THE QT AND RELATED INTERVALS,

PHYSIOLOGICAL PACING AND

THE PERFORMANCE OF

THE ´QT-RESPONSIVE´ (TX) PACEMAKER

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CONTENTS

PART TWO - ADVANTAGES OF PHYSIOLOGICAL PACING, THE PACED-VENTRICULAR RATE/STIMULUS-T INTERVAL RELATION AND THE PERFORMANCE OF THE RATE RESPONSIVE (TX) PACING SYSTEM.

THE PURPOSE OF THIS THESIS

The QT interval, hitherto thought to be determined largely if not solely by heart rate, has become the focus of increased interest recently through the realization that the QT interval also shortens during periods of increased sympathetic nervous system activity under circumstances where heart rate remains unchanged, such as during exercise in fixed-rate ventricular pacing in patients in complete heart block, and the successful use of this principle by the TX pacemaker to provide a rate response during periods of increased metabolic demand.

The aim of the first part of this thesis is to obtain a better understanding of factors which affect the duration of the QT interval.

Initially the error in estimating QT intervals is calculated and an attempt is made to define ´normal´ resting QT interval values.

The heart rate/QT interval during exercise is examined to determine which regression equation provides the best curve fit, which could then be used for comparison of data presented subsequently in the thesis.

Heart rate/QT interval relation during atrial pacing at rest is compared with exercise heart rate/QT interval relations during exercise as any significant differences between these two relations would indicate the importance of factors other than heart rate which control the

duration of the QT interval.

As some of the studies which are described in the literature and in the thesis involve patients who are paced ventricularly, the relations between paced-atrial rate and QT interval and paced-ventricular rate and QT interval are compared and the rate of adaptation of the QT interval to changes in pacing rate is also examined during ventricular pacing.

Studies to date which have examined the contribution of factors other than heart rate to exercise-induced QT interval shortening have relied on different groups of subjects. Patients with atrial synchronized ventricular pacemakers afford the opportunity of evaluating this on a within-patient basis by exercising the same group of patients during fixed-rate and atrial synchronized ventricular pacing modes and examining the respective atrial rate/QT interval and heart rate/QT interval relation.

Crucial to the success of the QT-responsive (TX) pacing system is the extent to which the heart rate/QT interval relation is subject to patient variation. The exercise data in normal subjects and that in patients undergoing atrial and ventricular pacing at rest are therefore examined to determine the extent to which, if any, the heart rate/QT interval relation varies in different patients. Patients with implanted atrial synchronized pacemakers also permits the quantification of

inter-patient and intra-patient variation affecting the contribution of heart rate to QT interval changes by examining the data in patients who were exercised on more than one occasion.

The role of heart rate and sympathetic nervous system activity in determining the extent of changes in the QT interval during exercise, is further examined by studying the effect of beta adrenergic receptor blockade on the atrial/QT interval and heart rate/QT interval changes during fixed-rate and atrial synchronized ventricular pacing modes, respectively. Heart rate/QT interval relation is also examined in normal subjects before and after acute beta adrenergic receptor blockade.

It has been suggested in the literature (Vaughan Williams, 1975 and 1977) that the effects of acute and chronic beta adrenergic receptor blockaded on the duration of the QT interval vary. This may have important implications in patients with TX pacing system who require or are on beta blocker medication. The heart rate/QT interval relation following acute beta adrenergic receptor blockade is therefore compared with the heart rate/QT interval relation during exercise in patients who are on long term beta blocker therapy.

Any significant patient variation affecting the heart rate/QT interval relation would render Bazett´s formula invalid. Bazett´s constant QTc which corrects the measured QT for changes in heart rate is therefore

examined under circumstances where both heart rate and autonomic nervous system activity act on the QT interval, such as during exercise and the results are compared to that in subjects in whom heart rate alone is altered, for example during pacing, or who are beta blocked.

Both ventricular effective refractory period and QT interval are affected by heart rate. This thesis therefore addresses itself to the relations between heart rate, QT interval and ventricular effective refractory period and the effect of two class III antiarrhythmic drugs, namely amiodarone and sotalol, on these relations.

The overall aim of the first part of this thesis is to provide information on factors which govern the heart rate/QT interval relations and hence obtain a greater understanding of the performance of the QT-responsive (TX) pacing system.

The second part of the thesis examines the whole concept of physiological pacing and its advantages compared with fixed-rate ventricular demand pacing.
The relative contributions of heart rate and atrio-ventricular synchrony to exercise performance are discussed and in this exercise performances during rate responsive (TX) pacing, fixed-rate and atrial synchronized ventricular pacing modes are compared.

The paced-ventricular rate/Stimulus artefact to

T wave interval relation is compared with the heart rate/QT interval and in particular is examined to determine if it is also affected by patient variation.

The effect of alternating various programmable indices on rate response during treadmill exercise tests is defined and suggestions are made as to the best method of programming this pacemaker and possible future developments.

THE PLAN OF THIS THESIS

This thesis is divided into two major parts.

In the first part, an introductory review is given of current knowledge concerning factors which determine the duration of the QT interval and formulae which have been proposed in the literature to correct the QT interval for heart rate. An account is given of the methods used and results achieved during the examination of the contributions of heart rate and autonomic nervous system activity to QT interval changes under various circumstances. The effects of heart rate on QT interval and ventricular effective refractory period are defined and the changes produced by amiodarone and sotalol on the heart rate/QT/ventricular effective refractory period relations are compared. The first part is concluded by a discussion of the findings and their probable relevance to the performance of the new QT-responsive (TX) pacing system.

The second part of the thesis is introduced by a discussion of physiological pacing and its reported advantages compared to fixed-rate ventricular pacing. This is followed by a description of methods used to quantify improvements in haemodynamic indices and exercise performance during atrial synchronized ventricular pacing mode compared to fixed-rate ventricular pacing, examination of the role of the chronotropic response to improvements in exercise performance and the performance of the rate responsive TX pacemaker. This is followed by sections which report and discuss the findings.

PART ONE

QT AND RELATED INTERVALS

ABSTRACT

The QT interval of the standard electrocardiogram is a clinical measure of the action potential duration. Heart rate has hitherto been regarded as its most important determinant and Bazett's formula $QT = k\sqrt{RR' \text{ Interval}}$ is usually used to correct QT interval for differences in heart rate.

In the first part of this thesis it is shown that the heart rate/QT interval relation during exercise, can equally satisfactorily be expressed by the linear regression equation, QT = 494 - 1.581 x Heart Rate. QT interval changes induced at rest by pacing;
QT = 433 - 0.99 x Heart Rate, were less than those seen during exercise. Furthermore, QT interval shortened with exercise during fixed-rate ventricular pacing;
QT = 515 - 0.85 x atrial rate. These studies suggest that heart rate is not the sole determinant of exercise-induced QT interval changes and that the autonomic nervous system also plays a significant role in this respect.

QT interval was found to take about a minute to adapt fully to changes in pacing rate. The slopes of linear regression equations describing the paced-ventricular rate/QT interval (broad QRS complexes) and paced-atrial/QT interval relations were similar.

The separate contributions of heart rate and factors other than heart rate, to QT interval shortening during exercise was assessed on a within-patient basis, by exercising patients with atrial synchronized ventricular pacemakers during atrial synchronized and fixed-rate ventricular pacing modes. In each subject the QT interval shortened with exercise fixed-rate ventricular pacing at 70 beats per minute and in each case the QT interval shortening during fixed-rate ventricular pacing was less than that during atrial synchronized ventricular pacing mode. Only about half of the QT interval changes could be attributed to heart rate alone.

The contribution made by heart rate was subject to wide inter-patient and intra-patient variation. Acute beta adrenergic receptor blockade abolished the QT interval changes with exercise during fixed-rate ventricular pacing mode. Acute beta adrenergic receptor blockade also reduced the slope of the heart rate/QT interval regression line in subjects with normal conduction. Autonomic nervous system activity therefore has an important role in determining exercise-induced QT interval changes. Chronic beta adrenergic receptor blockade however, had little effect on the slope of the heart rate/QT interval linear regression equation, presumably due to adaptive changes affecting this relation and occurring at a cellular level. QT interval prolongation may reflect a cardiac state with greater than normal disparity of recovery times rather

than one where simply prolonged recovery is present. This inhomogeneity of recovery times may predispose to arrhythmia susceptibility. Class III antiarrhythmic drugs may act by reducing this inhomogeneity by having a greater effect on cells with shorter recovery times. Ventricular effective refractory:QT interval ratio may be a useful index of homogeneity of myocardial recovery times. The heart rate/ventricular effective refractory period/QT relations were explored during pacing and the effects of sotalol and amiodarone on these relations were studied. Of the two drugs, amiodarone had the greatest effect on ventricular effective refractory period compared to changes in QT interval.

In the second part of the thesis it is shown that atrial synchronized ventricular pacing improves exercise performance in the vast majority of patients with stable second or third degree atrio-ventricular block. This enhanced exercise performance is due to the chronotropic response to exercise rather than to the maintenance of the proper sequence of cardiac chamber activation.

A new rate responsive pacemaker has been designed based on the principles that sympathetic activity governs in part QT interval changes and that heart rate changes contribute significantly to haemodynamic adaptations to increased physiological demand: the TX pacing system (Vitatron) senses the T waves of paced-ventricular complexes and alters heart rate in response to changes in the Stimulus-T

interval. The TX pacemaker was implanted and its performance evaluated in 14 patients. The effect of the programmable indices: T wave sensitivity, slope and T wave sensing window on rate responsiveness during exercise are described. T wave sensing problems arose in 3 patients. The TX pacemaker improved exercise performance in the majority of patients and provided satisfactory rate responses to varying physiological needs as assessed by Holter monitoring. The paced-ventricular rate/Stimulus-T interval relation at rest was subject to significant inter-patient and intra-patient variation. Consequently, the onset of rate response and the programmed upper heart rate limit was attained at different stages of identical exercise protocols. Repeated exercise testing and programming changes were necessary to adjust for this variation and to ensure that the pacemaker continued to function optimally. Suggestions are made about possible future developments of this pacing system.

CHAPTER 1 INTRODUCTION

The QRST complex of the standard electrocardiogram describes ventricular depolarization and repolarization. The QT interval is thought to reflect the resultant of action potential durations of all ventricular muscle cells.

The QT interval has recently been the subject of increasing interest, because of (a) the reported association between prolonged QT intervals and serious ventricular arrhythmias (Jervell and Lange-Nielson, 1957; Romano et al., 1963; Ward, 1964; Krikler and Curry, 1976; Ahnve et al., 1978; Ahnve et al., 1980; Taylor et al., 1981; Palatini et al., 1984), the identification of QT prolongation as a prognostic index of sudden death (Schwartz and Wolf, 1978; Ahnve et al., 1980; Boudoulas et al., 1984), (b) the use of amiodarone and sotalol, which have antiarrhythmic properties but which paradoxically prolong the QT interval (Rosenbaum et al., 1976), (c) the realization of the importance the autonomic nervous system in determining the duration of the QT interval and (d) the availability of the QT responsive (TX) pacing system.

Factors Affecting the Duration of the QT Interval:

Several factors are known to influence the duration of the QT interval. Abnormalities of the QT interval have been described in association with electrolyte disturbances

(Lepeschkin and Suarawicz, 1952; Weidmann, 1956), drugs (Pick, 1957; Kelly et al., 1963; Weber et al., 1972; Reynolds, 1976), neurogenic mechanisms (Burch et al., 1954), hypothermia (Clements and Hurst, 1972), hypothyroidism (Surawicz et al., 1977) as well as cardiac states such as mitral valve prolapse (Swartz et al., 1977), myocardial ischaemia (Sareli et al., 1980), myocardial infarction (Elek et al., 1953; Doroghazi and Childers, 1978), use of liquid-protein-modified diets (Isner et al., 1979; Siegel et al., 1981), anorexia nervosa (Isner et al., 1985), drug-free depressed states (Rainey et al., 1982) and pulmonary tumours (Petrovich et al., 1978).

The Role of Heart Rate -

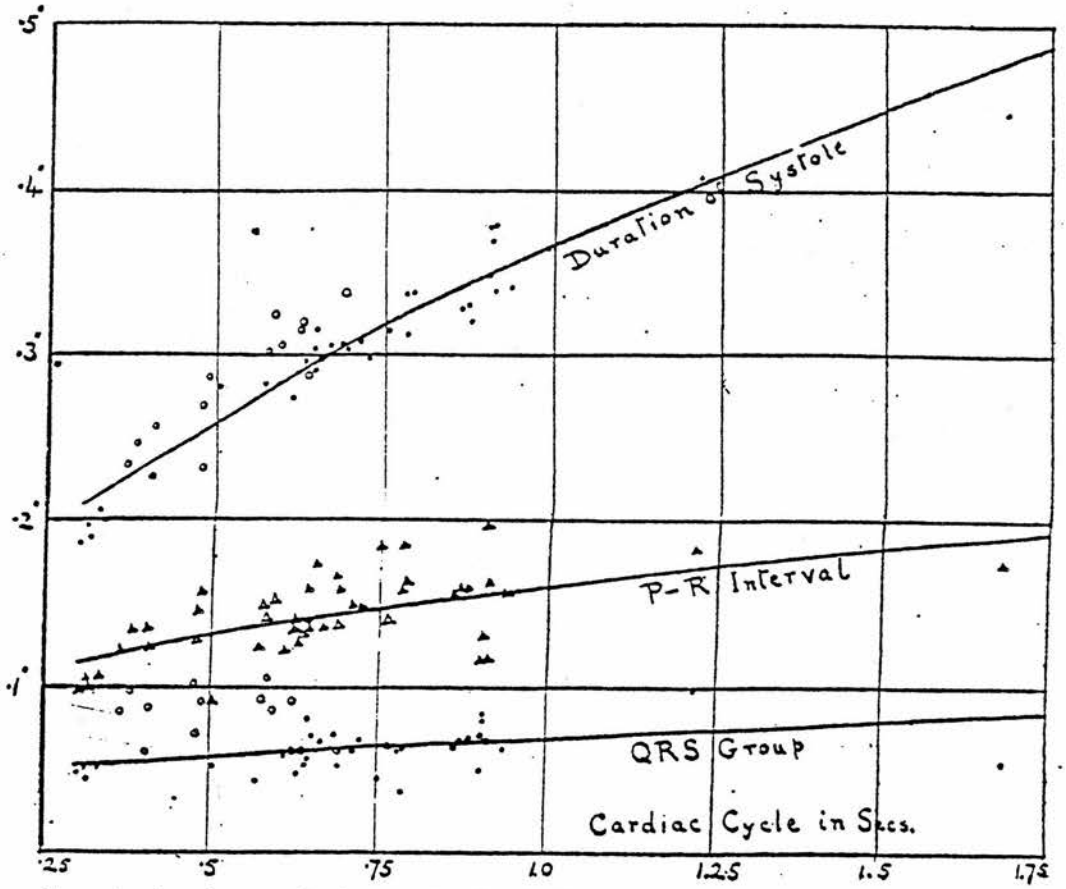
Historical Background:

Traditionally heart rate has been regarded as the most important determinant of the QT interval and various formulae have been proposed to take into account the effect of heart rate on the measured QT interval. Waller in 1891 was the first person to point to an inverse relation between mechanical systole and heart rate. Lombard and Cope (1919) confirmed from their studies on the carotid pulse that the duration of mechanical systole was inversely related to the square root of the pulse rate - mechanical systole = $60/k\sqrt{\text{pulse rate}}$, where k was a constant. The value of k for standing posture was 28.5,

for sitting, 26 and for lying down, 25. Systolic times were longer during exercise and in women. They postulated that the latter finding may have been due to "the fact that most women take little exercise"!

Formulae Proposed in the Literature to Correct the Measured QT Interval for Differences in Heart Rate:

Bazett (1920), reported on ´electrical systole´ as well as ´mechanical systole´, values for the latter having been borrowed from Weitz, 1918. He argued that as electrocardiographic measurement of systole correlated well with mechanical systole, a similar formula may be used to describe the relation of heart rate and electrical systole. He was able to find a hyperbolic relation between electrical systolic times and cardiac cycle length (Figure A) - Electrical Systole = k x $\sqrt{\text{Cardiac Cycle Length}}$. Of all the suggested correction factors his has remained the most popular because of its simplicity.
As the QTc which corrects the measured QT interval for an arbitary heart rate of 60 beats per minute: [QTc = measured QT interval/k$\sqrt{[\text{cardiac cycle length (seconds)}]}$ is widely used for comparison of data, a more detailed examination of the original data on which it is based is called for: Bazett´s data dealing with electrical systole consisted of the following groups of subjects:
20 normal men; (28 values - heart rate; 34 to 105 beats per minute);



Normal values for ventricular systole (electrical), the *P-R* interval, and the duration of the *Q.R.S.* group in men, including also five observations on infants, which form the five resting values at the extreme left of the curve.

Electrical Systole ..	Resting	●	On the top curve.
„ „	After exercise	○	On the top curve.
P-R Interval ..	Resting	▲	
„ „	After exercise	△	
Q.R.S. Group ..	Resting	●	On the lowest curve.
„ ..	After exercise	○	On the lowest curve.

Figure A . Bazett´s hyperbolic heart rate/QT interval relation. (Heart 1918-20, Volume VII, page 358).

