3.17. The changes in resting heart rate correspond with those in resting cycle length in the electrophysiological studies although the mean resting heart rate prior to exercise was consistently higher than during electrophysiological studies (by seven to 13 bpm). Despite this discrepancy there was a strong linear correlation between these measurements ($r=0.84$, $R^2=70\%$).

When the changes in peak heart rate are expressed as a percentage of heart rate reserve to adjust for changes in resting heart rate a different pattern emerges (figure 3.18). There is an initial increase in response between three and six weeks, no change between six weeks and three months and a further increase in response at six months ($p<0.001$). The pattern of exercise response throughout each test also changed over the course of the study period in a very similar way to the peak exercise response. This is illustrated in figure 3.19.

The variation in heart rate reserve at peak exercise also increases with time after transplantation and is particularly large by six months. At six months, five of 31 subjects (16%) achieved in excess of 75% of their heart rate reserve at peak exercise (range 76%

to 124%). These subjects also had a significantly greater heart rate response to exercise during earlier tests although the difference was not as large (figure 3.20). The exercise response continued to improve in the five subjects with an enhanced response whereas there was no significant change after the sixth postoperative week in the remainder. Exercise times and thus workload achieved were similar in both groups throughout the duration of the study.

Chronotropic incompetence by some criteria suggested for innervated hearts was, as expected, frequent. Using Rosenquist's[1990] definition of maximal peak heart rate of less than 120 beats per minute the incidence of chronotropic incompetence was 79% at three weeks, 35% at six weeks, 32% at three months and 19% at six months. However using Wiens's[1984]definition (heart rate <85 at 4 METS and <100 at 6 METS) the incidence was consistently lower. At 4 METS the incidences were 5%, 7%, 0% and 4% and at 6 METS 20%, 13%, 14% and 9% at three and six weeks, three and six months respectively.

Changes in heart rate during recovery

Figure 3.22 illustrates heart rate changes in the first five minutes of recovery after exercise at different times after transplantation. From two minutes into the recovery period the fall in heart rate is significantly greater with increasing time after transplantation ($p<0.01$). However, when the five subjects with an enhanced exercise response (greater than 75% heart rate reserve at peak exercise at six months) were eliminated from the analysis, the changes with time were no longer significant (figure 3.23). Figure 3.24 details the individual changes in heart rate during recovery three and six months after transplantation. A discriminant value between those with an enhanced response to exercise (greater than 75% of heart rate reserve at peak exercise) and other

subjects is readily identifiable at but not before six months: a decrease in heart rate of 10 bpm at three minutes and 20 bpm at five minutes. There were two exceptions. The single subject with a more delayed recovery despite an enhanced exercise response was the subject with late sinus node dysfunction. One subject with a rapid fall in heart rate after exercise had achieved a maximum of only 54% of heart rate reserve.

Exercise response in subjects with sinus node dysfunction

Of seven subjects with sinus node dysfunction by electrophysiological criteria in this study, five were able to undertake exercise tests. Of these three underwent exercise testing at a time when sinus node function was abnormal.

One of these three had late sinus node dysfunction. The chronotropic response is illustrated in figure 3.25. Compared with other subjects six months after transplantation the response was normal. The peak heart rate of 150 bpm compares with a mean of 135 ± 20 bpm in the group as a whole.

Two subjects with persistent and two with resolved early sinus node dysfunction underwent exercise testing three weeks after transplantation. Table 3.5 summarises the chronotropic response in these individuals in comparison with other subjects. Figure 3.26 compares the same responses analysed by heart rate reserve and metabolic reserve criteria. The subject indicated as symptomatic experienced presyncope and lethargy at a very low workload which was readily corrected by temporary pacing.

The range of exercise responses in subjects with sinus node dysfunction overlapped considerably with those of subjects with normal sinus node function. Consequently resting heart rate was the only reliable discriminant factor between subjects with and without sinus node dysfunction. Although maximal heart rates were also low in the subjects with persistent sinus node dysfunction, two subjects with normal sinus

node function had lower heart rates at peak exercise. One such subject exercised without symptoms for nine minutes 34 seconds (estimated workload 4 METS) achieving a maximum rate of only 89 beats per minute.

Table 3.5: Chronotropic response in four subjects with early sinus node dysfunction

	Sinus node dysfunction				Group mean
	Persistent		Resolved		
Subject number	15	33	14	37	
Resting heart rate (bpm)	70	64	96	90	87 ± 13 (range 64-110)
Duration of exercise (minutes, seconds)	4'24"	6'07"	6'20"	11'01"	8'05" ± 2'0"
Heart rate at peak exercise (bpm)	90	98	103	115	110±12 (range 84-131)
Increase in heart rate (bpm)	20	34	7	25	23 ± 8 (range 7-41)
Percentage heart rate reserve at peak exercise	16	34	11	31	27 ± 9 (range 11-46%)
Symptomatic	Yes	No	No	No	

The chronotropic response remained relatively impaired in three of the four subjects with early sinus node dysfunction six weeks after transplantation (figure 3.27). However, none was symptomatic and all achieved a workload of at least five METS. Six months after transplantation the chronotropic response was comparable with the rest of the group (figure 3.28). The subject with a relatively poor response exercised for 13 minutes and achieved a workload of eight METS.

None of the proposed definitions for chronotropic incompetence[Wicns 1984, Rosenquist 1990] for innervated hearts was useful in distinguishing the chronotropic response of

subjects with and without sinus node dysfunction. All subjects with early sinus node dysfunction achieved a heart rate of less than 120 beats per minute[Rosenquist 1990] three weeks after transplantation but 76% of subjects with normal sinus node function also failed to reach 120 beats per minute. No subject with early sinus node dysfunction achieved a heart rate of less than 85 at 4 METS workload[Wiens 1984].

Correlation with sinus node electrophysiology, rejection, operative ischaemia and age

A weak linear correlation was identified between peak heart rate and corrected sinus node recovery time six weeks after transplantation ($r=-0.52$, $R^2=27\%$, $p<0.01$). This relationship was not consistent over time however ($r=-0.41$, $r=-0.3$, $r=-0.36$ at three weeks, three and six months respectively, p=NS).

Three subjects underwent exercise tests at times when they were subsequently found to have moderate rejection. None had a history of sinus node dysfunction. The chronotropic response was significantly reduced compared with other subjects. The peak heart rates were 92,104 and 107 bpm compared with a mean of 127 ± 13 bpm in other subjects ($p=0.01$). The percentages of heart rate reserve used at peak exercise were 18, 36 and 22 compared with 41 ± 11.2 in the other subjects ($p=0.03$). This difference was not due to impaired exercise capacity (exercise times: 713, 768 and 457 seconds compared with 661 ± 153 seconds, p=NS).

The response in these three subjects was also significantly impaired three months after transplantation when they did not have moderate rejection (peak heart rates: 104, 118, 100 compared with 129 ± 14.8 bpm, $p=0.04$). Six months after transplantation there was no significant difference. However when the chronotropic response was analysed according to whether subjects had ever experienced moderate rejection no significant differences were found in the response at any time between those who had and those

who had not.

There was no evidence of any relationship between duration of operative ischaemia and exercise response when first tested three weeks later ($r=0.24$ with peak heart rate, $r=0.36$ with percentage heart rate reserve at peak exercise, p=NS). There was no relationship between any parameter of exercise response and donor or recipient ages.

Drug effects

Four subjects who underwent exercise testing were treated with diltiazem and four were treated with anticonvulsants during the study period. No consistent changes in exercise response could be identified. The effects of preoperative amiodarone treatment are detailed in chapter 5.

DISCUSSION

Changes in exercise response and recovery with time after transplantation

This is the first serial study of changes in exercise response with time after transplantation. The time scale of the present study focusing on the first six months also differs from previous cross sectional studies[Quigg 1989, Rudas 1991] both of which compared recipients one to two months and approximately 12 months after transplantation.

The improvement in chronotropic response between the third and sixth weeks after transplantation demonstrated in this study has not previously been described. The reasons for this change are unclear. It is unlikely to be due to the increase in the ratio of β_2 to β_1 adrenergic receptors described by Brodde and colleagues[1991] as the time course (peak at four months) is incompatible. The gradual development of presynaptic catecholamine supersensitivity following autonomic denervation at surgery is a more likely explanation. Although the time course of these changes has not been described in detail they are established in subjects studied between one and three months after transplantation[Gilbert 1989]. Serial studies of sensitivity to catecholamine infusions over the first six weeks after transplantation would be required to confirm this hypothesis.

The enhanced exercise response seen six months after transplantation in some subjects suggests efferent sympathetic reinnervation. Although further enhancement of presynaptic supersensitivity could be postulated as an alternative mechanism the rapid fall in heart rate during the recovery period seen in 80% (four of five) of these subjects is more in keeping with a rapidly acting direct neural mechanism. The finding of an improved heart rate response to exercise in the same subjects from as early as three weeks after transplantation does not support this conclusion as such rapid structural sympathetic reinnervation would seem very unlikely. The rapid fall in heart rate during recovery seen at six months is not, however, evident at three months. The combined

pattern of exercise response and recovery seen in four of these five subjects is directly comparable with that described in previous reports[Rudas 1991, Johnson 1991] and attributed to efferent sympathetic reinnervation. Johnson and colleagues[1991] confirmed sympathetic reinnervation by intracoronary tyramine testing. An enhanced early exercise response mediated by an alternative mechanism may, therefore, be predictive of future sympathetic reinnervation although an explanation for this hypothesis is not evident. There have been no previous reports of recipients with this pattern of exercise response or with other evidence of sympathetic reinnervation at such an early stage after transplantation. The subject with an enhanced exercise response and delayed recovery had late sinus node dysfunction defined by electrophysiological testing. The mechanism of enhanced chronotropic response may have been different in this case.

Chronotropic competence and sinus node dysfunction

This study has shown that definitions of chronotropic competence suggested for innervated hearts are not applicable to the denervated transplanted human heart.

The importance of chronotropic incompetence as regards limitation of exercise capacity is unclear. Although the peak heart rate was less than 100 bpm in both subjects with persistent sinus node dysfunction, only one was symptomatic and two subjects with normal sinus node function also had peak heart rates of less than 90 bpm without substantial limitation of exercise. Differences in stroke volume due to variation in ventricular compliance may be responsible for the observed anomalies. Measurements of cardiac output during exercise would be required to assess this hypothesis further.

Thus no useful definition of chronotropic incompetence in transplant recipients can be proposed on the basis of these data. The routine use of rate responsive pacemakers in transplant recipients with sinus node dysfunction is illogical in view of

similar chronotropic responses without limitation of exercise in other recipients. Rate responsive pacemakers should probably be reserved for those patients who have symptomatic chronotropic incompetence and who have been shown to benefit from temporary pacing during exercise.

Determinants of the chronotropic response in transplant recipients

This results of this study suggest that acute rejection may cause impairment of the chronotropic response to exercise despite a normal exercise capacity and that the effects may persist for some time after effective treatment. This observation has not been previously reported but it must be interpreted with caution given the very small number of subjects studied during rejection episodes.

The lack of correlation with any electrophysiological index of sinus node function suggests that intrinsic sinus node function is not a primary determinant of the chronotropic exercise response. Early changes in catecholamine sensitivity and later direct sympathetic reinnervation in some subjects are more likely to be important.

Conclusions

The chronotropic response to exercise is markedly impaired early after surgery in heart transplant recipients. It improves significantly by the sixth week. By six months some recipients have both an enhanced exercise response and a rapid decline in heart rate during recovery suggesting efferent sympathetic reinnervation. The chronotropic response is relatively impaired in subjects with early sinus node dysfunction but these subjects cannot be reliably separated from those transplant recipients with normal sinus node function. Symptoms related to an impaired heart rate response to exercise are infrequent and not predicted by the severity of chronotropic incompetence.

SECTION 3
24 HOUR AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

METHODS

Twenty four hour ambulatory ECG recordings were planned on six occasions for each of 40 subjects at one, two, three and six weeks, three and six months after transplantation. The Reynolds Medical "Tracker" system was used. Ambulatory recordings were performed primarily to assess the incidence of bradyarrhythmias. They were therefore omitted when subjects were continuously paced. Recordings were also omitted if the patient developed an acute complication likely to distort heart rate data such as a pyrexial illness.

Pacing policy

Temporary epicardial pacing was used in the first three weeks after transplantation to maintain a heart rate of at least 50 bpm in all subjects. In the first week it was judged clinically necessary in some subjects to maintain a heart rate of at least 90 bpm. Thereafter a requirement for continued pacing was defined by the occurrence of symptomatic bradyarrhythmias during normal activity or symptomatic chronotropic incompetence on exercise after withdrawal of temporary pacing.

Analysis

All recordings were analysed using the Reynolds Medical "Pathfinder 3" analyser. The minimum heart rate and minimum day time heart rate were determined automatically by the analyser using two minute sample periods and were individually

verified by direct inspection. The mean heart rate over 24 hours was calculated from automated QRS counts provided the recording was of sufficient quality to produce reliable data. Sinus pauses of greater than two seconds, any pacemaker activity and any second or third degree AV block were individually documented.

Statistical methods

Changes in heart rates over time were analysed using one way analysis of variance. The associations between heart rates during ambulatory monitoring and electrophysiological measurements of sinus node function, donor and recipient ages and perioperative ischaemic time were assessed by linear correlation analysis. The Wilcoxon signed rank test was used to compare heart rates before and after treatment with diltiazem in five subjects.

RESULTS

At the time of proposed ambulatory monitoring one week after transplantation continuous temporary pacing 90 bpm was judged clinically necessary in eight subjects. A total of 14 recordings were lost due to the deaths of five subjects, two of these died before undergoing any ambulatory monitoring. Thirty eight recordings were unavailable because subjects refused ambulatory monitoring at that time or had developed acute complications. Of the remaining 185 recordings 166 (90%) were suitable for analysis; 19 were lost due technical failures or were of insufficient quality. Very high quality recordings were required for the calculation of mean heart rate and 134 (81% of those analysed) were suitable.

Minimum and mean heart rates

Figure 3.29 illustrates the changes in overall minimum and daytime minimum heart rates with time after transplantation. There was no significant change over time. There was a trend towards higher 24 hour mean heart rates with increasing time after transplantation (figure 3.30) but this was not statistically significant. Paced heart rates are not included in these analyses. The exclusion of five subjects with electrophysiological evidence of sinus node dysfunction on at least one occasion (corrected maximal sinus node recovery time >525 msec or sinoatrial conduction time >250 msec) did not affect these analyses. These subjects frequently required temporary pacing in the first few weeks and sinus node dysfunction had usually resolved during subsequent ambulatory monitoring.

Bradyarrhythmias and pacing requirements

Five subjects with electrophysiological evidence of sinus node dysfunction on at least one occasion were studied by ambulatory monitoring. Table 3.6 summarises the findings and concurrent electrophysiological measurements in these subjects.

Continuous pacing at 50 bpm was observed on only one occasion in each of two subjects with clearly abnormal sinus node function by electrophysiological criteria (corrected maximal sinus node recovery time <525 msec, sinoatrial conduction time <250 msec). One subject had nodal rhythm, the other had sinus bradycardia with a corrected maximal sinus node recovery time of 2385 msec.

A requirement for intermittent temporary pacing (50 bpm) one week after transplantation was more common and was not reliably associated with abnormal sinus node function by electrophysiological criteria. Three subjects with normal sinus node function (corrected maximal sinus node recovery time range 360 to 410 msec) and two of three subjects with abnormal sinus node recovery times required intermittent pacing.

After the first week intermittent pacing was only observed in subjects with current or previous sinus node dysfunction by electrophysiological criteria. Only the subject (number 33) who paced intermittently (50 bpm) three weeks after transplantation paced intermittently during long term follow up (up to six months).

Late sinus node dysfunction (three to six months after transplantation) observed in a single subject was not associated with a requirement for pacing. The minimum recorded heart rate was 54 bpm in this subject despite corrected maximal sinus node recovery times of up to 1825 msec.

Table 3.6: Ambulatory monitoring and electrophysiological data in subjects with sinus node dysfunction

Subject number		14	15	16	33	37
Week 1	Ambulatory monitoring	Pacing dependent at 50 bpm	Intermittent pacing at 50 bpm	Paced at 90 bpm	Intermittent pacing at 50 bpm	Minimum heart rate 72 bpm
	$CSNRT_{max}$	Nodal rhythm	Nodal rhythm	260 msec	795 msec	575 msec
	SACT	Nodal rhythm	Nodal rhythm	80 msec	159 msec	298 msec
Week 2	Ambulatory monitoring	Minimum heart rate 68 bpm	Intermittent pacing at 50 bpm	Minimum heart rate 52 bpm	Pacing dependent at 50 bpm	Technical failure
	$CSNRT_{max}$	675 msec	1430 msec	255 msec	2385 msec	450 msec
	SACT	270 msec	312 msec	110 msec		334 msec
Week 3	Ambulatory monitoring	Minimum heart rate 75 bpm	Minimum heart rate 55 bpm	Missing data	Intermittent pacing at 50 bpm	Minimum heart rate 82 bpm
	$CSNRT_{max}$	460 msec	565 msec	235 msec	1325 msec	345 msec
	SACT	256 msec	294 msec	116 msec	197 msec	249 msec
Permanent pacemaker		NO	YES	NO	YES	NO
Week 6	Ambulatory monitoring	Minimum heart rate 82 bpm	Minimum heart rate 57 bpm	Minimum heart rate 56 bpm	Intermittent pacing at 50 bpm	Minimum heart rate 72 bpm
	$CSNRT_{max}$	315 msec	405 msec	365 msec	485 msec	400 msec
	SACT	133 msec	235 msec	4 msec	243 msec	199 msec
Month 3	Ambulatory monitoring	Minimum heart rate 79 bpm	Minimum heart rate 65 bpm	Minimum heart rate 54 bpm	Minimum heart rate 54 bpm	Technical failure
	$CSNRT_{max}$	230 msec	280 msec	1825 msec	445 msec	290 msec
	SACT	145 msec	200 msec	75 msec	271 msec	163 msec
Month 6	Ambulatory monitoring	Minimum heart rate 73 bpm	Technical failure	Minimum heart rate 57 bpm	Intermittent pacing at 50 bpm	Missing data
	$CSNRT_{max}$	255 msec	265 msec	1460 msec	450 msec	385 msec
	SACT	186 msec	109 msec	126 msec	269 msec	295 msec

Key: $CSNRT_{max}$ = corrected maximal sinus node recovery time, SACT = sinoatrial conduction time
Pacing dependent = continuous pacing

Permanent pacing

Two subjects received permanent pacing systems. The subject (number 33) who required intermittent pacing three weeks after transplantation received an atrial demand (AAI) system. Six weeks after transplantation an ambulatory recording showed intermittent pacing (50 bpm) and sinus rhythm. At three months the minimum recorded heart rate was 54 bpm with no pacing. At six months ambulatory recording showed further intermittent pacing but only at night. This return of pacing activity coincided with an increase in a previously normal sinoatrial conduction time to 269 msec. The patient was fully active and asymptomatic with the pacing rate programmed to 50 bpm.

The other subject who received a permanent pacemaker had a minimum heart rate of 55 bpm during ambulatory monitoring three weeks after transplantation but had a very limited heart rate response to exercise and became presyncopal. The symptoms were relieved by temporary pacing. In addition the atrioventricular refractory period was 460 msec (600 msec drive), the Wenckebach cycle length was 550 msec and the PR interval was 200 msec. A dual chamber pacemaker was therefore implanted which was programmed to 50 bpm DDD mode. Six weeks after transplantation the minimum recorded heart rate was 54 bpm with no atrial pacing on that or any subsequent recording. Ventricular pacing and atrial tracking was constant during subsequent recordings with underlying first degree heart block (PR interval 250 msec).

Other than in the few hours immediately after surgery no subject had any bradyarrhythmias related to atrioventricular block.

Correlations with electrophysiology results, ischaemic time, donor and recipient ages

There was a close linear correlation between spontaneous cycle length measured during electrophysiological study and heart rates on ambulatory monitoring. The

strongest correlation was with minimum daytime heart rates at between -0.71 and -0.85 (figure 3.31). The association with corrected maximal sinus node recovery time was strongest with 24 hour mean heart rates at six weeks to six months (figure 3.32). There was no correlation between sinoatrial conduction time and heart rates on ambulatory monitoring.

There were no relationships between heart rates during ambulatory monitoring and perioperative ischaemic time, donor or recipient ages.

Drug effects

Five subjects received diltiazem during the study. Figure 3.33 illustrates the mean heart rates before and after diltiazem treatment. The overall mean heart rate was 82.5 ± 6 bpm before and 82.7 ± 7.8 bpm after diltiazem ($p > 0.99$). The analysis separating subjects who had taken preoperative amiodarone is detailed in chapter five but the differences between the whole group and those not treated with preoperative amiodarone were minimal. No consistent changes in heart rates were observed in the four subjects taking carbamazepine and phenytoin (see Appendix 1.2).

DISCUSSION

Heart rates

The absence of any clear trend towards higher mean and minimum heart rates with increasing time after transplantation is a little surprising in view of the trends in resting cycle length during electrophysiological studies. This is probably explained by the necessary elimination of paced heart rates from the analysis (mostly in the first week).

The close correlation between heart rates and resting cycle length measured at electrophysiological study is reassuring as regards the reliability of the method for calculating mean heart rate during ambulatory monitoring. Similarly the correlation between corrected maximal sinus node recovery time and mean heart rates closely parallels the correlation between resting cycle length and corrected maximal sinus node recovery time.

There have been two previous studies which have measured mean heart rate in transplant recipients by ambulatory monitoring techniques. Heinz and colleagues[1992a]reported a mean heart rate of 94.2 ± 9 bpm in 51 subjects three months after transplantation. Alexopoulos and colleagues[1988]reported a mean rate of 99 ± 11 bpm in 19 subjects between six months and three years after transplantation. In comparison the mean heart rates found in the current study are lower. The fall in mean heart rate at six months in the present study is probably artefactual. The calculation of mean heart rate by the method used required very high quality recordings and there was a considerable quantity of data unsuitable for full analysis at six months.

Bradyarrhythmias, sinus node dysfunction and pacing requirements

In this study ambulatory monitoring was of limited usefulness in the first week after transplantation. Temporary pacing at 90 bpm was judged clinically necessary in 20% of

subjects and several subjects with no subsequent bradycardia or abnormal electrophysiology required intermittent pacing at 50 bpm.

After the first week the results may be more significant although caution is required in view of the small number of subjects with bradyarrhythmias. In this study both subjects who required intermittent or continuous pacing at two weeks subsequently required permanent pacemakers and the subject who paced intermittently at three weeks continued to pace intermittently long term.

There have been no previously published studies which have employed 24 hour ambulatory ECG monitoring in the first three weeks after transplantation in an attempt to assess the need for permanent pacing. Two groups of authors have published the results of ambulatory monitoring in long term transplant survivors. Bexton and colleagues[1983a]reported "relative bradycardia" in three of four subjects with electrophysiological evidence of sinus node dysfunction between four and 14 months after transplantation. Two of these subjects had ventricular pacemakers programmed to 70 bpm, the other had a minimum recorded heart rate of 57 bpm. Heinz and colleagues[1992a]reported that 44% of subjects with early sinus node dysfunction (corrected maximal sinus node recovery time >520 msec) had ambulatory ECG evidence of persistent sinus node dysfunction three months after transplantation. However the definitions of sinus node dysfunction used were non standard. Permanent pacemakers had been implanted in some subjects and were programmed to 70 bpm as compared with 50 bpm in the current study and the definition of normal sinus node function included a 24 mean heart rate of at least 80 bpm. In the current study two subjects who were completely asymptomatic with consistently normal electrophysiological indices of sinus node function would have been classified as having sinus node dysfunction by these criteria. It is of note that six of 17 subjects (35%) defined as having ambulatory ECG

evidence of sinus node dysfunction were asymptomatic.

The selection of a relatively low temporary pacing rate of 50 bpm during early ambulatory monitoring was, we believe, essential in order to separate out subjects with relative bradycardia but no clinically significant arrhythmias. Although this rate may be disadvantageous to some subjects in the first week, all were able to tolerate it from the second week with no ill effects.

Conclusions

Ambulatory ECG monitoring may be useful in assessing the need for permanent pacing in transplant recipients between two and three weeks after transplantation. Patients who pace continuously or intermittently three weeks after transplantation may require long term pacing. It is essential that temporary pacing rates are set low (50 bpm) to adequately distinguish patients who may require pacemakers from those with relative but clinically insignificant bradyarrhythmias. These data should however be interpreted with caution in view of the small numbers of subjects with clinically important bradyarrhythmias in this study.

Figure 3.1: Changes in sinus node recovery time in subjects with normal sinus node function

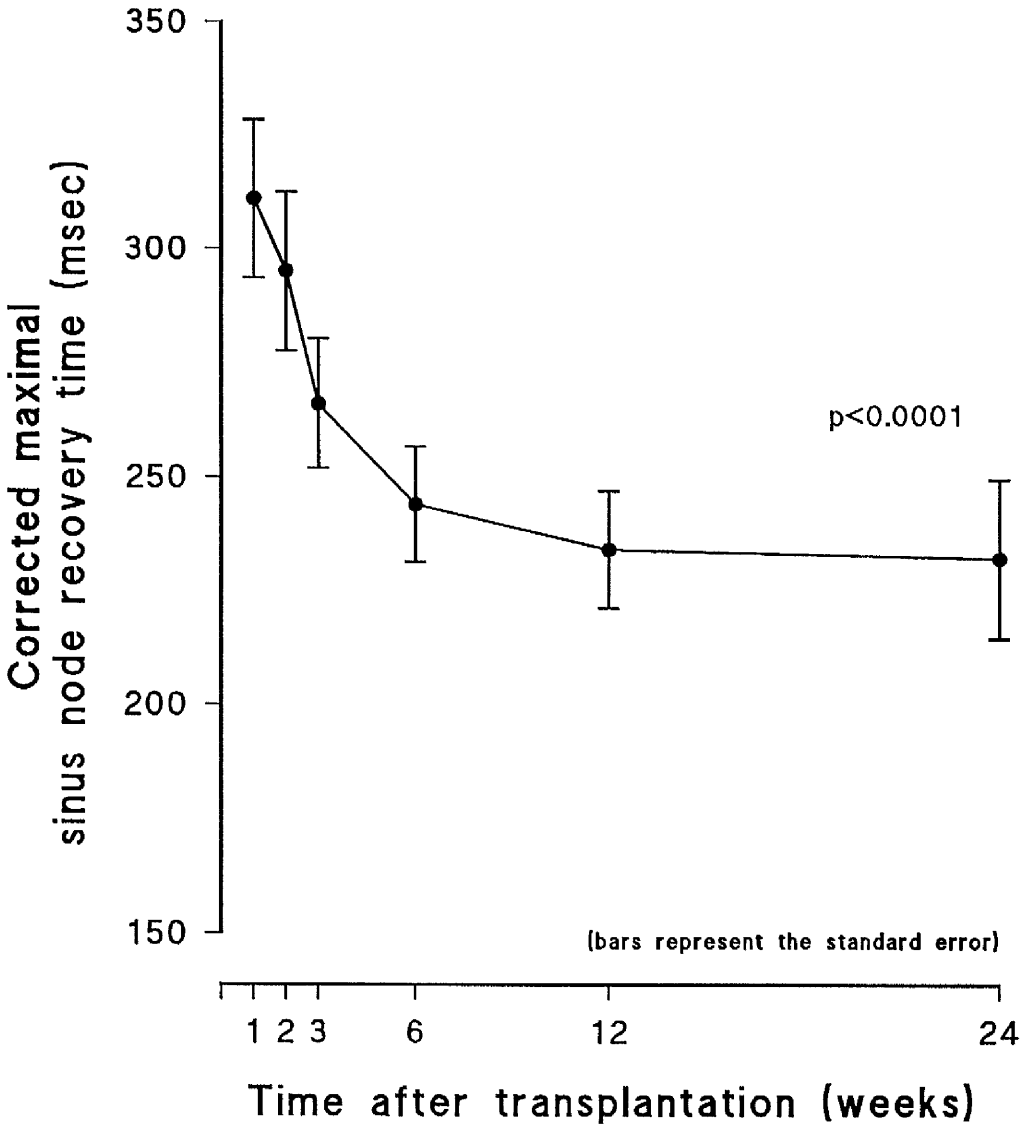


Figure 3.2: Changes in sinus node recovery in subjects with normal sinus function

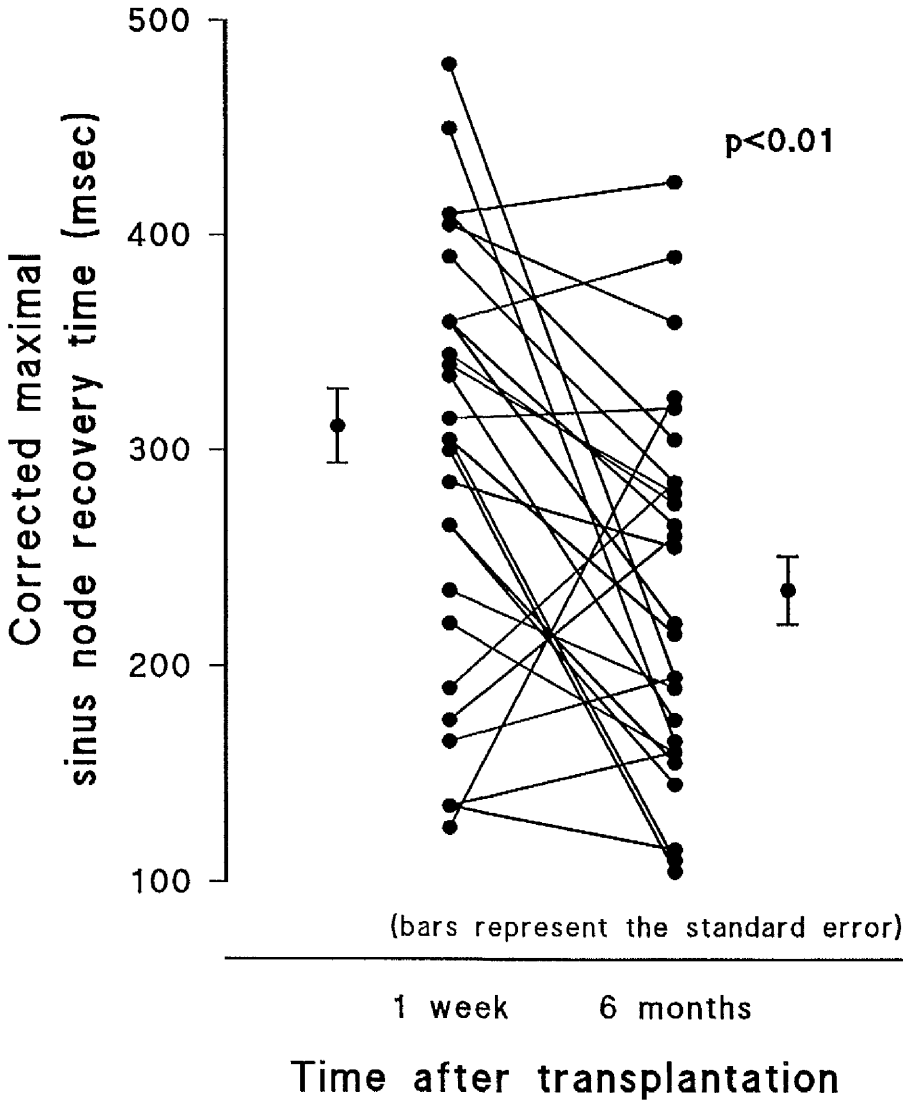


Figure 3.3: Changes in resting cycle length in subjects with normal sinus node function

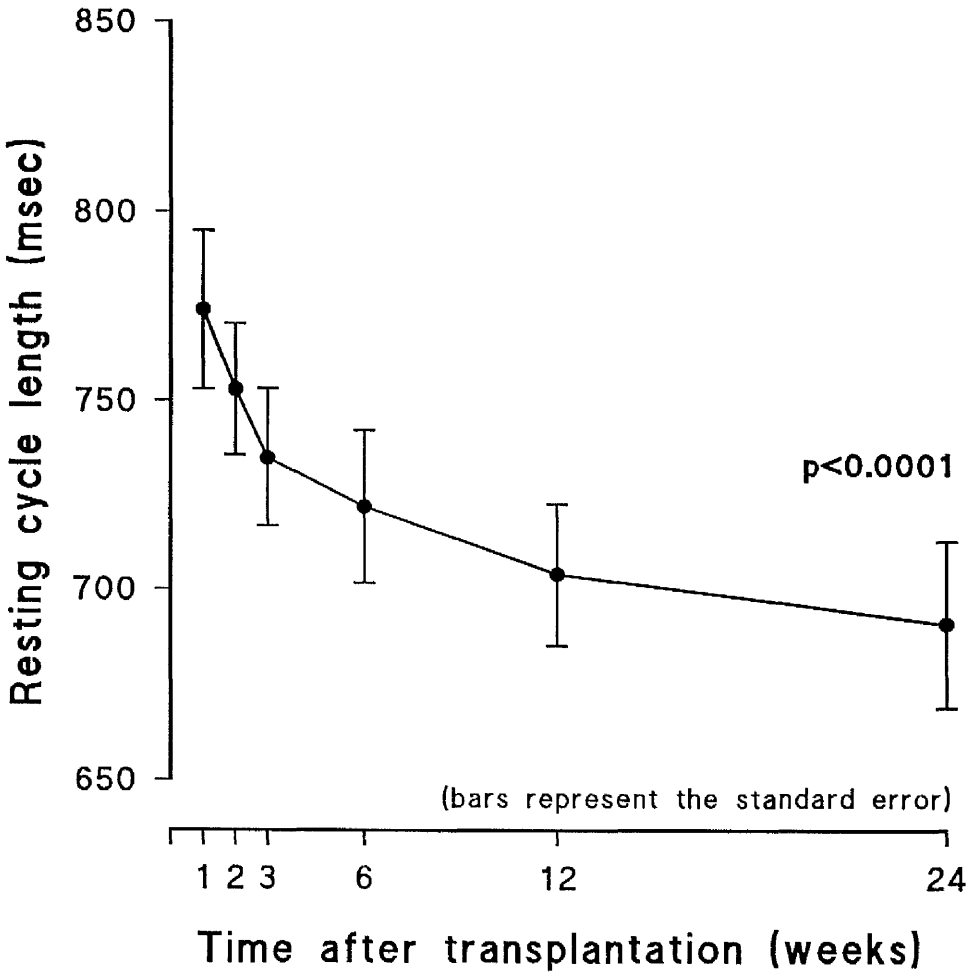


Figure 3.4: Changes in resting cycle length in subjects with normal sinus function