19 normal women; (31 values; heart rate, 65 to 105 beats per minute);
5 children aged 1 day to 2 months (heart rates; 114 to 198 beats per minute) and 16 'exercise QT values' in 3 men. The formula which he provided apparently included all the measurements on these cases, although this is not definitely stated to be the case.
Despite its acceptance through common usage, Bazett's QTc has therefore some serious obvious weaknesses, largely resulting from the fact that the heart rate/QT interval relation was derived from very inhomogenous data:

(i) The data included both resting and post-exercise values.

(ii) Resting heart rates varied from 34 to 198 bpm (!).

(iii) There were no true exercise data, as he was unable to record the electrocardiogram during exercise; his 'exercise' values were recorded after 0.5 to 13 minutes rest and with only 8 'exercise' heart rates being greater than 100 bpm.

(iv) No clinical information was provided about the patients beyond their sex. In particular he did not mention any drug therapy the subjects may have been taking which could have affected the results.

Bazett himself was aware that his k was anything but

constant under a variety of situations such as rest and during exercise. He reported larger k values for women (males, k=0.37; females, k=0.40) and suggested that this reflected the effect of differences in heart size. In support of this, he referred to studies by Meakins (1919), which had shown that the duration of the electrical systole was increased in patients with large hearts. But as Bazett himself pointed out, Meakins´ conclusions had referred to mechanical systole and not the QT interval, the relation between the two variables being different in patients with diseased and enlarged hearts due to differences in sympathetic activity (Wiggers, 1917). Furthermore, mechanical systole is sensitive to afterload but not the QT interval.

Other Proposed Correction Formulae:

That heart rate/QT interval relation was intrinsically subject to patient variation which depended on factors other than heart rate was apparently forgotten in the following sixty years. During this period, attempts were made to improve on Bazett´s formula (Table IA). Fenn (1922), Cheer and Li (1930), Shipley and Halloran (1936) and Hegglin and Holtzmann (1937) provided square root formulae which approximated Bazett´s. Fridericia (1920) proposed a cube root formula, which was supported by other workers (Miki, 1922; and Schlomka and Raab, 1936). Staniforth (1983), using atropine, hyoscine and

exercise to obtain a range of heart rates, proposed a power formula which approximates to the cube root formula of Fridericia (1920) as providing the best curve fit. Mayeda (1934) also derived a power curve formula to describe the cardiac cycle length/QT interval relation whilst Adams (1936), Schlamowitz (1946), Rickards et al., (1979) and Rickards and Norman (1981) have reported that this relation is essentially linear. Simonson et al., (1942) proposed a loglinear relation between QT interval and cardiac cycle length. Ashman (1939 and 1942) and Manion et al., (1980) have also reported that a logarithmic formula is better than Bazett´s formula at correcting the measured QT interval for differences in heart rate.

Apart from Bazett, other workers have noted that sex (Cheer and Li, 1930; Adams, 1936 and Shipley and Halloran, 1936) and age (Schlomka and Raab, 1936 and Simonson et al., 1942) or both (Ashman, 1939 and 1942 and Ashman et al., 1945), had a small but significant effect on the QT interval.

Many of these studies contain experimental bias that limit their value. In particular most of the equations are derived from data towards which each subject has often made only a single contribution. The heart rate/QT interval relation has not been analysed in any detail on a

within-patient basis. The equations may be relevant in comparing inter-population QT interval changes. They cannot be applied freely to situations where QT interval changes are studied in individual subjects or have been brought about by therapeutic manoeuvres.

The Effect of Autonomic Nervous System Activity on the Duration of the QT Interval:

Bazett in his classic paper (1920), draws attention to the "importance of the action of the vagus and sympathetic". He refers to the work of Hunt (1899) who "found that the vagus affected both systole and diastole, but the latter to a larger extent, while sympathetic stimulation caused greater changes in the duration of systole in proportion to the change in pulse rate", and the work of Patterson (1915), who had shown that adrenaline infusion caused a "lessening of k". His own results, which were based, as observed, on very limited data, indicated an increase in the value of k after exercise which he explained on the basis of "an absence of the normal balance between vagal and sympathetic activity".

Other workers have also noted that the heart rate/QT interval relation varies widely and consequently heart rate could not explain all the changes in the duration of the QT interval.

Ashman (1942) for instance reported that this relation in an individual patient varied when changes in heart rate were brought about by exercise from which occurred as consequence of a paroxysmal tachycardia. Simonson et al., (1942) discovered that although within the upper limits of normal, the various correction formulae provided similar QT intervals, a wide scatter existed when QT values were correlated with heart rate. He was unable to explain the variation in the QT interval in spite of analysing a host of factors with the aid of a computer. Only age appeared to make a small contribution. Geppert (1949) also analysed the relation between heart rate and QT intervals using linear and exponential formulae based on data derived on 600 occasions from one healthy individual. The variation of the ´constants´ for both formulae were enormous.

More recently, Manion and his colleagues (1980) have also emphasized the disparate nature of the heart rate/QT relation which they studied in eleven subjects - in one individual there were marked changes in the QT interval at nearly the same heart rate, but in another individual, the QT interval remained invariate through marked changes in heart rate. A similar observation has been made by Anderson (1981), who noted that, in children who demonstrated marked sinus arrhythmia, the uncorrected QT interval remained stable despite wide excursions in heart rate resulting in wide variations in the QTc.

These studies have been extended to show that QT interval changes during pacing at rest are less than those which occur during exercise. Rickards et al., (1979) compared the heart rate/QT interval relation in 3 groups of patients:

Group 1. Ten patients who were not on any medication which would be likely to affect the QT interval and who underwent maximal exercise tests. The results were initially reported as follows;

Heart Rate (bpm) = -0.45QT(ms) + 248 (r= 0.83), otherwise expressed as, QT (ms) = 551 - 2.22 x Heart Rate (bpm). The QT interval changes during exercise therefore appeared to be sensitive to small alterations in heart rate.

Group 2. Fifteen patients who were on beta adrenergic receptor blocking drugs and who also underwent maximal exercise tests. There was no significant difference between the slopes of the linear regression equations describing the heart rate/QT interval relations in groups 1 and 2.

Group 3. Fifteen patients who underwent an atrial pacing stress test in the cardiac laboratory. In this group of patients the authors did not record any change in QT interval and they therefore concluded that heart rate per se had no effect on the QT interval.

In a reappraisal of their data (Rickards and Norman, 1981), the following linear regression equations were provided to describe the heart rate/QT interval relations,

presumably for the same group of subjects:
QT (ms) = 522 - 1.87 x Heart Rate (Groups 1 and 2) and
QT (ms) = 399 - 0.66 x Paced-Atrial Rate (Group 3),
(Figure B).
Hence, two-thirds of the QT interval shortening during exercise could not be explained on the basis of an increase in heart rate.
In support of these findings a fourth group of patients in complete heart block with implanted ventricular pacemakers were exercised. Despite a constant ventricular rate, the QT interval did shorten with exercise. Furthermore, a close correlation existed between the independent atrial rate and the QT interval changes:
QT = 530 - 0.95 x Atrial Rate (n = 9). They presumed that there was no autonomic innervation of ventricular myocardium and hence concluded that most of the QT interval changes during exercise were brought about by circulating catecholamines. No mention was made about the heart rate/QT interval relation in individual subjects.
In a series of similar studies, Milne et al. (1980) examined the heart rate/QT interval relation during atrial pacing at 3 rates at rest - 100, 130 and 150 beats per minute - during ventricular pacing at 2 rates at rest - 88 and 138 beats per minute, and during exercise at a fixed-ventricular rate. The respective approximate linear regression equations were as follows;
QT (ms)= 500 - 1.46 x Paced-Atrial Rate (bpm),

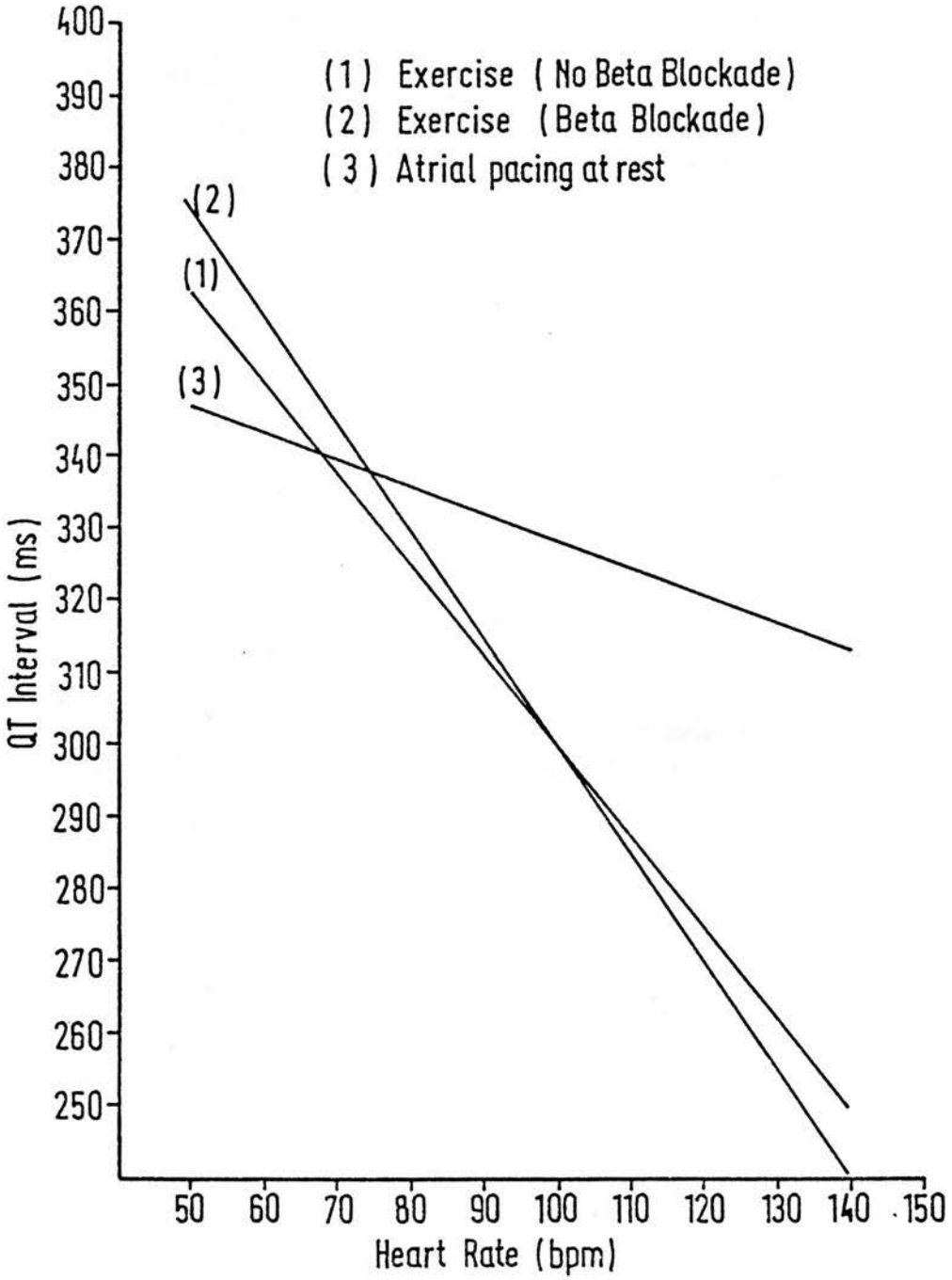


Figure B . Heart rate/QT interval relations based on observations of Rickards and Norman (1981).

QT (ms) = 548 - 1.22 x Paced-Ventricular Rate (bpm) and QT (ms) = 481 - 0.61 x Paced-Ventricular Rate (bpm). Their conclusions were also that sympathetic nervous system activity did shorten the QT intervals during fixed-rate ventricular pacing but their results suggested that the role of sympathetic nervous system was less important than heart rate in determining the duration of the QT interval.

A different approach has been to evaluate the contribution of the autonomic nervous system to QT interval changes by studying the effect of atropine and beta blockers to patients during fixed-rate atrial pacing. Browne et al., (1982) have reported that atropine shortened the atrially-paced QT interval but that propranolol had no effect in this respect. Atropine plus propranolol shortened the atrially paced QT interval from 330 $\pm$ 28 ms to 315 $\pm$ 27 ms. Ahnve et al., (1982) have also reported that for identical paced-rates, propranolol had no effect on the duration of the QT interval. They also found that the addition of atropine shortened the QT interval. These studies suggest that at rest sympathetic nervous system activity does not determine the duration of the QT interval and furthermore that the cholinergic nervous system has a direct effect on ventricular myocardium and QT interval.

Anatomic Basis for the Influence of Autonomic Nervous System on the QT Interval:

The heart is profusely innervated by sympathetic and parasympathetic divisions of the autonomic nervous system, which contain both afferent and efferent fibres (Levy and Martin, 1979).

The efferent pre-ganglionic sympathetic fibres emerge from the spinal column through white rami communicantes of the upper six thoracic segments to synapse about cells in the upper thoracic and cervical ganglia.

From these, post-ganglionic fibres emerge to form the sympathetic cardiac nerves.

The efferent cardiac parasympathetic nerves are derived from the dorsal nucleus of the vagus and from cells near the nucleus ambiguus and run in the cardiac branches of the vagus to synapse about cells in intra cardiac ganglia, usually close to structures innervated by post-ganglionic neurons.

Until recently the view was held that there was no vagal innervation of the mammalian ventricles (Sarnoff and Mitchell, 1962). Since then considerable evidence has accrued to support the concept of an appreciable vagal innervation of the mammalian ventricles (Duchene-Marullaz, 1973; Higgins et al., 1973; Levy, 1976; Levy and Martin, 1979). Choline acetyl tranferase, the enzyme that catalyzes the production of acetyl choline in parasympathetic nerves and muscarinic cholinergic

receptors has been shown to be present in mammalian ventricle (Schmid et al., 1978; Fields et al., 1978) and nerves that stained for acetylcholinesterase have been found in ventricular myocardium (Kent et al., 1974). Vagal efferent nerves approach the heart over the posterior atria and may reach the ventricular myocardium via the ventricular septum as well as the epicardium (Hirsch, 1971).

(i) Adrenergic Effects:

The effects of catecholamines are mediated through beta receptors located at the outside of the cell membranes (Reuter, 1974). Beta receptor activation may operate through an increase in cyclic AMP. This in turn is believed to activate a protein kinase (Reuter, 1974 and 1976; Fozzard, 1981) which catalyzes the phosphorylation of proteins associated with I_{si} channels and the sarcoplasmic reticulum (Watanabe and Besch, 1974; Tada et al., 1975). In this way the number of Ca^{++} channels are increased. In sarcoplasmic reticulum membranes protein phosphorylation leads to an increase in Ca^{++}-ATP-ase activity and Ca^{++} uptake by the organelles and thus to an increase in the rate of relaxation.

In sino atrial cells, catecholamines increase the rate of diastolic depolarization (hence the chronotropic effect), increase the maximal rate of depolarization, elevate the plateau height and slightly shorten the action

potential duration (Carmaliet, 1982). Catecholamines also increase the plateau amplitude and shorten the action potential duration and refractory period of Purkinje fibres (Wit et al., 1979; Zipes et al., 1981; Carmaliet, 1982).

Zipes et al. (1981), report that beta adrenoreceptor stimulation has little effect on ventricular action potential. Conversely, catecholamines are reported to lengthen or shorten the action potential, depending on the type of substance and its concentration (Quadbeck and Reiter, 1975 and 1975; Wit et al., 1979). Shortening of the action potential due to sympathetic stimulation is believed to be mediated through an increase in the K^+ current (Noble and Tsien, 1965). Intracellular studies have shown that ganglion blocking agents prolong the action potential, presumably by decreasing the amplitude of the K^+ channels in the membrane (Ito and Surawicz, 1981). Drugs that block the function of postganglionic adrenergic nerves have similar effects on myocardial repolarization. The prolongation of the repolarization phase of the ventricular action potential by bretylium tosylate has been well shown in vitro by Bigger and Jaffe, (1971). Similarly, bethanidine increases the duration of the ventricular action potential - the 'evoked response' (Donaldson and Rickards, 1982).

Adrenergic stimulation has been also been reported to shorten the ventricular refractory period

(Brookes et al., 1955; Reddy and Gettes, 1979). Beta blockade, however, has been shown to shorten only insignificantly the duration of the right ventricular effective refractory period (Prystowsky et al., 1980). The influences of the sympathetic nerve stimulation on the heart are modulated by cholinergic activity and are hence dependent to some extent on vagal innervation. Furthermore the effects of the right and left sympathetic nerves on ventricular refractory period are not uniform over large areas of both ventricles (Moore and Swain, 1960; Yanowitz et al., 1966; Kralios et al., 1975). This dispersion of refractoriness may provide one mechanism by which sympathetic neural output might result in ventricular arrhythmias.

The QT interval also prolongs following left stellate ganglion stimulation or interuption of the right stellate ganglion (Yanowitz et al., 1966). The long QT syndrome (Jervell and Lange-Nielson, 1957; Romano et al., 1963; Ward, 1964) , an inherited defect which causes some children to faint during exercise or emotional states associated with a prolonged QT interval and sometimes an alternating T-wave and a predisposition to ventricular fibrillation, may result from a congenital imbalance in cardiac sympathetic innervation, characterized by reduced right sympathetic activity and/or enhanced activity of the left stellate ganglion (Yanowitz et al., 1966; Moss and McDonald, 1971; Crampton, 1979).