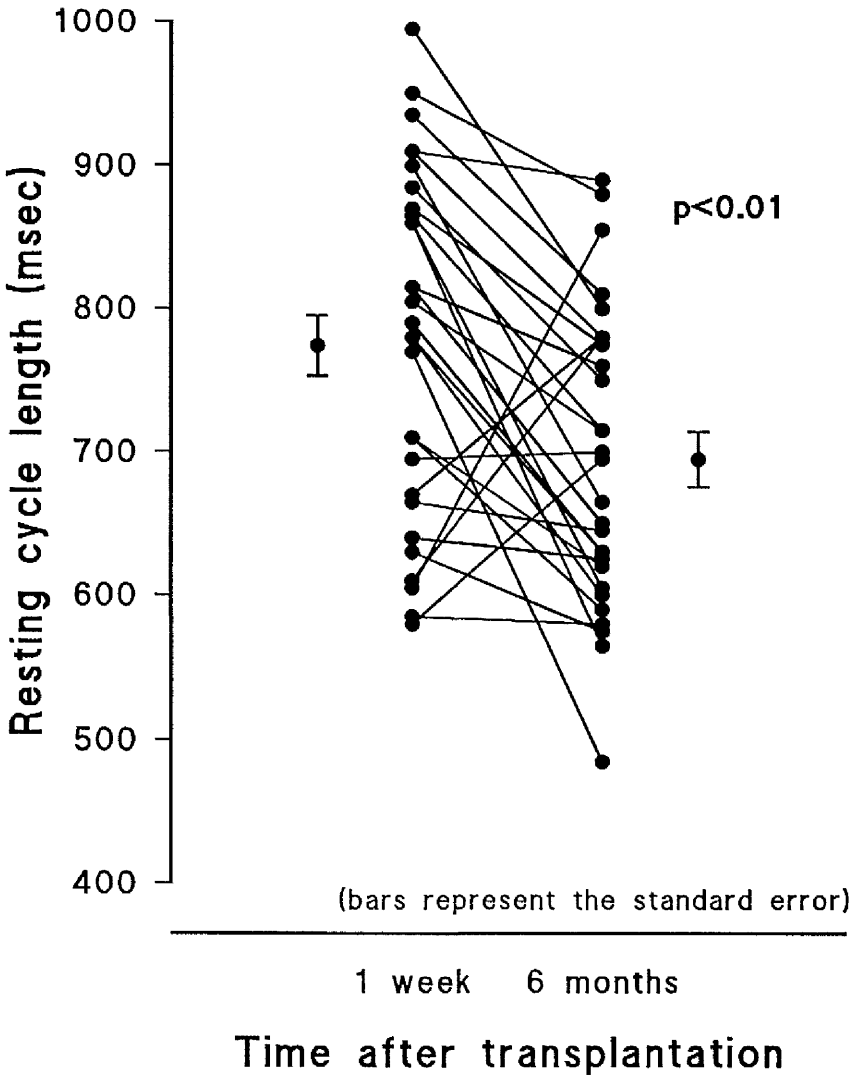


Figure 3.5: Changes in sinoatrial conduction time in subjects with normal sinus node function

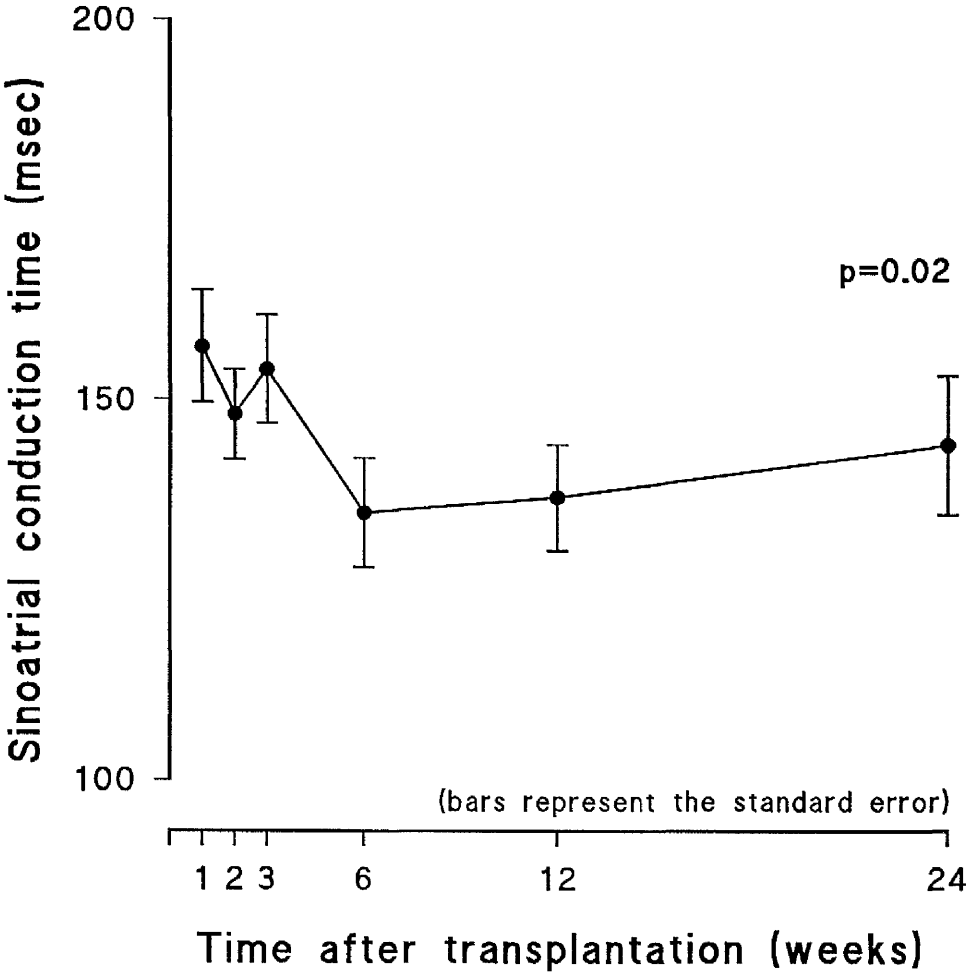


Figure 3.6: Changes in sinus node recovery time in seven subjects with sinus node dysfunction

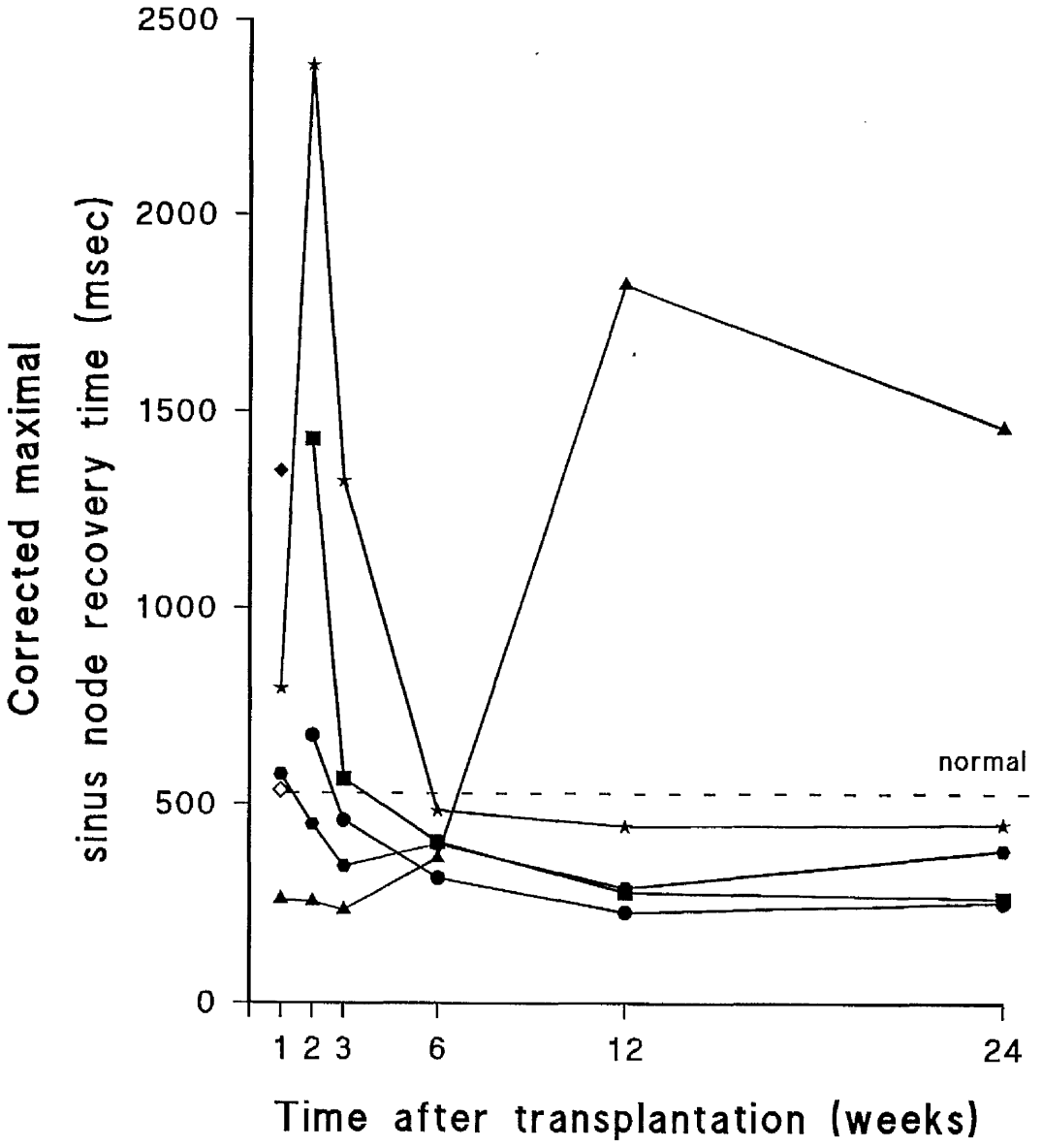


Figure 3.7: Changes in sinoatrial conduction time in subjects with sinus node dysfunction

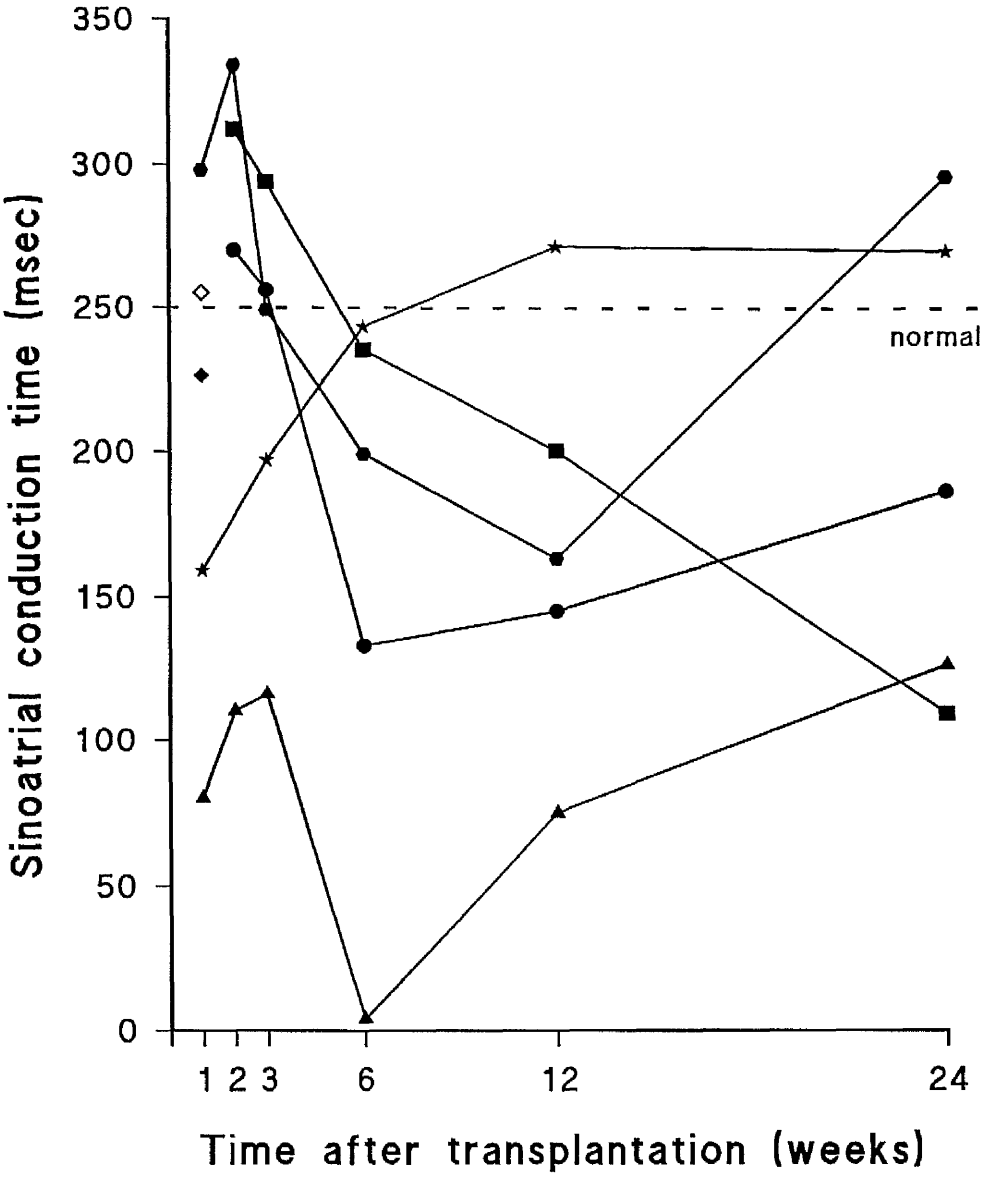


Figure 3.8: Changes in resting cycle length in subjects with sinus node dysfunction

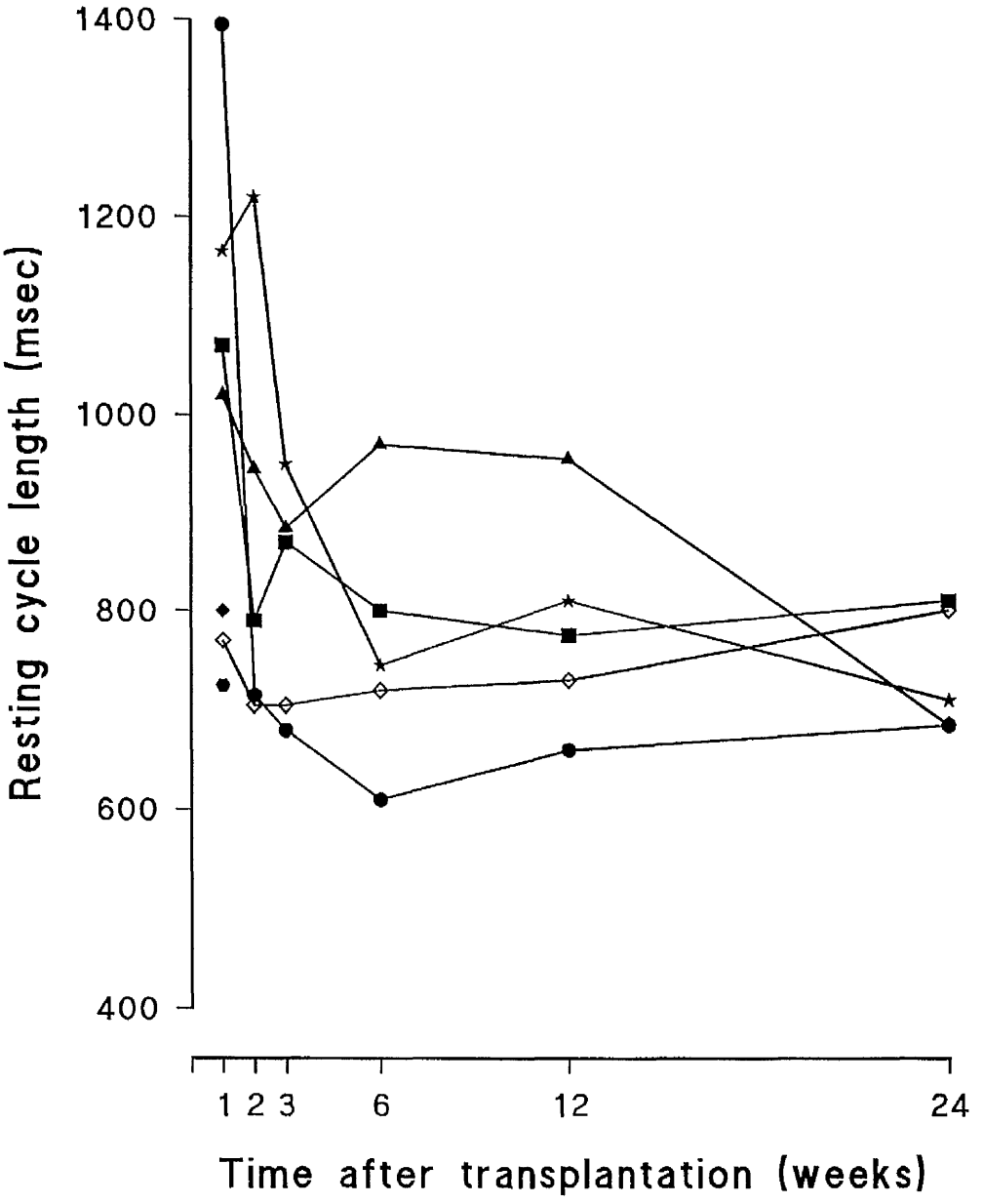
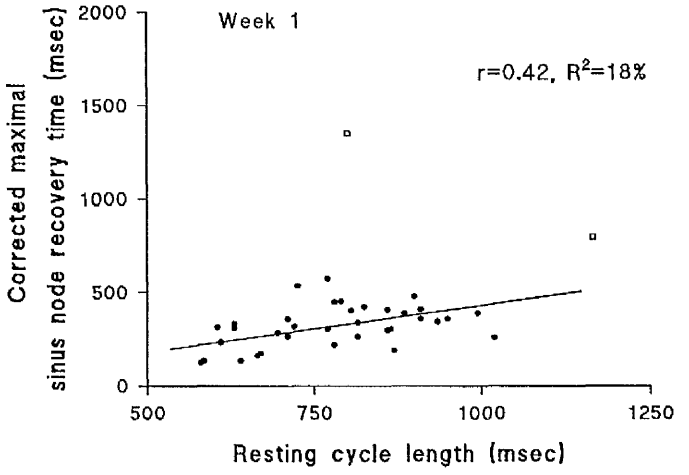
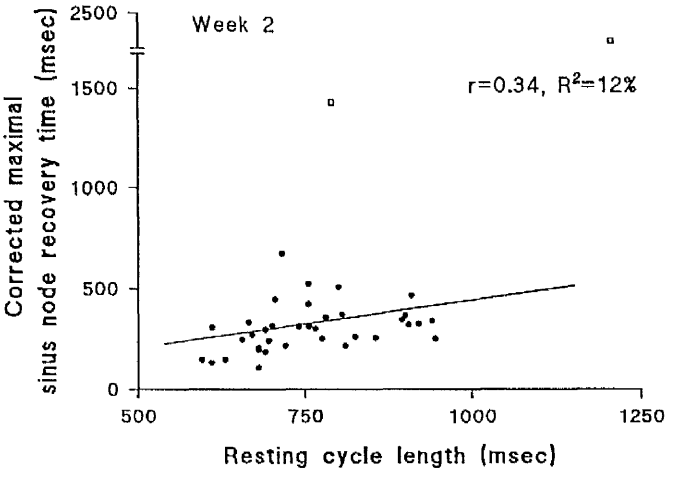
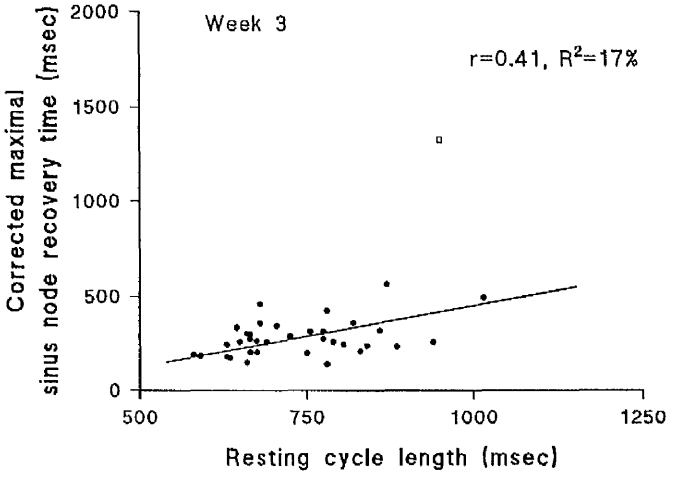


Figure 3.9: Correlation of sinus node recovery time and sinus cycle length early after transplantation

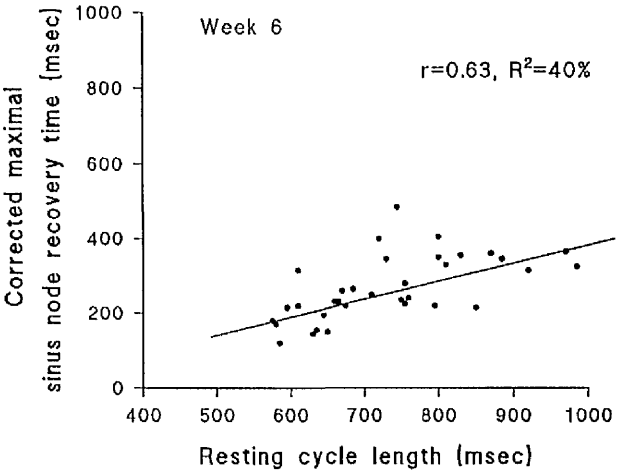


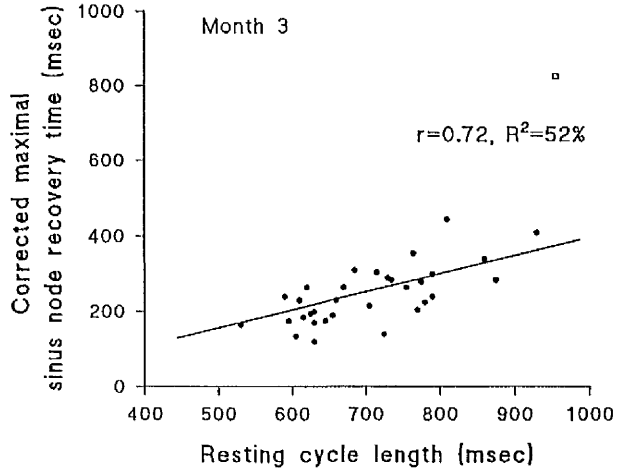


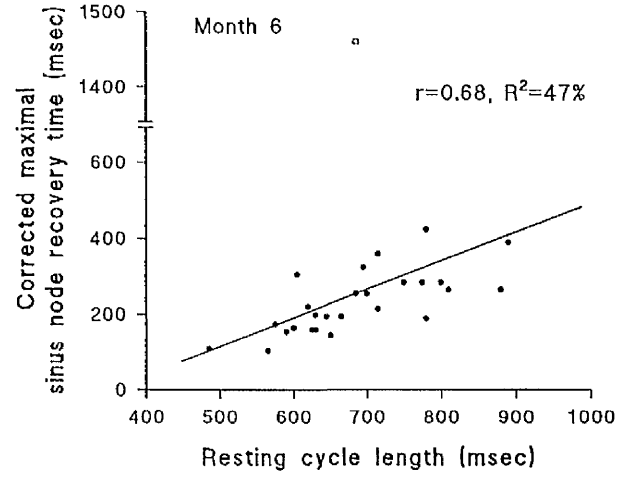


Key: □ = data point excluded from correlation analysis

Figure 3.10: Correlation of sinus node recovery time and sinus cycle length in longer term survivors







Key: □ = data point excluded from correlation analysis

Figure 3.11: Changes in sinus node recovery time in subjects receiving diltiazem

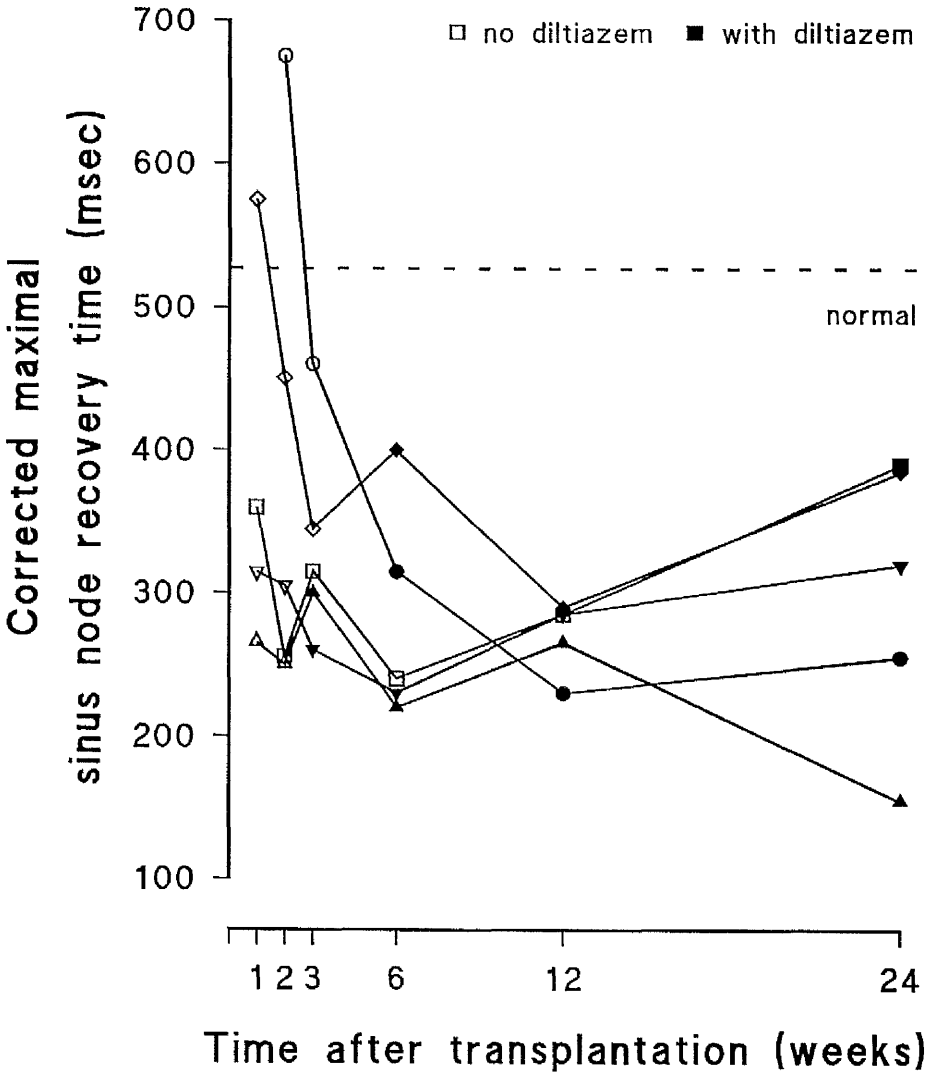


Figure 3.12: Changes in atrioventricular effective refractory periods with time after transplantation

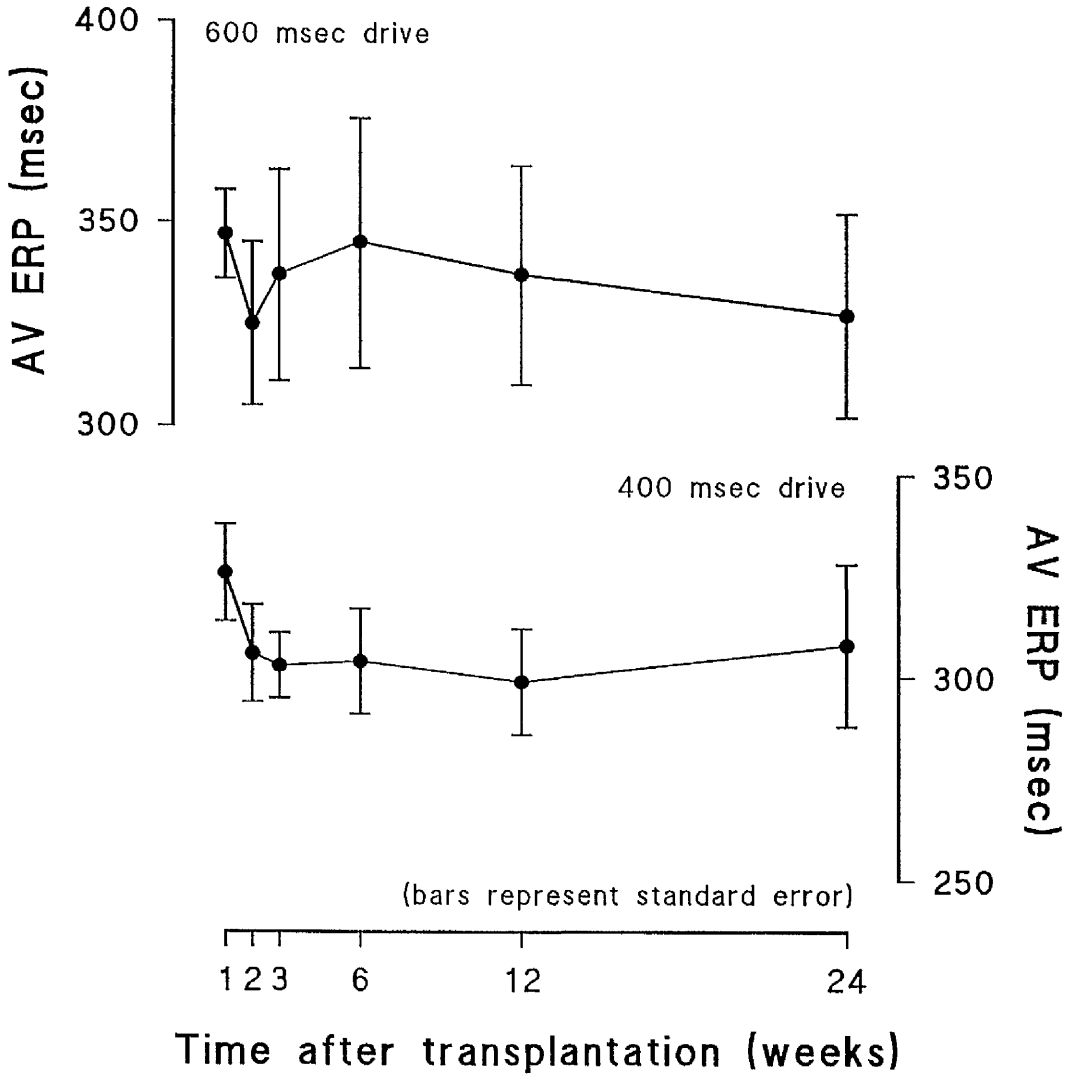


Figure 3.13: Changes in Wenckebach cycle length with time after transplantation

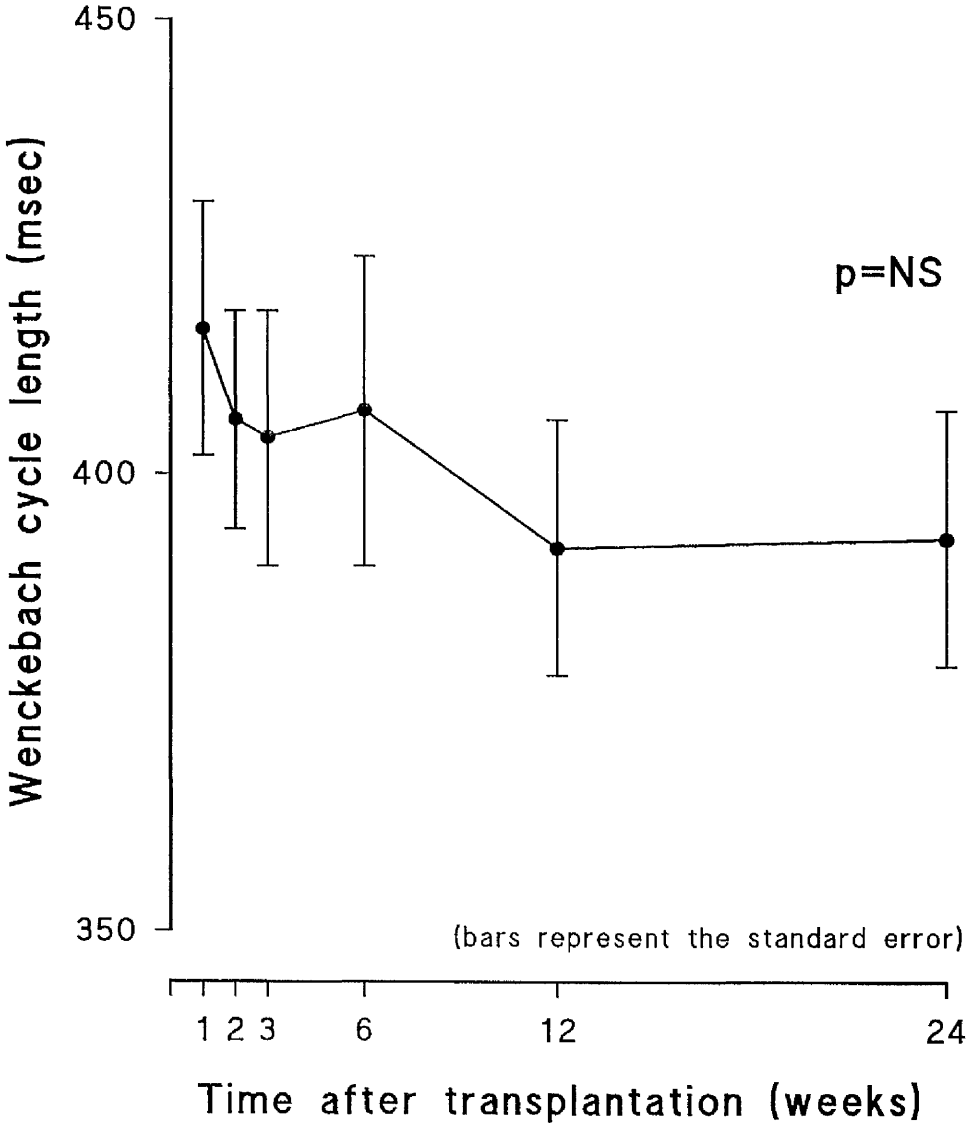


Figure 3.14: Correlation of atrioventricular effective refractory period and Wenckebach cycle length (600 msec drive)

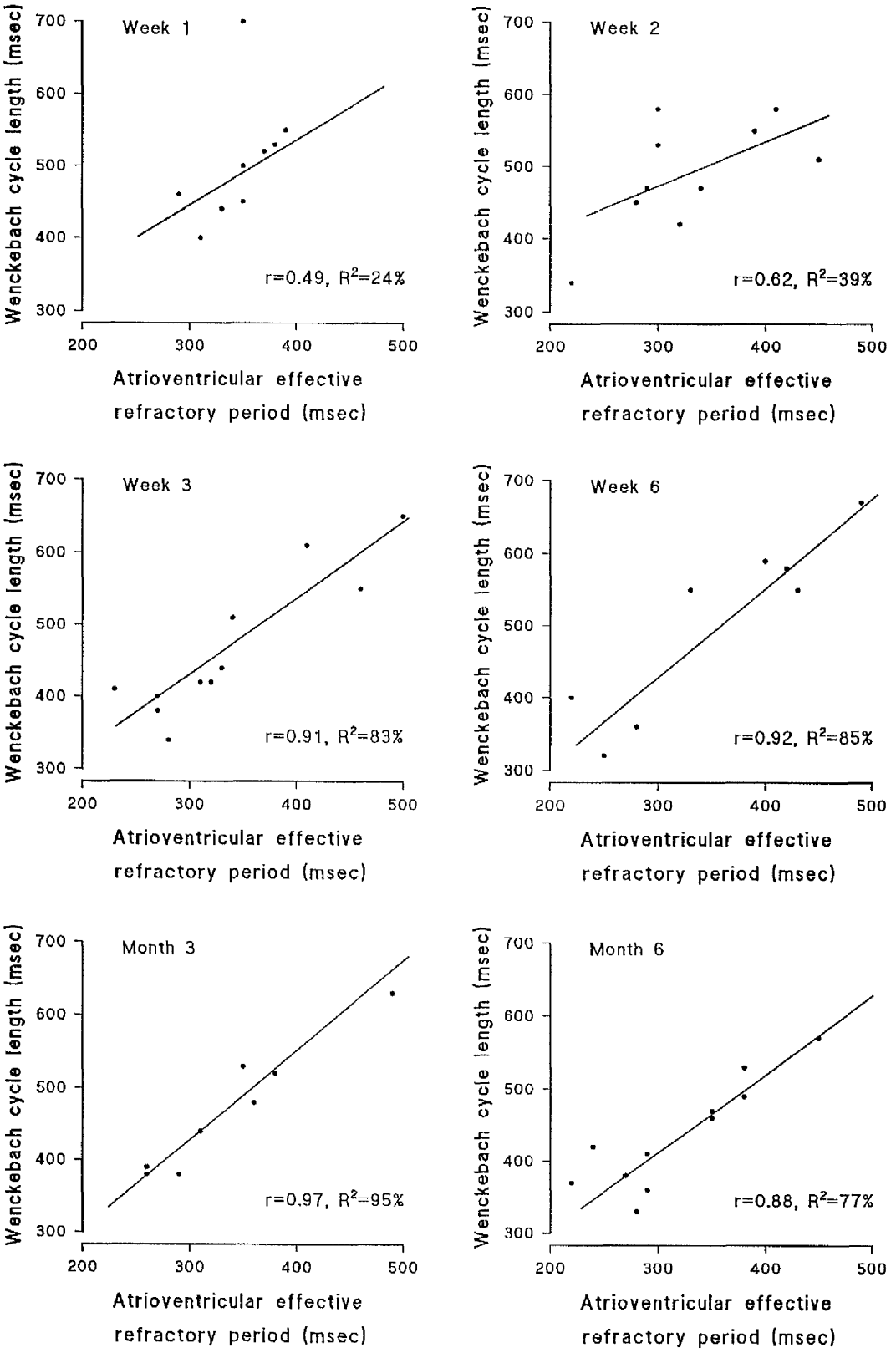


Figure 3.15: Correlation of atrioventricular effective refractory period and Wenckebach cycle length (400 msec drive)