(ii) Vagal Effects:

There are several examples of cholinergic-adrenergic interaction (Levy, 1977), notably (a) interneural e.g. presynaptic muscarinic inhibition of noradrenaline release by sympathetic nerve endings and (b) intracellular - muscarinic agonists modulate the effects of beta agonists through inhibition of beta-induced activation of adenylcyclase (Gardner 1976; Watanabe et al., 1978 and 1978; Muscholl, 1982).

Vagal effects on ventricular action potential duration and recovery of excitability are not settled.
Vagal stimulation has been shown to prolong ventricular effective refractory period by antagonizing sympathetic activity via muscarinic receptors (Zipes et al., 1981). The magnitude of vagal effects on the ventricular effective recovery would therefore be expected to be accentuated in the presence of increased sympathetic activity (Zipes et al., 1981). Ventricular effective refractory period is also shortened by intravenous atropine (Prystowsky et al., 1981; Browne et al., 1982). Thus the evidence currently suggests that resting vagal tone exerts a significant effect on human right ventricular refractoriness and that this effect can occur during beta adrenergic blockade (Zipes et al., 1981). Vagal-induced prolongation of the ventricular effective refractory period may be one mechanism by which

cholinergic stimulation may terminate a ventricular tachycardia (Waxman and Wald, 1979).

The resting parasympathetic tone affects the QT interval directly in man and withdrawal of the vagal tone shortens the QT interval (Browne et al., 1982; Ahnve et al., 1982).

Martins and Zipes (1980) studied the effect of right and left vagal nerve stimulation on the QT intervals measured from nine separate ventricular sites and found QT prolongation at all sites except the anterior right ventricle. This correlated with the effective refractory period measured at the same sites. This nonuniform response to vagal stimulation may result from unequal distribution of vagal or sympathetic innervation or unequal electrophysiological responses to autonomic influences and could play a role in the genesis of some arrhythmias (Zipes et al., 1981).

Electrophysiological Basis for the Heart Rate/Systolic Time Interval Relation:

It has been known for some time that an increase in heart rate is accompanied by an abbreviation of systolic time, thereby ensuring adequate time for diastolic filling of the ventricles. This is partly due to a purely rate-dependent shortening of the action potential (Hoffman and Cranefield, 1960; Boyett and Jewell, 1978) and partly to the action of adrenaline on the myocardium

(Morad et al., 1972). Experiments on mammalian cardiac muscle have shown that cathecholamines not only cause a rate dependent shortening of the action potential but also abbreviate systole by enhancing the rate of myocardial relaxation through an action which is independent of heart rate (Boyett and Jewell, 1978).

The electrolyte currents responsible for the production of the action potential are illustrated in Figure C. The duration of the action potential depends in part on the processes responsible for repolarization of the cell membrane. The factors which are believed to be involved in this process are:

1. Inactivation of the slow inward current.
2. Growth of the outward current.
3. Return of K^+ conductance (inward rectification).

Repolarization is then followed by a period of membrane recovery during which the slow inward current recovers from inactivation and the outward current decays to resting values.

Increased rate of myocardial stimulation may interfere with the processes of repolarization and membrane recovery and thereby shorten the action potential by several mechanisms (Vaughan Williams, 1980):

1. Triggering of an action potential before the recovery phase is complete may reduce the amount of slow inward current that can be activated (Gettes et al.,

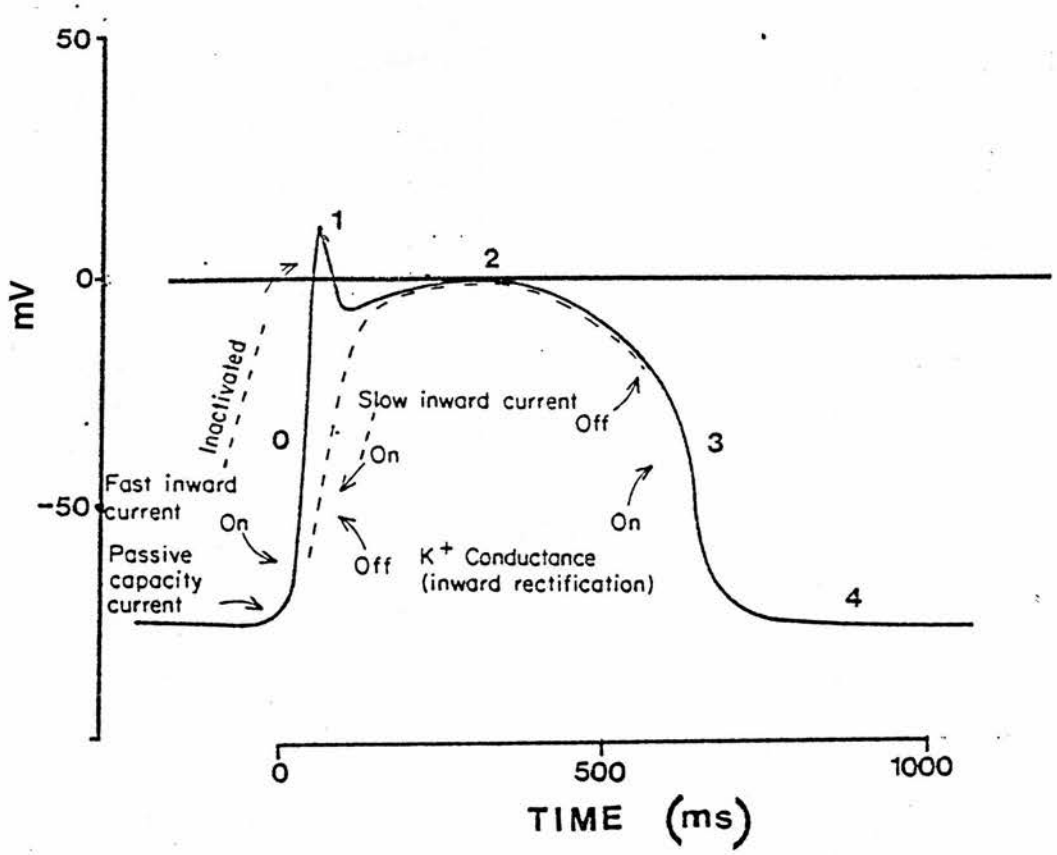


Figure C . Electrolyte currents responsible for the production of the action potential.

1974). Furthermore the outward current may not have had time to decay fully (de Hemptinne, 1971; Hauswirth et al., 1972).

2. Accumulation of Ca^{++} intracellularly may reduce the electrochemical gradient for the slow inward current (Reuter, 1973), or increase the outward current through an action on the K^{+} membrane permeability (Meech, 1976; Bassingthwaigthe et al., 1977; Gelles, 1977; Isenberg, 1977).
3. Accumulation of K^{+} in the extracellular clefts (Noble and Tsien, 1965; Kline and Morad, 1976).

The relative importance of these mechanisms in causing a rate-dependent shortening of the action potential is as yet ill defined. However, mechanisms 2 and 3 are believed to play a greater role in contributing to action potential reduction at rates in excess of 100 beats per minute (Vaughan Williams, 1980).

The Effect of Beta Adrenergic Receptor Blockade on the QT Interval:

(i) Acute Versus Chronic Beta Adrenergic Blockade:

It is now believed that the secondary effects of prolonged beta-adrenoreceptor blockade can be distinguished from the

acute effects. Microelectrode studies of rabbit cardiac muscle (Vaughan Williams et al., 1975; Vaughan Williams, 1978) have shown that prolonged beta-blockade significantly prolonged action potentials in animals, in contrast to the absence of acute beta-blockade action on cardiac action potential duration. The QT interval steadily lengthens after a week, reaching a plateau at 3 to 4 weeks. Similar observations have been made in man. Seides et al., (1974) reported that intravenous propranolol had no effect on the duration of the QT interval.

Chronic treatment with beta-blockers has been reported to cause a relative prolongation of the QT interval (Raine and Pickering, 1977). Edvardsson and Olsson (1981) have also shown that prolongation of monophasic action potential duration occurs with chronic but not acute administration of metoprolol.

Adaptation of the Heart Rate/QT Interval Relation to Prolonged Beta Adrenergic Blockade:

Vaughan Williams (1980) noted that prolongation of the action potential due to chronic beta blocker therapy persisted after cessation of treatment. He distinguished the therapeutic response and QT interval changes due to prolonged beta adrenergic blockade while patients were still taking the drug from 'adaptation' to treatment i.e. from effects which persisted after treatment had been

interrupted for a sufficient length of time to permit all drugs to be eliminated from the body.

As part of their studies Vaughan Williams et al., (1980 and 1982) recorded the electrocardiogram in a group of normal subjects at rest and during exercise, before and after intravenous beta blocker therapy [Cardioselective drugs; atenolol (5mg) and metoprolol (10 mg) and non-selective drugs; pindolol (0.4 mg) and propranolol (1 mg)]. The subjects were subsequently put on the corresponding oral preparations of beta blocker therapy for four weeks, (total daily dose: 100 mg atenolol, 200 mg metoprolol, 15 mg pindolol and 160 mg propranolol, respectively). The electrocardiogram was re-examined at rest and on exercise 52 hours after the last dose of beta blocker drugs.

The heart rate responses while the subjects were taking the drug were different in the two groups. In the cardioselective group there was a significant bradycardia at rest which was absent in the non-selective group. Adaptation to prolonged beta-adrenoreceptor therapy was also different in the two groups; the resting and exercise heart rates were lower after 52 hours of cessation of treatment with the cardioselective drugs but a similar effect was not seen with the non-selective drugs. Adaptations in the heart rate/QT interval relation were also observed with the cardioselective drugs. (The QT interval was expressed as a function of the R-R interval

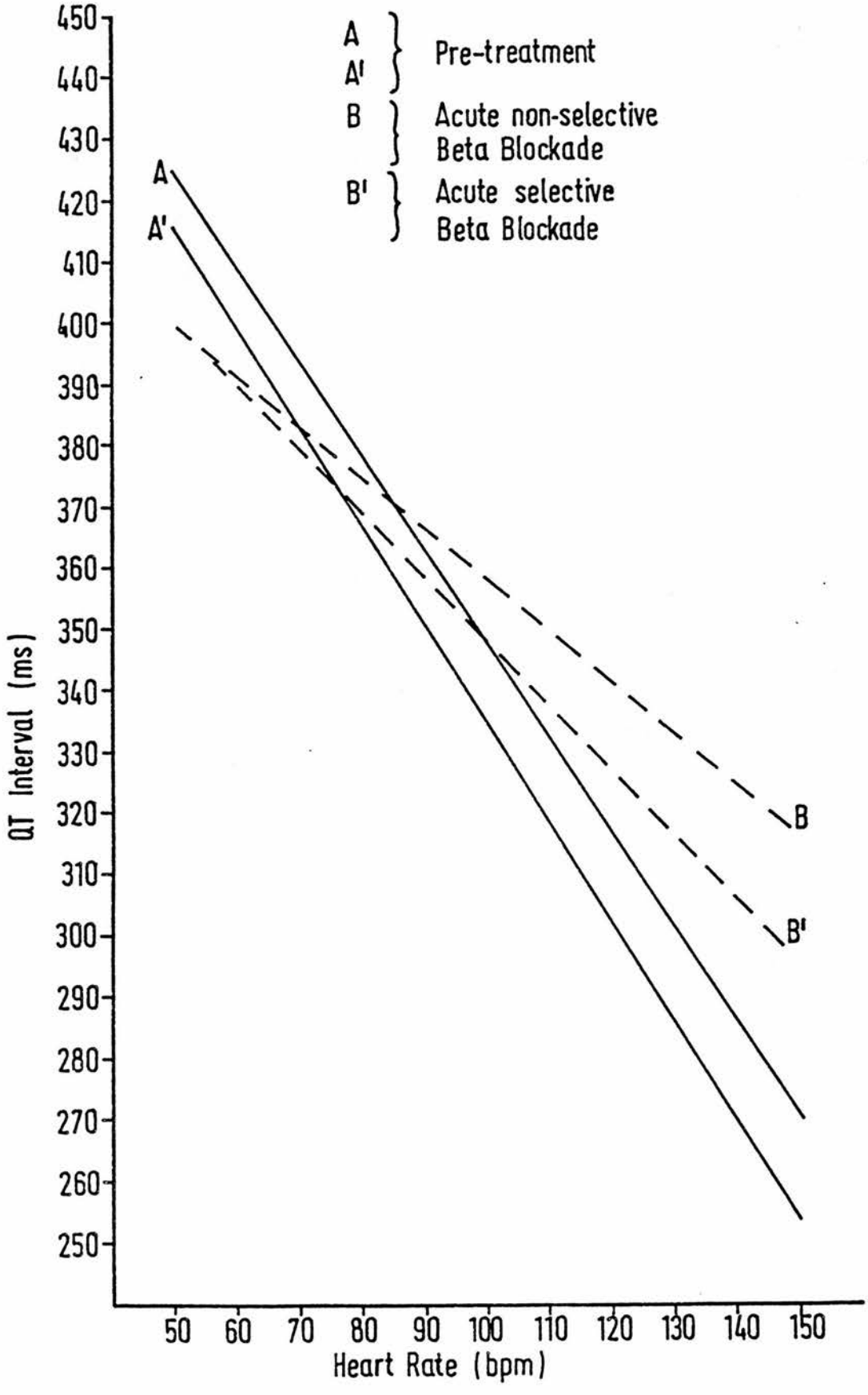
using linear regression equations. For the sake of simplicity the QT intervals are expressed as a function of heart rate here). Table IB and Figure D show the results in the two groups of patients.

Their interpretation of these results was that no 'adaptation' of the heart rate/QT interval relation had occurred after 4 weeks with the non-selective drugs although the QT interval had prolonged by 16 ms. On the other hand the slope of the heart rate/QT regression had flattened at rest and on exercise with the selective beta adrenergic blockers.

Although there was a considerable flattening of the slopes of the regression equations after acute beta adrenergic blockade at rest and to a much smaller extent during exercise with the non-selective drugs, it is difficult to understand why a similar change in the heart rate/QT interval relation was not seen during exercise with the cardioselective drugs. The equations also surprisingly suggest that the QT interval shortened at the lower heart rates after acute beta adrenergic blockade with both types of drugs.

Rickards and Norman (1981) had also studied the heart rate/QT interval relation during exercise in patients who were not on any beta blockers and in patients who were taking propranolol chronically. They did not observe any difference in the slopes of the regression equations of the two groups. To reconcile this finding with their

Figure D. The effect of beta adrenergic receptor blockade on the heart rate/QT interval relations based on the observations of Vaughan Williams (1980 and 1982).


A
A'
Pre-treatment
B
Acute non-selective
Beta Blockade
B'
Acute selective
Beta Blockade
A
A'
B
B'
QT Interval (ms)
450
440
430
420
410
400
390
380
370
360
350
340
330
320
310
300
290
280
270
260
250
50
60
70
80
90
100
110
120
130
140
150
Heart Rate (bpm)

belief that the sympathetic activity accounted for most of the changes in the QT interval during exercise, they advanced the explanation that the 'effect of propranolol in blocking the sinus response to circulating catecholamines is accompanied by a similar blocking of the effect of circulating cathecholamines on repolarisation time (QT interval) of the ventricular myocardium' (Akhras and Rickards, 1980). Closer examination of this statement, however, shows that this hardly explains why over even a small range of heart rate changes during exercise (such as that which occurs after beta blockade) the QT interval should shorten so rapidly if heart rate per se is not an important factor in influencing changes in the QT interval, the effect of the sympathetic nervous system activity having presumably been totally blocked.

Adaptation to Beta Blocker Therapy:

Two distinct factors have been postulated which may control the relation between heart rate and QT interval (Vaughan Williams, 1980);

1. A 'metabolic' factor, perhaps related to the level of intracellular glycogen and glycolytically-produced sub-sarcolemmal ATP (Cowan and Vaughan Williams, 1977 and 1980). The availability of this factor could be a function of the level of beta-adrenoreceptor activation.
2. A 'biophysical' factor, purely related to heart

rate, and under the control of the time-and-voltage 'gating' of the ionic channels.

It is proposed (Vaughan Williams, 1980) that acute beta adrenergic receptor blockade, or adaptation to prolonged beta adrenergic receptor blockade, could attenuate the metabolic factor, leaving the rather feeble regression of the rate-dependent biophysical factor.