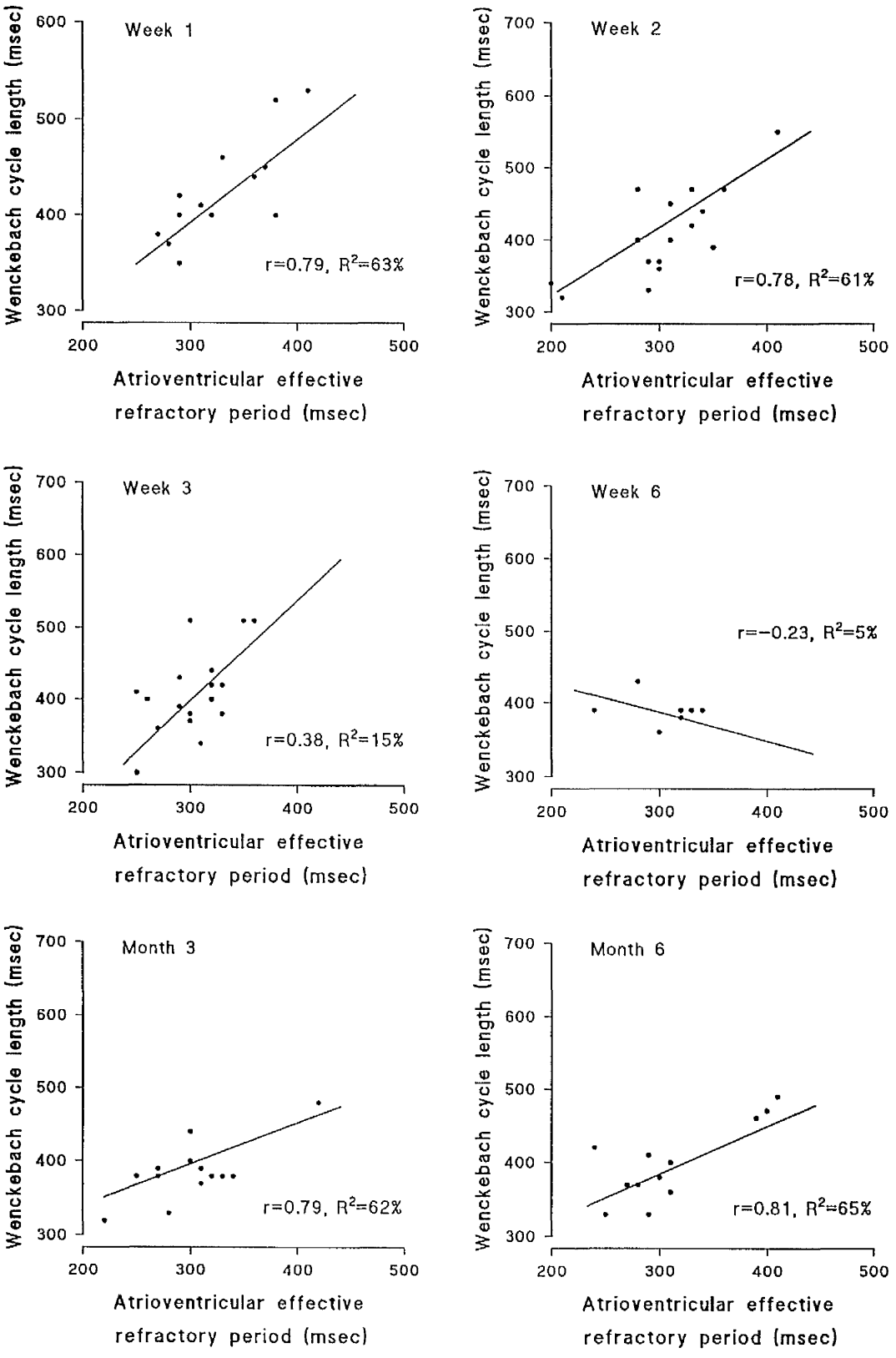


Figure 3.16: Changes in exercise duration with time after transplantation

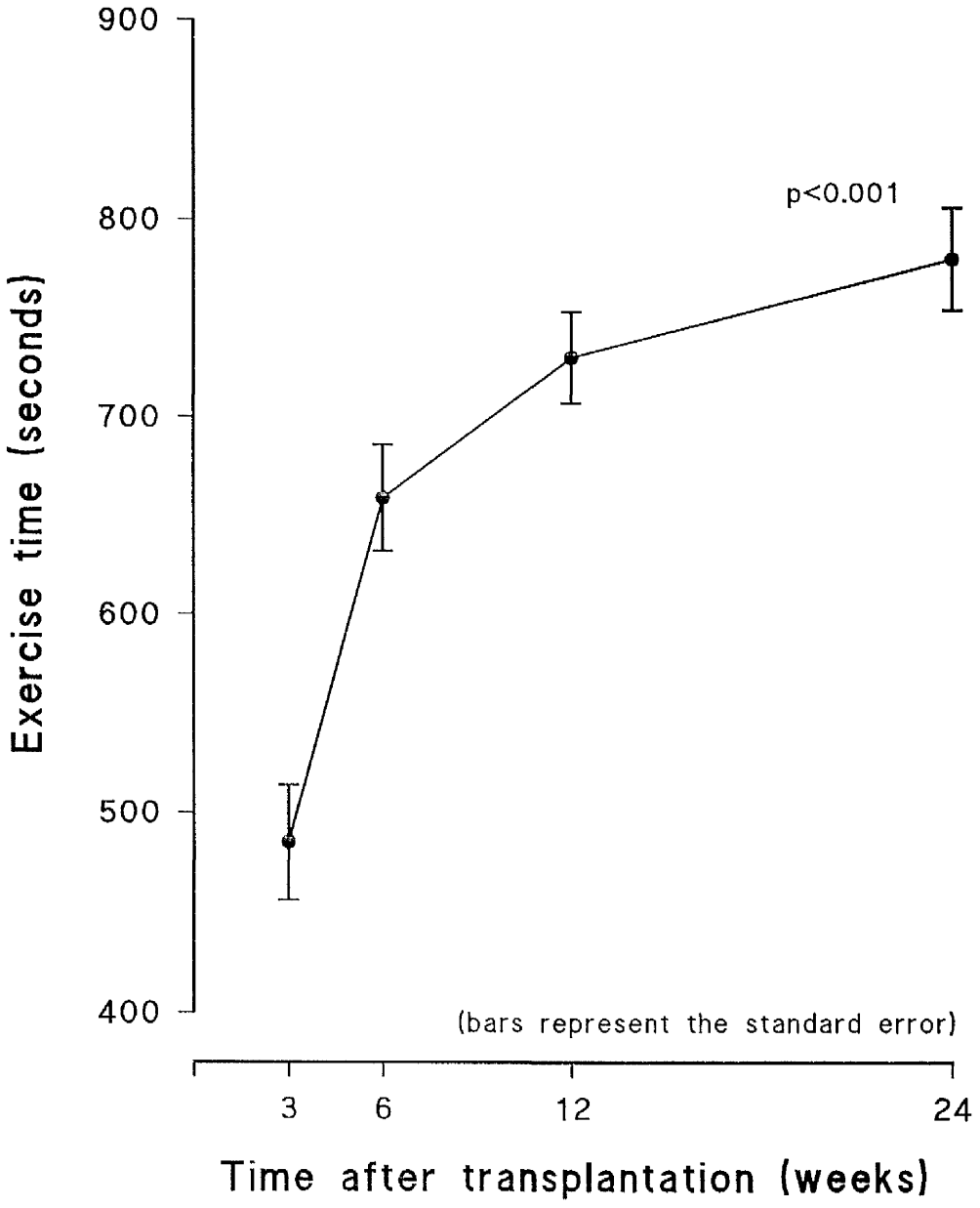


Figure 3.17: Changes in heart rate at rest and peak exercise with time after transplantation

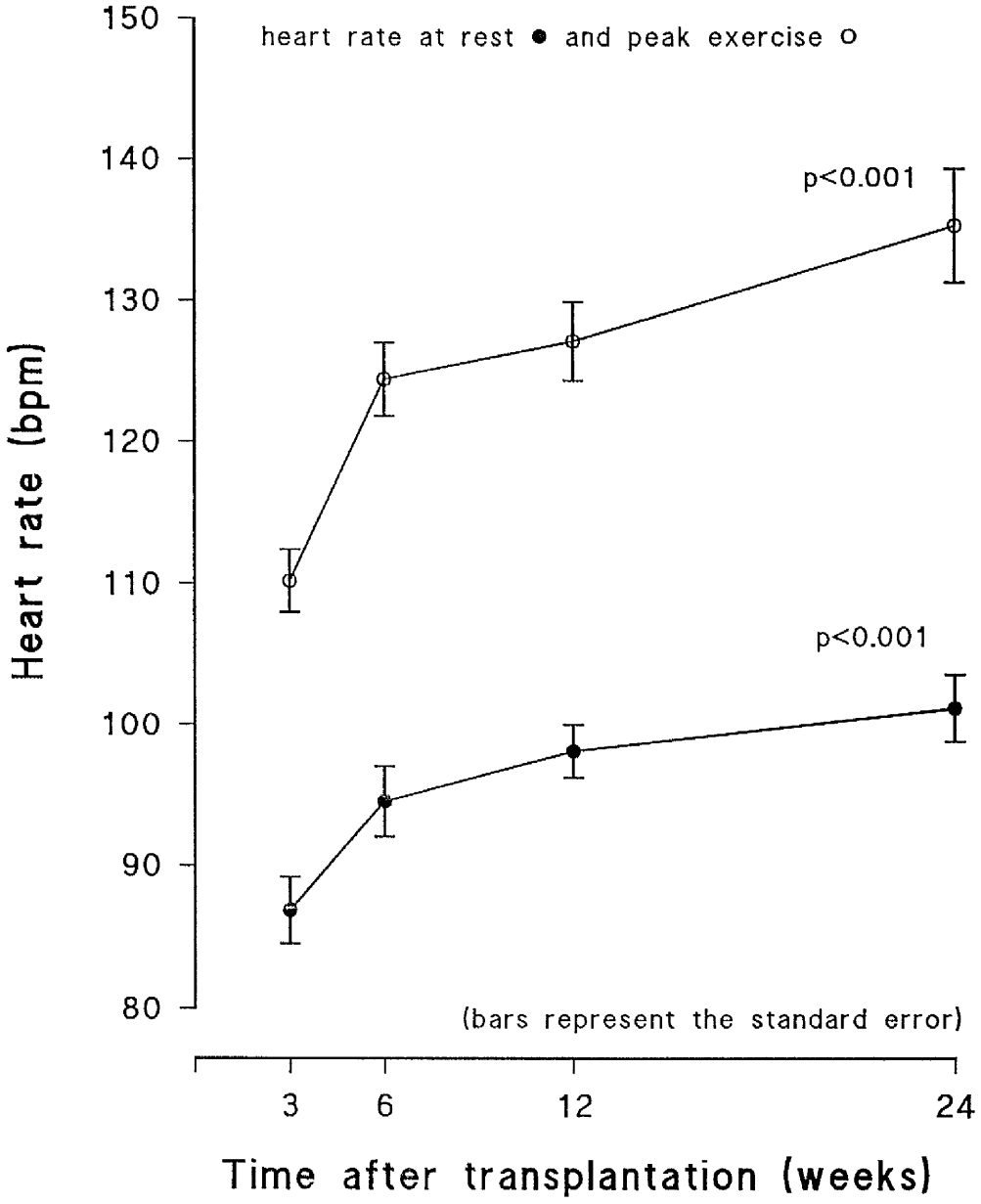


Figure 3.18: Changes in heart rate reserve used at peak exercise with time after transplantation

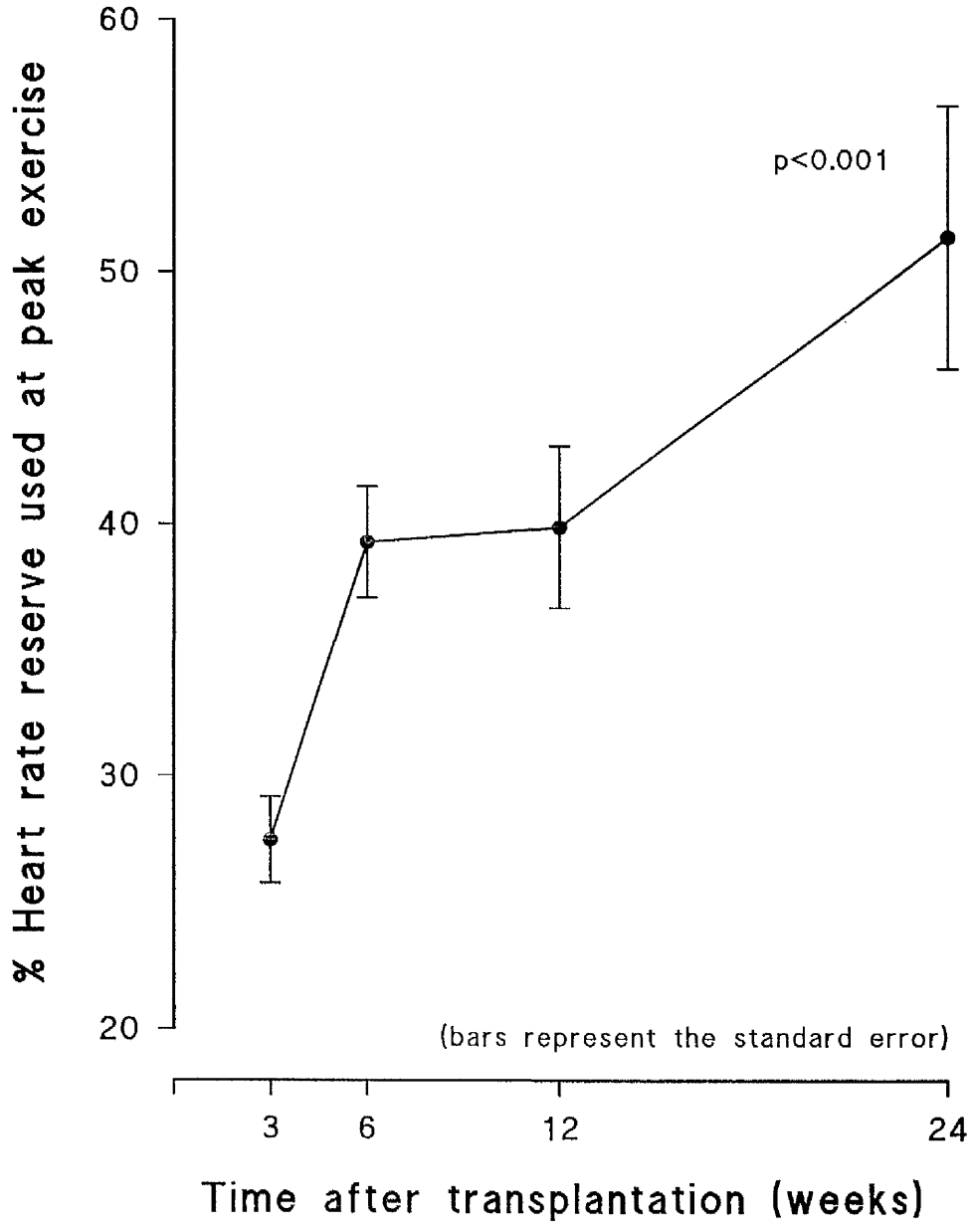


Figure 3.19: Changes in the chronotropic response with time after transplantation

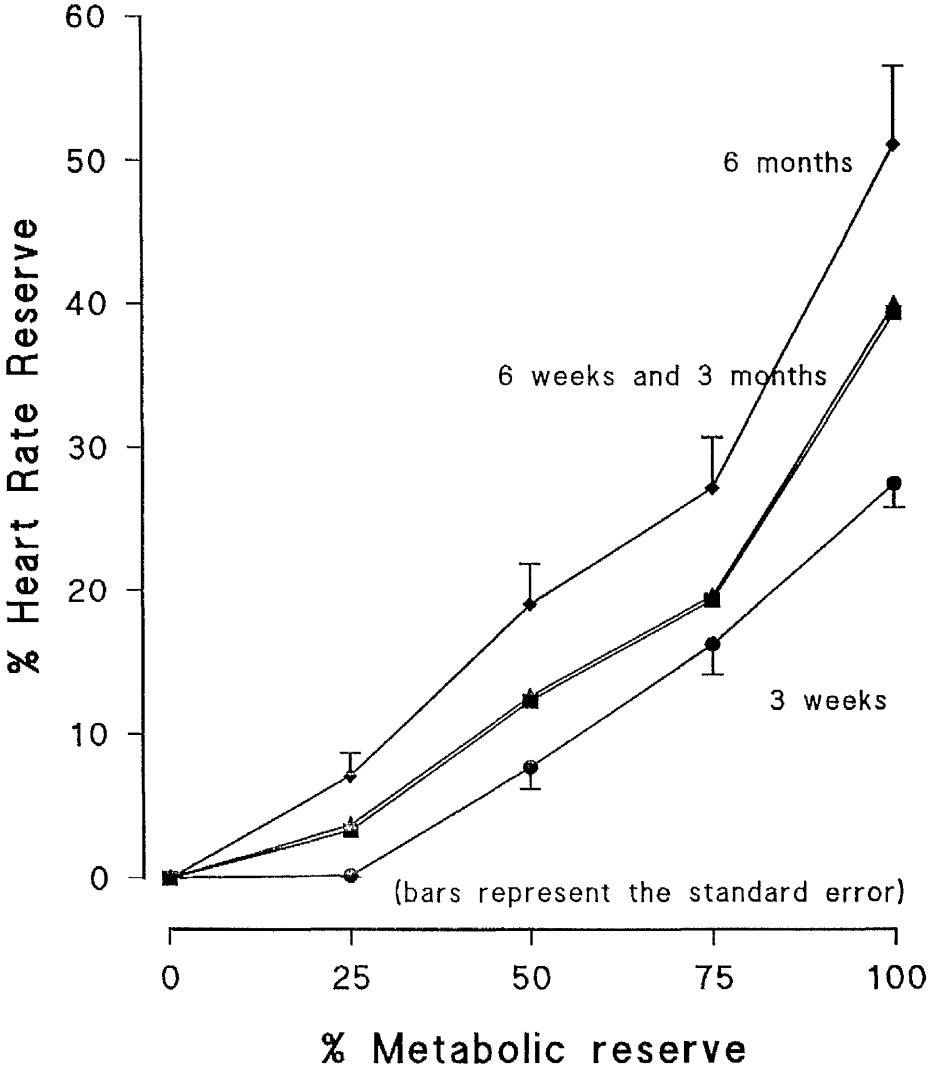


Figure 3.20: Heart rate reserve at peak exercise in subjects with an enhanced exercise response

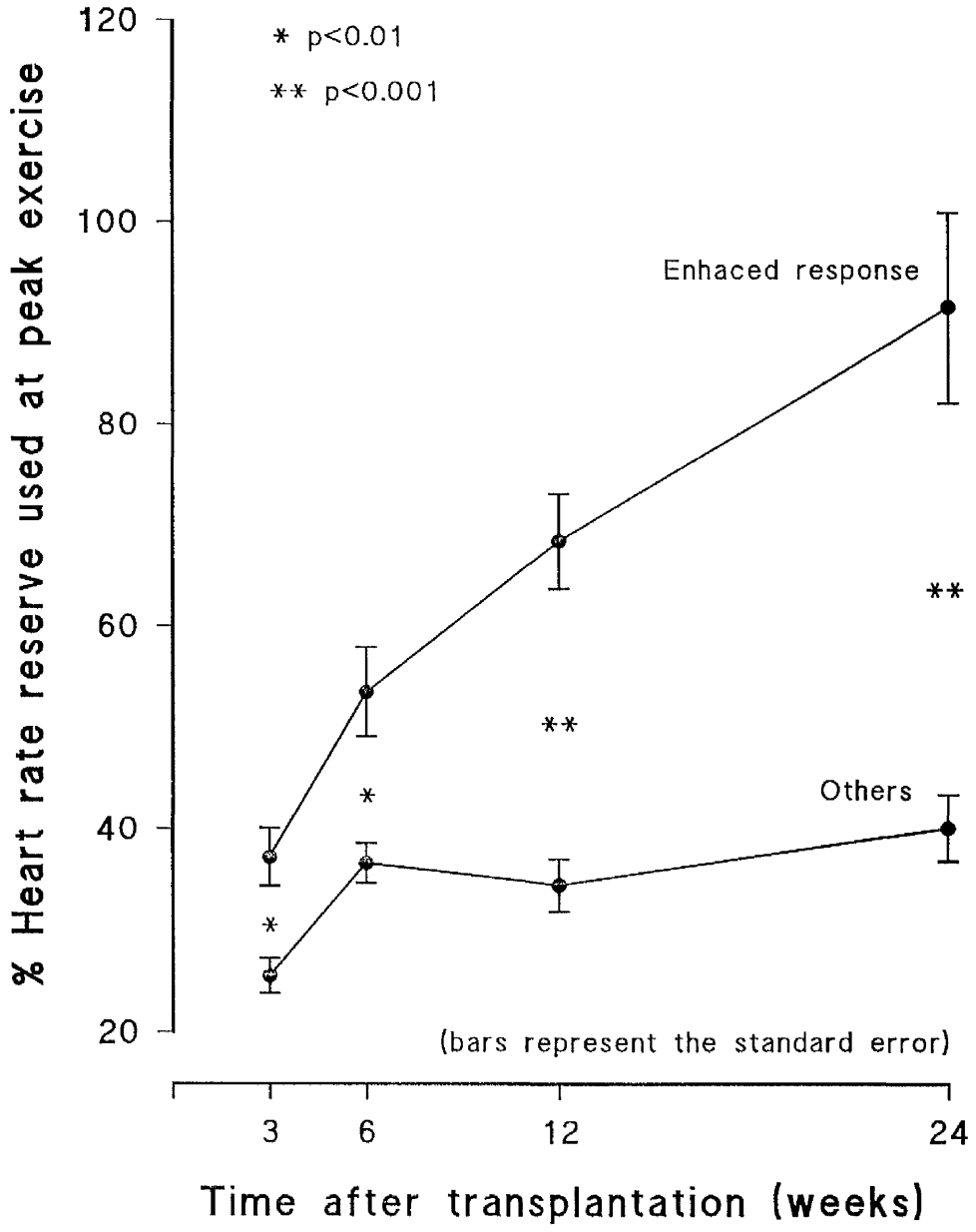


Figure 3.21: Differences in exercise time in subjects with an enhanced exercise response

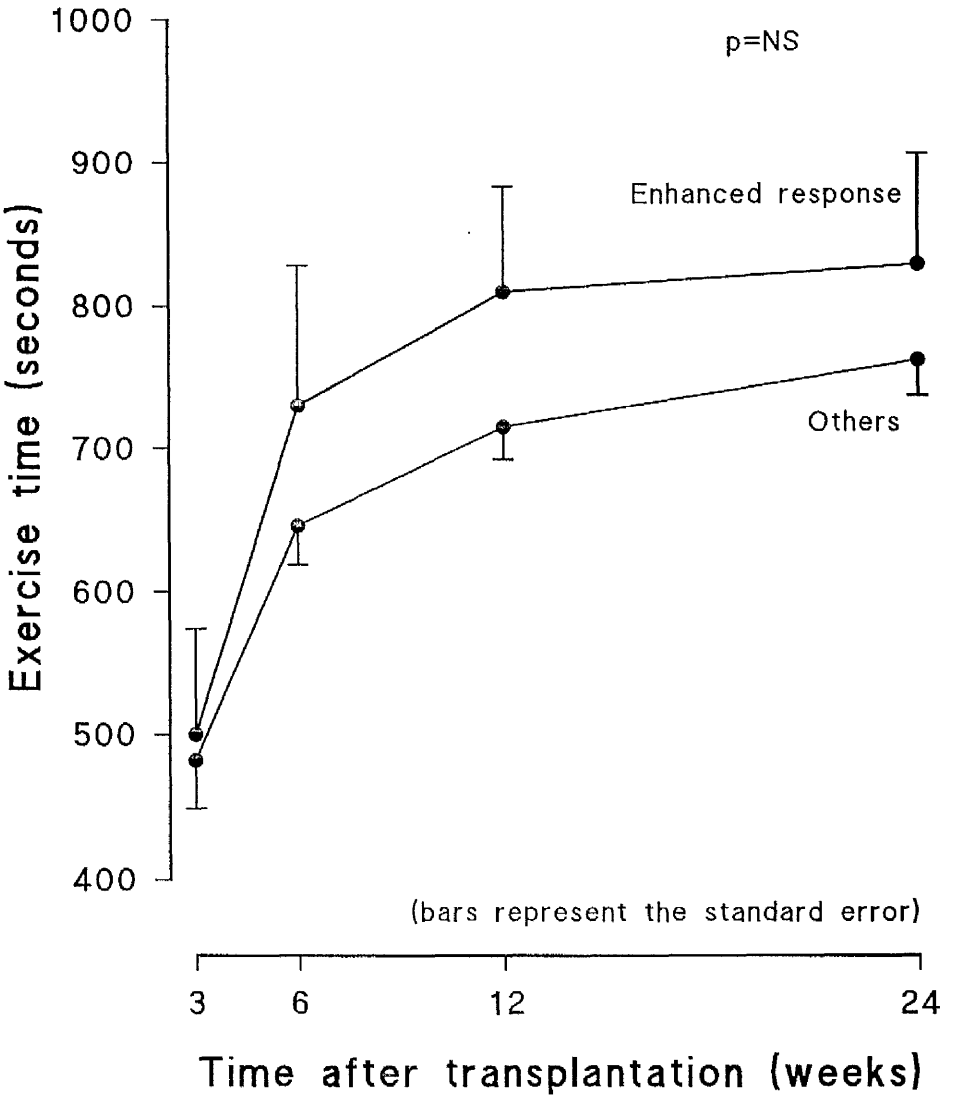


Figure 3.22: Changes in heart rate during recovery and time after transplantation

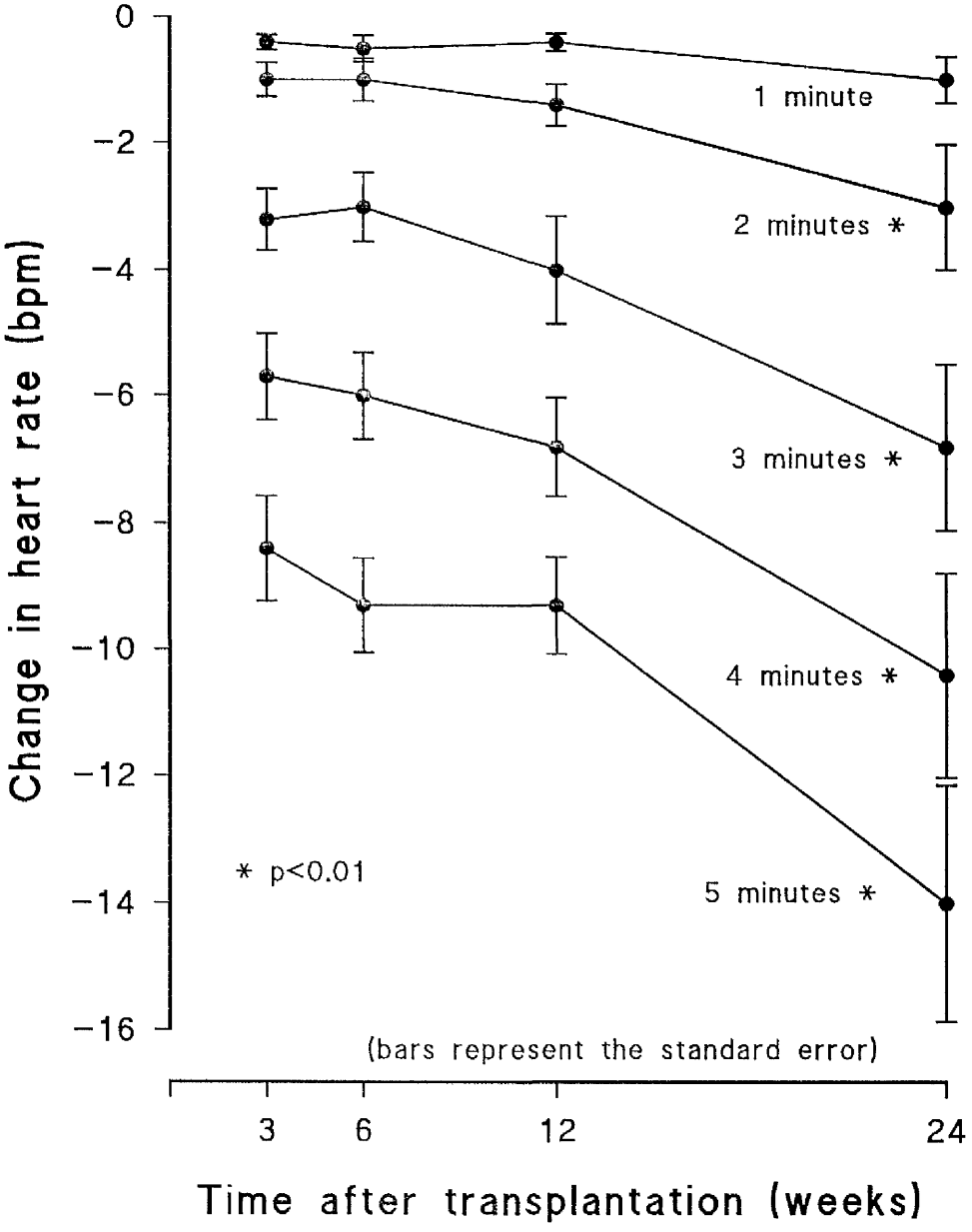


Figure 3.23: Changes in heart rate during recovery and time after transplantation (5 subjects with enhanced exercise response excluded)

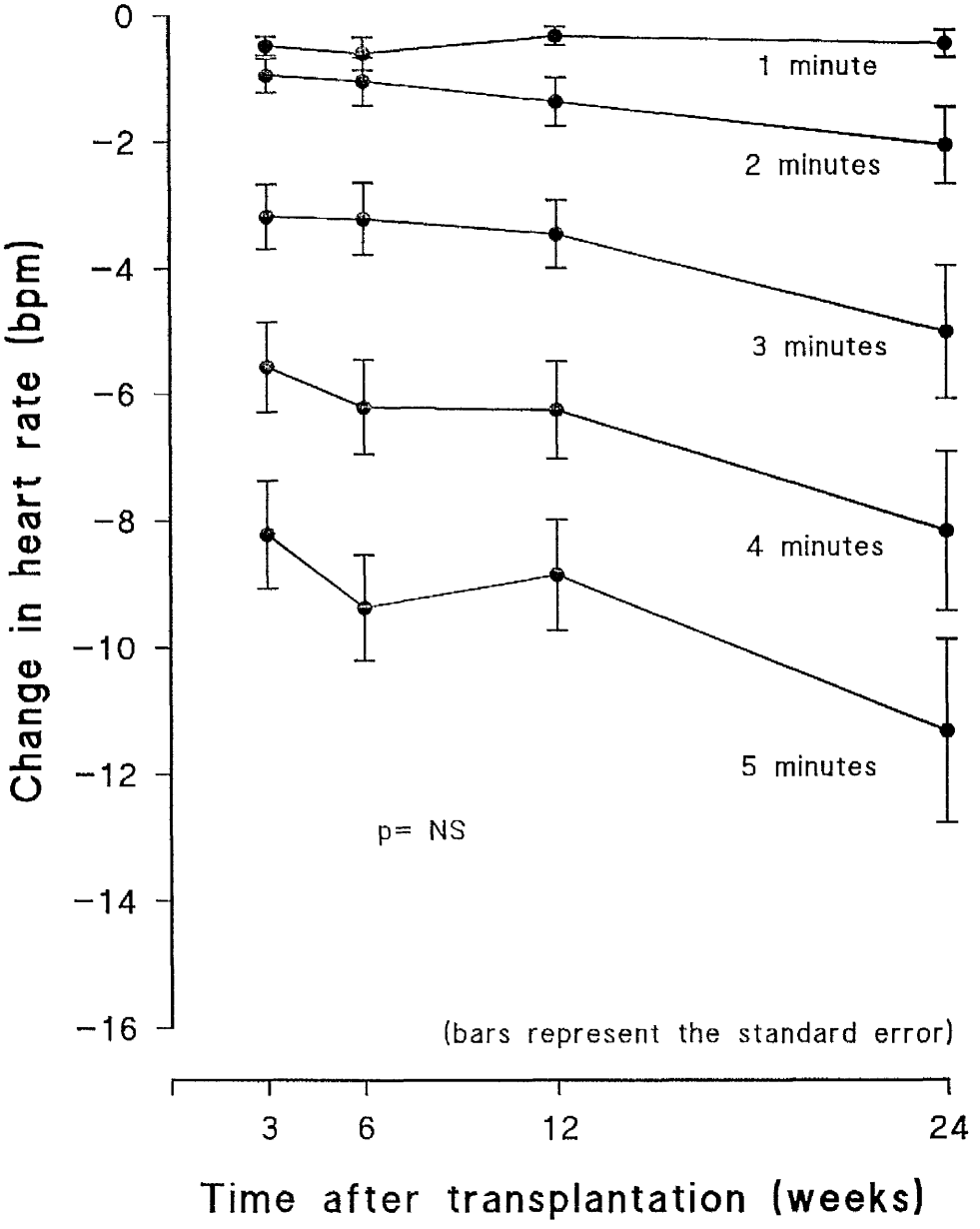


Figure 3.24: Decrease in heart rate during recovery and time after transplantation