Heart Rate/Ventricular Effective Refractory Period/QT Interval Relations:

Introduction:

The QT interval is thought to reflect the sum of the action potential durations of all ventricular muscle cells. In common with the QT interval, ventricular refractoriness is influenced by heart rate (Mendez et al., 1956). A covariation has also been described between QT interval duration and the refractoriness of ventricular myocardium (Guss et al., 1976). However, the relation of QT interval and ventricular recovery time is complex in that factors which alter recovery time may result in paradoxical effects on the QT interval (Lewis and Drury, 1926; Hoffman, 1960; Janse et al., 1969; Denes et al., 1974). For example, left stellate ganglion stimulation which frequently results in prolongation of the

QT interval, reduces the refractory period in the innervated area (Janse et al., 1969; Denes et al., 1974). This suggests that prolongation of the QT interval may sometimes reflect a cardiac state with greater than normal disparity of recovery times rather than one in which simply prolonged recovery is present. The degree of inequality of recovery times in cardiac muscle has been documented as a possible factor in arrhythmia susceptibility (Drury, 1936; Mendez et al., 1956; Bigger and Heissenbuttel; 1969; Spear et al., 1973; Castellanos et al., 1973; Castellanous et al., 1973; Guss et al., 1975; Kastor et al., 1975). Increases in the ratio 'effective refractory period:action potential duration' have been observed when antiarrhythmic drugs are administered, and have been suggested to be an important feature of the effectiveness of such drugs (Bigger and Heissenbuttel, 1969). Preliminary studies in patients support some of these in vitro findings (Guss et al., 1975 and 1976). The present study examines the relations of ventricular effective refractory period and the QT interval to changes in heart rate induced by pacing. The heart rate/QT interval/ventricular effective refractory period relations were also explored following administration of amiodarone and sotalol - drugs with reputed Class III antiarrhythmic properties.

Amiodarone:

Amiodarone is very effective in the treatment of atrial, junctional and ventricular tachyarrhythmias (Dreifus and Ogawa, 1977; Fidelle et al., 1976; Wheeler et al., 1979; Kaski et al., 1981). Its antiarrhythmic properties are principally due to prolongation of the transmembrane action potential duration and hence refractory period of myocardial contractile fibres (Olsson et al., 1973; Coumel et al., 1978; Fananapazir et al., 1984) and the specialized conducting system (Cabasson et al., 1976; Rosenbaum et al., 1974; Wellens et al., 1976; Nadamanee et al., 1982). Amiodarone also exerts a non-competitive beta-receptor blocking effect (Charlier, 1970; Singh and Vaughan Williams, 1970). Its advantage over many other antiarrhythmic agents resides in its extreme effectiveness, long half-life which facilitates patient compliance and the absence of any significant negative inotropic effect.

Sotalol:

Sotalol was initially described as a pure beta adrenergic antagonist with class II antiarrhythmic action, but lacking cardioselectivity, intrinsic sympathomimetic effect, or local anaesthetic properties (Lish et al., 1965; Fitzgerald, 1969; Vaughan Williams, 1970). Subsequent animal investigations have shown that sotalol

also increases the action potential duration, similar to that seen with amiodarone (Singh and Vaughan Williams, 1970; Strauss et al., 1970). Edvardsson et al., (1980) also noted prolongation of right ventricular monophasic action potentials in man and recently Bennett (1982) and Nathan et al. (1982) have reported prolongation of the atrial (AERP) and ventricular (VERP) refractory periods. These effects are consistent with class III action (Vaughan Williams, 1970).

The effect of intravenous (0.4mg/Kg) sotalol on the VERP and the QT interval in the study of Nathan et al., was as follows:

VERP prolonged from 231±30 ms to 242±31 ms (by 11 ms)

AERP prolonged from 216±38 ms to 233±40 ms (by 17 ms).

The atrially-paced QT interval prolonged from 388±43 ms to 400±37 ms (i.e. by 12 ms)

Bennett (1982) measured the refractory periods 10 to 20 minutes after completion of an infusion of 1.5 mg/kg sotalol, given over 5 minutes:

VERP prolonged from 209±23 ms to 245±20 ms (36 ms)

AERP prolonged from 224±37 ms to 264±49 ms (40 ms)

The QT interval changes were not documented in this study.

Summary:

The literature indicates that both heart rate and autonomic nervous system affect the duration of the QT interval for which there appears to be good anatomical and physiological bases.

The first part of this thesis addresses itself to examining in greater detail factors which determine the duration of the QT interval and the related ventricular effective refractory period and the effect of certain drugs on these intervals.

Table IA Proposed formulae in the literature for the correction of measured QT interval for differences in heart rate and comparison of QT intervals based on these formulae and derived for three heart rates.

Author (year)	Subjects	Correction Formula	A	B	C
Bazett (1920)	20 males	$QT=0.37\sqrt{RR'Interval}$	370	290	230
	19 females	$QT=0.40\sqrt{RR'Interval}$	400	310	250
	(plus 5 children and 16 'exercise' values in 3 men)				
Fridericia (1920)	50 men, women and children	$QT=0.0822\sqrt[3]{100xRR'Interval}$	382	322	281
Fenn (1922)	10 males and females	$QT=0.39\sqrt{RR'Interval}$	390	300	250
Cheer and Li (1930)	75 males	$QT=0.374\sqrt{RR'Interval}$	374	290	240
	43 females	$QT=0.3877\sqrt{RR'Interval}$	388	300	250
Mayeda (1934)	135 males	$QT=[0.2574(100xRR')]^{0.604}$	461	339	265
	61 females				
Adams (1936)	males	$QT=0.1536(RR')+0.2462$	399	338	308
	females	$QT=0.1259(RR')+0.2789$	405	354	329
Schlomka and Raab (1936)	age, 20-40 k=0.0795	$QT=k\sqrt[3]{100xRR'}$	369	311	272
	41-60 k=0.0802		373	314	274
	61-70 k=0.0815		379	319	279

Table IAcontinued:

Author (year)	Subjects	Correction Formulae	A	B	C
Shipley and Halloran (1936)	(n=200) males	$QT=0.397\sqrt{RR'}\pm0.04$	397	308	251
	females	$QT=0.415\sqrt{RR'}\pm0.04$	415	321	262
Hegglin and Holtzmann (1937)	(n=700)	$QT=0.39\sqrt{RR'}$	390	302	247
Simonson (1942)		$\log QT=0.320\log RR'+0.000354age-0.4185$ or $QT=0.2423+0.14RR'+0.003age$	382	326	298
Ashman and Hall (1945)	younger men and children	$QT=K \times \log[10(RR' + k)]$ (K=0.375, k=0.07)	396	318	260
	>45 years, males	(K=0.380, k=0.07)			
	>45 years females	(K=0.390, k=0.70)			
Schlamowitz (1946)	1419 cycle lengths in 650 soldiers	$QT=0.205RR' + 0.167$	410	335	249
Rickards and Norman (1980)	n=25	$QT=522-1.87\times Rate$	410	335	242

A, B and C = QT intervals (ms) estimated at hearts of 60, 100 and 150 beats per minute, respectively.

Table IB. The heart rate/QT interval relations before and after beta adrenergic receptor blockade and after withdrawal of therapy with non-selective and cardioselective drugs, based on the observations of Vaughan Williams (1980 and 1982).

Type of Beta-blocker	Period	Heart Rate/QT Interval Relation QT = a - b x Heart Rate
Non-selective	Pre-Treatment	498 - 1.63x Heart Rate
	IV/BB Rest	453 - 1.05x Heart Rate
	IV/BB Exercise	464 - 1.42x Heart Rate
	Day 29/52hr after cessation of BB - Rest	503 - 1.56x Heart Rate
	Day 29/52hr after cessation of BB -exercise	513 - 1.86x Heart Rate
Cardioselective	Pre-Treatment	503 - 1.56x Heart Rate
	IV/BB Rest	440 - 0.82x Heart Rate
	IV/BB Exercise	499 - 1.65x Heart Rate
	Day 29/52hr after cessation of BB - Rest	448 - 0.75x Heart Rate
	Day 29/52hr after cessation of BB - Exercise	476 - 1.36x Heart Rate

Abbreviations; BB=beta blocker; IV=intravenous.

CHAPTER II PATIENTS AND METHODS

QT-INTERVAL MEASUREMENT

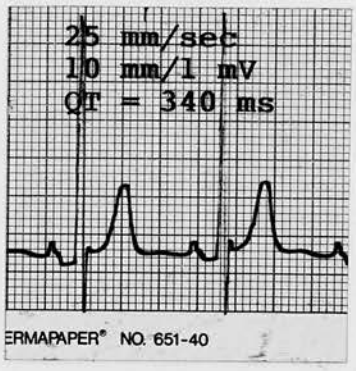
Accurate measurement of the QT interval is hindered by several factors including observer variation. The onset and termination of electrical activity of the surface electrocardiogram is dependent on the lead recorded. The onset is earliest in leads V_{1-3} and the termination is usually latest in the Standard limb lead II (Lepeschkin and Surawicz, 1952).

Recordings of a single lead may give differences of duration of the QT interval as great as 40 ms, as alterations in the T wave vector may masquerade as changes in the QT interval. Wherever possible, therefore, 3 more or less orthogonal leads were recorded.

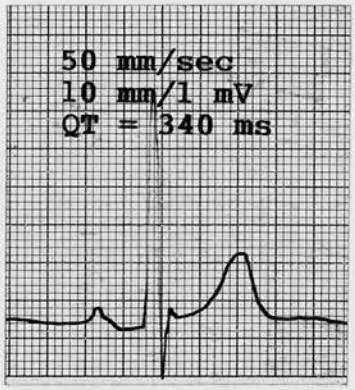
Care was taken not to include QT intervals of QRS complexes of different widths in the same data. The same set of leads was used in any particular patient or study. Measurements were made using the lead with the longest QT interval and the most distinct termination of the T wave. The QT interval was measured using a pair of dividers, from the onset of the q wave or the R wave in the absence of a q wave, or the pacing artefact during ventricular pacing to the termination of the T wave, i.e. the point where the downslope of the T wave met the isoelectric baseline (Figure 1A-C), (Ashman, 1942 and 1947; Lepeschkin, 1951). The mean of 4 estimates of each QT

Figure 1. Examples of QT intervals of normal QRS complexes, measured at a paper speed of 25 mm per second (A), 50 mm per second (B), and pre- and post-exercise at 25 mm per second (C); QT interval of ventricularly- (D) and atrially-paced (E) complexes, measured at a paper speed of 50 mm per second.

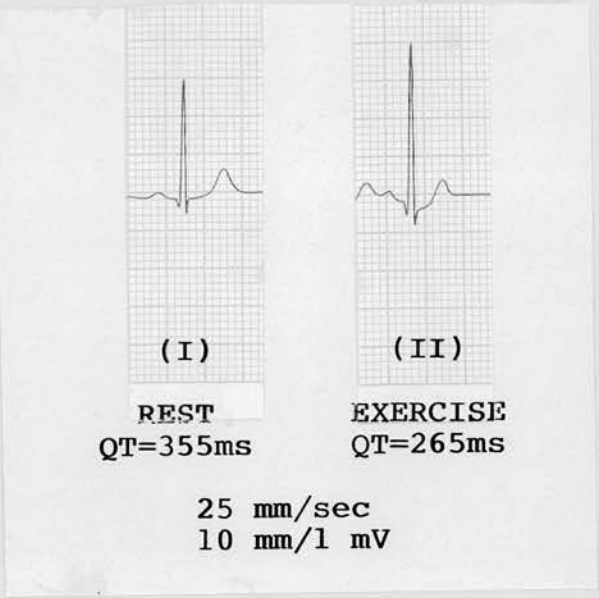
A


25 mm/sec
10 mm/1 mV
QT = 340 ms
ERMAPAPER® NO. 651-40

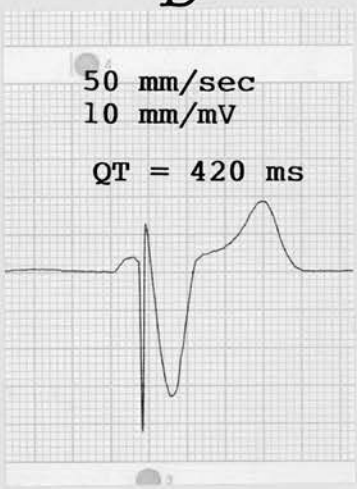
B


50 mm/sec
10 mm/1 mV
QT = 340 ms

C


(I)
(II)
REST
QT=355ms
EXERCISE
QT=265ms
25 mm/sec
10 mm/1 mV

D


50 mm/sec
10 mm/mV
QT = 420 ms

E

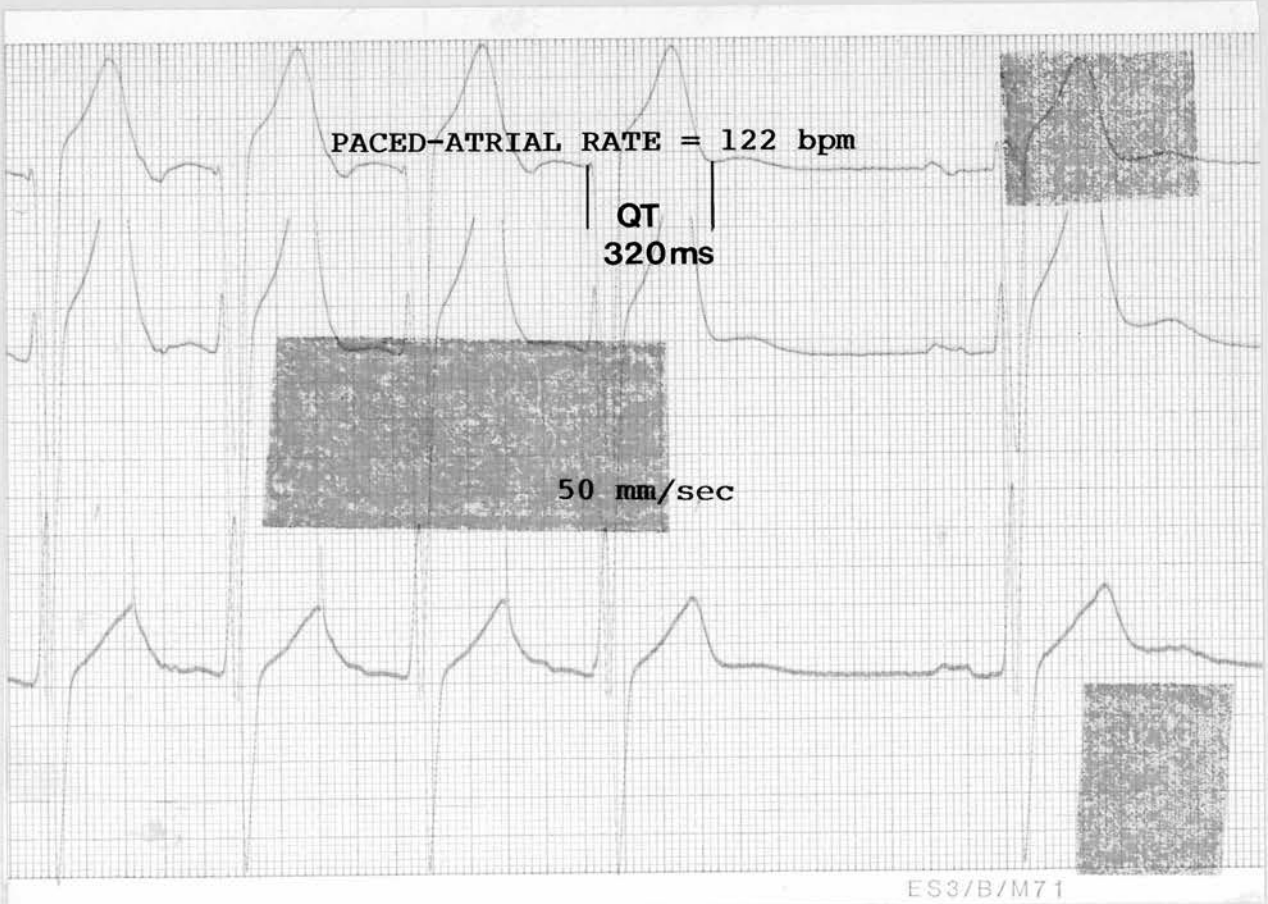

PACED-ATRIAL RATE = 122 bpm
QT
320ms
50 mm/sec
ES3/B/M71

Figure 2. Examples of QT intervals which were unsatisfactory for measurement.

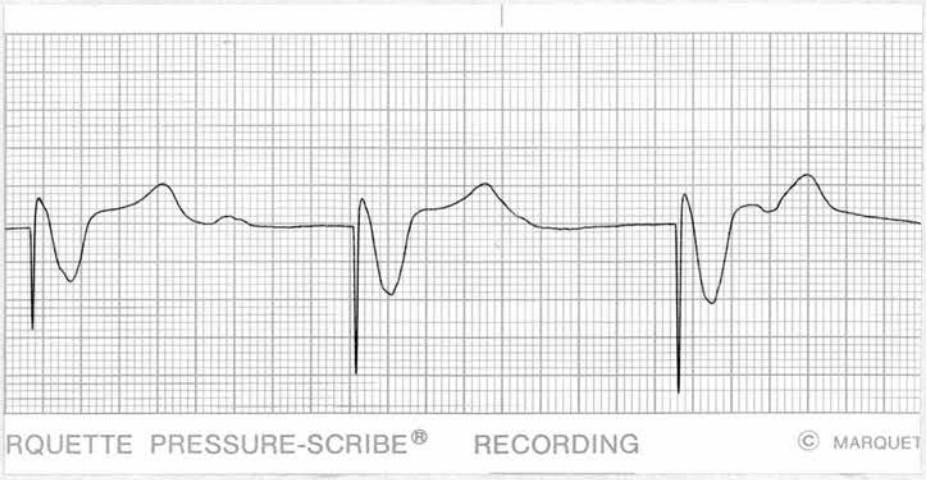
A - Collision of P waves with the terminal portion of the T wave.

B - Prominent U waves.

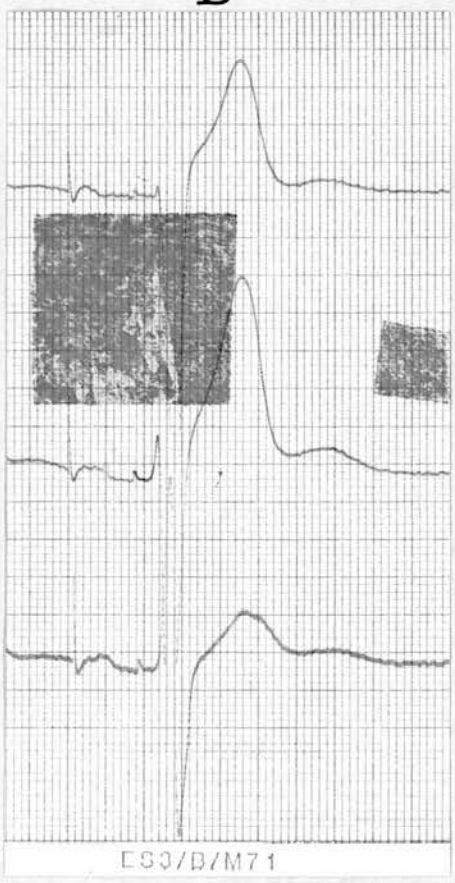
C - biphasic T wave.

D - unstable baseline.

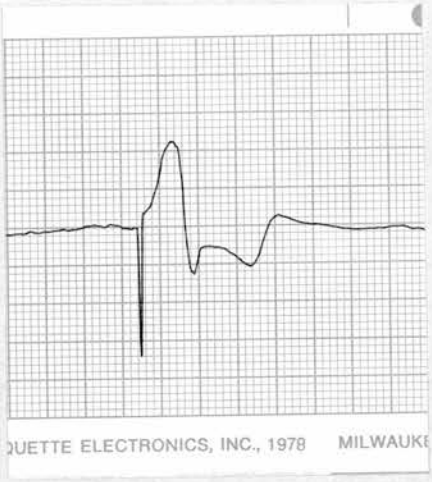
A


RQUETTE PRESSURE-SCRIBE®
RECORDING
© MARQUET

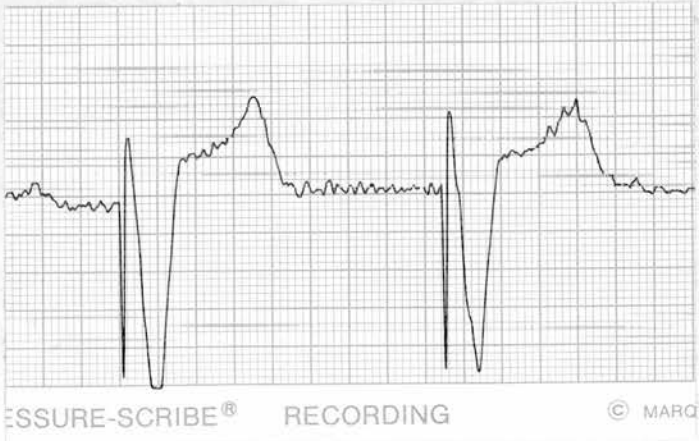
B


ES3/B/M71

C


UETTE ELECTRONICS, INC., 1978
MILWAUKE

D


ESSURE-SCRIBE®
RECORDING
© MARQ

interval was used in calculations.

At high pacing rates, the pacing artefact (or the resultant p wave during atrial pacing) may fuse with the preceding T wave, thereby rendering impossible any measurement of the QT interval. This was overcome by switching off the pacemaker and measuring the QT interval of the last of a sequence of paced-complexes (Figure 1D).

The following circumstances were regarded as unsatisfactory for QT interval measurements (Figure 2):

1. Presence of complexes where p or U waves obscured the terminal portion of the T wave.
2. Presence of notched, bifid, biphasic, flat or inverted T waves.
3. Presence of complexes with indistinct terminal portion of the T wave.
4. Presence of muscle tremor or irregular baseline.

Paper Speed:

Except were indicated, QT intervals were measured at paper speeds of 50 or 100 mm per second, (mostly on a six-channel electrocardiographic recorder, Mingograph, Siemens).

Exercise data presented in Sections C, E and F were recorded using a Marquette CASE Computer Assisted System for Exercising (MFG Milwaukee Marquette Electronics). This system provided only a paper speed of 25 mm per second. QT interval measurements were facilitated by the

provision of a stable baseline. Precision of measurement may be more difficult when assessing the QT interval with electrocardiographic recordings at a paper speed of 25 mm per second than at higher rates (Ahnve et al., 1978 and 1980; Crampton, 1979). However, QT interval measurements at a paper speed of 25 mm per second have also been used in larger studies (Haynes et al., 1978; Doroghazi and Childers, 1978; Schwartz and Wolf, 1978) without methodological problems. An advantage of this lower speed is the acute angle with which the T wave meets the isoelectric line. This end point often merges imperceptibly with the baseline at paper speeds of 100 mm per second.

Statistics

Regression Equations - Curve Fitting:

The following regression equations were used to express the relation between two variables e.g. heart rate and QT interval:

Linear regression line;	$y = a + bx$
Exponential regression curve;	$y = ae^{bx}$
Logarithmic regression curve;	$y = a + b.\ln.x$
Power curve;	$y = ax^{b}$

The correlation coefficient r is an index of the extent to

which the relation between the two variables x and y approaches the extreme situation in which every point on the scatter diagram falls on a straight line. It therefore indicates the quality of fit of each of the regression equations.

The linear regression describing the rate/QT interval relation for a group of subjects in whom the rate/QT interval relation had been determined individually, was calculated by estimating the mean QT interval over a range of heart rates, as predicted by the separate linear regression equations and deriving the rate/mean QT interval linear relation.

Correlation between two variables was also tested non-parametrically using Spearman's Correlation Test.

Significant Differences between paired-numbers were calculated using Wilcoxon's Signed Rank test and for non-paired numbers using Wilcoxon's Sum Of Ranks Test.

The Significance of the Difference in the Slope of Two Linear Regression Lines:

The significance of the difference between the slopes of two linear regression lines was calculated as follows: let S_{y1} be the standard error of the estimate for line 1, based on n pairs of observations, and S_{y2} be the

standard error of the estimate for line 2, based on n pairs of observations,

(a) Calculate $s^2 = \frac{[(n - 1)Sy_1^2 + (n - 1)Sy_2^2]}{n_1 + n_2 - 2}$

(b) Calculate standard error of the estimate of slopes $(b_1 - b_2)$:

$$SE(b_1 - b_2) = s\sqrt{\frac{1}{\sum(x - x)^2} + \frac{1}{\sum(x - \bar{x})^2}}$$

N.B. $\sum_{i=1}^{n}(x_i - x)^2 = \sum_{i=1}^{n}x_i^2 - \frac{(\sum x_i)^2}{n}$

and

(c) Test b_1 versus b_2: $t(n_1 + n_2 - 2) = \frac{b_1 - b_2}{SE\ (b_1 - b_2)}$

(A). Intra-Observer Error:

The intra-observer error of the QT interval measurements was estimated from the exercise data, as these were most likely to yield the largest intra-observer variation. Forty random QT interval measurements performed several months earlier were repeated without knowledge of the original estimates.

The estimate of within-subject (intra-observer) variance=

$\sigma^2 = \sum X^2 + \sum Y^2 - \frac{\sum(X+Y)^2}{2} \div n$

Where X and Y are respectively, estimates of the QT interval made on the first and second occasions and n = number of estimates per occasion.

Coefficient of intra-oberver error = $\frac{\sigma}{\text{Mean}}$ x 100 (%)

Where mean = $\frac{\sum(X+Y)}{2n}$

(B). Heart Rate/QT Interval Relation During Exercise - Curve Fitting:

The electrocardiographic recordings of 14 patients (age; 28 to 61 years, 10 males) who had undergone a treadmill exercise test as part of their investigations for suspected but unproven ischaemic heart disease, were examined. The electrocardiogram was normal in all subjects. None of the patients was on any medication. Correlation coefficients of linear, exponential, logarithmic and power curve regression equations describing the exercise heart rate/QT interval relation were compared.

(C). 'Normal Resting QT Interval':

Resting QT interval values were examined in 2 studies:

(i) Recordings Made After a Period of Rest in Patients with Normal Atrio-Ventricular Conduction:

The electrocardiogram was recorded in the supine position, at 5 minute intervals, after at least 2 hours of bed rest in a quiet room. A total of 122 electrocardiographic recordings were made in 10 subjects (aged 34 to 65 years, 7 males). The electrocardiogram was normal in all subjects. One subject had received a mild sedation

(valium 5mg) 2 hours prior to the study. None of the remaining subjects was on any medication.

(ii) Electrocardiographic Recordings Made During Sleep in Patients with Normal Atrio-Ventricular Conduction:

Two electrocardiographic recordings, separated by an interval of 15 minutes, were made in each of 12 subjects during deep slumber of at least 30 minutes duration. Six subjects had received a mild sedation (5mg to 10mg valium). Subjects with abnormal resting electrocardiograms were excluded from the study.

(D). Heart Rate/QT Interval Relation During Exercise:

Patients and methods were as described in section B.

(E-i And E-ii). Comparison of Resting Paced-Atrial Rate/QT Interval and Paced-Ventricular Rate/QT Interval Relations:

Eleven patients, aged 56 to 72 (mean 63) years, underwent atrial and vetricular pacing in the coronary care unit, at rates of 60 to 170 bpm, in increments of 5 to 10 bpm. Seven patients were being paced for sinoatrial disease and 4 patients were under investigation for suspected ischaemic heart disease.

(E-iii) The Rate of Adaptation of the QT Interval to Changes in Ventricular Pacing Rate:

The rate at which the QT interval adapts to a lower paced-ventricular rate was estimated in 6 patients (aged 56 to 77 years; 3 males) with third degree atrio-ventricular block who were awaiting implantation of a permanent pacing system and who were not on any medication. The studies were performed in a quiet room in the supine position. Right ventricular pacing was performed via a temporary electrode, at a rate of 110 beats per minute (bpm), for 10 minutes. At the end of this period, the electrocardiogram was recorded at a paper speed of 50 mm per second for 15 seconds and pacing then

suddenly switched to a rate of 50 bpm whilst recording the electrocardiogram continuously for a further 5 minutes. The QT intervals of complexes just before the change in heart rate and of consecutive complexes thereafter were measured.

(F). Contribution of Heart Rate to QT Interval Shortening During Exercise:

Twenty four patients with implanted atrial synchronized ventricular pacemakers (Cordis models 208A and 308A) were studied. Their ages ranged from 20 to 76 (mean 47) years; 14 patients were male. None of the patients was receiving medication. Maximal exercise testing was performed on a treadmill using the Bruce protocol (Bruce, 1971), with the pacemaker programmed to one or another of two pacing modes selected randomly;

(1) fixed-rate ventricular pacing at 70 bpm (VOO) and

(2) atrial synchronized ventricular (VAT) pacing mode.

The pacemaker was then reprogrammed to the other pacing mode and the exercise repeated after at least 30 minutes rest.

In individual patients, the contribution of factors other than heart rate to the total QT interval shortening during exercise was estimated by comparing the slopes of their regression equations describing the atrial rate/QT interval relation in the VOO and VAT pacing modes:

QT interval shortening at atrial rates of x_1 and x_2 during VOO pacing mode

$v = a_1 - b_1.x_1$ minus $a_1 - b_1.x_2$

$= b_1(x_2 - x_1)$

Similarly, QT shortening at a heart rate of x_1 and x_2 during VAT pacing mode

$= a_2 - b_2.x_1$ minus $a_2 - b_2.x_2$

$= b_2(x_2 - x_1)$

Hence for a given increase in atrial rate from x_1 to x_2, the QT interval shortening during VOO mode pacing (due to factors unrelated to heart rate), compared with that during VAT pacing mode and for a similar change in atrial rate (due to all factors), equals:

$$\frac{b_1}{b_2} \frac{(x_2 - x_1)}{(x_2 - x_1)}$$

or $\frac{\text{slope of regression equation during VOO mode}}{\text{slope of regression equation during VAT mode}} \times 100(\%)$

(G). Heart Rate/QT Interval Relation - Inter-Patient and Intra-Patient Variation:

(i) Exercise Heart Rate/QT Interval Relation in Patients with Normal QRS Configuration and Atrio-Ventricular Conduction:

Linear regression equations describing the heart rate/QT interval relation was examined in Section C patients to determine the extent to which this relation exhibited patient variation.

(ii) Exercise Paced-Ventricular Rate /QT Interval Relation in Patients with Atrial Synchronized Ventricular Pacemakers - Inter-Patient Variation:

(a) QT interval variability was examined at a paced-ventricular rate of 70 bpm at rest.

(b) Variability of paced-ventricular rate/QT interval relation during exercise in VAT pacing mode was examined in the 24 patients with atrial synchronized ventricular pacemakers (Section F).

(c) Contribution of Heart Rate to Exercise-Induced QT Interval Shortening - A Within Patient Study of Inter-Patient and Intra-Patient Variation:

In 11 of the 24 patients with atrial synchronized ventricular pacemakers discussed in Section F, treadmill exercise tests during both pacing modes (VOO and VAT) were repeated after an interval of 8 to 12 weeks.

Changes in the paced-ventricular rate/QT interval relation with the passage of time were examined on a within-patient basis by comparing the linear regression equations of the two pairs of exercise tests in each subject.

(H). Effect of Acute Beta Adrenergic Receptor Blockade on the Heart Rate/QT Interval Relation:

(i). Effect of Acute Beta Adrenergic Receptor Blockade on the Paced-Ventricular Rate/QT Interval Relation in Patients with Atrial Synchronized Ventricular Pacemakers:

In 3 patients with atrial synchronized ventricular pacemakers treadmill exercise tests were performed during fixed-rate, 70 bpm, and atrial synchronized ventricular pacing modes, with at least an hour of rest in between tests. The patients were re-exercised 2 hours after beta adrenergic receptor blockade with an oral dose of 100 mg oral atenolol. Each patient therefore had a total of 4 exercise tests.

(I-i). Paced-Ventricular Rate/QT Interval/Ventricular Effective Refractory Period Relations:

Ventricular Effective Refractory Period:

Fourteen patients participated in the study. The patients were those with complete heart block who were awaiting implantation of a permanent pacing system and who had temporary ventricular leads, or who were undergoing electrophysiological studies. None of the patients was on any medication which was likely to affect the QT interval or ventricular effective refractory period.

Each subject underwent ventricular pacing at a randomly selected rate for a period of two minutes, following which the ventricular effective refractory period was measured by the extrastimulus technique (Curry, 1975) using a programmable stimulator (Devices) and 5 ms decrements, at a pulse duration of 1.0 ms and at twice diastolic thresholds. Ventricular effective refractory period was defined as the longest coupling interval of ventricular extrastimuli which did not result in ventricular depolarization (Figure 3). The electrocardiogram was simultaneously recorded at a paper speed of 50 or 100 mm per second. The paced-ventricular rate/QT interval and paced-ventricular rate/ventricular effective refractory period relations were established in individual subjects, by repeating the above exercise for as many paced-ventricular rates as possible.

(ii) Effect of Acute Beta Adrenergic Receptor Blockade on the Heart Rate/QT Interval Relation During Exercise, in Normal Subjects:

The effects of acute beta adrenergic receptor blockade on the heart rate/QT interval relation during exercise were examined in 9 normal subjects, aged 28 to 40 years (8 males). Each subject underwent an identical treadmill exercise test before and 2 hours after an oral dose of 100 mg atenolol.