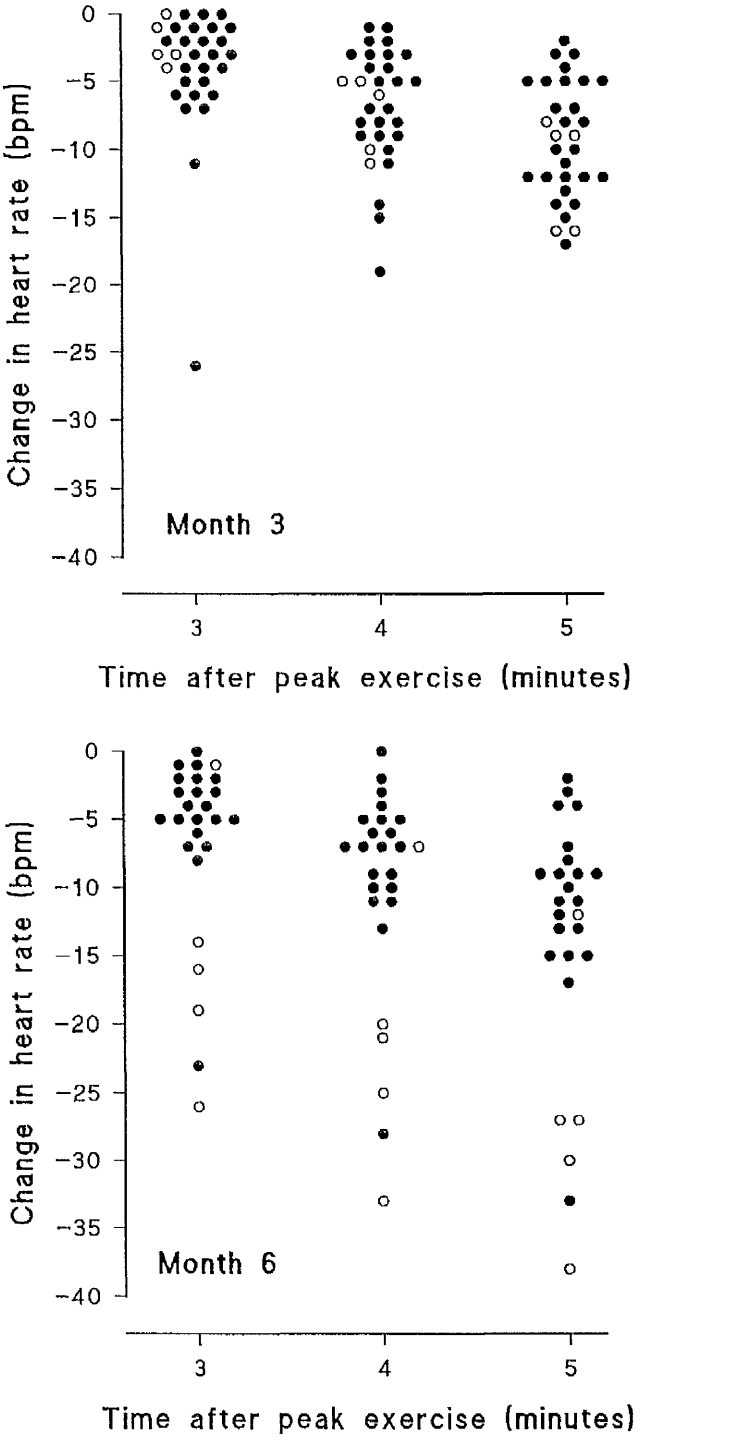


Figure 3.25: Chronotropic response in a subject with late sinus node dysfunction

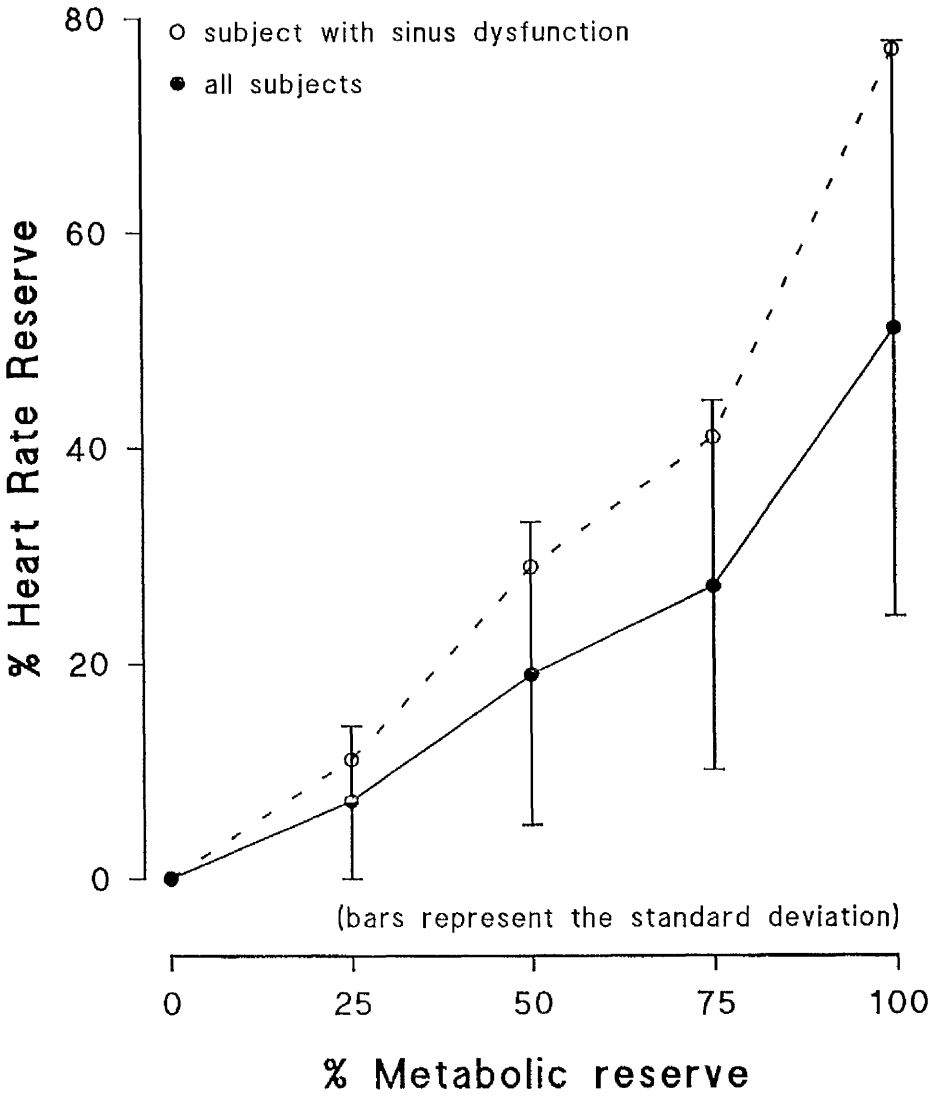


Figure 3.26: Chronotropic response in subjects with early sinus node dysfunction

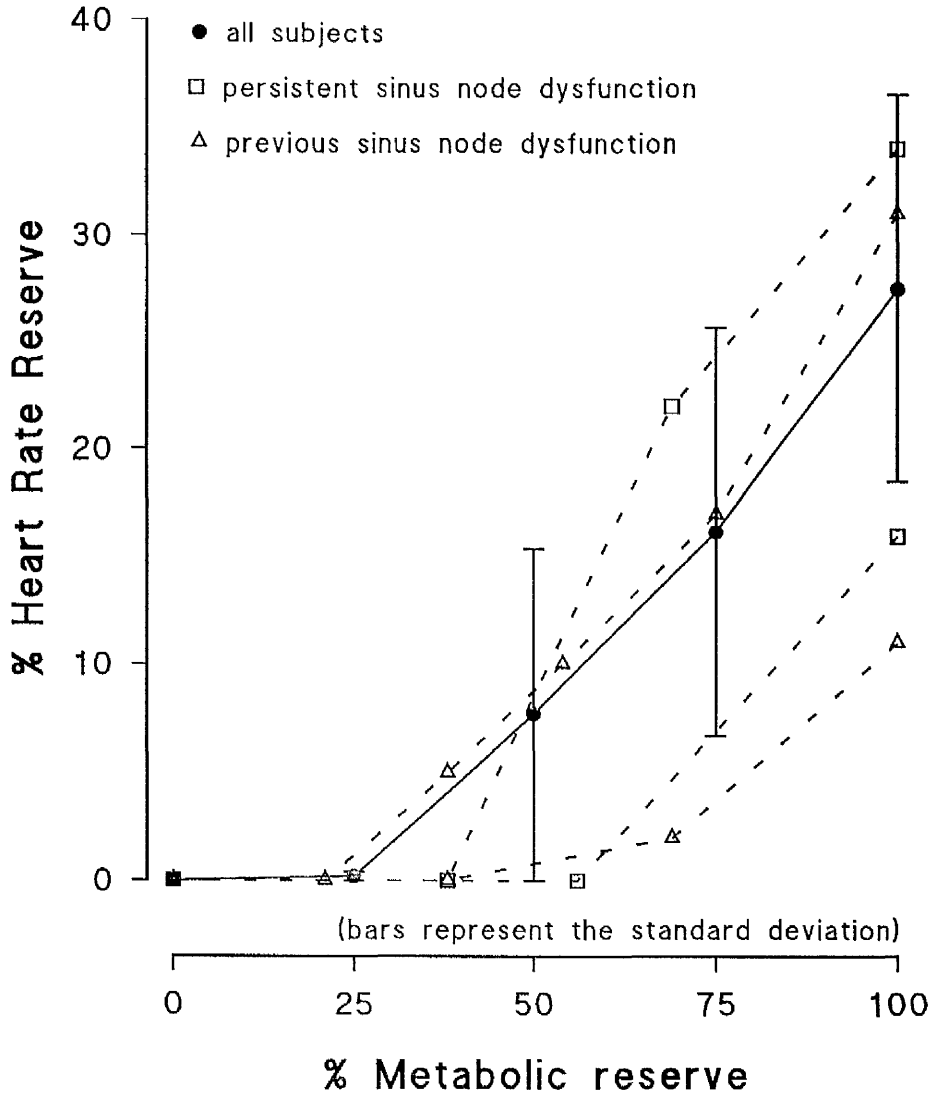


Figure 3.27: Chronotropic response at six weeks in subjects with previous sinus node dysfunction

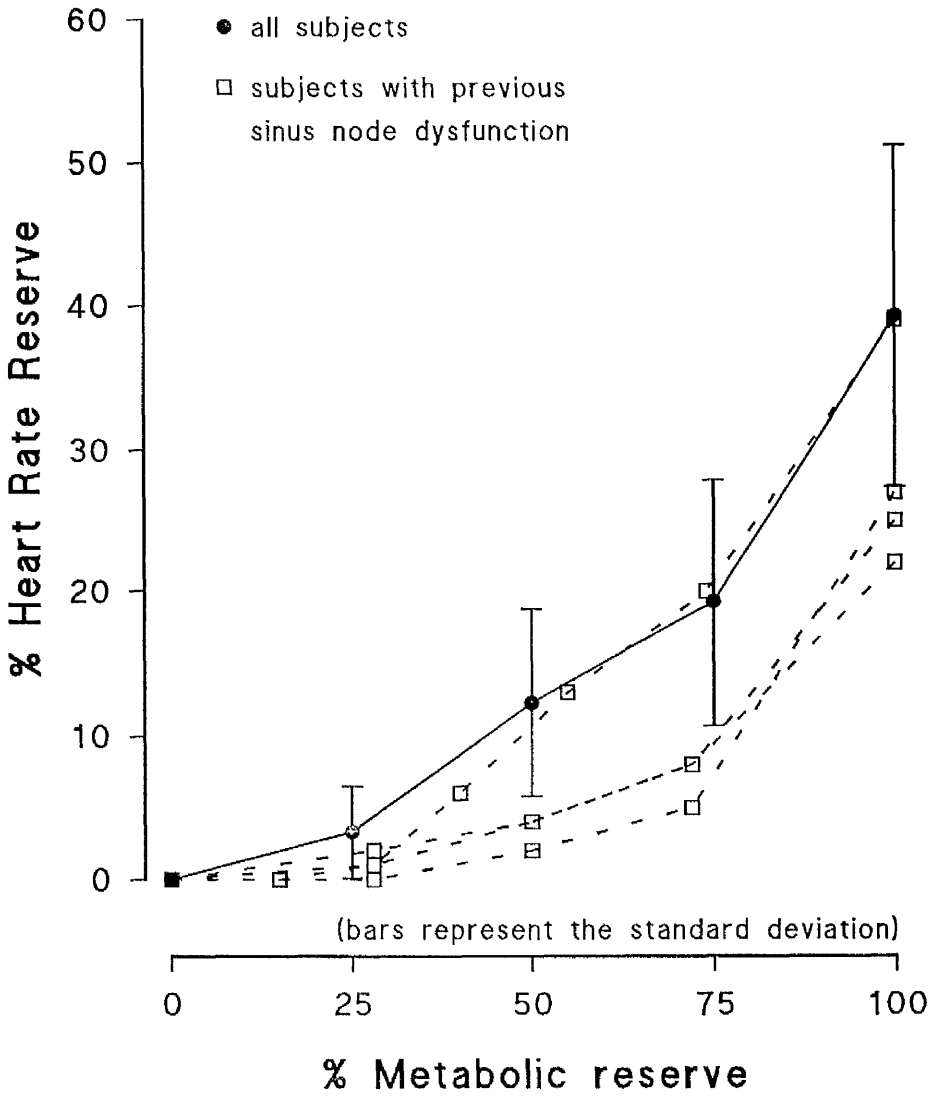


Figure 3.28: Chronotropic response at six months in subjects with previous sinus node dysfunction

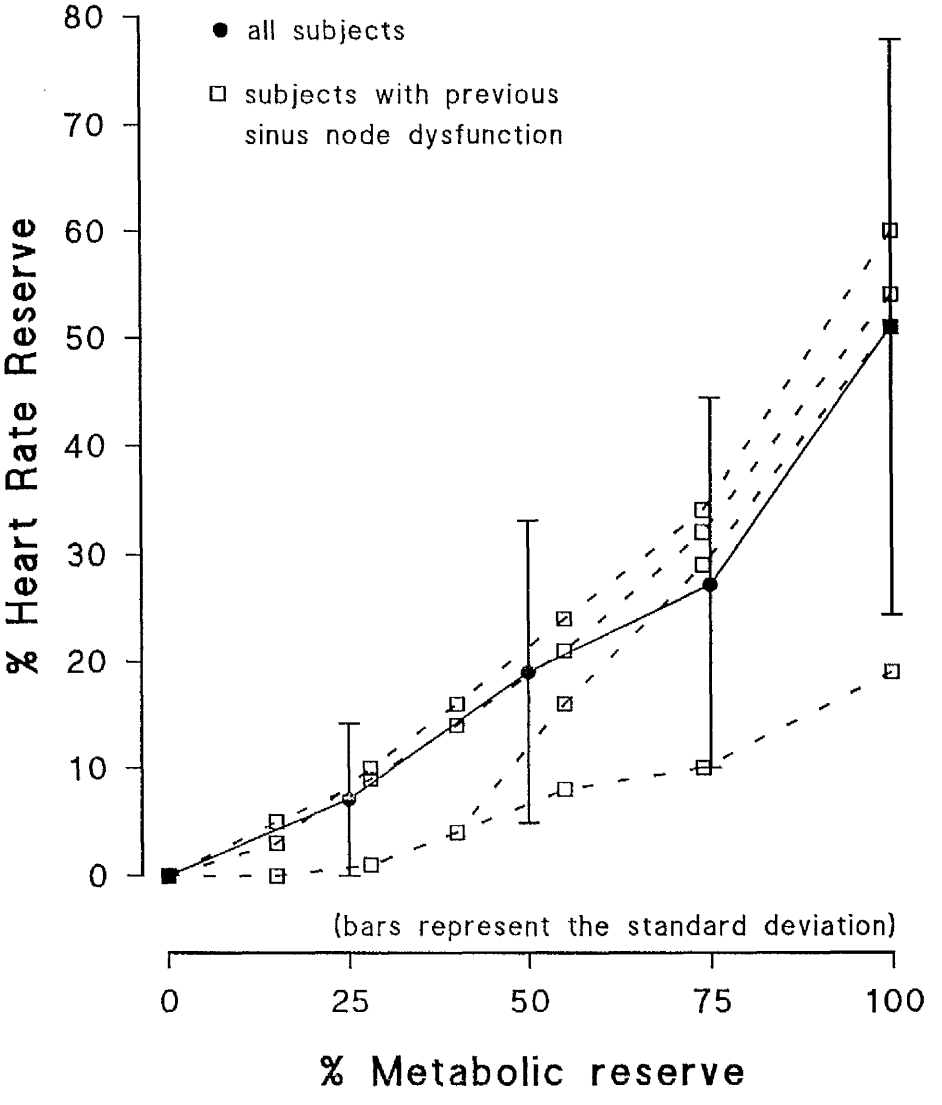


Figure 3.29: Minimum heart rates during ambulatory monitoring and time after transplantation

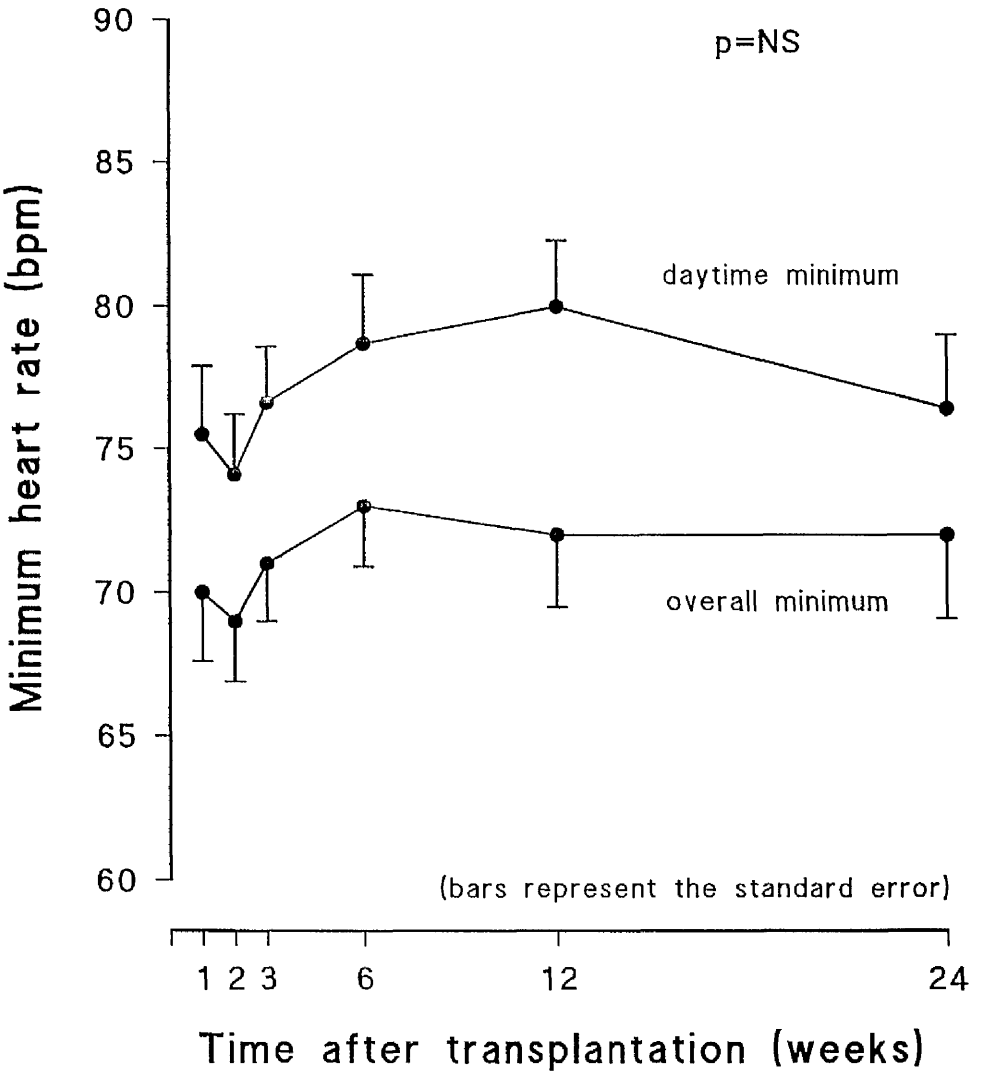


Figure 3.30: Mean heart rates during ambulatory monitoring and time after transplantation

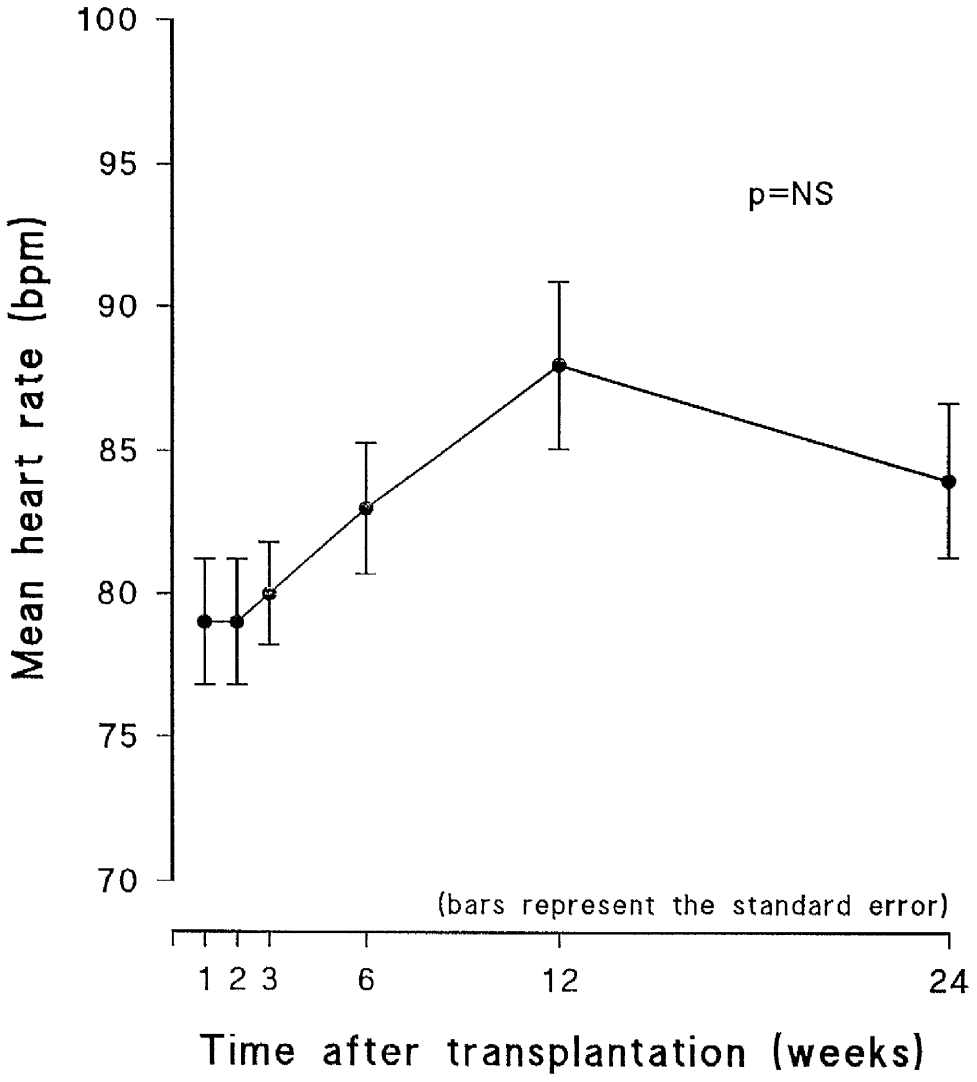


Figure 3.31: Correlation of minimum daytime heart rate during ambulatory monitoring and spontaneous cycle length at electrophysiological study

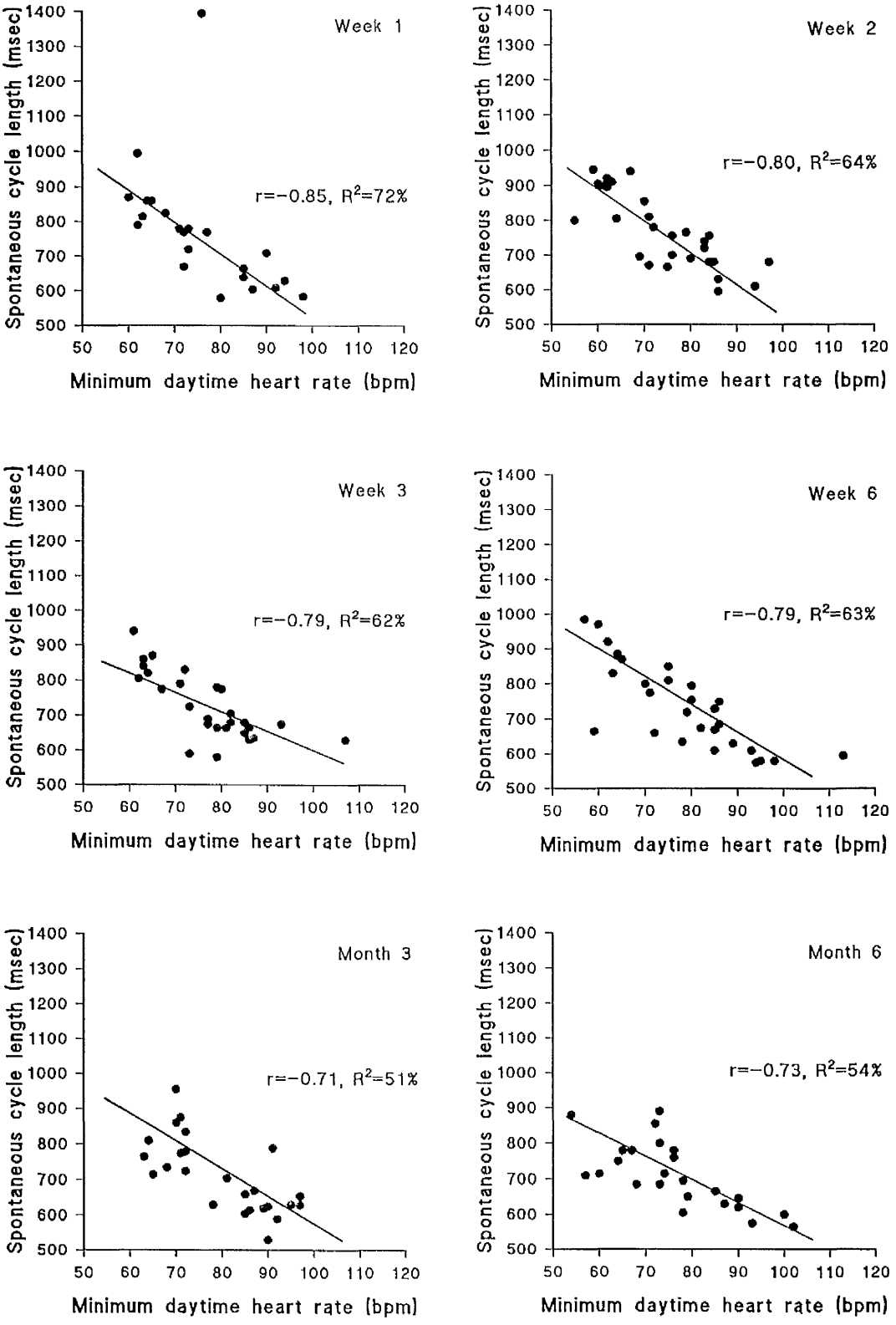


Figure 3.32: Correlation of mean heart rate during ambulatory monitoring and corrected maximal sinus node recovery time at electrophysiological study

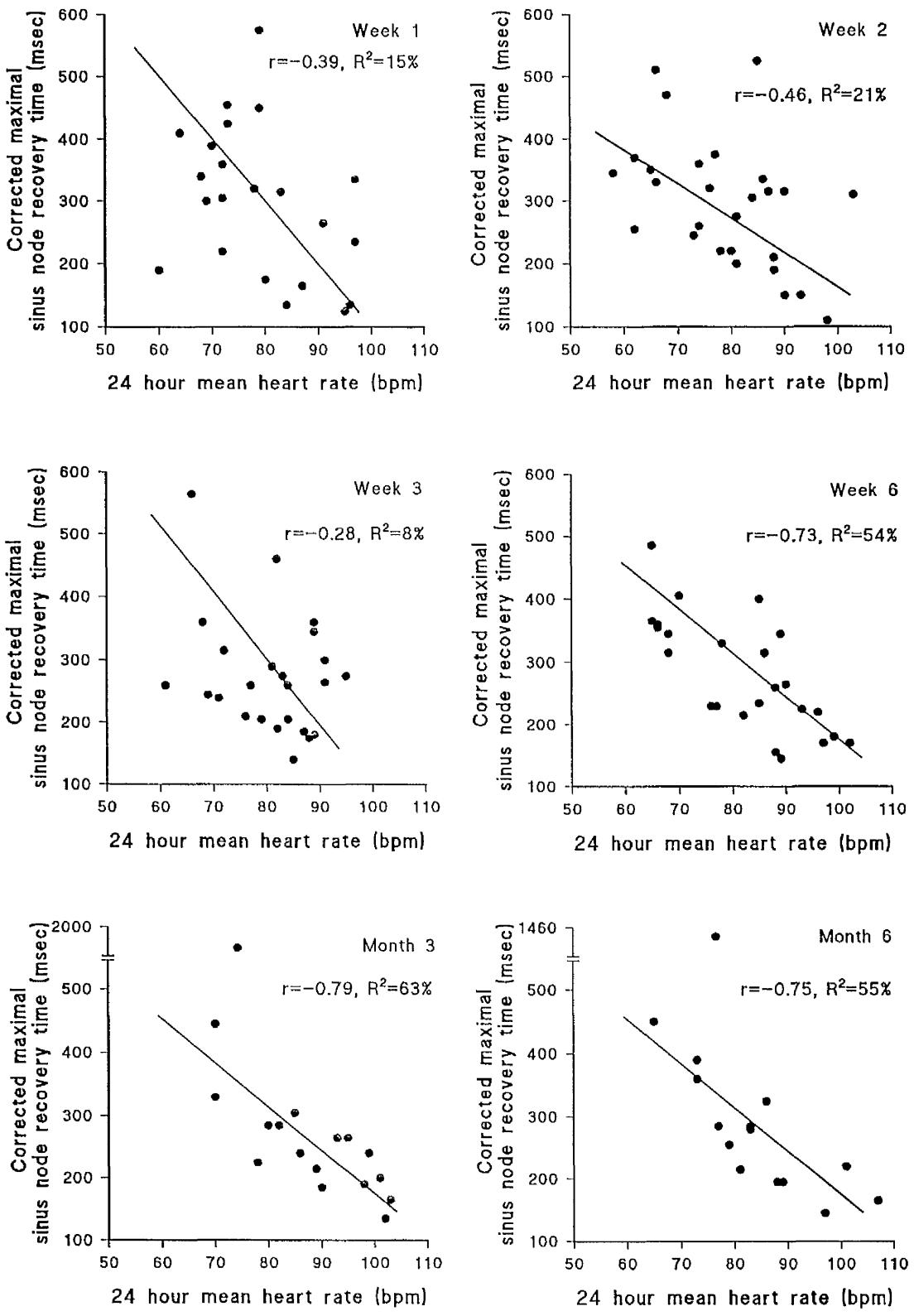
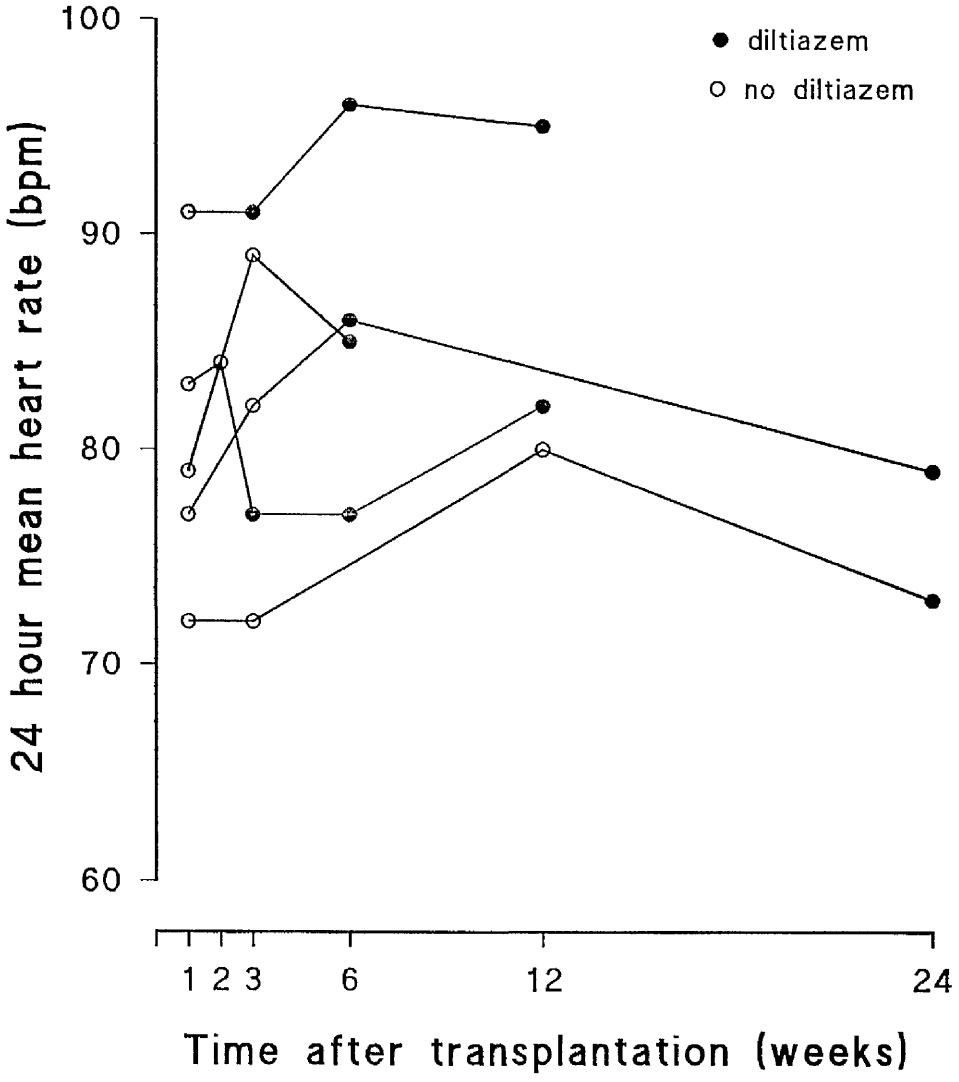


Figure 3.33: Mean heart rates during ambulatory monitoring and diltiazem treatment



CHAPTER 4

REPRODUCIBILITY OF ELECTROPHYSIOLOGICAL MEASUREMENTS IN TRANSPLANT RECIPIENTS

Introduction

In the normal innervated heart there is considerable variation in electrophysiological indices of sinus node function[Cinca 1986, Bergfeldt 1991]. Variation in atrioventricular node function indices is not as great[Cinca 1986, Bergfeldt 1991]but is nonetheless sufficient to be of importance.

The resulting poor reproducibility, particularly of sinus node function tests, has potential implications for their usefulness in the diagnosis of disease and for the significance of changes during serial studies. Variation in autonomic tone is a likely cause of the observed variation and pharmacological autonomic blockade has previously been shown to enhance the reproducibility of sinus node function tests[Alboni 1983].

The transplanted human heart is not subject to changes in direct autonomic tone. Thus the reproducibility of electrophysiological measurements may be improved and their clinical reliability enhanced. This hypothesis has not been tested in any previously published studies and the effects of variations in circulating catecholamines may be a confounding factor. This is the first study of the reproducibility of electrophysiological measurements of sinus and atrioventricular node function in the denervated transplanted human heart.

Methods

Six adult heart transplant recipients were studied at between 10 and 18 days after transplantation. Electrophysiological studies were repeated on five occasions at two hourly intervals over the course of single day between approximately 0900 and 1700. All subjects were studied in the supine position after resting for at least 15 minutes. A 1 1 studies were performed with a programmed stimulator delivering a constant voltage (square wave form) pulse of two msec duration standardised at twice diastolic threshold. Temporary epicardial pacing wires attached to the donor atrium (two pairs) and ventricle (one pair) at the time of transplantation were used for pacing and recording of electrograms. The surface ECG was monitored using standard lead I and chest lead V1. Signals were recorded using a Gould electrostatic recorder at a paper speed of 100mm per second and measurements were made to an accuracy of five msec.

The resting cycle length was calculated from the average of ten cycles prior to any other studies. Sinus node recovery time, sinoatrial conduction time, atrioventricular Wenckebach cycle length, effective refractory period of the atrioventricular conduction system and atrial refractory periods were measured using standard techniques as described in the previous chapter. Atrial and atrioventricular refractory periods were measured during sinus rhythm and at two different drive cycle lengths: 600 msec and 400 msec or 500 msec. Ventricular effective refractory periods were measured using single extrastimuli after eight beat drives at 600 msec and 400 msec.

Statistical analysis

The coefficients of variation (C_v) were calculated for each variable in each subject and the averages of all six coefficients of variation for each variable were calculated. The relative contributions of intra and inter subject variation to total variation were

calculated by analysis of variance. Changes in the mean of electrophysiologic variables between each study at progressively later times of the day were also assessed by one way analysis of variance.

Results

Sinus node function

No subject had abnormal sinus node function by standard criteria (corrected maximal sinus node recovery time >525msec). There were no significant changes in the mean of any of the indices of sinus node function over the course of the study. The mean and ranges of coefficients of variation and relative contributions of inter and intrasubject variation are shown in table 4.1.

Table 4.1: Reproducibility of electrophysiological indices of sinus node function

Variable	range of C_v	mean C_v	intersubject variation	intrasubject variation
Resting cycle length	<0.1% - 3.8%	1.7%	90%	10%
$CSNRT_{max}$	2.8% - 10.5%	5.9%	72%	28%
SACT	1.3% - 5.6%	3.3%	94%	6%

Key: $CSNRT_{max}$ - Corrected maximal sinus node recovery time
SACT - Sinoatrial conduction time
C_v - Coefficient of variation

Atrioventricular conduction

Measurement of the effective refractory period of the atrioventricular conducting system (AVERP) was frequently limited by longer atrial effective refractory period (AERP) or drive Wenckebach conduction. With a 600 msec drive AERP was greater

than AVERP in all studies in two subjects and four of five studies in another. Statistical analysis was restricted to the remaining three subjects in whom only one value was unobtainable. With a 400 msec or 500 msec drive AVERP was consistently measurable in four of six subjects. The Wenckebach cycle length was measurable in all studies.

The AVERP was normal by accepted criteria for AV node ERP (<450 msec with a 600 msec drive) on all occasions. The Wenckebach cycle length ranged from 380msec to 490 msec. There were no significant differences mean AVERP or Wenckebach cycle length over the course of the study. The mean and ranges of coefficients of variation and proportions of inter and intrasubject variation are shown in table 4.2.

Table 4.2: Reproducibility of indices of atrioventricular node function

Variable	range of C_v	mean C_v	intersubject variation	intrasubject variation
AVERP 600	1.6% - 5.2%	3.2%	<1%	100%
AVERP 400/500	1.3% - 2.7%	2%	74%	26%
Wenckebach cycle length	1% - 5.4%	2%	92%	8%

Key: AVERP - Effective refractory period of the atrioventricular conducting system
600,400,500 - drive cycle length in milliseconds.
C_v - Coefficient of variation.

The unusual distribution of the components of variation in AVERP with a 600 msec drive is a result of close similarity of the means: 336, 336 and 328 msec in the three subjects. This did not occur at the other cycle length.

Atrial and ventricular effective refractory periods

The reproducibility of atrial and ventricular effective refractory periods are detailed in table 4.3. There were no significant changes in these variables with time over the duration of the study.

Table 4.3: Reproducibility of atrial and ventricular effective refractory periods

Variable	range of C_v	mean C_v	intersubject variation	intrasubject variation
AERP 600	2.3% - 5.5%	3.6%	91%	9%
AERP 400	2.1% - 4.3%	3.2%	93%	7%
VERP 600	1.6% - 4.1%	2.4%	95%	5%
VERP 400	1.8% - 4.6%	3%	92%	8%

Key: AERP - atrial effective refractory period
VERP - ventricular effective refractory period
600, 400 - drive cycle length in milliseconds
C_v - Coefficient of variation

Discussion

Sinus node function

The most comprehensive study of variability of electrophysiological measurements in the innervated heart to date was undertaken by Cinca and colleagues[1986] who performed 10 to 15 measurements over a 24 hour period in 12 subjects. Most of these patients were undergoing electrophysiological study for assessment of supraventricular tachycardia. The reported mean coefficients of variation were 10.4% for resting cycle length, 32.5% for corrected sinus node recovery times and 46.8% for corrected maximal sinus node recovery time ($CSNRT_{max}$). These compare with 1.7% for resting cycle length and 5.9% for $CSNRT_{max}$ in the current study of denervated transplanted hearts. Cinca and colleagues[1986]included nocturnal electrophysiological measurements which increased the variation compared with daytime studies alone. This effect was quite marked with the resting cycle length. A zenith was observed between midnight and 04.00 but there was no clear pattern for $CSNRT_{max}$. It is unlikely to account for the large differences from the current study and nocturnal variations in electrophysiological measurements are unlikely to affect their reliability in normal clinical practice. The observations in normal subjects are probably explained by enhanced vagal tone at night which would be absent in transplant recipients.

Other investigators have also studied the reproducibility of sinus node function tests but although they have studied considerable numbers of patients most have only undertaken two studies in each subject with consequent limited statistical analysis. Bergfeldt and colleagues[1991] reported longer term reproducibility in 10 subjects studied on two occasions several weeks apart. The coefficients of variation were 6% for resting cycle length and 33% for $CSNRT_{max}$. Jewell and colleagues[1980]studied 16 subjects on two occasions but their analysis was restricted to comparing mean values in all subjects

and does not adequately describe the intrasubject variation. De Marneffe and colleagues[1986]reported mean percentage changes (not equivalent to the coefficient of variation) of 7.3% and 24.4% in resting heart rate and corrected maximal sinus node recovery time between two studies in 50 subjects.

Alboni and colleagues[1983] studied reproducibility of sinus node function tests after pharmacological autonomic blockade. Two studies were performed in 15 subjects both before and after autonomic blockade. The mean percentage change in resting cycle length was 12.6% before and 2.9% after autonomic blockade. The corresponding changes in $CSNRT_{max}$ were 30.5% and 7.7%. Although these crude indices of variation are not directly comparable with the coefficients of variation quoted above the results of pharmacological studies are probably similar to those in denervated transplanted hearts.

Atrioventricular conduction

A limitation of this study as regards atrioventricular conduction measurements was the absence of His bundle recordings. Thus AV nodal refractory periods could not be reliably separated from those of the more distal parts of the AV conducting system. However, as discussed in chapter 3, this is unlikely to have led to significant errors as His bundle ERP rarely exceeds nodal ERP in normal subjects[Akhtar 1975] and there are no reports of this occurring in transplant recipients.

In the current study the coefficients of variation in atrioventricular ERP of between 2% and 3.2% depending on the drive cycle length are also substantially lower than the 8.3% and 12% reported by Cinca[1986]and Bergfeldt[1991] respectively in innervated hearts. The variation in Wenckebach cycle length of 2% compares with 7% reported by Bergfeldt[1991]; Cinca and colleagues[1986] did not measure Wenckebach cycle

length. Reddy and colleagues[1975] also measured AV node function on two occasions in 22 subjects but the statistical analysis was inadequate to assess reproducibility.

The distribution of variation of atrioventricular effective refractory period at a drive cycle length of 600 msec is unusual. This is probably due to serendipitous close approximation of the mean values in the limited number of subjects for whom a full set of data was available.

Atrial and ventricular refractory periods

The reproducibility of ventricular effective refractory periods in innervated hearts has previously been shown to be good. Cinca and colleagues[1986] reported a 3.3% coefficient of variation and Olsson and colleagues[1977] produced similar results albeit with less satisfactory study numbers and analysis. The variation in the current study of between 2.4% and 3% is very similar. Atrial effective refractory periods have also been readily reproducible in innervated hearts with a reported coefficient of variation of 5.5%[Cinca 1986] compared with between 3.2% and 3.6% in the current study.

Conclusion

This study has confirmed that the reproducibility of electrophysiological measurements of sinus and atrioventricular node function in the transplanted heart is much greater than in the innervated heart. The effect is more striking on the indices of sinus node function which have greater variability in the normal heart. Measurements of atrial and ventricular effective refractory periods are very reproducible in both normal and transplanted hearts. The results of previous studies using pharmacological autonomic blockade are similar to the current study suggesting that autonomic denervation is primarily responsible for the improved reproducibility of electrophysiological

measurements in the transplanted human heart.

The consistent dominance of intersubject over intrasubject variation in this study suggests that the clinical reliability of electrophysiological measurements in transplant recipients is good. This increases the likelihood that changes observed in serial studies are genuine rather than due to random variation.

CHAPTER 5

THE EFFECTS OF PREOPERATIVE AMIODARONE TREATMENT AFTER HEART TRANSPLANTATION

Introduction

Amiodarone is a highly effective antiarrhythmic agent[Heger 1981, Neri 1987] with little or no negative inotropic action[Cleland 1987, Hamer 1989]. As a consequence it is particularly suitable for patients with end-stage cardiac disease awaiting transplantation.

However, its unusually large volume of distribution and high lipid affinity result in very slow elimination from the body after discontinuation of therapy[Holt 1983]. The possibility of redistribution of amiodarone from extracardiac stores to the (amiodarone free) transplanted heart thus arises. Previous studies[Cameron 1988, Macdonald 1991, Chelimsky-Fallick 1992, Heinz 1992a] have suggested that preoperative amiodarone does affect the transplanted heart. These observations however, have been limited to indirect or imprecise measurements such as the duration atrial pacing required after transplantation and isolated measurements of resting heart rate.

The aim of this study is to examine in detail, the cardiac electrophysiological effects of preoperative amiodarone after transplantation. A further aim is to determine the pharmacokinetics of amiodarone in these subjects and to correlate electrophysiological effects with serum and tissue concentrations of amiodarone and its active metabolite desethylamiodarone. No existing studies directly correlate tissue levels of amiodarone with its electrophysiological effects in humans. The availability of cardiac tissue in transplant recipients afforded by a programme of surveillance endomyocardial biopsies provides a unique opportunity to undertake such a study.

Methods

Eleven of the 40 subjects recruited for the study of sinus and atrioventricular node function described in chapter 3 had received preoperative amiodarone therapy. The daily dose and duration of treatment were recorded and a cumulative dose calculated.

Electrophysiology

Sinus and atrioventricular node function were assessed by electrophysiological techniques on six occasions as part of the previous study described in chapter 3 (one, two, three and six weeks, three and six months after transplantation).

In four subjects who had received preoperative amiodarone and five transplant recipients who had not, the ventricular effective refractory period was also measured. Temporary epicardial ventricular pacing wires were employed for the first three studies at one, two and three weeks after transplantation. Thereafter a single quadripolar electrode catheter was introduced via the right internal jugular vein and placed in the right ventricular apex using fluoroscopy. Programmed stimulation was carried out using a constant voltage source (square wave form) at twice diastolic threshold. The ventricular effective refractory period (VERP) was defined as the maximum interval between an eight beat drive and an extrastimulus which fails to evoke a ventricular response[Josephson 1979]. The VERP was measured at 600 and 400msec drive cycle lengths on each occasion.

Amiodarone assays

Tissue and serum levels of amiodarone and desethylamiodarone were measured on six occasions in six of eleven subjects who had received preoperative amiodarone treatment.

Venous blood was drawn immediately prior to each electrophysiological study. It was placed in lithium heparin tubes, centrifuged and frozen at -30°C for storage. Endomyocardial biopsy specimens were taken on the day of electrophysiological study one, two and three weeks after transplantation. In later studies they were taken immediately prior to electrophysiological study. Specimens were snap frozen in liquid nitrogen and stored in liquid nitrogen for subsequent analysis.

The concentrations of amiodarone and desethylamiodarone were measured in cardiac tissue and serum samples by high performance liquid chromatography. The details of this method have been previously described[Hutchings 1986]. No sample was stored for more than six months before analysis.

Statistical analysis

The relationship between sinus node dysfunction and amiodarone therapy was assessed using Fisher's exact test. Comparisons of patient characteristics and electrophysiological measurements between subjects who had and had not received preoperative amiodarone were made using the Mann-Whitney U test. The relationship between concentrations of amiodarone and desethylamiodarone and electrophysiological variables was examined by linear correlation analysis. Results are expressed as mean $\pm$ one standard deviation unless otherwise indicated.

Results

Subject characteristics

There were no significant differences in donor or recipient ages between those patients who had received preoperative amiodarone and those who had not. The mean donor ages were 38±10 and 34±11 years and respectively. The mean recipient ages were 46±13 and 48±9 years. The operative ischaemic time in subjects who received amiodarone was 170±56 minutes compared with 183±49 minutes in the remainder ($p=0.48$).

All subjects who had taken preoperative amiodarone were taking amiodarone immediately before transplantation. The daily dose of preoperative amiodarone ranged from 200mg to 800mg. Treatment had been continued for between four and 60 preoperative months. The cumulative dose of preoperative amiodarone ranged from 24g to 360g with a mean of 138±122g. In the six subjects in whom serum and tissue levels were subsequently measured it ranged from 24g to 216g with a mean of 82±72g.

Sinus node function

Preoperative amiodarone treatment was not associated with sinus node dysfunction after transplantation. Sinus node function was abnormal by standard electrophysiological criteria (corrected maximal sinus node recovery time >525msec or sinoatrial conduction time >250msec) on at least one occasion in one of 11 subjects who received preoperative amiodarone compared with six of 29 subjects who did not ($p=0.69$). The subjects with abnormal sinus node function were excluded from the subsequent analyses.

The average resting cycle length was significantly longer in subjects who had received preoperative amiodarone treatment compared with the remainder throughout the

first three months of the study (figure 5.1). Figure 5.2 illustrates the changes in 24 hour minimum heart rate during ambulatory monitoring. Although the mean minimum rate was consistently lower in amiodarone treated subjects the differences were much smaller and did not achieve statistical significance at any time. The differences in 24 hour mean heart rates were greater and were significant at two and six weeks after transplantation. The mean corrected maximal sinus node recovery times were also longer in amiodarone treated subjects but the difference was only significant from two to six weeks after operation (figure 5.4). Figure 5.5 illustrates changes in sinoatrial conduction time. There were no significant differences at any stage.

Atrioventricular node function

In subjects who had received preoperative amiodarone the Wenckebach cycle length increased over the first three weeks after transplantation, during which time it decreased in other subjects. This resulted in significant differences at two, three and six weeks after transplantation. Thereafter Wenckebach cycle length decreased again in the amiodarone treated group with no further changes in the remainder (figure 5.6).

The measurement of the ERP of the atrioventricular conducting system (AVERP) was as previously noted frequently limited by atrial refractoriness. With a drive cycle length of 600msec the atrial ERP was longer than AVERP during 63% of studies in subjects treated with preoperative amiodarone and 75% of other subjects. The corresponding proportions with a 400msec drive were 64% for amiodarone subjects and 48% for others.

Figure 5.7 illustrates the changes in AVERP over time. The mean AVERP was generally longer in subjects who had received preoperative amiodarone although the difference was only significant three weeks after transplantation with a 600msec drive.

Atrial and ventricular refractory periods

Changes in atrial effective refractory periods in subjects who received and did not receive preoperative amiodarone are shown in figure 5.8. The atrial ERP was again consistently longer in the amiodarone group although the difference did not achieve statistical significance. The measurement of ventricular effective refractory periods in a small number of subjects (four amiodarone, five others) produced very similar findings although the difference achieved statistical significance on one occasion (figure 5.9).

Amiodarone and Desethylamiodarone levels in tissue and serum

Amiodarone was detectable in both serum and endomyocardial biopsy specimens in all subjects from the first week until at least three months after transplantation. The active metabolite desethylamiodarone was also readily detectable from the first week until at least six weeks in all subjects. Figure 5.10 illustrates the changes in mean serum levels and figure 5.11 the changes in mean cardiac concentrations with time after transplantation. The pattern of changes over time is different with peak mean serum levels at three weeks but peak mean tissue levels in the first week after transplantation.

The pattern of individual changes in serum and tissue levels of amiodarone and desethylamiodarone over time was quite variable. Figures 5.12 and 5.13 illustrate the individual changes in serum and cardiac amiodarone concentrations. Figures 5.14 and 5.15 illustrate the corresponding changes in desethylamiodarone concentrations.

Correlation of preoperative dose and serum and tissue levels

There was no identifiable relationship between cumulative dose of preoperative amiodarone and peak or mean serum levels of amiodarone or desethylamiodarone. Similarly there was no relationship between dose and peak or mean tissue levels of

amiodarone or desethylamiodarone. The highest cardiac levels of amiodarone and desethylamiodarone were recorded in subjects who had received cumulative doses of only 24g and 36g respectively.

Correlation of amiodarone levels and electrophysiological effects

There was no demonstrable relationship between serum levels of amiodarone or desethylamiodarone and any electrophysiological variable measured: corrected maximal sinus node recovery time, sinoatrial conduction time, resting cycle length, Wenckebach cycle length, AV, atrial and ventricular ERP. The correlation coefficients ranged from -0.12 to 0.41 (R^2 from 2% to 17%).

The most consistent relationship between cardiac concentrations of amiodarone and desethylamiodarone and electrophysiological measurements was with ventricular ERP. Figures 5.16 and 5.17 illustrate the relationship between ventricular effective refractory periods and cardiac amiodarone and desethylamiodarone concentrations respectively. Although the individual data points in these regression analyses are not independent the separate analyses at each time point were limited by small numbers of data points. There were no significant changes in ventricular ERP over time in subjects who did not receive preoperative amiodarone which lends further credibility to this analysis. The individual correlation coefficients for ventricular ERP are shown in table 5.1. Correlation of atrial ERP and tissue amiodarone and desethylamiodarone concentrations revealed weak associations with overall r values between 0.5 and 0.6 (R^2 between 25% and 36%). Individual analyses at separate time points were again limited by small amounts of data with r ranging from -0.81 to 0.98 (R^2 from less than 1% to 96%).

Table 5.1: Correlation coefficients between ventricular effective refractory periods and cardiac levels of amiodarone and desethylamiodarone.

Time after transplantation	VERP 600 vs amiodarone	VERP 400 vs amiodarone	VERP 600 vs desethyl-amiodarone	VERP 400 vs desethyl-amiodarone
Week 1	0.99	0.99	0.93	0.94
Week 2	0.36	0.14	-0.16	-0.39
Week 3	2 points only	2 points only	2 points only	2 points only
Week 6	0.74	0.61	0.88	0.79
Month 3	0.99	0.96	0.99	0.97
Month 6	0.98	-0.51	0.93	-0.71
Overall	0.84 R^2=70%	0.70 R^2=50%	0.81 R^2=66%	0.63 R^2=40%

Key: VERP= ventricular effective refractory period, 600= 600msec drive, 400= 400 msec drive,

There were no direct correlations between cardiac amiodarone levels and other electrophysiological variables measured: sinus node recovery time, sinoatrial conduction time, resting sinus cycle length and Wenckebach cycle length (r ranged from 0.07 to 0.33, R^2 from less than 1% to 11%). A weak correlation was identified between cardiac desethylamiodarone concentrations and Wenckebach cycle length. The overall correlation coefficient was 0.55, R^2 30%. Separate analyses at individual time points revealed correlation coefficients between 0.04 and 0.95 (R^2 between less than 1% and 90%). A similar weak correlation was identified between cardiac desethylamiodarone concentration and resting sinus cycle length (overall r=0.57, R^2 33% separate analysis: r ranged from 0.16 to 0.74, R^2 3% to 56%).

The effects of amiodarone on the chronotropic response to exercise

As would be anticipated from the electrophysiological and ambulatory monitoring data the resting heart rate was significantly slower in subjects treated with preoperative amiodarone three and six weeks after transplantation (figure 5.18). The peak heart rate exhibits a similar pattern (figure 5.18) but when the chronotropic response is analysed as percentage of heart rate reserve used at peak exercise it is clear that preoperative amiodarone does not significantly effect the exercise response (figure 5.19).

Discussion

The pharmacokinetics of preoperative amiodarone after transplantation

This study has confirmed previous suspicions[Cameron 1988, Macdonald 1991] that amiodarone, taken preoperatively, is subsequently redistributed to the transplanted heart.

Serum concentrations of amiodarone for the first three weeks of this study (around 1 ug/ml) were comparable with those measured in subjects taking regular amiodarone[Holt 1983, Mitchell 1989]. In one subject similar levels were maintained until the third postoperative month. The serum concentrations of the active metabolite desethylamiodarone were consistently higher than those of the parent compound in all subjects. This is consistent with the report by Bandyopadhyay and colleagues[1987]that desethylamiodarone concentrations were higher in subjects who had discontinued therapy. This may also be true of subjects taking long term amiodarone[Barbieri 1986].

For the first three months after transplantation myocardial levels of amiodarone in this study (10 to 20 ug/g) were also directly comparable with those reported in subjects taking regular amiodarone[Barbieri 1986, Giardina 1990]. Myocardial desethylamiodarone concentrations were consistently higher than amiodarone concentrations and comparable with previous reports of subjects taking regular amiodarone[Barbieri 1986, Giardina 1990]. Desethylamiodarone was more persistent, remaining detectable in myocardium throughout the whole of the six month study period in all subjects but one.

The lack of any relationship between duration of therapy or cumulative dose of amiodarone and subsequent tissue or serum levels in this study is consistent with a previous report in other subjects[Giardina 1990].

Electrophysiological effects

The effects observed in this study of preoperative amiodarone on the transplanted heart are very similar to the previously reported electrophysiological effects of amiodarone[Touboul 1979, Mitchell 1989]. Resting cycle length, corrected maximal sinus node recovery time and Wenckebach cycle length were significantly prolonged compared with subjects who had not received amiodarone. There was no demonstrable effect on sinoatrial conduction time. Atrioventricular, atrial and ventricular effective refractory periods were also consistently longer in subjects who had taken preoperative amiodarone but the differences did not achieve statistical significance. The differences in minimum heart rate during 24 hour ambulatory monitoring between amiodarone treated subjects and others were noticeably smaller than those in resting cycle length and 24 hour mean heart rates. This may relate to the anti-adrenergic effects of amiodarone[Polster 1976] which may result in more depression of higher rather than lower heart rates. There was, however, no demonstrable effect of amiodarone on exercise capacity. This is in keeping with a previous study [Cleland 1987] which showed slower resting heart rates but no impairment of exercise capacity in non-transplant patients taking amiodarone.

The time course of these changes was generally compatible with the observed changes in myocardial drug concentrations. However the differences in several electrophysiological parameters were not significant until two weeks after transplantation despite higher tissue levels at one week. The reason for this is unclear. Serum levels of amiodarone continued to increase throughout the first three weeks in some subjects but there was no correlation between serum levels and electrophysiological effects.

Despite the demonstrable electrophysiological effects of preoperative amiodarone there is no evidence from this or any other study[Cameron 1988, Macdonald 1991, Chelimsky-Fallick 1992, Heinz 1992a]that clinically significant bradyarrhythmias result.

Correlation of cardiac drug levels and electrophysiological effects

This is the first study which has reported simultaneous results of electrophysiological studies and cardiac amiodarone and desethylamiodarone concentrations. Despite the small number of subjects we have demonstrated a clear linear correlation between ventricular ERP and amiodarone concentration. A less consistent relationship was found with atrial ERP. The lack of a direct relationship between amiodarone or desethylamiodarone concentrations and other electrophysiological variables despite clear evidence of the effects of amiodarone is probably due to unpredictable individual dose responses.

Conclusions

Amiodarone is rapidly redistributed from extracardiac stores to the transplanted heart in subjects who received preoperative treatment. For the first three to six weeks serum levels of amiodarone and desethylamiodarone are directly comparable with those reported in other subjects taking regular oral amiodarone. Myocardial amiodarone concentrations remain at comparable levels for three months and myocardial desethylamiodarone persists for at least six months after discontinuation of therapy. Cardiac levels of amiodarone are independent of the duration of prior treatment and of cumulative dose.

Preoperative amiodarone treatment has significant electrophysiological effects after transplantation. These effects are directly comparable with those reported in non-transplant subjects receiving conventional oral treatment. The time course of changes in electrophysiological effects is generally compatible with measured cardiac drug levels although the first week may be an exception.

Cardiac amiodarone and desethylamiodarone concentrations were strongly correlated with ventricular ERP and to a lesser degree with atrial ERP. There was no correlation with other electrophysiological variables despite clear evidence of the effects of preoperative amiodarone.

Figure 5.1: Changes in resting cycle length and preoperative amiodarone treatment

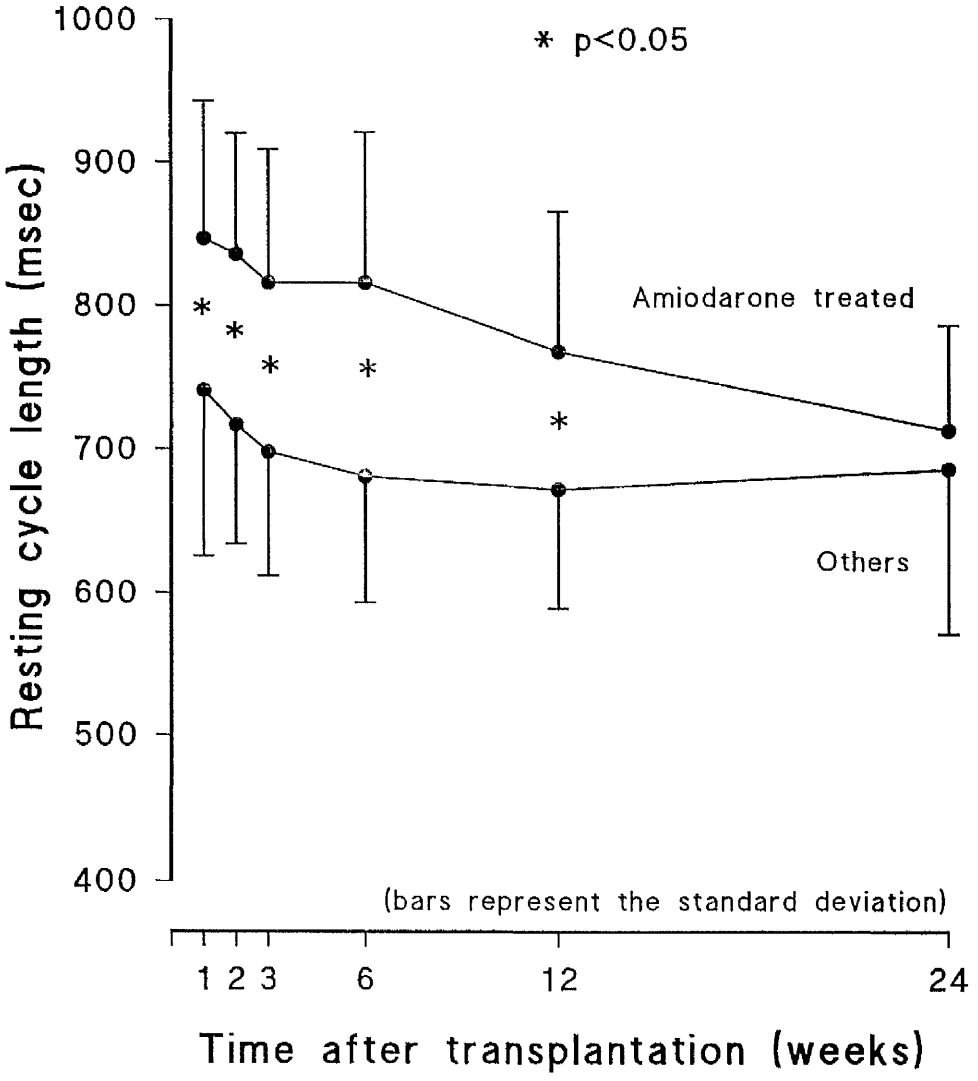


Figure 5.2: Minimum heart rate during ambulatory monitoring and preoperative amiodarone treatment

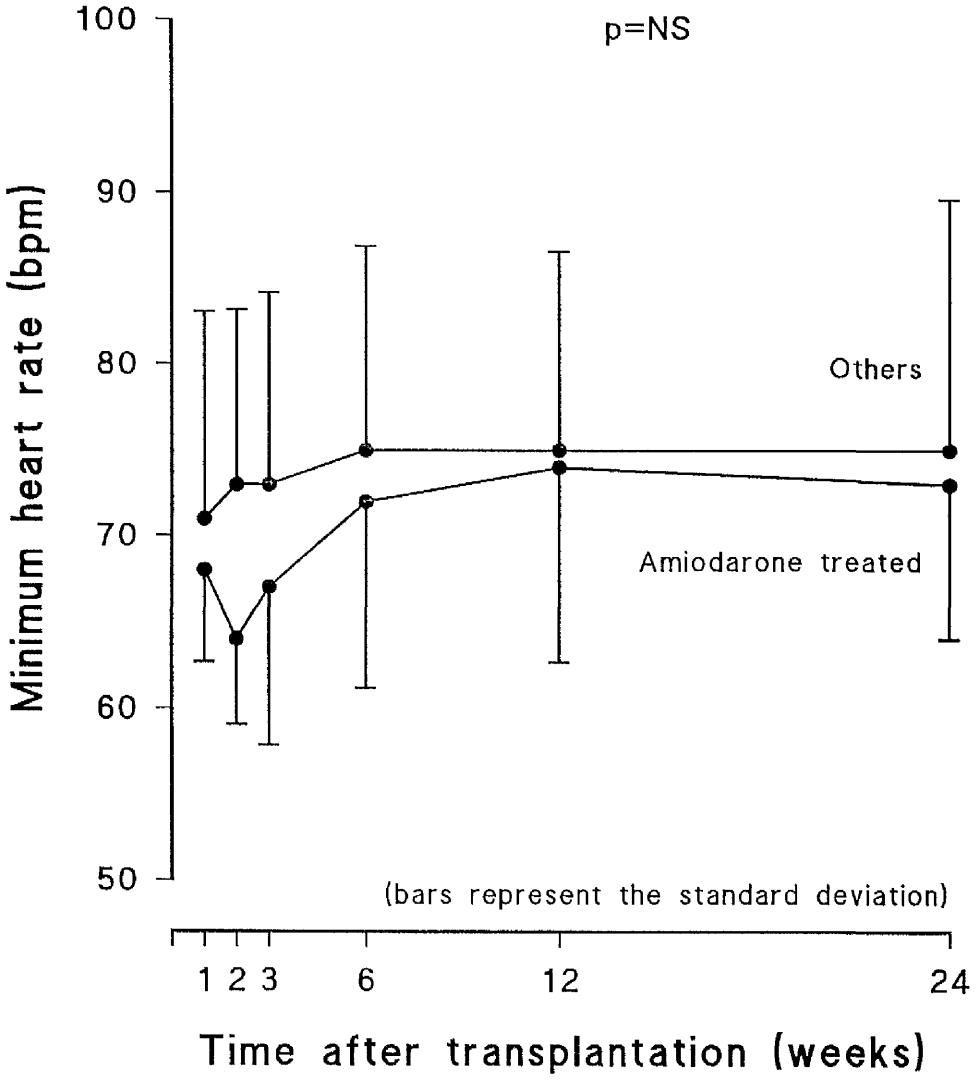


Figure 5.3: Mean heart rate during ambulatory monitoring and preoperative amiodarone treatment

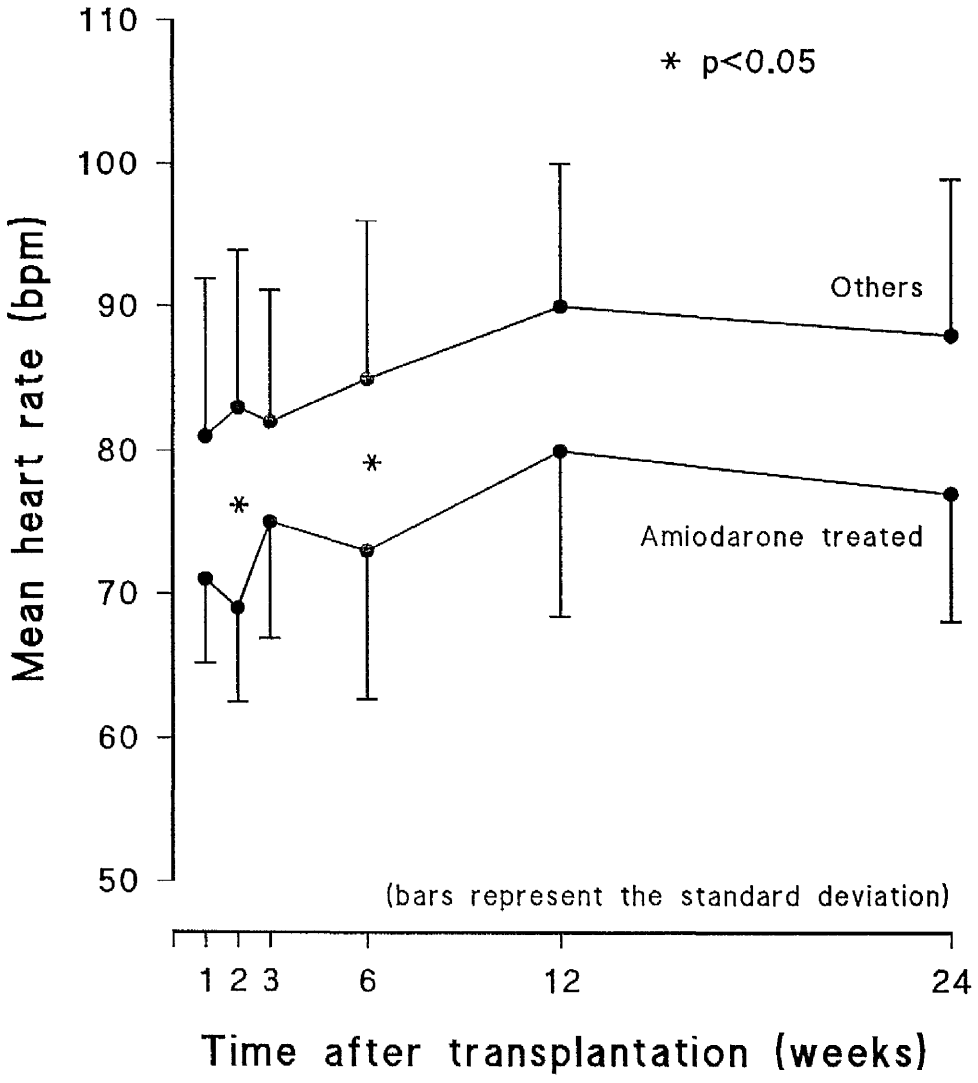


Figure 5.4: Changes in sinus node recovery time and preoperative amiodarone treatment