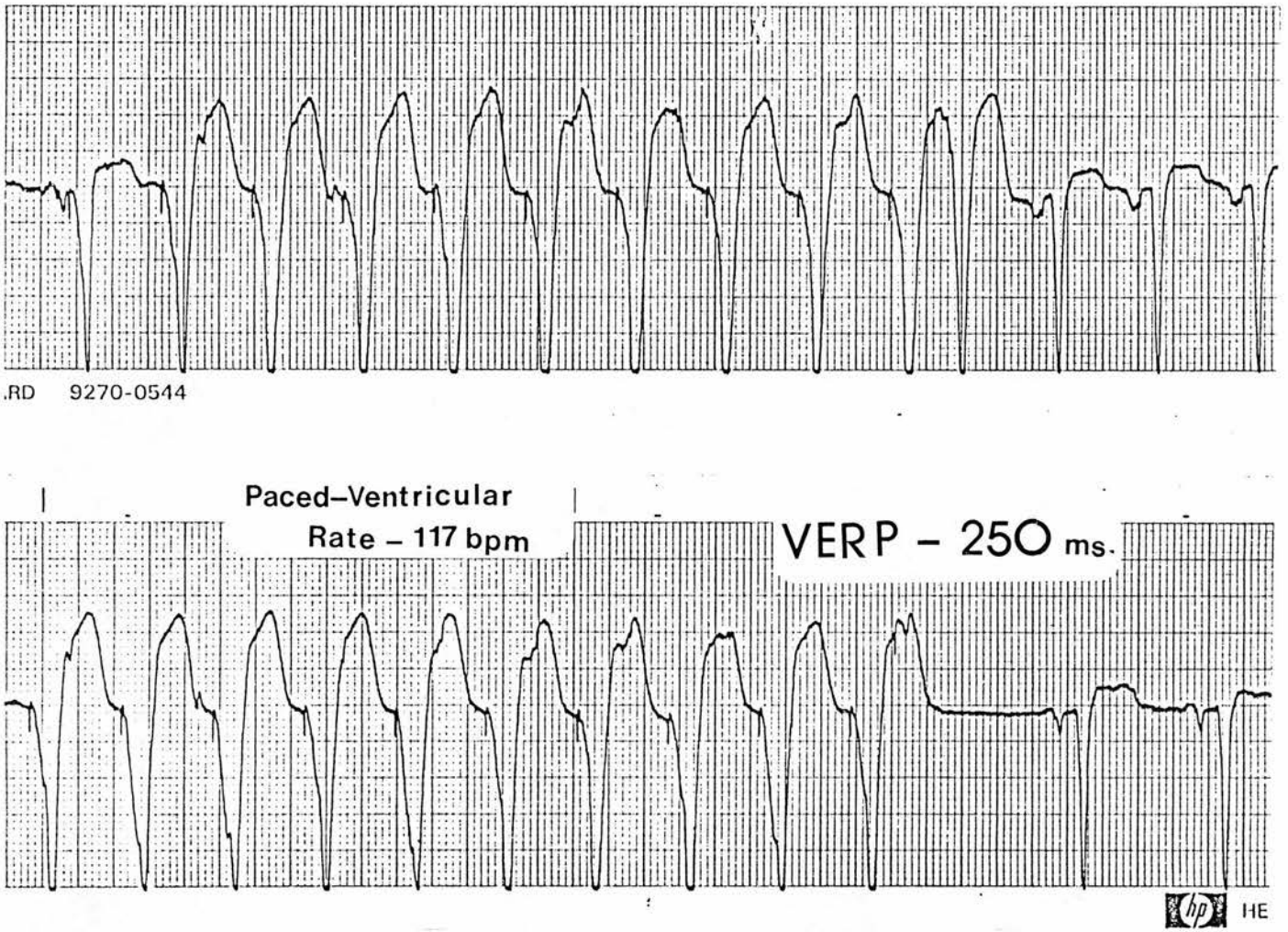
(iii). The Effect of Chronic Beta Adrenergic Receptor Blockade on the Heart Rate/QT Interval Relation During Exercise:

The effects of prolonged beta adrenergic receptor blockade on the heart rate/QT interval relation were studied by examining the exercise electrocardiograms of 22 patients who were on a daily oral dose of 100 mg atenolol and had been on this medication for more than 3 months (mean 5.5 months; range 3.5 to 10 months). Patients with significant exercise-induced ischaemic ST/T wave changes were excluded from the study.

(ii) Effect of Amiodarone on the Paced-Ventricular Rate/QT Interval/Effective Ventricular Refractory Period Relations:

The effects of amiodarone on the QT interval and ventricular refractory period was studied in 10 patients who were being treated in the coronary care unit for a variety of tachyarrythmias which had proven resistent to conventional therapy. There were 9 males. The average age of the patients was 63 years (range, 50 to 73 years). Five drug half-lives separated previous medication and institution of amiodarone therapy. Each patient was treated with a 5 mg/kg intravenous amiodarone, given over 30 minutes, followed by a further 1000 mg intravenous drug over 24 hours. This was followed by a once or twice daily dose of 400 mg amiodarone for two weeks. Once every twenty four hours, the patients were paced at a ventricular rate of 120 beats per minute for a period of 2 minutes and the ventricular effective refractory period and QT interval were then measured at the same paced-ventricular rate.

Figure 3. Measurement of ventricular effective refractory period (VERP) by the extra-stimulus technique.



(iii) Effect of Sotalol on the Paced-Ventricular Rate/QT Interval/Effective Ventricular Refractory Period Relations:

Using the electrocardiographic and refractory period measurements from 13 patients provided kindly by Dr. D.H. Bennett, QT intervals and ventricular effective refractory period changes were compared at a paced-ventricular rate of 120 beats per minute, before and 10 to 20 minutes after the completion of an infusion of sotalol hydrochloride, 1.5 mg per kg body weight, given over 5 minutes.

CHAPTER III RESULTS

(A). Estimation of Error of QT Interval Measurements - Intra-Observer Error:

In order to assess the error of QT interval measurements, 40 QT interval estimations were repeated by the author, 3 to 6 months after the original QT interval calculations to determine the intra-observer error.

The QT intervals estimated on the first and second occasions, X and Y respectively, are shown in Table II.

The within-subject variance for the two sets of QT interval measurements σ^2 is given by the following equations: $\sum X^2 + \sum Y^2 - \frac{\sum (X+Y)^2}{2} \div 40 = 37.$

Hence σ equals 6.08 and the coefficient of intra-observer error equals $\frac{6.08}{389} \times 100 = 1.56\%$

The data was based on exercise data where the paper speed was 25 mm per second and therefore most likely to provide the largest differences in calculations of QT interval performed on the two occasions. The intra-observer error however was satisfactorily small. It is probably even smaller at paper speeds of 50 or 100 mm per second, which was the method most commonly adopted in the thesis, and where QT intervals were measured at rest at a single

heart rate, for example during pacing.
Possible sources of error include indistict terminal portion of the QT interval, presence of prominant T waves and unstable baseline, which were all avoided as far as possible.

(B). Determination of the Regression Equation which Best Describes the Heart Rate/QT Interval Relation - Curve Fitting:

QT intervals measured at various heart rates recorded during treadmill exercise tests in 14 patients are shown in Table III. The data was subjected to linear, exponential, logarithmic and power curve regression analysis to determine which equation best described the heart rate/QT interval relation. Table IV compares their respective coefficients of correlation.
Exponential and linear regression equations provided the most frequent best curve fit (5 patients each, Table IV). The differences were small but exponential regression equations provided the highest mean coefficient of correlation. Coefficients of correlation for exponential equations were significantly higher than those for logarithmic regression equations ($p<0.05$). There were no significant differences between the remaining comparisons.

It was therefore decided to subsequently use linear regression equations to describe the heart rate/QT interval relation, as this facilated comparison of data.

(C-i) QT Interval Values and Heart Rate/QT Interval Relation Determined at Rest:

Heart rate/QT interval relation was examined after prolonged rest in 10 subjects in an attempt to reduce the effect of autonomic nervous system activity on the duration of the QT interval and thus define a narrow range of 'normal' QT intervals. A total of 122 electrocardiographic recordings were made and the measured QT intervals at the various heart rates are shown in Table V.

The mean ($\pm$ 1 S.D.) heart rate and QT interval recorded in each subject is shown in Table VI which shows that, despite prolonged bed rest, there was a significant range of heart rates and that the QT interval varied from 358 $\pm$ 12 ms to 398 $\pm$ 11 ms (mean $\pm$ 1 S.D.) in individual subjects.

A reasonable negative correlation was found between the resting heart rates and QT intervals, which varied in each subject.

The linear regression equation describing the heart rate/QT interval relation in individual subjects was as follows:

Subject	QT = a - b x Heart Rate	r
1.	535 - 2.12 x Heart Rate	-0.86
2.	552 - 2.00 x Heart Rate	-0.62
3.	526 - 2.04 x Heart Rate	-0.66
4.	493 - 1.69 x Heart Rate	-0.68
5.	521 - 2.04 x Heart Rate	-0.70
6.	540 - 2.53 x Heart Rate	-0.79
7.	495 - 1.86 x Heart Rate	-0.85
8.	515 - 1.97 x Heart Rate	-0.70
9.	538 - 2.25 x Heart Rate	-0.75
10.	534 - 1.98 x Heart Rate	-0.83

Bazett´s correction formula provides the following wide range of QT values for a heart rate of 60 beats per minute: 419, 414, 416, 403, 407, 392, 391, 406, 411, 427 ms. From the regression equations the following QT interval values may be derived for the same heart rate: 408, 432, 404, 392, 399, 388, 383, 397, 403 and 415 ms (mean $\pm$ 1 S.D. QT interval - 402 $\pm$ 14 ms).

Hence, it was not possible by this method to eliminate inter-subject and intra-subject variation.

(C-ii) QT Interval and Heart Rate/QT Interval Relation Examined During Sleep:

As heart rate and QT interval measurements during prolonged bed rest may still have been associated with a certain degree of anxiety which may have accounted for the patient variability affecting the heart rate/QT interval relation, electrocardiographic recordings were also made on two occasions during sleep in 12 subjects.

The mean QT intervals and heart rates on the two occasions are shown in Table VII.

Heart rates recorded during sleep were lower than the resting heart rates reported in section C-i. However, the QT intervals again differed significantly from patient to patient; range 370 to 435 ms.

The correlation between heart rate and QT interval was less good because of the small range of these values. Linear regression equation provided the best curve fit and the relation between heart rate and QT interval during sleep for the group could be represented as follows:

QT (ms)= 516 - 1.75 xHeart Rate (bpm), $r = 0.6073$, $p<0.01$.

(The coefficient of correlation for the corresponding exponential, logarithmic and power regression equations, were 0.6136, 0.6044 and 0.6103, respectively).

(D). Heart Rate/QT Interval Relation During Exercise:

Heart rate changes during exercise are mediated through vagal (largely at the beginning) and sympathetic (responsible for most of the changes at maximal exercise test) nervous system activity. The corresponding QT interval changes may be due to alterations in heart rate and autonomic nervous system activity. The heart rate/QT interval relation was examined during exercise in 14 patients to determine whether this differed from that described at rest.

Table VIII shows the linear regression equations describing the heart rate/QT interval relations during treadmill exercise tests in individual subjects.

The results indicated the following:

(a) the exercise heart rate/QT interval relation was subject to significant patient variation and

(b) despite a greater level of sympathetic activity, the slope of the exercise linear regression equation for the group (QT = 493 - 1.57 x heart rate) was less than the resting or sleep regression equations. The heart rate/QT interval relation therefore is linear at heart rates of 68 to 188 beats per minute during exercise, but if the data includes a significant number of resting heart rate and QT interval values (i.e. a combination of Tables III and V) the heart rate/QT interval relation would be more curvilinear.

(E). The Heart Rate/QT Interval Relation at Rest During Pacing:

(i) Atrial Pacing

Heart rate changes during rest and sleep are brought about by fluctuations in autonomic nervous system activity and are largely due to variations in vagal activity. QT interval changes during pacing are more purely rate-related.

The heart rate/QT interval relation was therefore examined during atrial pacing at rest and compared with the heart rate/QT interval relation obtained during exercise.

Linear regression equations describing the atrial rate/QT interval relation at rest in 11 subjects are shown in Table IX.

The slopes of the regression equations obtained at rest during atrial pacing were significantly less ($P<0.01$) than slopes of exercise regression equations (section D).

The overall relation between the paced-atrial rate and QT interval was defined by the following regression equation:

QT Interval (ms) = 465 - 0.98 x Atrial Rate (bpm).

The slope of this regression equation was also significantly less ($p<0.01$) than the slope of the linear regression equation describing the overall heart rate/QT interval relation during exercise (section D).

(ii) Comparison of Paced-Atrial Rate/QT Interval and Paced-Ventricular Rate/QT Interval Relations Determined at Rest:

Certain studies reported in the literature and undertaken in this thesis involve studying the heart rate/QT interval relation with ventricular pacing. This section defines the paced-ventricular rate/QT interval relation at rest and compares the heart rate/QT interval relation during atrial pacing (normal QRS confuguration) and ventricular pacing (broad QRS complexes) at rest in the same group of 11 subjects.

The paced-atrial and ventricular rate/QT interval relations in individual subjects are compared in Table IX.

There was no correlation between the slopes of the paired linear regression equations describing the atrial and ventricular/QT interval relations, probably partly because of the small range of available slopes. There was no significant difference ($p>0.1$) between the slopes of the paced-atrial rate/QT interval and paced-ventricular rate/QT interval regression equations.

The overall paced-ventricular rate/QT interval relation was described by the following linear regression equation: QT Interval (ms) = 537 - 0.99 x Ventricular Rate (bpm). For example, the QT interval at an atrial pacing rate of 60 and 150 beats per minute equals 374 ms and 284 ms i.e. a QT interval shortening of 86 ms and the QT intervals for

identical pacing rates equal 477 ms and 388 ms or a similar QT interval of 89 ms.

(iii) The Rate Of Adaptation of the QT Interval to Changes in Heart Rate:

Heart rate changes constantly during exercise and the heart rate and QT interval measurements are therefore random. During pacing, however, QT interval measurements are made at a constant heart rate after a specified length of time. It was therefore decided to determine whether the QT interval was subject to hystereis in relation to pacing rate. Six patients underwent right ventricular pacing for 10 minutes at a rate of 110 beats per minute. The pacing rate was then suddenly reduced to 50 beats per minute and the duration of the QT interval for each complex thereafter was measured to determine the time it took, if any, for the QT interval to reach a constant value in response to the heart rate.

The results in each subject are illustrated in Figure 4. The missing data was due to collision of p waves with the terminal portion of the T wave. QT interval adaptation to the new lower pacing rate was most rapid in the first 20 seconds, with most of the adaptation completed by 45 seconds.

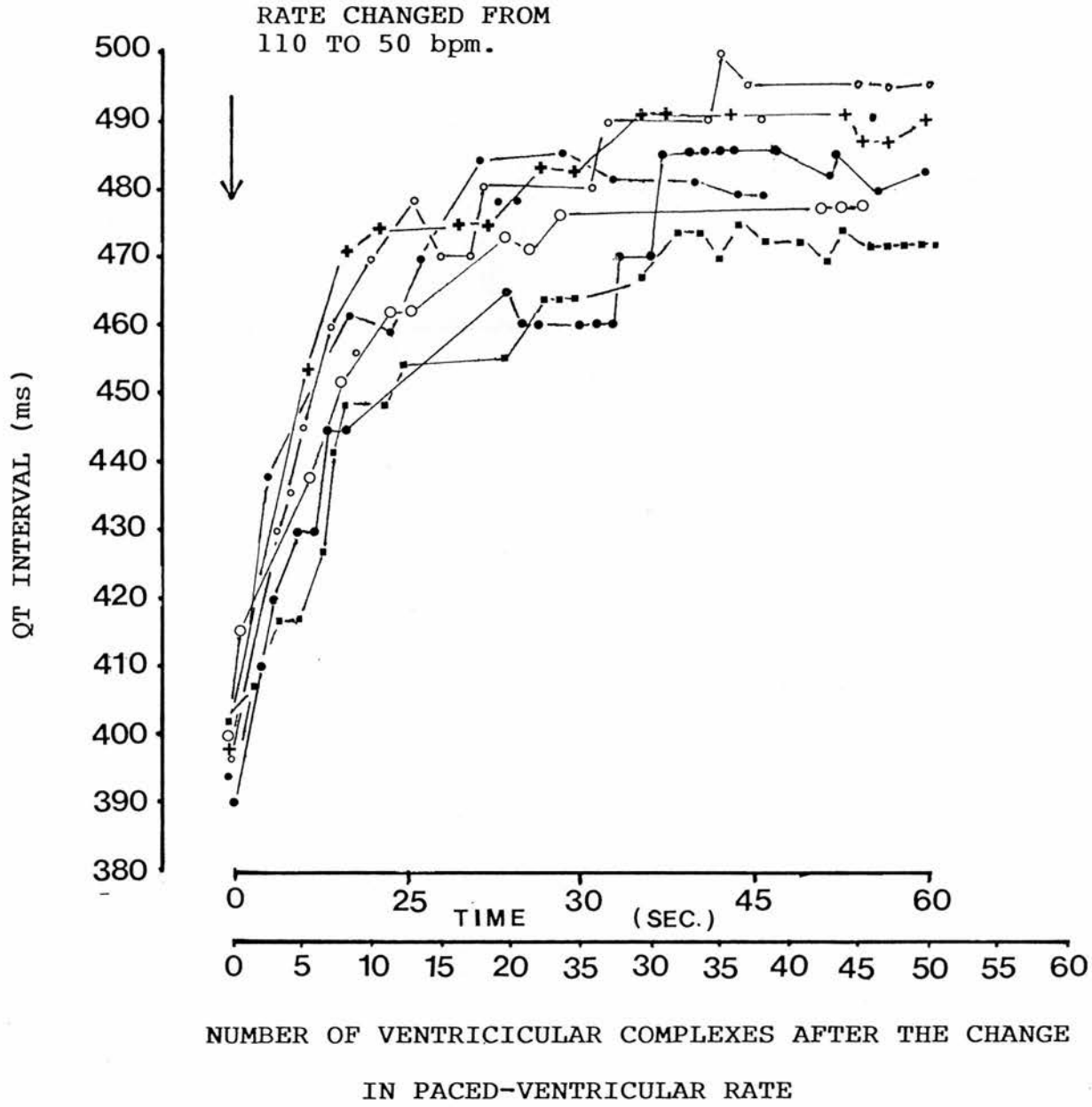


Figure 4. Consecutive QT intervals determined following a change in paced-ventricular rate from 110 to 50 beats per minute.