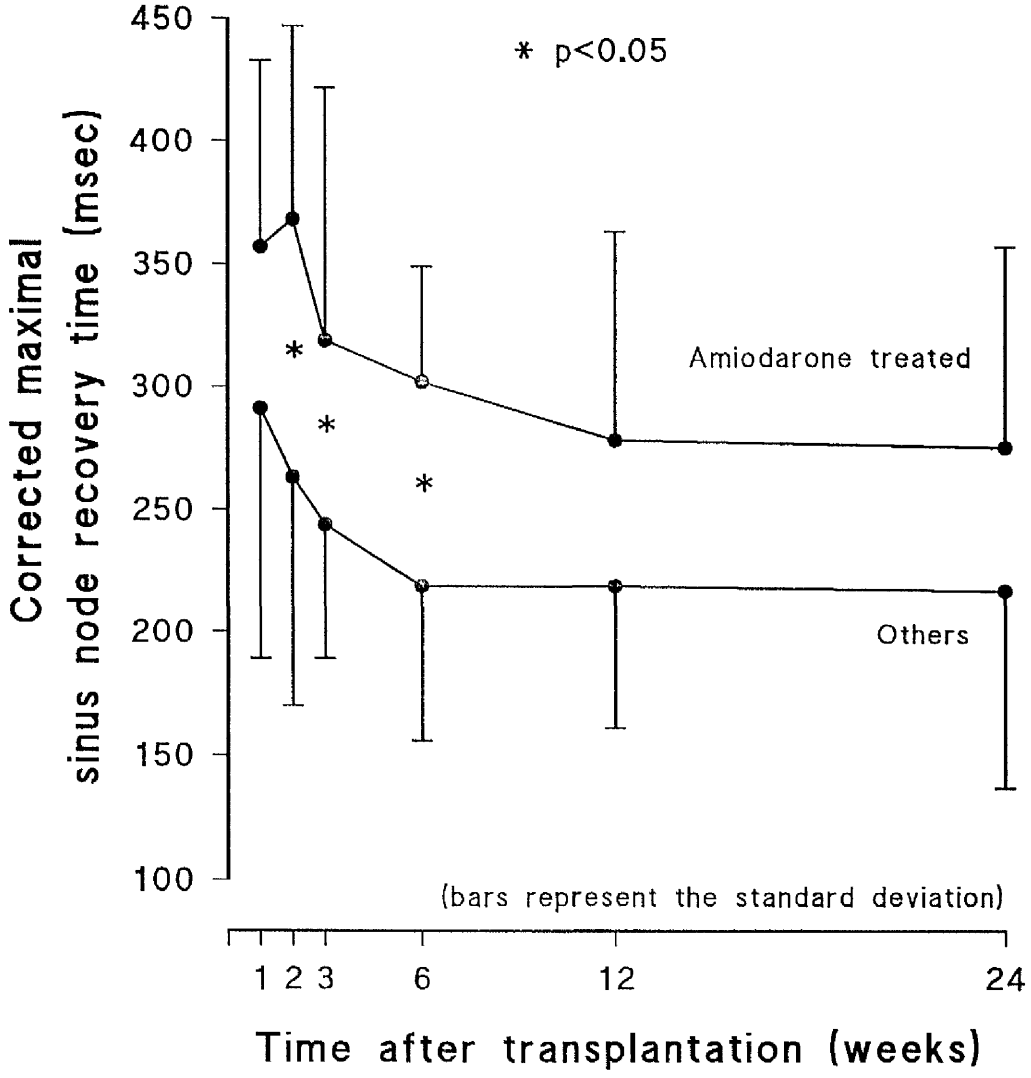


Figure 5.5: Changes in sinoatrial conduction time and preoperative amiodarone treatment

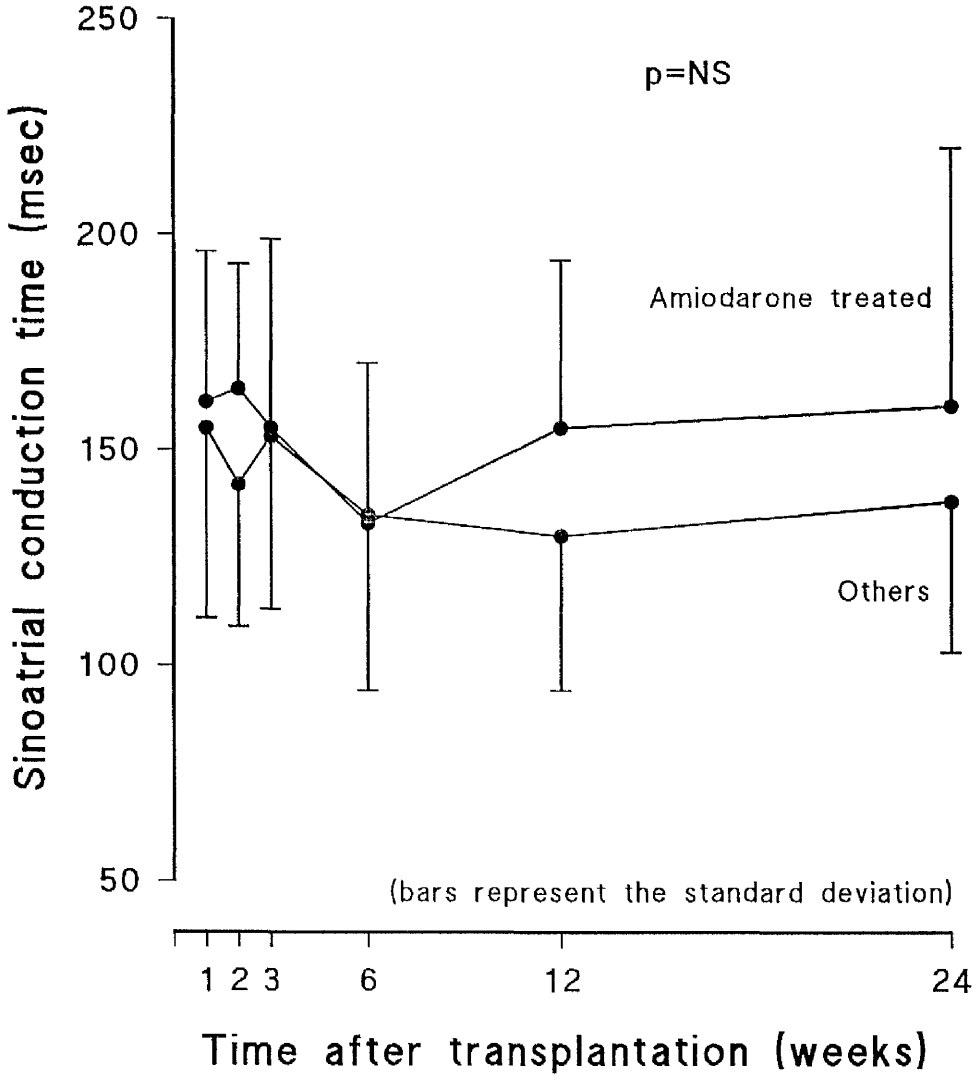


Figure 5.6: Changes in Wenckebach cycle length and preoperative amiodarone treatment

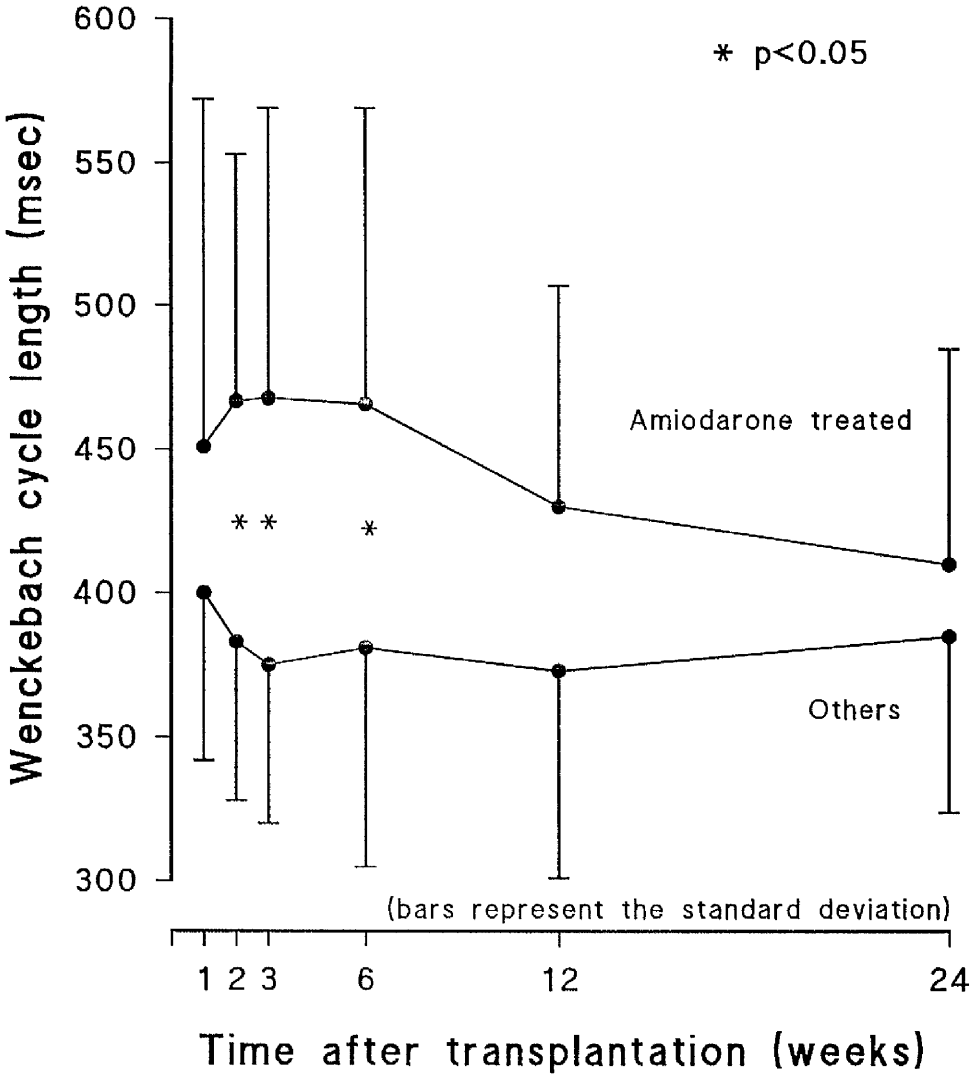


Figure 5.7: Changes in AV effective refractory period and preoperative amiodarone treatment

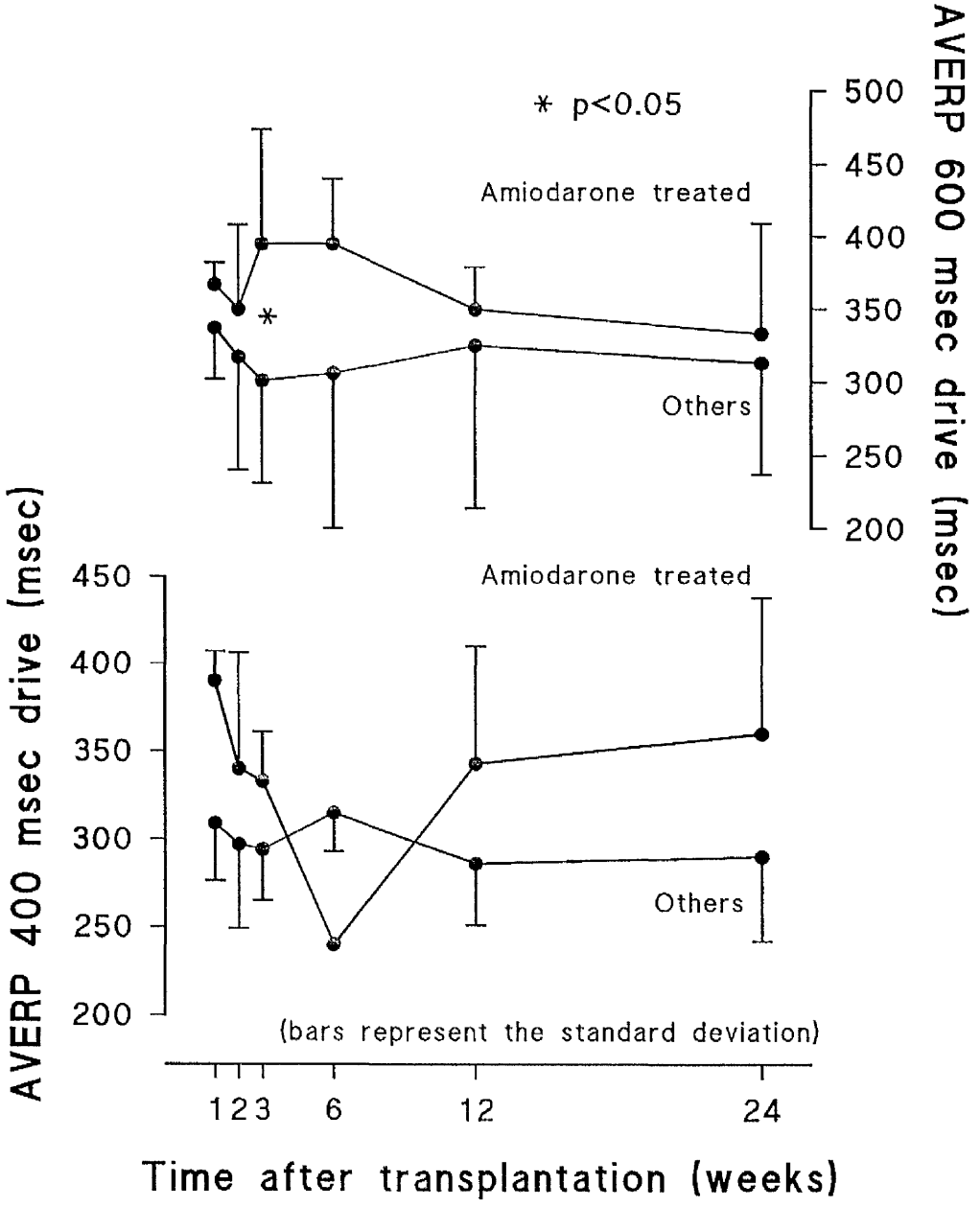


Figure 5.8: Changes in atrial effective refractory period and preoperative amiodarone treatment

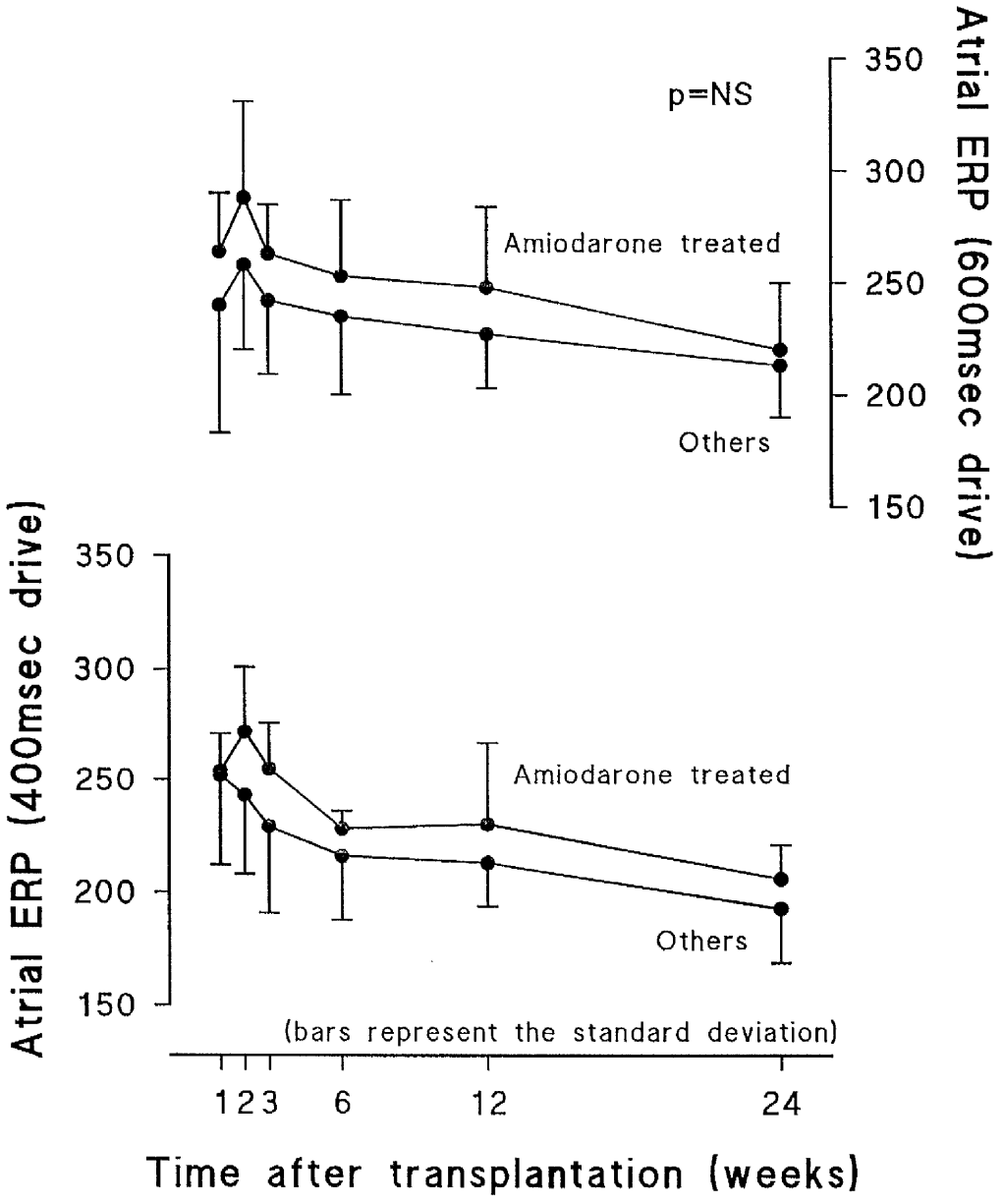


Figure 5.9: Changes in ventricular effective refractory period and preoperative amiodarone treatment

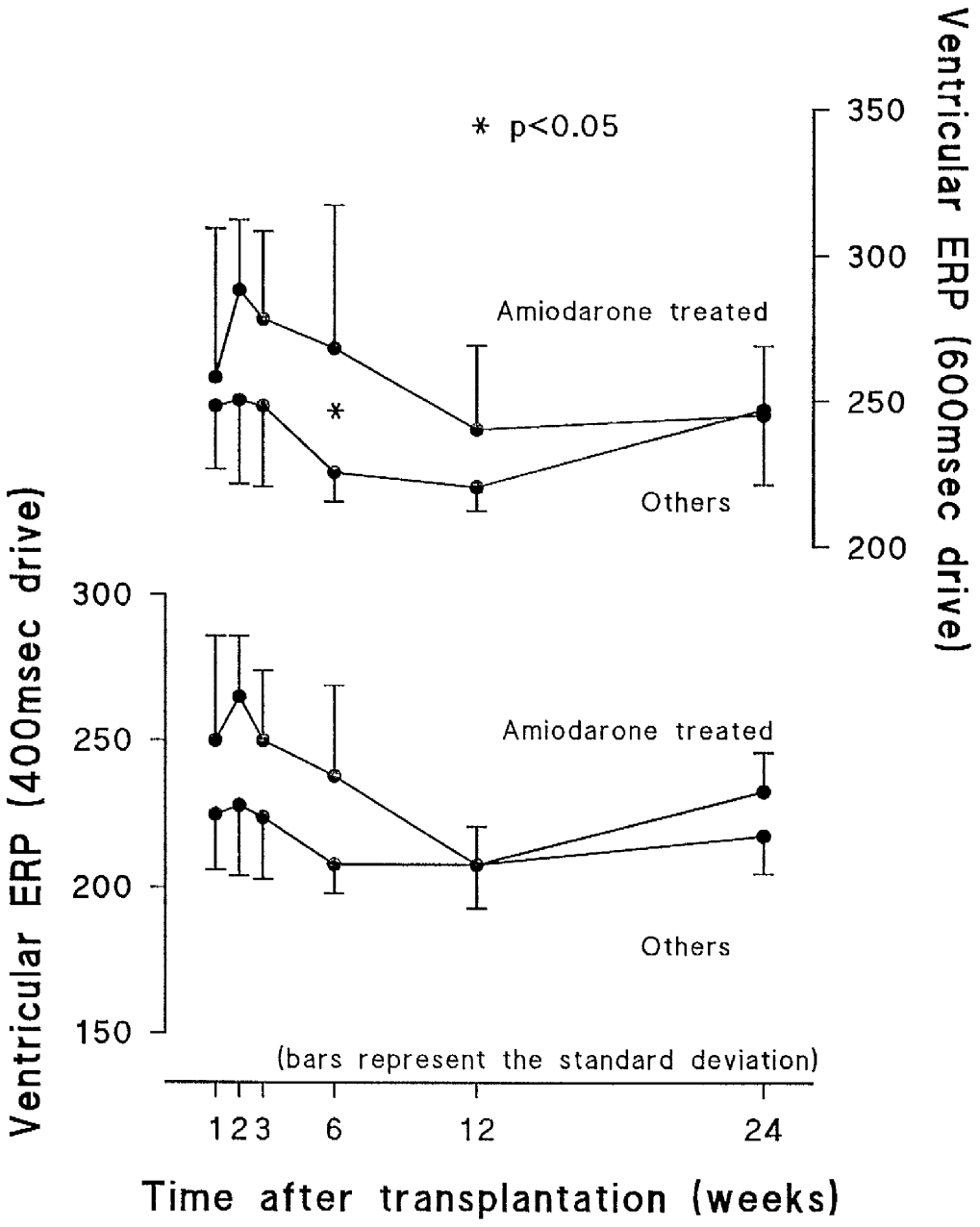


Figure 5.10: Serum amiodarone and desethylamiodarone concentrations and time after transplantation

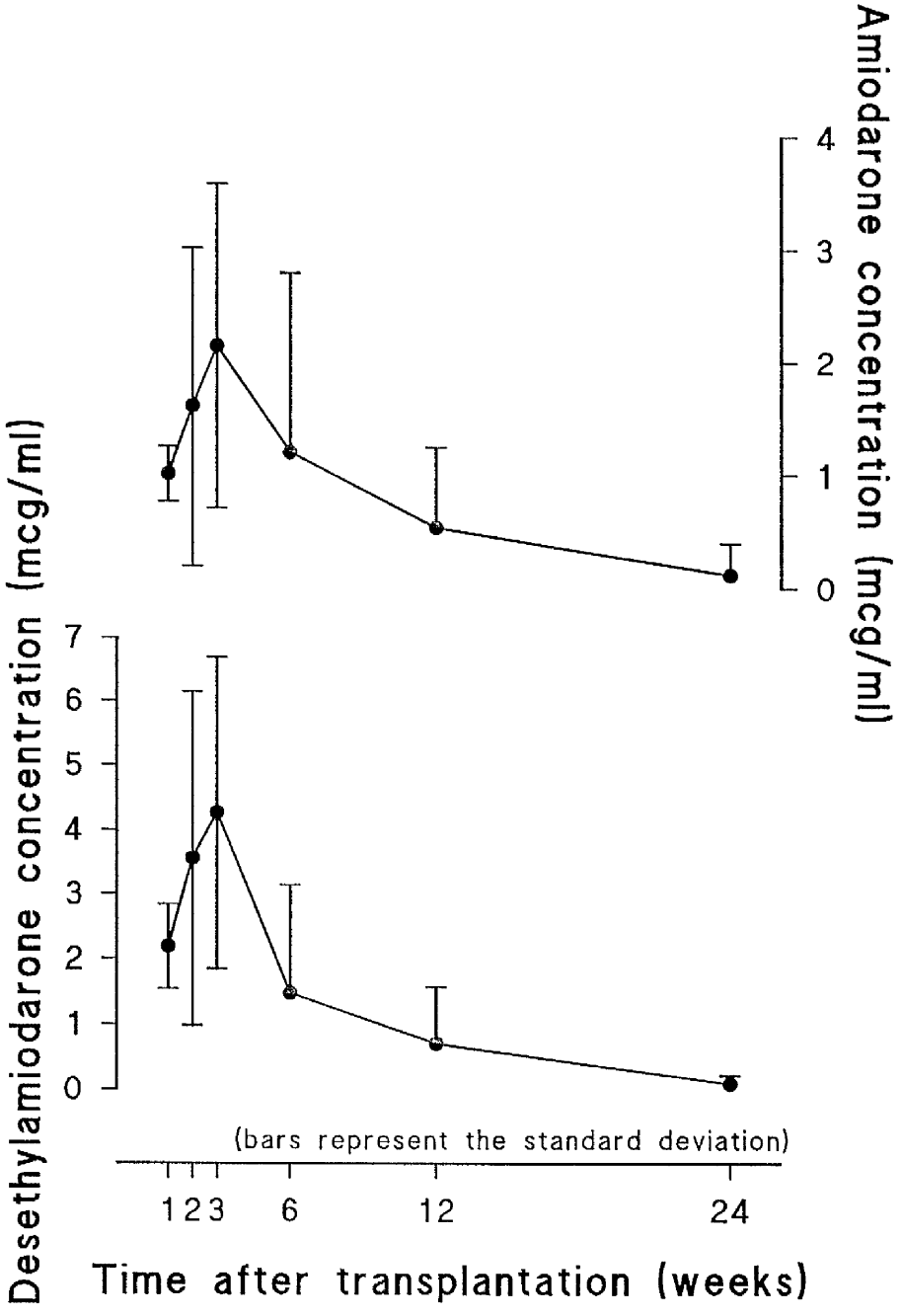


Figure 5.11 Concentrations of amiodarone and desethylamiodarone in cardiac tissue and time after transplantation

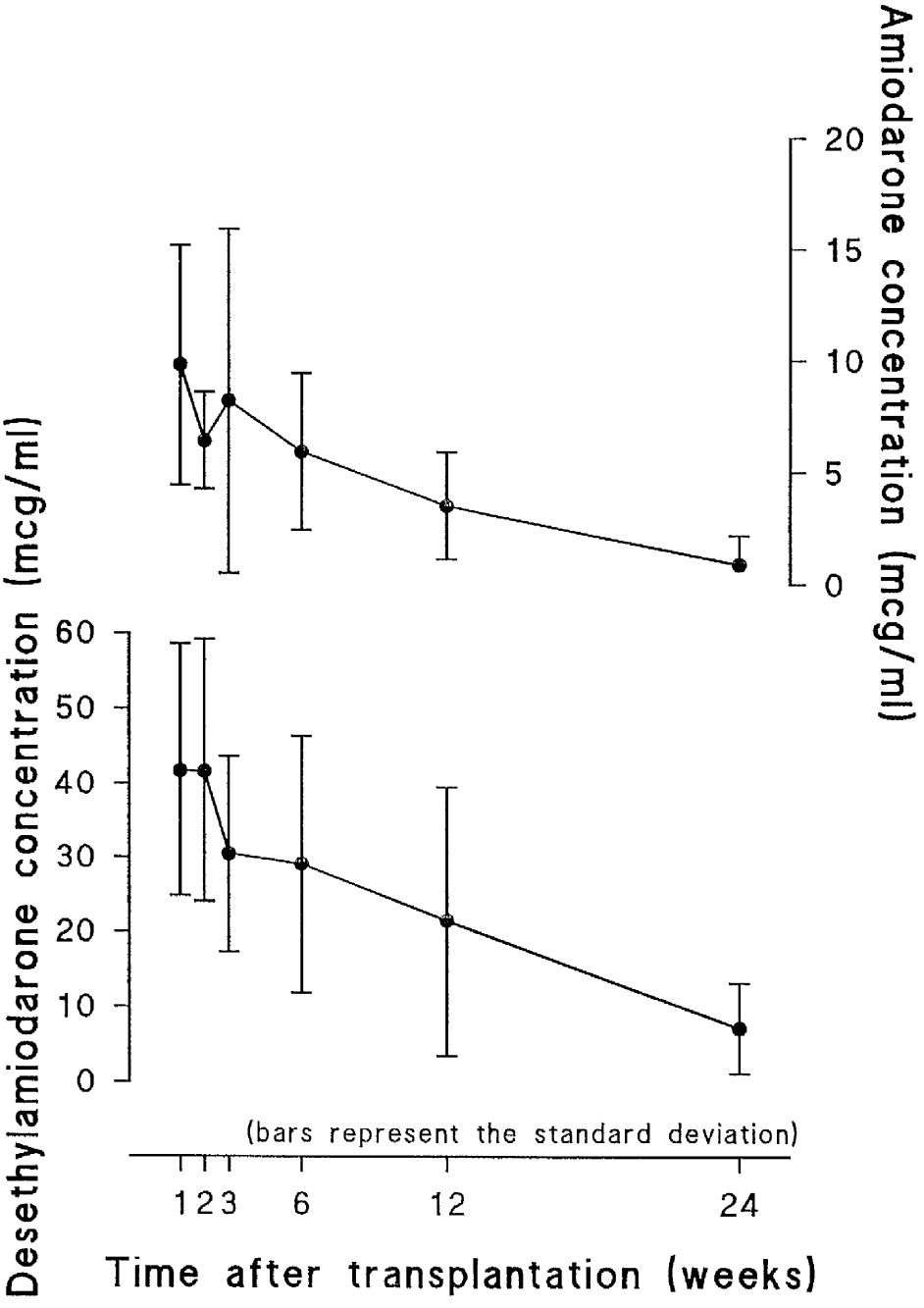


Figure 5.12: Individual changes in serum amiodarone concentration and time after transplantation

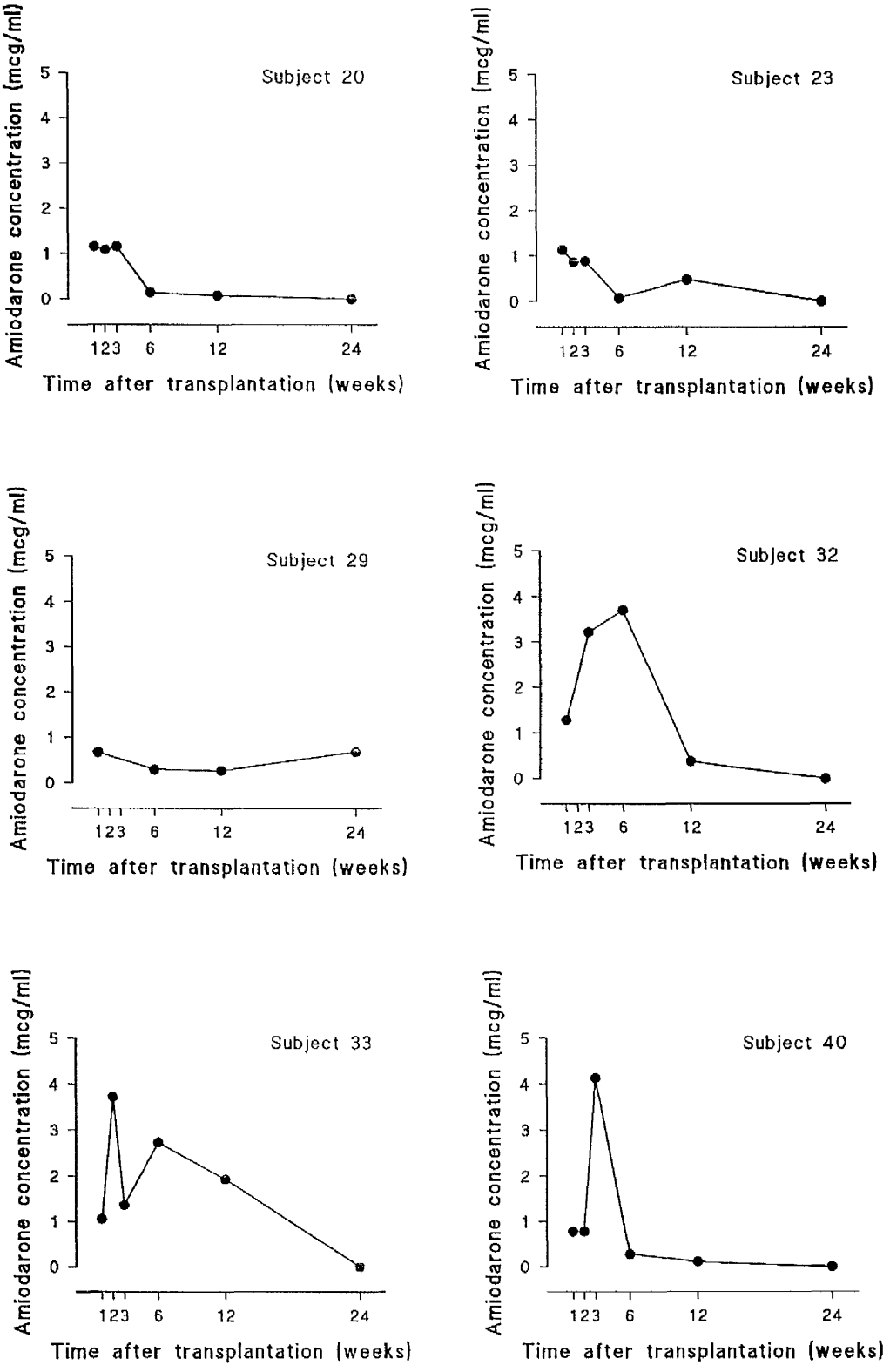


Figure 5.13: Individual changes in cardiac amiodarone concentration and time after transplantation

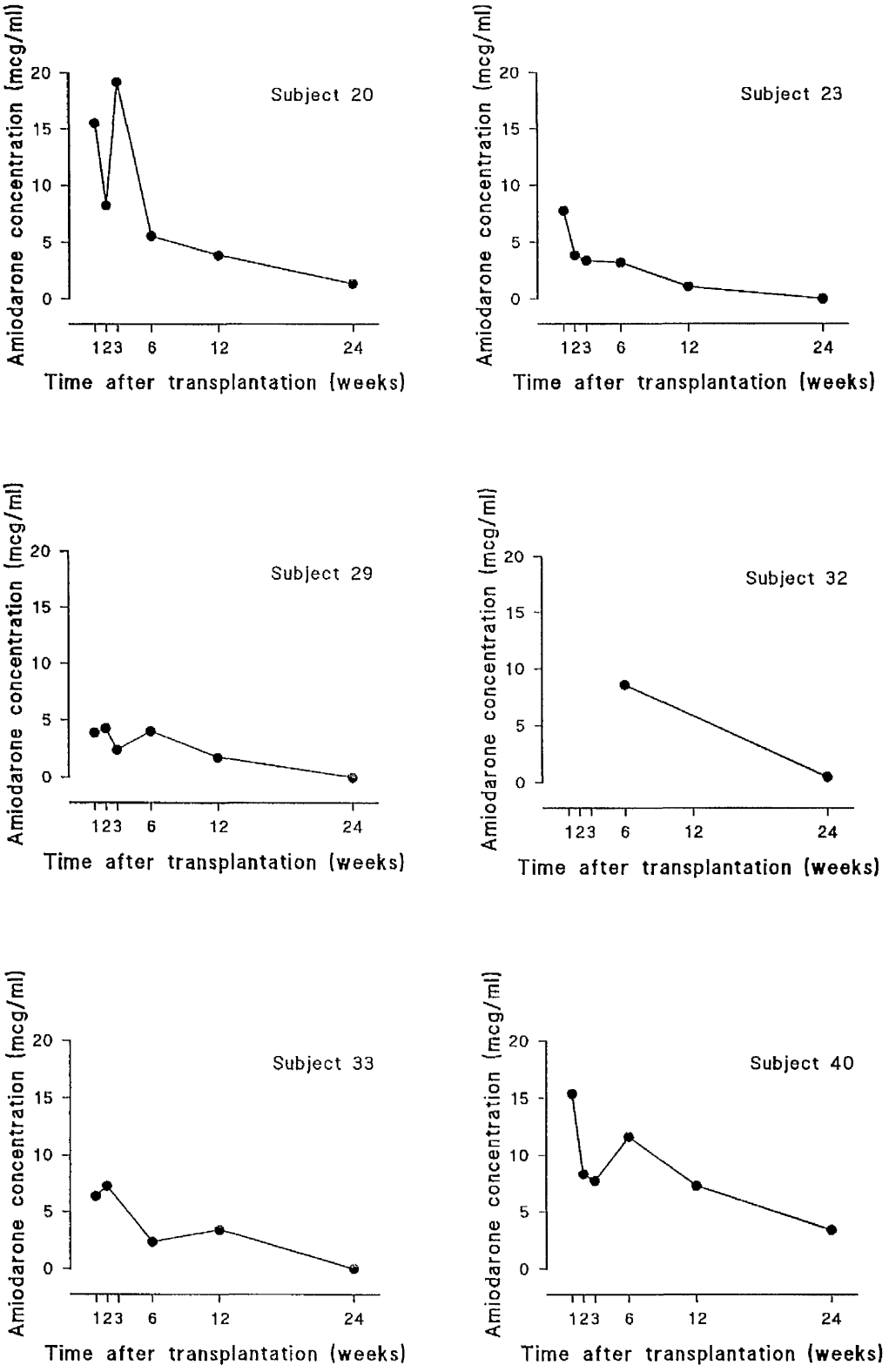


Figure 5.14: Individual changes in serum desethylamiodarone concentration and time after transplantation