In each patient, however, exercise-induced QT interval changes during VOO pacing mode were less than the QT interval changes which occurred during VAT pacing for a given increase in atrial rate (Table XI). This is also shown by comparing the slopes of the linear regression equations describing the overall atrial rate/QT interval and paced-ventricular rate/QT interval relations during VOO and VAT pacing modes, respectively;

Fixed-Rate Ventricular Pacing Mode:

QT Interval (ms)= 531 - 0.96x Atrial Rate (bpm) and

Atrial Synchronized Ventricular Pacing Mode:

QT Interval (ms)= 563 - 1.75x Paced-Ventricular Rate (bpm).

Comparison of the slopes of these two regression equations further indicates that only 45% of the QT interval shortening recorded during exercise may be attributed to heart rate.

(F). Contribution of Heart Rate to QT Interval Shortening During Exercise

Patients with implanted atrial synchronized ventricular pacing systems provided the opportunity to quantify the contribution of heart rate to QT interval shortening during exercise on a within patient basis. With the pacemaker programmed externally to fixed-rate, 70 beats per minute ventricular pacing mode (VOO), any QT interval shortening would occur as a result of factors other than heart rate, whilst during atrial synchronized ventricular pacing mode (VAT), heart rate and factors unrelated to heart rate, act on the QT interval.

QT intervals measured in each of the 24 patients with VAT pacemakers at various atrial rates during VOO pacing mode and ventricular pacing rates during VAT pacing modes with exercise are shown in Table X.

The linear regression equations describing the atrial rate/QT interval (VOO mode) and paced-ventricular rate/QT interval (VAT mode) relations during exercise in each subject are compared in Table XI.

The QT interval did shorten during exercise in the absence of a chronotropic response during VOO pacing mode. The QT interval changes during fixed-rate ventricular pacing moreover correlated well with the independent atrial rate, as shown in Table XI and Figures 5 and 6.

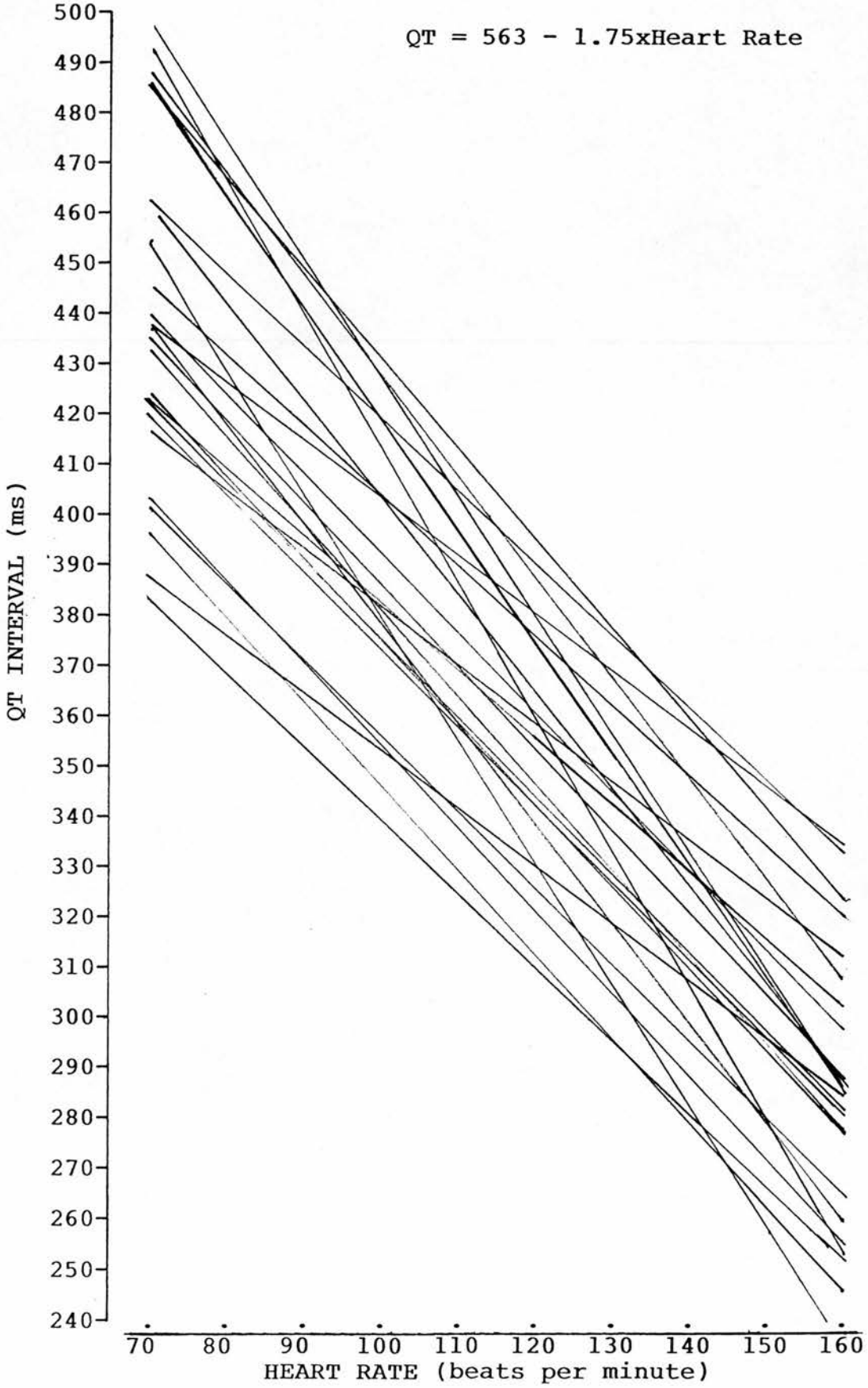


Figure 5. Regression lines describing heart rate/QT interval relations during exercise in atrial synchronized ventricular pacing mode.

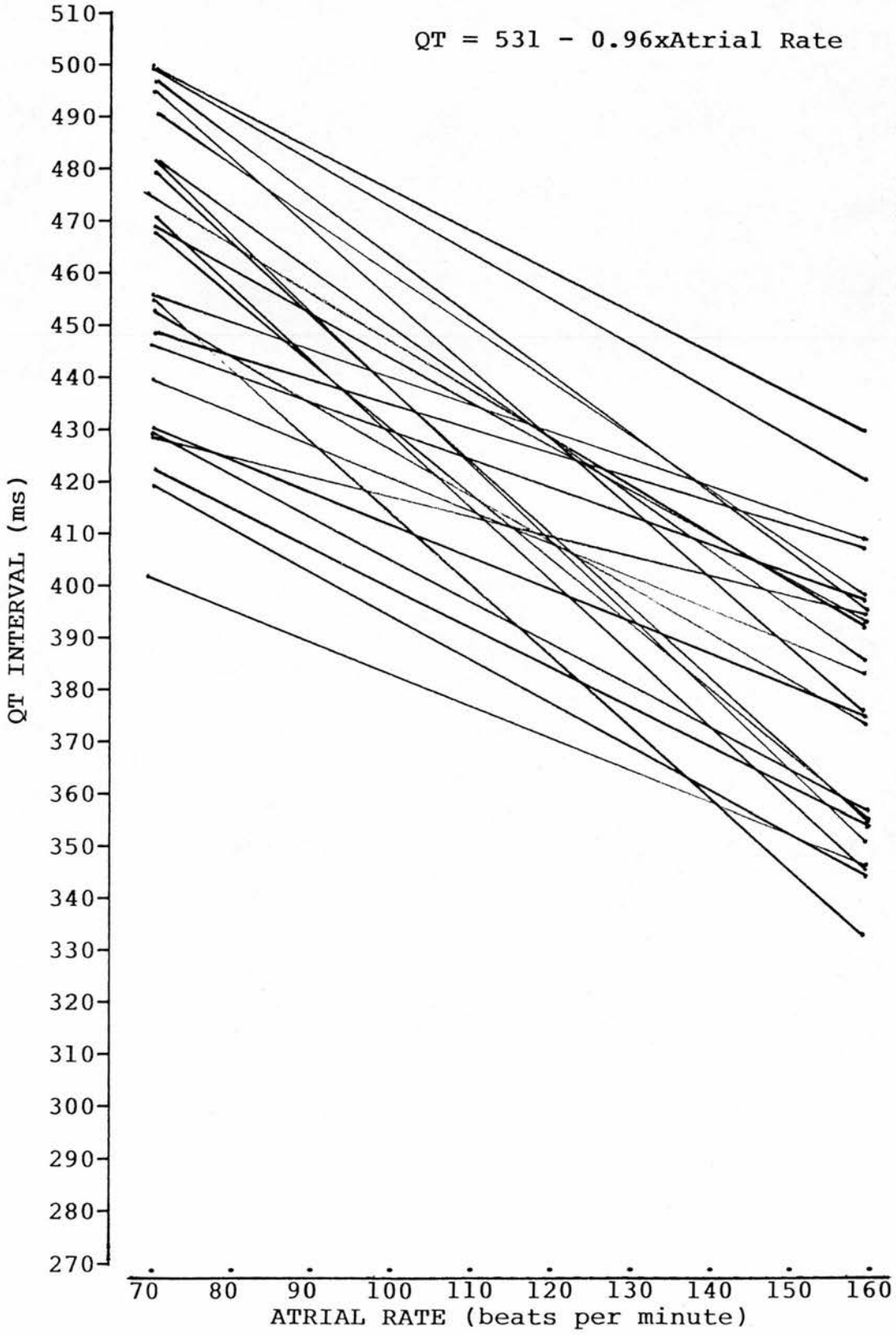


Figure 6. Regression lines describing atrial rate/QT interval relations during exercise in fixed-rate, 70 beats per minute, ventricular pacing mode.

(G) Heart Rate/QT interval Relation - Inter-Patient And Intra-Patient Variation

Examination of the data of several studies indicates that the heart rate/QT interval relation is subject to significant patient variation:

(i) Exercise Heart Rate/QT Interval Relations in Patients with Normal Electrocardiograms:

Comparison of the linear regression equations describing the relation between heart rate and the QT interval during exercise in normal subjects, discussed in section B and detailed in Table IV, shows that the heart rate/QT interval relation varied sigificantly from one subject to another. For example, the regression equations suggest that at a heart rate of 60 beats per minute, the QT interval would vary between 360 ms to 421 ms, or a difference of 61 ms. Similarly, at a heart rate of 150 beats per minute, the QT interval would vary from 209 ms to 328 ms, an even larger variation of 119 ms (Figure 5).

(ii) Evidence from Studies Involving Patients with Implanted Atrial Synchronized Ventricular Pacing Systems:

(i) Variation in the Duration of the QT Interval, Measured During VOO Pacing Mode Prior to Exercise Tests:

The QT interval after 30 minutes of rest measured during

fixed-rate ventricular pacing at 70 beats per minute in the 24 patients with implanted VAT pacing systems prior to the onset of exercise tests showed that the QT interval varied from 395 ms to 510 ms (Table X).

(ii) The Paced-Ventricular Rate/QT Interval Relation:

The heart rate/QT interval relation during VAT pacing mode as shown in Figure 5 also varied significantly from patient to patient. For example, the QT interval is estimated to vary from 400 ms to 528 ms, at a ventricular pacing rate of 60 beats per minute and 264 ms to 384 ms at a ventricular pacing rate of 150 beats per minute. Similarly, the contraction in the duration of the QT interval, associated with an increase in pacing rate from 70 to 150 beats per minute, varied from 105 ms to 236 ms (Figure 5).

(iii) Contribution of Heart Rate to Exercise-Induced QT Interval Shortening:

(a) Inter-Patient Variation:

The VAT pacemaker model provides also information as to the extent to which the contribution of heart rate to QT interval shortening during exercise is subject to patient variation. By comparing the slopes of paired regression equations, derived during exercise in VOO and VAT pacing modes, the contribution of heart rate to QT interval changes was derived for individual patients and as shown

in Table XI varied between 16% to 75%.

(b) Inter-Patient and Intra-Patient Variation in Patients Who Had Two Sets of Exercise Tests:

The linear regression equations in the 11 subjects who had two sets of exercise tests during VOO and VAT pacing modes are compared in Table XII. In this subgroup, the minimum and maximum contributions of 'factors which were unrelated to heart rate' to exercise-induced QT interval shortening are shown for each patient and for the group in Figure 7. The contribution of heart rate to QT interval changes varied from 20% to 75% in different subjects and from 23% to 75%, in the same patient from one occasion to another (patient 5, Table XII).

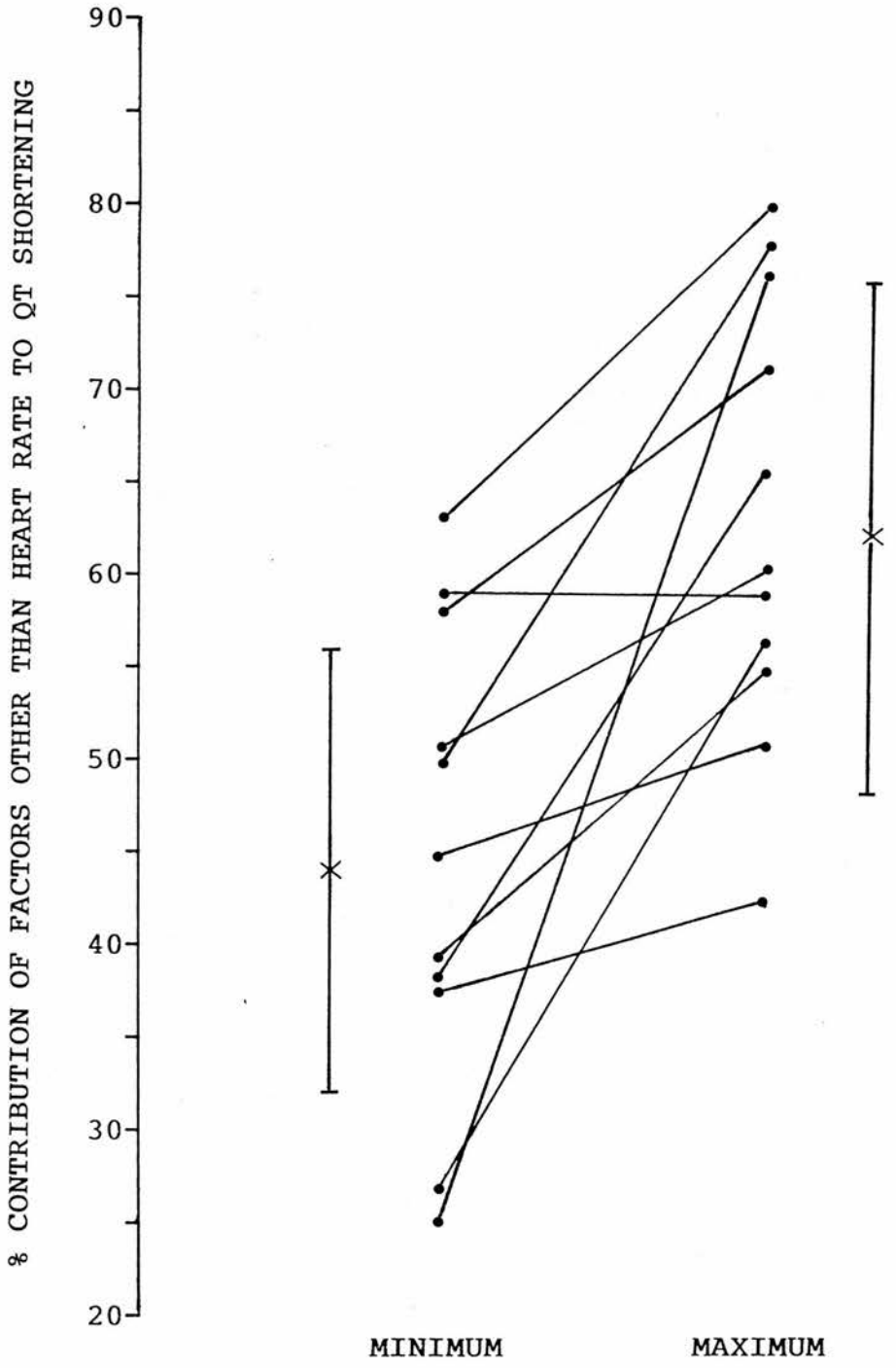


Figure 7. Minimum and maximum contributions made by factors other than heart rate to QT interval shortening during exercise tests performed on two separate occasions.

H. The Effect of Beta Adrenergic Receptor Blockade on the Heart Rate/QT Interval Relation During Exercise

(i) Effect of Acute Beta Adrenergic Receptor Blockade on the Atrial Rate/QT Interval and Paced-Ventricular Rate/QT Interval Relations in Patients with Atrial Synchronized Ventricular Pacing Systems:

The correlation between atrial rate and QT interval shortening during fixed-rate ventricular pacing mode, as described in section F, suggested that autonomic nervous system activity plays an important part in determining QT interval changes during exercise. This finding was investigated further by examining the atrial rate/QT interval and paced-ventricular rate/QT interval relations during VOO and VAT pacing modes, respectively, in 3 patients, before and 2 hours after an oral dose of a 100 mg atenolol. Linear regression equation describing (A) the paced-ventricular rate/QT interval before beta adrenergic receptor blockade during VAT pacing mode, (effect of heart rate and autonomic nervous system activity), (B) atrial rate/QT interval relation during VOO pacing mode before beta adrenergic receptor blockade (effect of autonomic nervous system activity), (C) the paced-ventricular rate/QT interval relation during VAT pacing mode after atenolol therapy (effect of heart rate and parasympathetic nervous system activity) and (D) atrial rate/QT interval relation during VOO pacing mode

after atenolol therapy (effect of parasympathetic nervous system activity alone) in the 3 subjects are illustrated in Figures 8, 9 and 10 and further compared in Table XIII.