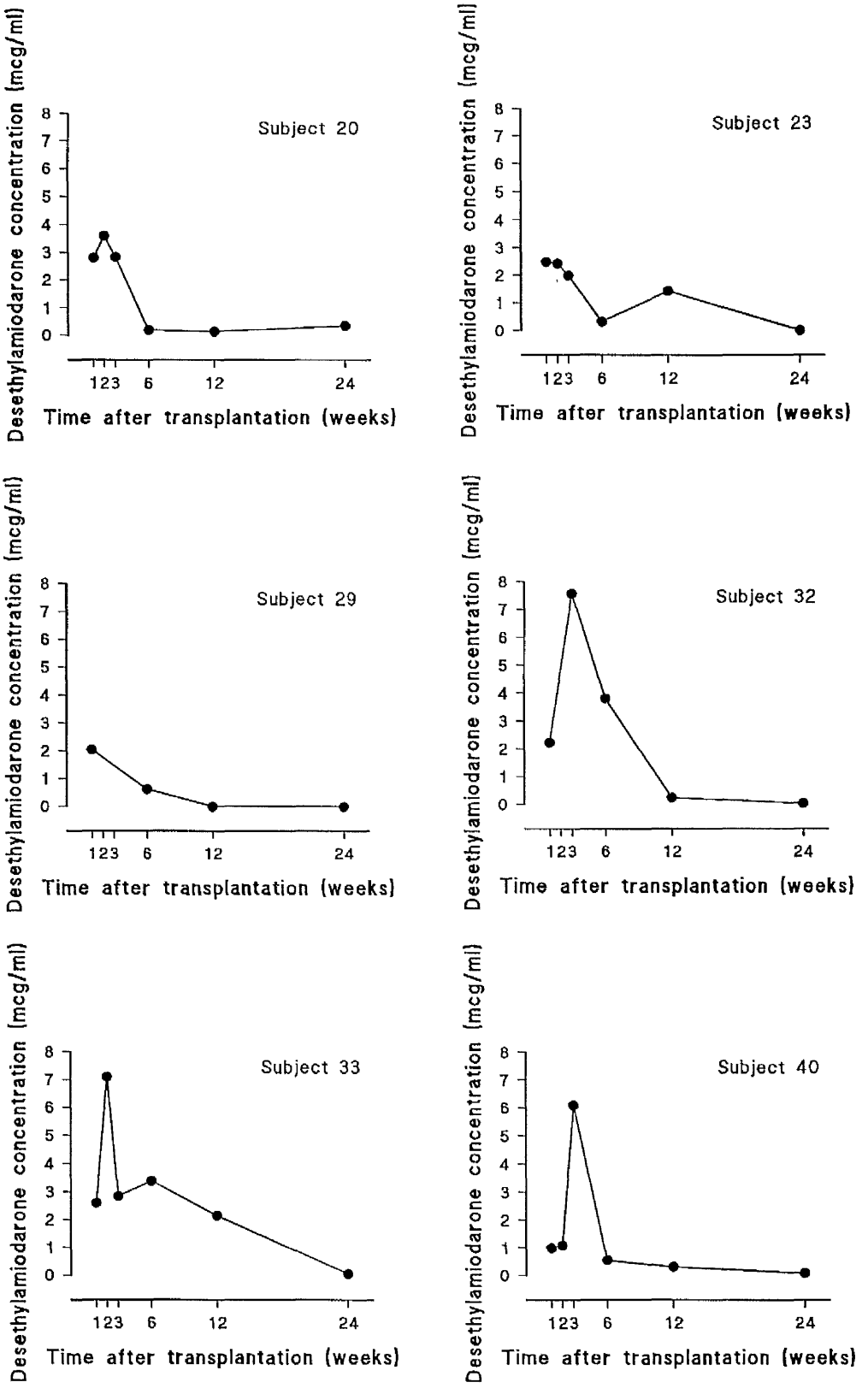


Figure 5.15: Individual changes in cardiac desethylamiodarone concentration and time after transplantation

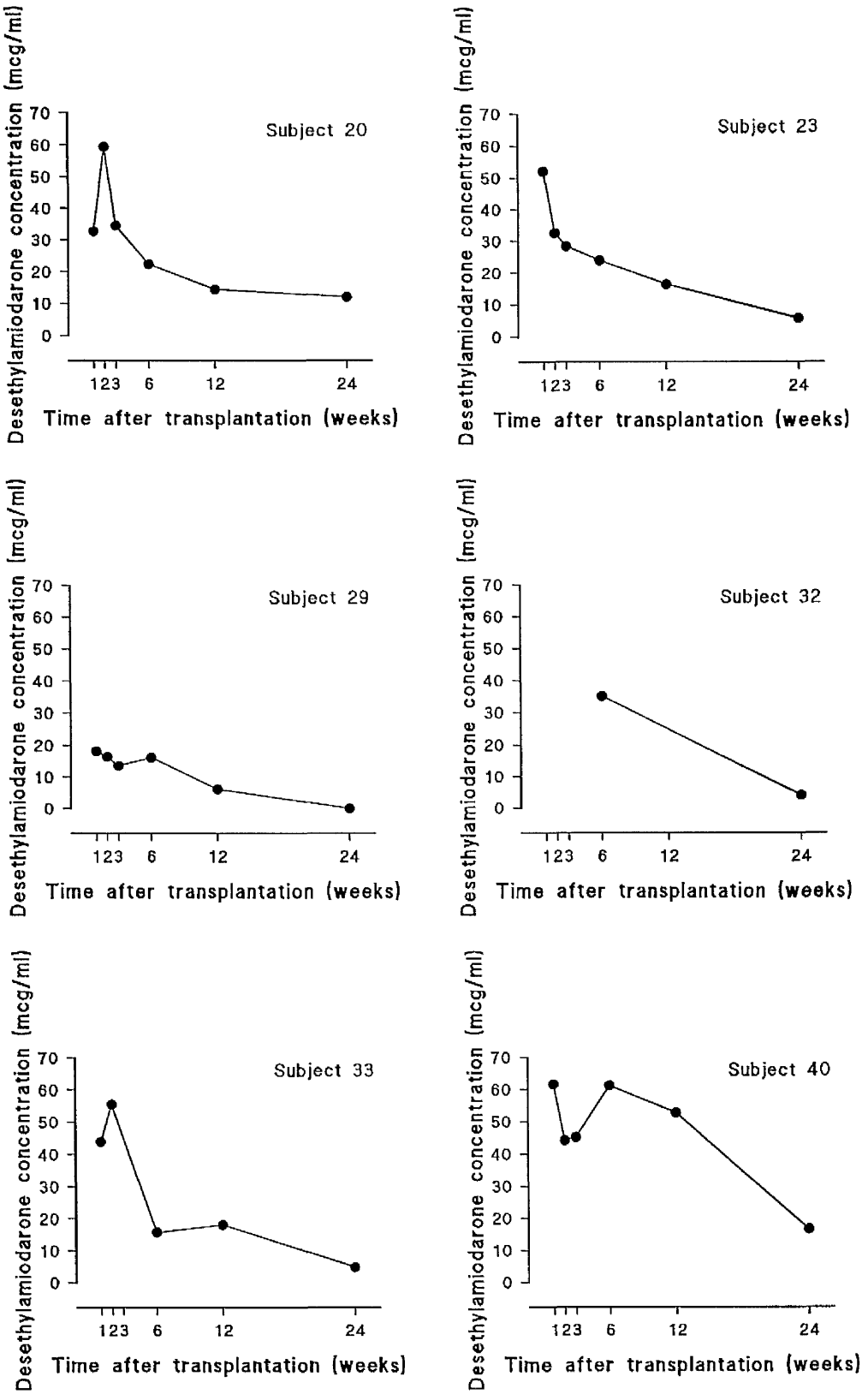
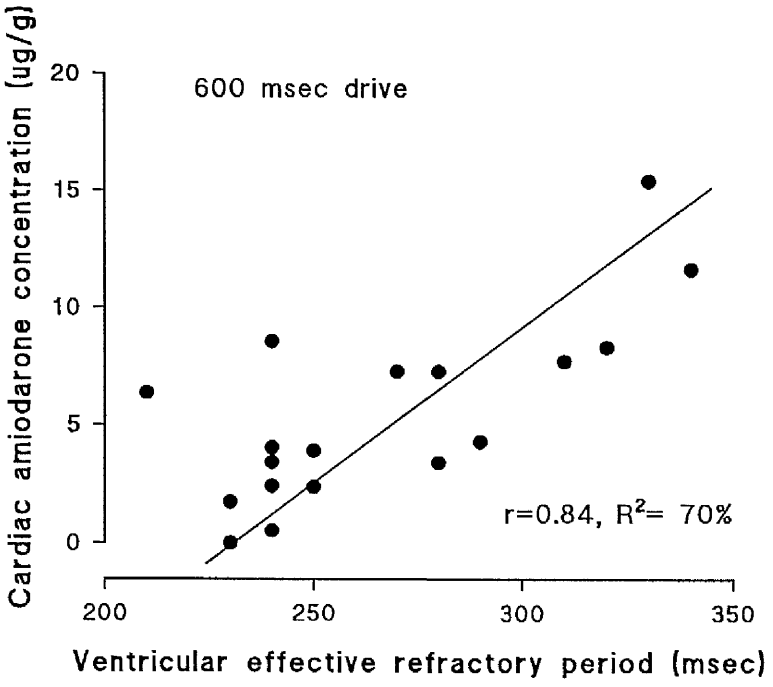


Figure 5.16: Correlation of cardiac amiodarone concentrations and ventricular effective refractory periods



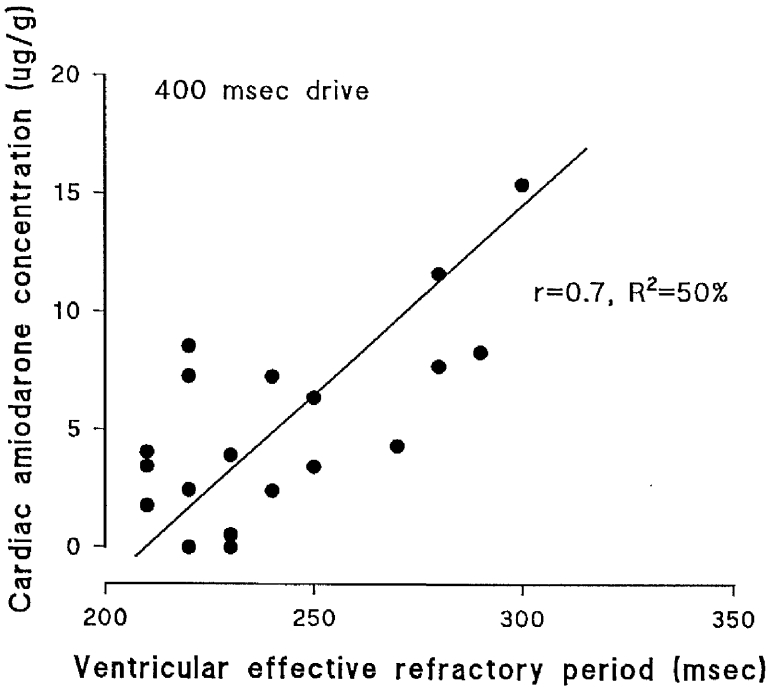
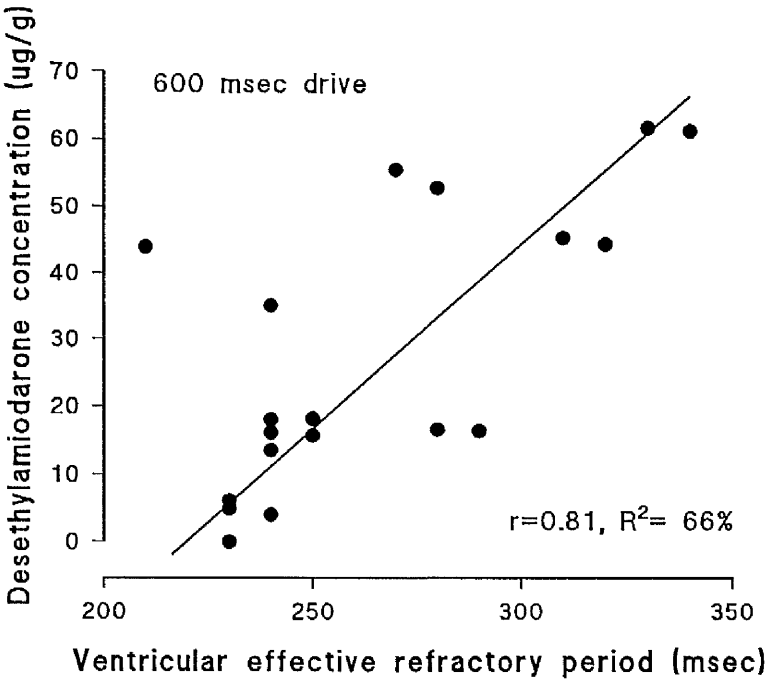


Figure 5.17: Correlation of cardiac desethylamiodarone concentrations and ventricular effective refractory periods



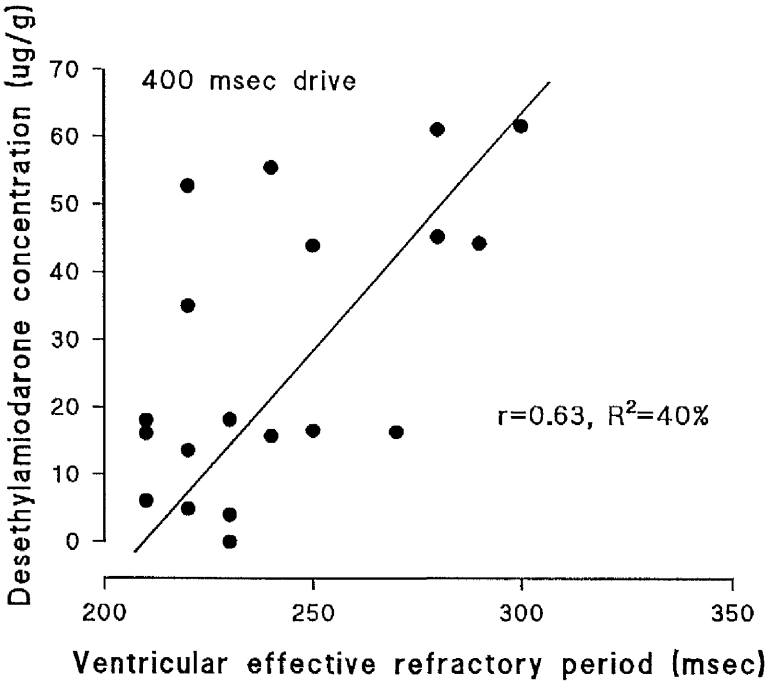


Figure 5.18: Rest and peak heart rates on exercise and preoperative amiodarone

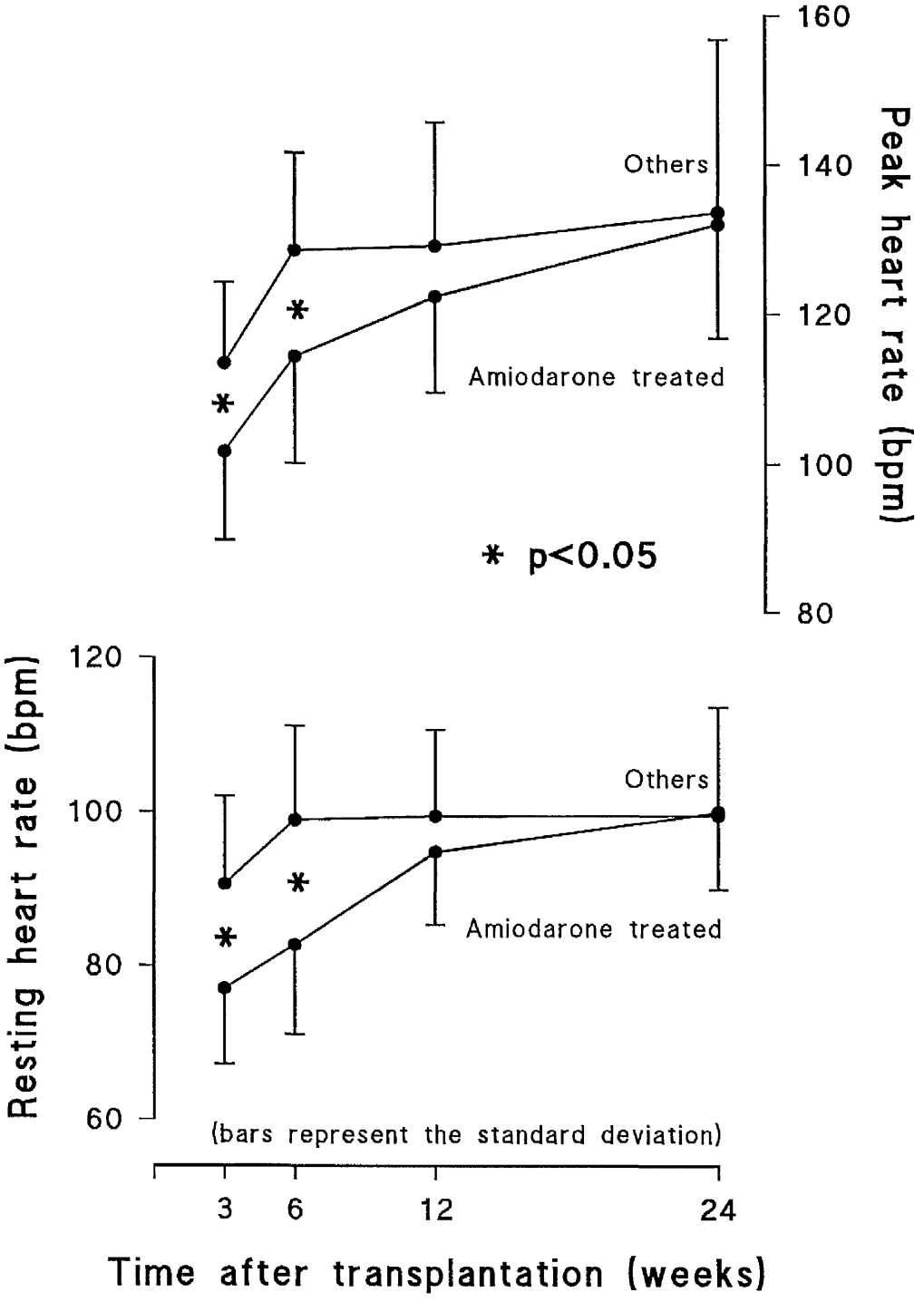
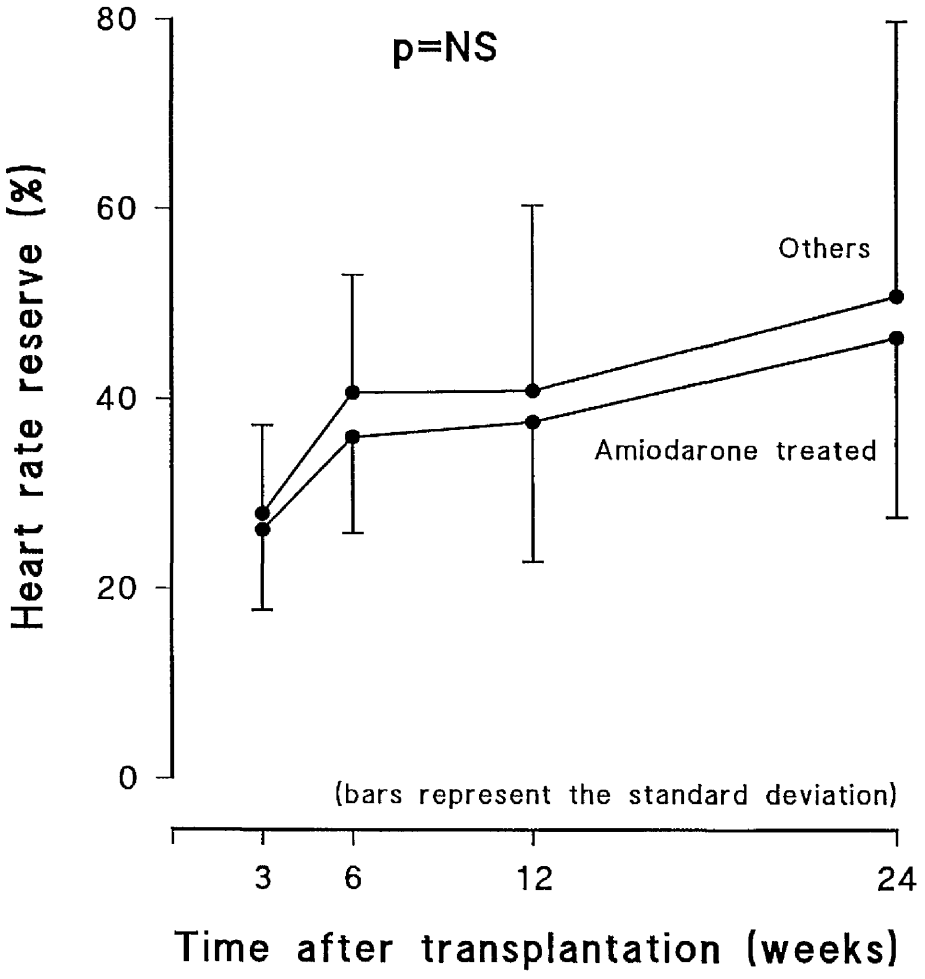


Figure 5.19: Heart rate reserve used at peak exercise and preoperative amiodarone



CHAPTER 6

SUMMARY OF CONCLUSIONS

REVIEW OF TRANSPLANT RECIPIENTS WITH PERMANENT PACEMAKERS

A retrospective study revealed that of 218 consecutive transplant recipients 21 received permanent pacemakers. The indication for pacing was sinus node dysfunction in 13 (62%) and atrioventricular block in eight (38%). Prospective study of 18 of 19 surviving pacemaker recipients using ambulatory monitoring at between three and 65 months after transplantation confirmed a clinical suspicion that long term pacing was infrequently needed. Patients who received pacemakers for sinus node dysfunction were more likely to require long term pacing than those who had atrioventricular block. In retrospect several pacemakers were probably implanted unnecessarily in the first two weeks after transplantation.

SERIAL PROSPECTIVE STUDIES

This is the first serial prospective study of sinus and atrioventricular node function in heart transplant recipients. The study period ran from the time of surgery until six months after transplantation. Serial electrophysiological studies, exercise testing and ambulatory monitoring were undertaken in 40 consecutive adult recipients.

Electrophysiology

Prospective serial electrophysiological studies in 40 consecutive transplant recipients showed that the mean sinus node recovery time shortened significantly with increasing time after transplantation. This was true both of 33 subjects with normal sinus

node function and of seven with sinus node dysfunction by standard criteria. This suggests that there is relative depression of sinus node automaticity in the first few weeks after transplantation and that the normal range for sinus node recovery time for innervated hearts may not be directly applicable to the denervated transplanted heart.

Early sinus node dysfunction (from the first week) was relatively common after transplantation (15% incidence). Sinus node function consistently improved from the second week onwards and sinus node dysfunction invariably resolved by the sixth week. Measurement of corrected maximal sinus node recovery time may be useful in predicting need for permanent pacing. In this study both subjects with abnormal corrected maximal sinus node recovery times three weeks after transplantation received a permanent pacemaker and one continued to pace at six months. The subject who required long term pacing had a much longer corrected maximal sinus node recovery time in excess of 1000 msec compared with 565 msec in the subject who became independent of pacing. Late sinus node dysfunction (from three months) was uncommon (one of 40 subjects) and was not associated with clinically significant bradyarrhythmias. The differing clinical profile of late sinus node dysfunction suggests a different aetiology.

No specific aetiological factors were identified for sinus node dysfunction after transplantation. In particular donor and recipient age and perioperative ischaemic time were unrelated to the subsequent development of sinus node dysfunction.

Abnormalities of electrophysiological measurements of atrioventricular conduction were uncommon after transplantation (two of 40 subjects) and invariably resolved within the study period. No clinically significant arrhythmias resulted. There were no changes in electrophysiological indices of atrioventricular conduction with time after transplantation in subjects without such abnormalities.

Ambulatory monitoring

Ambulatory monitoring may be useful in the assessment of subjects with sinus node dysfunction two to three weeks after transplantation when temporary pacing is restricted to 50 bpm on demand. In this study only one subject paced at 50 bpm during ambulatory monitoring three weeks after operation. This subject was one of two who received permanent pacemakers but was the only one who paced during ambulatory monitoring six months after transplantation. The relatively low temporary pacing rate is important. Higher pacing rates would have failed to distinguish subjects who required long term pacing from those with relative bradycardia and normal sinus node function on electrophysiological testing who did not experience clinically relevant arrhythmias. These data should be interpreted with caution, however, in view of the small number of subjects who eventually needed permanent pacing.

Exercise testing

Exercise testing revealed significant impairment of the chronotropic response as would be expected in denervated hearts. No definition of chronotropic incompetence proposed for innervated hearts could usefully be applied in order to distinguish transplant recipients with more severe impairment of the chronotropic response. Serial exercise testing showed significant improvements in the chronotropic response between the third and sixth weeks. This may in part result from improved general fitness after major surgery but analyses which correct for workload exhibited the same changes. This suggests that there are genuine changes in chronotropic response over this period which may relate to changes in responsiveness to circulating catecholamines.

The variation in chronotropic response steadily increased with time after transplantation. This was entirely explained by the identification of a subgroup of 16%

(five of 31) of subjects with an enhanced exercise response which continued to improve further throughout the study. Four of these five also had a rapid fall in heart rate during recovery which was first observed six months after transplantation. The exercise response was unchanged between after the sixth week in the remaining 26 subjects. The combination of enhanced exercise response and rapid fall in heart rate during recovery suggests efferent sympathetic reinnervation. Sympathetic reinnervation has not previously been described as early as six months after transplantation.

The chronotropic response to exercise was generally worse in subjects with sinus node dysfunction than in those with normal sinus node function. However, exercise testing could not reliably distinguish subjects with persistent sinus node dysfunction from those in whom it had resolved and was not useful in determining the prognosis of sinus node dysfunction. Symptoms related to an impaired chronotropic response were infrequent and not predicted by the severity of chronotropic incompetence. Exercise testing to detect symptoms may, therefore, be useful in assessing the need for rate responsive pacing.

The ability of several subjects in this study to exercise normally with a very limited heart rate response calls into question the routine use of rate responsive systems advocated by some transplant centres.

Reproducibility of electrophysiological measurements in transplant recipients

This study has confirmed that reproducibility of electrophysiological measurements is improved in the denervated transplanted heart compared with the normal. This is particularly true of indices of sinus node function which are more variable than those of atrioventricular conduction in the normal heart. The improved reproducibility is almost certainly due to the absence of variation in autonomic tone.

This finding has important implications for the clinical reliability of the differences observed during serial electrophysiological studies. It is more likely in the light of these findings that the changes we have observed are genuine and not a result of random variation.

The pharmacokinetics and effects of preoperative amiodarone after transplantation

Amiodarone is rapidly redistributed from extracardiac sites to the transplanted heart in transplant recipients who have taken preoperative treatment. From the first week until six weeks after transplantation serum concentrations of amiodarone and desethylamiodarone are directly comparable with those reported in patients taking long term oral amiodarone. Cardiac drug levels are comparable with patients taking amiodarone for three months after transplantation and in some subjects are detectable up to six months.

Strong correlations of cardiac amiodarone and desethylamiodarone concentrations with ventricular effective refractory periods were identified. A weaker association was found with atrial effective refractory periods. No other electrophysiological variable correlated quantitatively with cardiac drug levels and no electrophysiological variable correlated with serum drug levels.

Preoperative amiodarone has significant electrophysiological effects after transplantation. Resting cycle length, sinus node recovery time and Wenckebach cycle length are the most consistently affected and for up to three months after transplantation are significantly longer in recipients who took preoperative amiodarone than in those who did not.

Clinical implications

This study has, therefore, confirmed that the need for permanent pacing after transplantation is less frequent than formerly thought. Sinus node dysfunction, which is the most common indication for pacing, consistently improves with time after transplantation. In a very small proportion of recipients, however, the improvement is insufficient for them to become independent of pacing. The indications for permanent pacing in transplant recipients should be similar to those in the general population: bradyarrhythmias which are symptomatic or which are known to place the patient at risk. There is no evidence to suggest that "prophylactic" pacing for asymptomatic relative bradycardia in transplant recipients is necessary. The routine use of rate responsive pacemakers has not, as yet, been shown to be beneficial. Rate responsive pacing should probably, therefore, be reserved for patients with symptomatic chronotropic incompetence.

The previously suspected redistribution of amiodarone taken before transplantation to the transplanted heart has been proven. The electrophysiologic effects of preoperative amiodarone have been confirmed but it is clear that it does not cause clinically significant bradyarrhythmias after the first week.

APPENDIX 1: PATIENT DETAILS

Appendix 1.1
Biopsy histology

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	NER	MILD	MILD	NER	MILD	NER
2	NER	MILD	-	-	-	-
3	NER	NER	NER	NER	MILD	NER
4	NER	NER	NER	NER	NER	MOD
5	NER	NER	NER	NER	NER	NER
6	NER	NER	MILD	NER	MILD	NER
7	MILD	MILD	MILD	MOD	MILD	NER
8	NER	NER	MILD	MOD	MILD	MILD
9	NER	MILD	MILD	MILD	MILD	MILD
10	NER	MILD	NER	NER	MILD	NER
11	NER	MILD	MILD	-	-	-
12	NER	MOD	NER	NER	NER	NER
13	NER	NER	MILD	NER	NER	NER
14	NER	NER	NER	MILD	NER	NER
15	NER	MOD	MILD	MILD	MILD	NER
16	NER	MILD	MILD	MILD	NER	NER
17	NER	NER	MILD	MILD	MILD	NER
18	MILD	MOD	MILD	MILD	MILD	NER
19	MOD	-	-	-	-	-
20	NER	NER	NER	NER	NER	NER
21	NER	-	-	-	-	-
22	MOD	MILD	NER	NER	MILD	MILD
23	MILD	MILD	NER	MOD	NER	MILD
24	NER	NER	NER	MILD	NER	NER
25	NER	NER	NER	MILD	NER	-
26	NER	NER	NER	NER	NER	NER
27	MILD	MOD	NER	NER	NER	NER
28	MILD	NER	NER	MILD	NER	NER
29	MILD	MILD	NER	MILD	NER	NER
30	NER	MILD	MILD	NER	NER	NER
31	MILD	MILD	MILD	NER	NER	NER
32	NER	MILD	NER	MILD	NER	NER
33	MILD	NER	NER	NER	NER	NER
34	MILD	MILD	MILD	NER	NER	MILD
35	MILD	NER	MILD	MILD	MILD	NER
36	MILD	MILD	MILD	MILD	NER	NER
37	NER	MILD	MILD	NER	NER	NER
38	MILD	NER	MILD	MILD	MILD	NER
39	MILD	MILD	MILD	-	-	-
40	MILD	NER	MILD	MILD	NER	NER

Key: NER - no evidence of rejection, MILD - mild rejection, MOD - moderate rejection (Billingham classification)

Appendix 1.2
Additional drug therapy

1.21 Diltiazem (mg/day)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
6	-	-	-	-	-	180
14	-	-	-	180	360	360
18	-	-	180	180	180	180
36	-	-	120	180	360	480
37	-	-	-	180	360	180

1.22 Carbamazepine (mg/day)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
6	-	-	-	-	400	400
30	-	400	400	400	400	400

1.23 Phenytoin (mg/day)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
6	-	-	300	300	-	-
14	-	-	300	300	300	300
18	-	350	350	400	400	400

Appendix 1.3
Donor and recipient ages, perioperative ischaemic time

Subject number	Recipient age	Donor age	Ischaemic time (mins)
1	29	25	199
2	39	38	104
3	50	40	119
4	55	47	235
5	58	44	238
6	49	20	215
7	17	43	160
8	41	30	128
9	61	37	228
10	26	22	236
11	33	24	125
12	46	41	260
13	58	41	248
14	59	27	103
15	28	25	165
16	54	21	256
17	56	45	187
18	22	33	189
19	31	36	187
20	51	51	99
21	53	39	167
22	60	43	200
23	59	47	232
24	54	23	80
25	52	56	180
26	53	25	222
27	54	20	192
28	60	50	170
29	35	31	197
30	30	18	169
31	51	41	152
32	52	24	104
33	57	37	235
34	52	28	275
35	42	24	195
36	55	42	130
37	49	29	160
38	44	49	110
39	47	49	162
40	42	45	180

Appendix 1.4
Perioperative rhythms

Subject number	Defibrillation	Off Bypass	return to ITU
1	Junctional	Sinus	Sinus
2	Sinus	Sinus	Sinus
3	Sinus	Sinus	Sinus
4	AV dissociation	AV dissociation	Sinus
5	AV dissociation	AV dissociation	AV dissociation
6	Sinus	Sinus	Sinus
7	AV dissociation	Sinus	Sinus
8	AV dissociation	Sinus	Sinus
9	Asystole	Asystole	AV dissociation
10	Sinus	Sinus	Sinus
11	Sinus	Sinus	Sinus
12	Sinus	Sinus	Sinus
13	Sinus	Sinus	Sinus
14	Sinus	Junctional	Junctional
15	AV dissociation	AV dissociation	AV dissociation
16	Sinus	Junctional	Sinus
17	AV dissociation	Sinus	Sinus
18	Asystole	Asystole	Junctional
19	Sinus	Junctional	Junctional
20	Asystole	AV dissociation	Junctional
21	AV dissociation	Sinus	Sinus
22	Sinus	Sinus	Sinus
23	AV dissociation	AV dissociation	AV dissociation
24	Sinus	Sinus	Sinus
25	AV dissociation	Sinus	Sinus
26	Sinus	Sinus	Sinus
27	Junctional	Sinus	Sinus
28	Sinus	Sinus	Sinus
29	AV dissociation	Sinus	Sinus
30	Sinus	Sinus	Sinus
31	Sinus	Sinus	Sinus
32	Sinus	Sinus	Sinus
33	Asystole	Asystole	Sinus
34	Junctional	Sinus	Sinus
35	Sinus	Sinus	Sinus
36	Sinus	Sinus	Sinus
37	Sinus	Sinus	Sinus
38	AV dissociation	Sinus	Sinus
39	AV dissociation	Atrial fibrillation	Sinus
40	AV dissociation	AV dissociation	AV dissociation

APPENDIX 2: ELECTROPHYSIOLOGY RESULTS

Appendix 2.1
Corrected maximal sinus node recovery time (msec)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	300	220	210	345	190	105
2	310	315	-	-	-	-
3	410	370	320	280	140	305
4	390	330	360	345	410	285
5	305	425	425	350	310	215
6	360	225	315	240	285	390
7	360	375	200	215	205	265
8	405	510	495	325	300	360
9	360	335	260	170	240	220
10	335	310	245	180	175	175
11	320	360	305	-	-	-
12	265	320	290	225	215	145
13	235	315	260	220	265	190
14	Nodal	675	460	315	230	255
15	Nodal	1430	565	405	280	265
16	260	255	235	365	1825	1460
17	165	200	205	215	185	195
18	265	250	300	220	265	155
19	1350	-	-	-	-	-
20	285	275	315	250	240	255
21	535	-	-	-	-	-
22	-	220	180	145	195	200
23	410	350	-	360	340	425
24	390	260	245	330	225	285
25	455	110	150	150	120	-
26	450	525	360	265	200	165
27	305	210	265	170	165	110
28	190	345	260	355	355	285
29	220	265	275	235	170	160
30	135	135	205	120	135	160
31	125	150	190	230	305	325
32	480	470	140	260	265	195
33	795	2385	1325	485	445	450
34	135	150	185	195	175	115
35	340	245	275	220	230	280
36	315	305	260	230	285	320
37	575	450	345	400	290	385
38	175	190	175	155	190	260
39	425	300	335	-	-	-
40	345	325	240	315	330	275

Appendix 2.2
Sinoatrial conduction times (msec)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	120	146	146	227	118	95
2	178	150	-	-	-	-
3	163	184	157	156	101	170
4	222	187	170	136	176	157
5	139	204	242	189	172	235
6	148	117	140	145	139	174
7	124	147	105	107	105	122
8	171	149	141	86	213	171
9	216	204	192	142	136	198
10	222	198	176	178	137	160
11	125	186	165	-	-	-
12	145	160	163	69	77	91
13	199	206	208	112	149	93
14	Nodal	270	256	133	145	186
15	Nodal	312	294	235	200	109
16	80	110	116	4	75	126
17	112	128	116	159	126	133
18	133	125	161	124	164	131
19	226	-	-	-	-	-
20	143	130	133	104	97	91
21	255	-	-	-	-	-
22	-	111	107	65	107	98
23	-	-	-	158	174	241
24	143	109	96	164	112	143
25	110	84	114	86	60	-
26	249	-	195	151	129	135
27	183	124	167	121	125	100
28	126	166	172	198	203	201
29	116	122	86	80	-	75
30	83	108	122	107	107	115
31	102	112	149	150	156	160
32	168	143	185	132	145	105
33	159	-	197	243	271	269
34	131	129	135	119	85	93
35	191	173	225	184	193	192
36	185	130	146	124	140	139
37	298	334	249	199	163	295
38	126	124	99	107	170	142
39	191	164	226	-	-	-
40	200	173	120	160	158	191

Appendix 2.3
Resting cycle lengths (msec)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	860	810	830	730	655	565
2	630	740	-	-	-	-
3	860	900	860	755	725	605
4	995	920	820	885	930	800
5	865	755	780	800	685	715
6	910	775	775	760	875	890
7	950	805	750	850	770	880
8	805	800	1015	985	790	715
9	710	665	650	580	590	620
10	630	610	630	575	595	575
11	720	780	660	-	-	-
12	815	700	725	755	705	650
13	610	755	690	795	755	780
14	1395	715	680	610	660	685
15	1070	790	870	800	775	810
16	1020	945	885	970	955	685
17	665	680	675	595	615	645
18	710	655	665	610	620	590
19	800	-	-	-	-	-
20	695	670	755	710	790	700
21	725	-	-	-	-	-
22	-	720	630	630	625	630
23	910	895	870	870	860	780
24	885	855	805	810	780	750
25	790	680	660	650	630	-
26	780	755	680	685	630	600
27	770	680	675	580	530	485
28	870	940	940	830	765	775
29	780	825	775	750	630	630
30	640	610	665	585	605	625
31	580	630	580	665	715	695
32	900	910	780	670	670	665
33	1165	1220	950	745	810	710
34	585	595	590	645	645	580
35	815	695	665	675	610	760
36	605	765	790	660	735	855
37	770	705	705	720	730	800
38	670	690	635	635	655	780
39	825	690	645	-	-	-
40	935	905	840	920	835	810

Appendix 2.4
Two way analysis of variance table: Corrected maximal sinus node recovery times

n=30 subjects
7 subjects with sinus node dysfunction and 3 with <50% of observations available were excluded
4 subjects with some missing data included

Source of variation	Sequential sum of squares	degrees of freedom	Adjusted sum of squares	Adjusted mean of squares	F	p
Subjects	654989	29	650603	22435	5.11	<0.0001
Times	131997	5	131997	26399	6.01	<0.0001
Residual	619558	141	619558	4394		
Total	1406545	175				

Appendix 2.5
Two way analysis of variance table: sinoatrial conduction times

n=29 subjects
7 subjects with sinus node dysfunction and 4 with <50% of observations available were excluded.
5 subjects with some missing data included

Source of variation	Sequential sum of squares	degrees of freedom	Adjusted sum of squares	Adjusted mean of squares	F	p
Subjects	135409	28	135743	4898	5.8	<0.0001
Time	11715	5	11715	2343	2.01	0.02
Residual	112753	135	112753	835		
Total	259876	168				

Appendix 2.6
Two way analysis of variance table: spontaneous cycle length

n=30 subjects
7 subjects with sinus node dysfunction and 3 with < 50% of observations available were excluded
3 subjects with some missing data included

Source of variation	Sequential sum of squares	degrees of freedom	Adjusted sum of squares	Adjusted mean of squares	F	p
Subjects	1367285	29	1352188	46627	11.0	<0.0001
Times	147545	5	147545	29509	6.96	<0.0001
Residual	601995	142	601995	3420		
Total	2116825	174				

Appendix 2.4
Wenckebach cycle lengths (msec)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	400	360	340	360	380	360
2	420	360	-	-	-	-
3	400	400	400	430	370	370
4	400	470	430	390	400	350
5	700	580	610	590	520	490
6	420	370	380	390	380	430
7	460	470	390	370	380	460
8	600	580	650	580	530	530
9	<300	310	320	310	300	330
10	400	420	420	380	400	400
11	410	510	440	-	-	-
12	410	440	380	410	420	420
13	320	370	350	390	380	380
14	370	340	320	310	340	350
15	450	510	550	670	630	570
16	390	360	360	370	390	390
17	370	370	420	380	320	370
18	400	390	380	390	390	390
19	380	-	-	-	-	-
20	400	400	420	430	440	390
21	440	-	-	-	-	-
22	-	340	340	340	330	340
23	520	550	510	550	480	470
24	500	450	420	430	390	400
25	460	440	410	400	380	-
26	410	400	420	390	380	410
27	320	370	320	320	300	<300
28	<300	320	310	<300	<300	<300
29	320	350	<300	<300	<300	<300
30	330	410	380	370	360	320
31	<300	330	300	330	330	330
32	330	370	350	330	340	330
33	350	400	360	340	320	320
34	350	370	380	380	380	380
35	350	320	320	310	310	330
36	<300	310	370	350	360	360
37	390	420	400	440	470	420
38	320	320	340	320	340	350
39	550	470	430	-	-	-
40	530	530	510	550	470	440

Appendix 2.5
Effective atrioventricular refractory period (600 msec drive)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	a	a	280	280	a	290
2	a	a	-	-	-	-
3	a	a	a	a	a	220
4	a	a	a	a	a	a
5	350	300	410	400	380	380
6	a	a	270	a	260	320
7	290	290	a	a	a	350
8	-	410	500	420	350	380
9	a	a	a	a	a	a
10	310	320	320	200	-	-
11	a	a	330	-	-	-
12	a	a	a	a	a	240
13	a	a	a	a	a	a
14	a	a	a	a	a	a
15	350	450	460	490	490	450
16	a	a	a	a	260	a
17	a	a	a	a	a	a
18	a	a	280	a	a	a
19	a	-	-	-	-	-
20	a	a	a	a	310	a
21	330	-	-	-	-	-
22	-	220	a	a	a	a
23	370	390	340	430	360	350
24	350	280	a	a	a	a
25	a	a	230	a	a	-
26	a	a	310	220	a	290
27	a	a	a	a	a	-
28	a	a	a	a	a	a
29	a	a	a	a	a	a
30	a	a	a	a	a	a
31	a	a	a	a	a	a
32	a	a	a	a	a	a
33	a	a	a	a	a	a
34	a	a	270	a	290	270
35	a	a	a	a	a	280
36	a	a	a	240	a	a
37	a	a	270	a	300	a
38	a	a	a	250	a	a
39	390	340	a	-	-	-
40	380	300	a	330	a	a

Key: a = atrial effective refractory period exceeds atrioventricular effective refractory period

Appendix 2.6
Effective atrioventricular refractory period (400 msec drive)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	290	300	310	300	320	310
2	-	a	-	-	-	-
3	-	a	320	a	310	270
4	380	330	a	240	a	a
5	-	-	-	-	-	410
6	290	a	330	320	250	340
7	330	280	290	a	270	390
8	-	-	-	-	-	-
9	a	a	a	a	a	a
10	320	330	330	320	300	310
11	a	-	350	-	-	-
12	a	a	320	a	a	240
13	a	a	a	340	330	a
14	a	a	a	a	a	a
15	370	-	-	-	-	-
16	a	a	270	a	270	a
17	280	290	300	a	220	280
18	290	350	310	360	330	320
19	270	-	-	-	-	-
20	a	a	a	a	300	a
21	360	-	-	-	-	-
22	-	200	a	a	a	a
23	380	410	360	-	420	400
24	-	310	a	280	310	310
25	a	340	250	a	270	-
26	310	310	320	330	340	290
27	a	300	a	a	a	a
28	a	a	a	a	a	220
29	a	a	a	a	a	a
30	a	290	250	a	280	a
31	a	a	a	a	a	250
32	a	280	a	a	a	a
33	a	a	a	a	a	a
34	a	a	300	a	330	300
35	290	210	a	a	a	290
36	a	a	310	280	300	300
37	a	a	260	a	360	a
38	a	a	a	a	a	a
39	-	360	290	-	-	-
40	410	a	300	-	a	a

Key: a = atrial effective refractory period exceeds atrioventricular effective refractory period

APPENDIX 3: EXERCISE TEST DATA

Appendix 3.1
Heart rates on exercise, Week 3 (bpm)

Time (minutes) Subject number	Rest	1	2	3	4	5	6	7	8	9	10	11	12	13	14	peak
1	81	81	81	84	87	91	95	98	103	107						107
3	68	67	69	71	74	77	79	80	81	84						89
5	79	79	81	84	88	92	96	101								108
6	80	81	82	85	87	89	90	93	96	98	100					103
7																
8																
9	97	96	98	103	109											114
10	98	98	99	102	105	108	111	115	119							127
12	92	96	101	105	109	111	113	116	117							119
14	96	95	94	96	97	98	100									103
15	70	71	73	78	82											90
16	70	82	88	92	94	98	100	105	108							111
17	89	88	90	93	100											106
18	100	99	100	100	102	102	104	105	105							112
20	84	83	82	82	85	88	92	95	97							102
22	106	107	107	108	110	113	115	119								120
23	72	72	72	75	78	80										84
24	75	75	78	82	86	88	91	93	95	100	105	110				113
26	92	92	96	100	104	108										113
27	93	96	96	96	97	97	98	100	101	104	106	110				117
28	77	78	79	80	82	84	86	88	90							96
29	83	82	82	83	84	85	87	88	90	91	93	96	101	106	112	121
30	91	93	95	97	100	105										115
31	107	110	112	116	119	121	122	123	125	125	127					131
32	94	94	95	96	97	98	98	99	99	100	100	101	106			110
33	64	71	79	83	86	90	93									98
34	99	100	103	111	117	122	127	131	131							131
35	110	110	110	109	112	113	115	116	117	120	124					129
37	90	90	90	92	94	96	98	101	104	106	109	114				115
38	90	91	92	96	100											110
40	72	72	74	76	79	83	87	90	94							101

Appendix 3.2
Heart rates on exercise, Week 6 (bpm)

Time (minutes) Subject number	Rest	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	peak
1	116	115	116	117	117	118	119	121	123	127	130	134	140	146	153			157
3	92	93	94	94	100	100	101	102	104	105	108	112	117	123				124
5	87	90	90	94	93	95	97	101	103	107	112							120
6	88	88	89	90	92	93	96	97	102	105	107	109						117
7	83	83	83	83	85	86	89	92	96	98	101							104
8	66	66	67	69	72	72	73	74	77	77	81	87	94	100				107
9	123	125	125	129	131	134	138											143
10	115	114	115	115	117	119	121	124	127	129	134							141
12	96	98	101	105	108	110	112	114	117	121	125							129
14	105	105	105	105	106	107	108	110	112	115								120
15	80	80	82	83	85	87	89	92	96	100								108
16	98	99	99	99	101	103	106	108	110	113	117	120	126	130	134			138
17	105	107	110	113	116	119	120	122	125	127								131
18	108	108	108	110	110	112	113	115	117	119	122	125						131
20	90	89	89	89	90	92	95	97	102	107	112							117
22	99	100	101	103	105	107	109	112	115	120	126							131
23	73	73	75	78	81	85	87	92										92
24	80	79	79	81	82	83	85	86	87	88	89	90	92	95	101			117
26	100	101	101	104	105	107	108	112	115	119	124	128						131
27	104	104	104	105	105	107	108	109	111	113	117	120	124					129
28	80	81	82	85	88	91	96	100	104									110
29	90	89	89	89	90	91	92	96	100	104	107	112	116	121	126			129
30	110	113	116	119	121	125	129											138
31	91	91	93	96	99	102	104	105	105	106	107	108	111	119	131			142
32	98	98	98	98	98	101	102	103	105	106	107	110	112	116	121	129		135
33	87	88	88	89	90	92	93	95	97	100								104
34	97	96	100	107	111	116	120	122	125									127
35	108	108	110	110	111	112	113	115	117	119	121	125	131					143
37	91	91	91	91	92	93	96	98	101	104	107	110	115	120				122
38	101	100	101	103	107	113												119
40	67	69	70	72	75	78	81	84	88	92	97							101

Appendix 3.3
Heart rates on exercise, Month 3 (bpm)

Time (minutes) Subject number	Rest	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	peak
1	104	105	107	108	110	111	114	116	119	121	124	127	131	136	142			149
3	106	105	105	105	106	107	110	112	113	115	117	120						122
5	98	98	98	99	101	104	107	110	114	120	124	128	135					141
6	83	83	85	86	87	88	89	90	91	92	93	94	96					98
7	90	90	91	92	93	94	95	96	97	100	101							104
8	92	92	93	95	96	97	99	100	101	104	106	109	112					118
9	109	110	111	115	120	123	127	131	136	141								142
10	115	115	115	115	117	119	119	120	122	125	127	131						136
12	107	107	108	110	113	115	117	117	117	117	119	120						126
14	100	100	101	101	102	103	105	107	106	108	109	114						120
15	88	86	87	89	91	94	96	98	102	105	109							116
16	81	80	81	83	85	89	92	96	99	103	107	112	120	127	134	149		149
17	98	98	98	99	101	102	104	107	109	111	114							117
18	107	107	108	108	108	110	110	119	113	115	115	118	120	122	127	134		141
20	97	98	100	101	102	104	107	108	110	113								115
22	110	110	110	111	113	115	117	119	122	127	131	136						141
23	84	85	85	85	87	89	90	93	95	98								100
24	88	88	88	89	89	90	91	91	92	94	96	97	101	104	109	115		129
26	104	104	104	105	107	108	110	112	115	119	121	125	129	133				136
27	125	125	126	127	127	127	129	129	130	131	131	133	134	139	142			142
28	87	87	88	89	89	90	92	93	96	97	101	104						111
29	105	105	106	107	107	108	108	111	112	114	115	116	118	121	126	133		134
30	110	110	110	112	115	117	120	125	129	134								139
31	98	101	102	105	108	110	113	114	115	117	118	121	126	131	138	141		151
32	101	102	104	104	105	105	107	107	108	110	113	115	117	119	125			136
33	93	93	94	94	95	98	98	100	102	105	108	113						120
34	96	97	100	103	107	110	113											114
35	97	96	96	96	96	97	97	99	101	102	106	110	115	125	136			150
37	88	88	88	88	89	89	90	90	91	92	94	96	98	100				102
38	104	104	104	108	112	113	117	120	122									127
40	77	78	78	80	83	85	87	90	92	96	100	105	112					115

Appendix 3.4
Heart rates on exercise, Month 6 (bpm)

Time (minutes) Subject number	Rest	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	peak
1																		
3	117	118	119	122	125	127	129	131	133	135	136	139						142
5	92	97	104	115	113	114	124	127	131	133	137	142	143	147				147
6	76	77	79	81	82	83	85	86	86	86	87							88
7	80	81	81	81	81	82	83	83	84	86	88	91						94
8	98	98	99	100	101	102	103	105	106	108	111	114	119	123	127			138
9	121	125	129	136	141	147	153	157	163	166								168
10	113	113	113	113	115	117	119	121	124	127	129	133	141					150
12	102	105	108	110	113	113	115	115	116	119	120	123						129
14	91	91	91	91	92	93	94	97	102	106	111	117	121					127
15	94	98	99	102	103	106	108	111	115	119	125	131	136	144				147
16	96	98	98	100	101	103	104	107	111	112	113	116	119	122	125	128	140	150
17	110	115	109	111	111	111	113	114	115	117	119	122						124
18	115	117	117	117	119	119	119	119	120	121	122	124	125	128	130	135	143	147
20	104	105	105	107	108	109	110	111	113	114	117							120
22	108	108	108	109	109	110	111	113	118	120	124							127
23	83	84	86	85	87	89	92	93	94	96	98	100						100
24	95	97	98	101	103	105	107	109	111	114	115	118	122	127	133	146		149
26	112	111	111	113	113	115	117	119	120	125	128	131	134					144
27	116	117	117	117	117	117	118	119	120	121	122	125	127	133	137			142
28	89	89	90	93	94	98	99	102	104	108	113							121
29	105	105	105	105	105	107	107	108	110	111	113	115	118	120	123	125		133
30																		
31	114	115	119	122	127	127	129	129	131	136	136	138	142	150	155	166		169
32	99	100	100	101	101	101	102	104	105	106	107	109	111	113	117	122	132	137
33	105	107	107	109	111	112	114	116	119	120	125	130	135					140
34																		
35	96	96	97	97	98	99	100	101	103	104	107	110	114	118	126	136		150
37	80	80	80	81	81	82	84	85	87	88	89	91	92	96				97
38	84	84	84	86	90	94	98	101	105	107	114							115
40																		

Appendix 3.5
Changes in heart rate during recovery, Weeks 3 and 6 (bpm)

	Week 3					Week 6				
Time (minutes)	1	2	3	4	5	1	2	3	4	5
Subject number										
1	0	2	6	9	13	1	2	4	8	11
3	1	1	3	7	9	0	2	6	10	13
5	0	0	2	3	6	0	0	0	3	6
6	0	2	6	9	12	6	9	13	15	18
7						0	1	3	5	6
8						1	0	1	2	4
9	1	0	1	3	5	0	0	0	5	8
10	0	0	1	1	4	0	0	1	5	9
12	0	3	8	13	17	0	3	7	13	18
14	0	1	1	2	2	0	0	1	2	4
15	0	1	2	2	7	2	0	1	3	7
16	0	5	9	14	19	0	5	9	14	18
17	0	1	3	5	8	0	2	5	9	11
18	2	0	2	4	6	0	1	3	5	7
20	1	0	1	3	4	0	2	5	8	11
22	0	0	4	6	9	0	0	2	5	7
23	0	0	0	2	3	0	1	4	5	8
24	0	2	5	10	14	1	0	0	2	6
26	0	0	2	6	10	0	0	3	6	9
27	0	2	4	9	11	0	0	4	9	12
28	1	0	2	5	7	1	2	4	8	11
29	2	0	0	1	4	0	0	0	0	3
30	0	0	2	5	7	2	0	0	3	7
31	0	0	2	5	7	1	0	0	3	8
32	0	0	3	7	9	1	0	4	9	14
33	1	0	0	0	1	1	0	1	2	5
34	2	5	10	13	17	0	1	6	11	16
35	0	2	4	5	9	0	0	1	3	7
37	0	0	3	4	7	0	0	1	3	6
38	1	0	2	4	6	0	1	2	6	10
40	0	2	4	7	10	0	0	2	5	8

Appendix 3.6
Changes in heart rate during recovery, Months 3 and 6 (bpm)

	Month 3					Month 6				
Time (minutes)	1	2	3	4	5	1	2	3	4	5
Subject number										
1	0	3	6	9	12					
3	2	6	7	9	14	0	0	5	9	13
5	0	0	3	10	16	1	9	14	21	27
6	0	3	5	8	10	0	3	5	7	9
7	0	0	2	3	5	0	2	3	3	4
8	0	0	2	3	5	1	0	2	7	10
9	1	1	4	6	9	6	13	19	25	30
10	0	0	0	3	7	0	0	1	6	9
12	1	1	4	8	11	0	3	7	11	15
14	3	2	2	4	5	0	2	5	7	11
15	0	1	3	5	8	4	12	23	28	33
16	0	2	3	11	16	0	1	1	7	12
17	0	1	1	1	2	0	1	2	4	4
18	0	0	1	5	5	0	0	3	5	8
20	0	1	4	5	8	0	2	4	6	9
22	0	1	5	8	12	0	2	5	9	12
23	1	4	26	19	10	1	3	1	2	3
24	2	1	0	5	9	3	11	16	20	27
26	0	0	1	4	7	0	1	3	7	11
27	0	4	7	11	14	1	4	8	13	17
28	1	0	0	1	3	1	1	2	5	9
29	0	0	1	3	4	0	0	0	0	2
30	0	2	6	15	15					
31	1	0	1	5	8	7	20	26	33	38
32	0	0	3	7	12	0	1	6	11	15
33	0	0	2	2	5	2	4	4	5	7
34	0	1	6	10	12					
35	0	0	3	7	12	0	1	5	10	15
37	0	0	0	2	3	0	0	0	2	4
38	1	7	11	14	17	0	2	7	10	13
40	0	1	4	9	13					

Appendix 3.7
Exercise times (seconds)

Time	Week 3	Week 6	Month 3	Month 6
Subject number				
1	540	864	875	
3	574	786	677	694
5	473	648	750	785
6	613	708	739	630
7		713	643	689
8		768	750	892
9	240	379	549	547
10	505	616	680	739
12	525	633	718	717
14	260	587	696	752
15	264	575	651	797
16	503	880	915	976
17	293	587	627	679
18	335	691	931	992
20	488	643	578	609
22	429	615	671	608
23	351	457	597	660
24	664	892	935	930
26	341	667	785	775
27	692	736	849	879
28	501	483	672	702
29	851	841	902	919
30	348	411	540	
31	619	851	900	909
32	724	840	898	961
33	367	572	700	733
34	482	509	540	
35	622	769	871	927
37	661	781	783	789
38	295	334	511	609
40	515	604	720	

APPENDIX 4: AMBULATORY MONITORING DATA

Appendix 4.1
Minimum heart rates (bpm)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	65	71	69	85	92	102
2	paced 90	80	-	-	-	-
3	59	56	60	61	65	74
4	62	62	61	62	-	62
5	paced 90	-	-	-	-	-
6	62	-	65	-	68	62
7	int.paced 50	64	-	54	-	54
8	int.paced 50	55	-	55	-	59
9	paced 90	74	72	91	84	88
10	91	90	107	94	-	92
11	69	71	-	-	-	-
12	paced 90	70	70	80	76	79
13	91	76	71	78	-	64
14	paced 50	68	75	82	79	73
15	int.paced 50	int.paced 50	55	57	65	-
16	paced 90	52	-	56	54	57
17	69	76	69	74	68	82
18	88	-	78	86	84	-
19	-	-	-	-	-	-
20	paced 90	70	-	-	71	-
21	-	-	-	-	-	-
22	-	79	80	79	84	87
23	int.paced 50	58	61	60	63	65
24	paced 90	63	60	65	64	64
25	62	88	-	-	88	-
26	73	72	82	80	91	96
27	65	76	73	88	84	-
28	54	51	52	63	60	-
29	67	-	73	72	60	-
30	78	-	74	-	80	-
31	80	80	69	59	63	68
32	-	51	70	77	84	84
33	int.paced 50	paced 50	int.paced 50	int.paced 50	54	int.paced 50
34	84	77	73	-	-	-
35	46	64	81	80	-	74
36	68	79	68	69	66	57
37	72	-	82	76	-	-
38	71	80	82	78	-	75
39	63	-	-	-	-	-
40	paced 90	60	62	62	64	-

Key: paced 50 = continuous pacing at 50 bpm, paced 90 = continuous pacing at 90 bpm, int.paced 50 = intermittent pacing with a programmed rate of 50 bpm.

Appendix 4.2
Minimum daytime heart rates (bpm)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	65	71	72	85	97	102
2	paced 90	83	-	-	-	-
3	64	61	63	71	72	78
4	62	62	64	64	-	73
5	paced 90	-	-	-	-	-
6	67	-	67	-	71	73
7	int.paced 50	64	-	75	-	54
8	int.paced 50	55	-	57	-	60
9	paced 90	75	85	95	92	90
10	94	94	107	94	-	93
11	73	72	-	-	-	-
12	paced 90	76	73	80	81	79
13	92	76	77	80	-	67
14	paced 50	76	85	85	85	73
15	int.paced 50	int.paced 50	65	70	71	-
16	paced 90	59	-	60	70	68
17	85	85	77	113	86	90
18	90	-	86	93	89	-
19	-	-	-	-	-	-
20	paced 90	71	-	-	91	-
21	-	-	-	-	-	-
22	-	83	86	89	90	87
23	int.paced 50	62	65	65	70	65
24	paced 90	70	62	75	72	64
25	62	97	-	-	97	-
26	73	84	82	86	95	100
27	72	84	93	98	90	-
28	60	67	61	63	63	-
29	71	-	80	86	78	-
30	85	-	79	-	85	-
31	80	86	79	59	65	78
32	-	63	79	85	87	85
33	int.paced 50	paced 50	int.paced 50	int.paced 50	64	int.paced 50
34	98	86	73	-	-	-
35	63	69	81	82	-	76
36	87	79	71	72	68	72
37	77	-	82	79	-	-
38	72	80	87	78	-	76
39	68	-	-	-	-	-
40	paced 90	60	63	62	72	-

Key: paced 50 = continuous pacing at 50 bpm, paced 90 = continuous pacing at 90 bpm, int.paced 50 = intermittent pacing with a programmed rate of 50 bpm.

Appendix 4.3
24 hour mean heart rates (bpm)

Time Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
1	69	78	76	89	98	-
2	paced 90	87	-	-	-	-
3	64	62	-	-	-	-
4	70	66	68	68	-	77
5	paced 90	-	-	-	-	-
6	72	-	72	-	80	73
7	int.paced 50	77	-	82	-	-
8	int.paced 50	66	-	-	-	73
9	paced 90	86	84	102	99	101
10	97	103	-	99	-	-
11	78	74	-	-	-	-
12	paced 90	76	81	93	89	97
13	97	90	-	-	-	-
14	paced 50	77	82	86	-	79
15	int.paced 50	int.paced 50	66	70	-	-
16	paced 90	62	-	65	74	78
17	87	81	79	-	90	88
18	91	-	91	96	95	-
19	-	-	-	-	-	-
20	paced 90	81	-	-	86	-
21	-	-	-	-	-	-
22	-	80	89	89	-	-
23	int.paced 50	65	69	66	-	-
24	paced 90	74	69	78	78	83
25	73	98	-	-	-	-
26	79	85	89	90	101	107
27	72	88	91	97	103	-
28	60	58	61	66	-	-
29	72	-	83	85	-	-
30	84	-	84	-	102	-
31	95	93	82	76	85	86
32	-	68	85	88	93	89
33	int.paced 50	paced 50	int.paced 50	int.paced 50	70	int. paced 50
34	96	90	87	-	-	-
35	68	73	95	96	-	83
36	83	84	77	77	82	-
37	79	-	89	85	-	-
38	80	88	88	88	-	-
39	73	-	-	-	-	-
40	paced 90	-	71	68	70	-

Key: paced 50 = continuous pacing at 50 bpm, paced 90 = continuous pacing at 90 bpm, int.paced 50 = intermittent pacing with a programmed rate of 50 bpm.

APPENDIX 5: AMIODARONE DATA

Appendix 5.1
Preoperative amiodarone dose

Subject number	daily dose (mg)	duration of treatment (months)	cumulative dose (g)
3	200	60	360
4	200	57	342
5	800	8	192
8	200	11	66
11	200	11	66
levels available for the following subjects			
20	200	4	24
23	variable	6	55
29	200	18	108
32	200	36	216
33	200	9	54
40	200	6	36

Appendix 5.2
Serum amiodarone concentrations (ug/ml)

Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
20	1.15	1.08	1.15	0.14	0.07	BQL
23	1.13	0.86	0.88	0.07	0.47	BQL
29	0.67	-	-	0.3	0.27	0.69
32	1.28	-	3.22	3.71	0.37	BQL
33	1.06	3.72	1.37	2.73	1.94	BQL
40	0.78	0.78	4.13	0.28	0.11	BQL

Key: BQL= Below quantifiable limit (<0.01 ug/ml)

Appendix 5.2
Serum desethylamiodarone concentrations (ug/ml)

Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
20	2.81	3.60	2.84	0.19	0.14	0.34
23	2.48	2.43	1.99	0.32	1.42	BQL
29	2.04	-	-	0.63	BQL	BQL
32	2.23	-	7.57	3.81	0.24	0.04
33	2.60	7.11	2.85	3.4	2.15	0.05
40	0.99	1.09	6.09	0.55	0.31	0.08

Key: BQL= Below quantifiable limit (<0.01 ug/ml)

Appendix 5.3
Concentration of amiodarone in cardiac biopsy specimens (ug/g)

Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
20	15.52	8.26	19.21	5.57	3.88	1.35
23	7.75	3.85	3.39	3.22	1.07	BQL
29	3.89	4.29	2.41	4.03	1.74	BQL
32	-	-	-	8.56	-	0.52
33	6.37	7.27	-	2.37	3.41	BQL
40	15.39	8.32	7.72	11.61	7.28	3.40

Key: BQL= Below quantifiable limit (<0.01 ug/g)

Appendix 5.4
Concentration of desethylamiodarone in cardiac biopsy specimens (ug/g)

Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
20	32.78	59.43	34.52	22.34	14.33	11.96
23	52.02	32.57	28.45	23.91	16.39	5.77
29	18.17	16.40	13.59	16.17	6.11	BQL
32	-	-	-	35.05	-	4.04
33	43.91	55.45	-	15.74	18.07	4.93
40	61.59	44.27	45.23	61.10	52.7	16.59

Key: BQL= Below quantifiable limit (<0.01 ug/g)

Appendix 5.5
Ventricular effective refractory periods in subjects who took preoperative amiodarone and controls (msec)

Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
600 msec drive						
Amiodarone treated						
29	250	290	240	240	230	230
32	240	270	270	240	210	240
33	210	270	290	250	240	230
40	330	320	310	340	280	280
Controls						
1	-	200	200	220	220	210
1	240	250	260	220	210	260
1	220	260	260	220	230	270
1	260	270	250	240	220	250
39	270	270	270	-	-	-
400 msec drive						
Amiodarone treated						
29	230	270	220	210	210	230
32	220	260	250	220	190	230
33	250	240	250	240	210	220
40	300	290	280	280	220	250
Controls						
1	-	190	190	200	200	200
1	220	220	240	210	200	220
1	200	240	220	200	230	220
1	240	250	230	220	200	230
39	240	240	240	-	-	-

Appendix 5.6
Atrial effective refractory periods in subjects who took preoperative amiodarone and controls (msec)

Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
600 msec drive						
Amiodarone treated						
3	270	290	250	240	250	-
4	310	290	300	200	300	260
5	-	-	-	-	-	-
8	-	-	-	-	-	-
11	280	380	-	-	-	-
20	250	250	270	280	-	190
23	-	-	-	-	-	220
29	230	290	250	250	200	210
32	250	260	230	230	250	190
33	240	240	270	270	240	250
40	280	300	270	300	-	-
Controls						
1	240	220	-	-	240	-
2	200	220	-	-	-	-
6	300	310	-	270	260	-
7	-	-	230	270	220	-
9	270	250	250	210	-	200
10	-	-	-	-	250	-
12	230	280	300	250	250	260
13	280	320	290	270	230	240
14	290	240	250	230	-	-
15	-	-	-	-	-	230
16	270	260	240	290	220	210
17	230	230	250	200	230	200
18	230	300	-	220	-	-
19	230	-	-	-	-	-
21	-	-	-	-	-	-
22	-	-	220	250	240	200
24	-	-	310	290	240	210
25	360	320	-	260	280	-
26	260	290	-	-	200	-
27	260	280	210	190	220	-
28	240	280	240	260	210	210
30	240	300	250	200	190	170
31	220	240	220	200	220	200
34	220	210	200	220	240	240
35	220	190	200	240	190	-
36	240	240	220	170	230	200
37	220	230	220	210	180	230
38	230	250	220	-	230	190
39	240	220	280	-	-	-

Appendix 5.6 continued

Subject number	Week 1	Week 2	Week 3	Week 6	Month 3	Month 6
400 msec drive						
Amiodarone treated						
3	-	290	-	220	-	-
4	-	-	290	-	290	220
5	-	-	-	-	-	-
8	-	-	-	-	-	-
11	280	-	-	-	-	-
20	260	240	260	240	-	190
23	-	-	-	-	-	210
29	240	290	250	230	190	210
32	250	260	230	220	230	180
33	240	240	240	230	210	210
40	-	310	260	-	230	220
Controls						
1	-	-	-	-	-	-
2	-	220	-	-	-	-
6	-	300	-	-	-	-
7	-	-	-	250	-	-
9	270	250	250	200	220	190
10	-	-	-	-	-	-
12	320	310	-	240	230	-
13	300	300	280	-	-	240
14	290	240	250	200	220	220
15	-	-	-	-	-	-
16	270	230	-	250	-	210
17	-	-	-	200	-	-
18	-	-	-	-	-	-
19	-	-	-	-	-	-
21	-	-	-	-	-	-
22	-	-	200	240	240	190
24	-	-	190	-	-	-
25	310	-	-	260	-	-
26	-	-	-	-	-	-
27	260	-	210	190	210	160
28	240	270	210	240	200	-
30	240	-	-	190	-	170
31	210	220	220	200	210	-
34	210	210	200	200	220	200
35	200	200	190	240	190	170
36	220	220	190	160	210	180
37	210	220	210	200	170	210
38	230	240	210	210	230	170
39	-	220	280	-	-	-

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RELEVANT PUBLICATIONS AND PRESENTATIONS

Parts of the work described in this thesis have been presented at the following scientific meetings: The North American Society for Pacing and Electrophysiology 1991; The European Congress of Cardiology of Cardiology 1991; The American College of Cardiology 1993.

Publications relating to this thesis:

1. Long term pacing after heart transplantation is usually unnecessary.
   Pac Clin Elect 1991;14:1792-6.
2. Permanent pacing after cardiac transplantation.
   Br Heart J 1993;69:399-403.
3. Bradyarrhythmias requiring pacemaker implantation after orthotopic heart transplantation: association with rejection.
   J Heart Lung Transplant 1993;12:534-5.