The results show that although the relations between the various regression equations varied from one subject to another, in all 3 patients, QT interval changes during VOO pacing mode were less than those during VAT pacing mode [QT(A) compared with QT(B)]. Secondly, acute beta adrenergic receptor blockade reduced the slopes of the regression equations during VAT and VOO pacing modes [QT(C) compared with QT(A) and QT(D) compared with QT(B)]. Thirdly, sympathetic nervous system appeared to account for most of the QT interval shortening during exercise in VOO pacing mode as shown by the effect of atenolol on the atrial rate/QT interval relation in this pacing mode [(QT(D) compared with QT(B)].

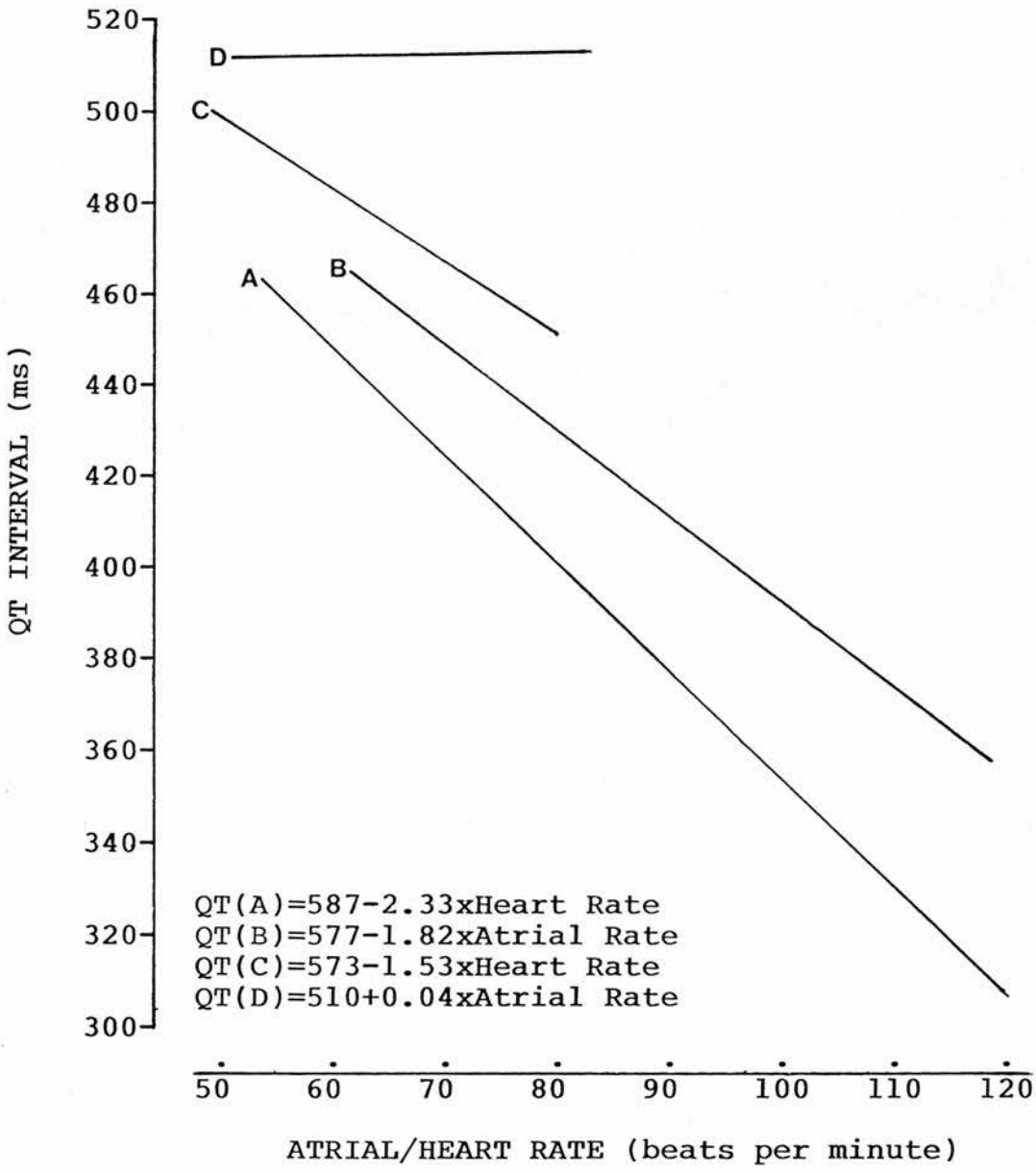


Figure 8. Patient A; Atrial/QT interval and heart rate/QT interval relations during exercise tests, performed during fixed-rate (VOO) and atrial synchronized (VAT) ventricular pacing modes, respectively, before and two hours after an oral dose of a 100 mg atenolol.
A = VAT; B = VOO; C = VAT + atenolol; D = VOO + atenolol.

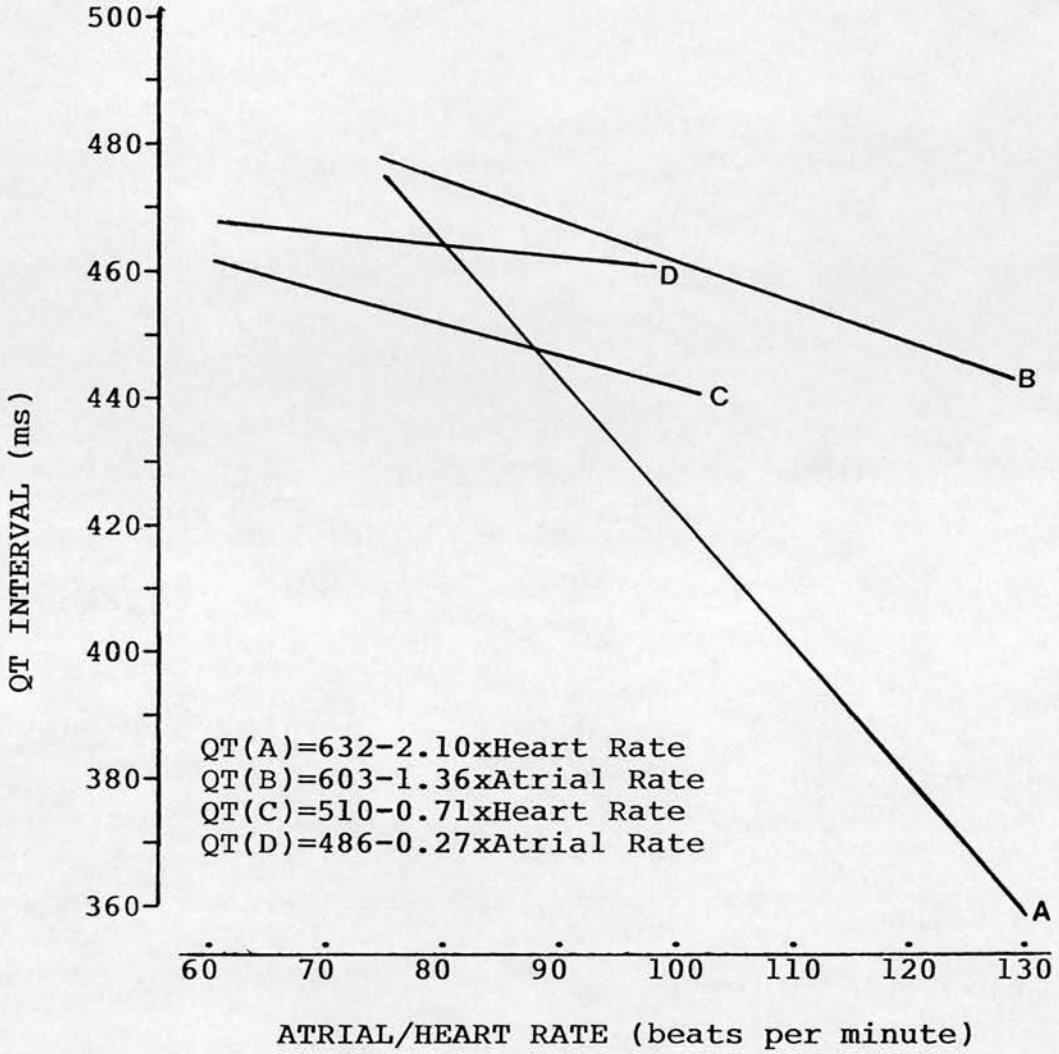


Figure 9. Patient B; Atrial/QT interval and heart rate/QT interval relations during exercise tests, performed during fixed-rate (VOO) and atrial synchronized (VAT) ventricular pacing modes, respectively, before and two hours after an oral dose of a 100 mg atenolol.
A = VAT; B = VOO; C = VAT + atenolol; D = VOO + atenolol.

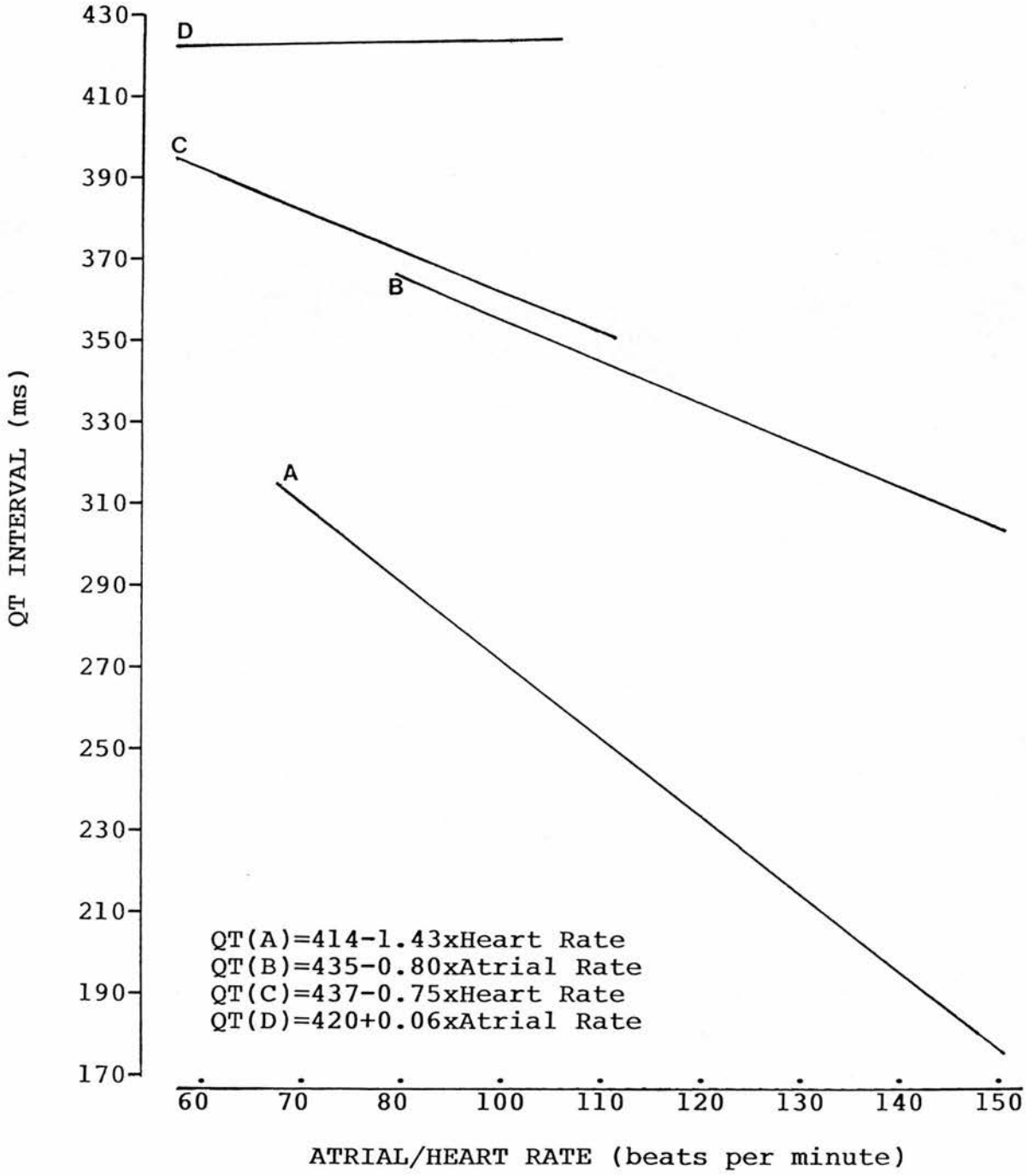


Figure 10. Patient C; Atrial/QT interval and heart rate/QT interval relations during exercise tests, performed during fixed-rate (VOO) and atrial synchronized (VAT) ventricular pacing modes, respectively, before and two hours after an oral dose of a 100 mg atenolol.
A = VAT; B = VOO; C = VAT + atenolol; D = VOO + atenolol.

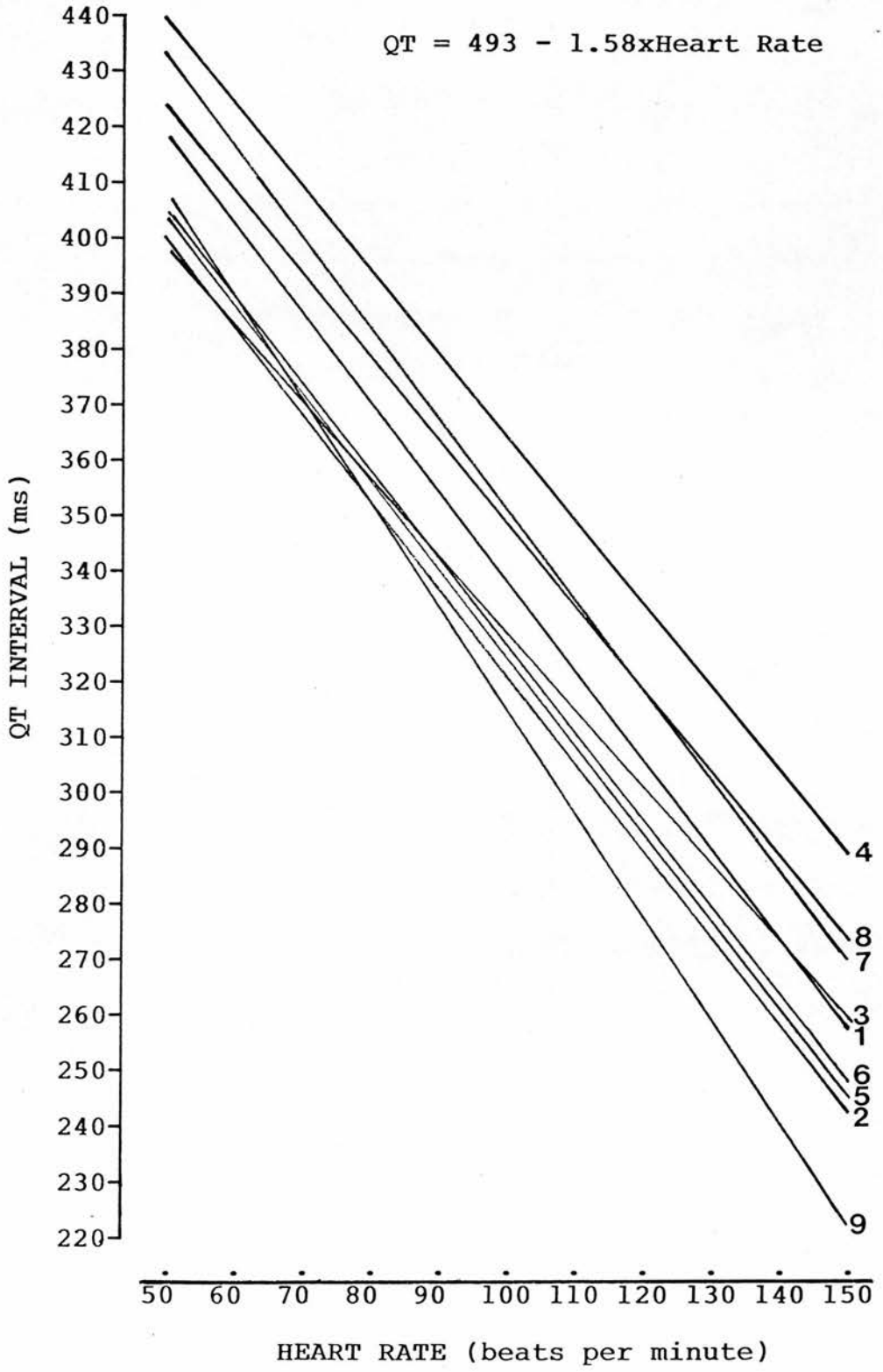


Figure 11a. Regression lines describing heart rate/QT interval relations in the 9 normal subjects during exercise, before beta adrenergic receptor blockade.

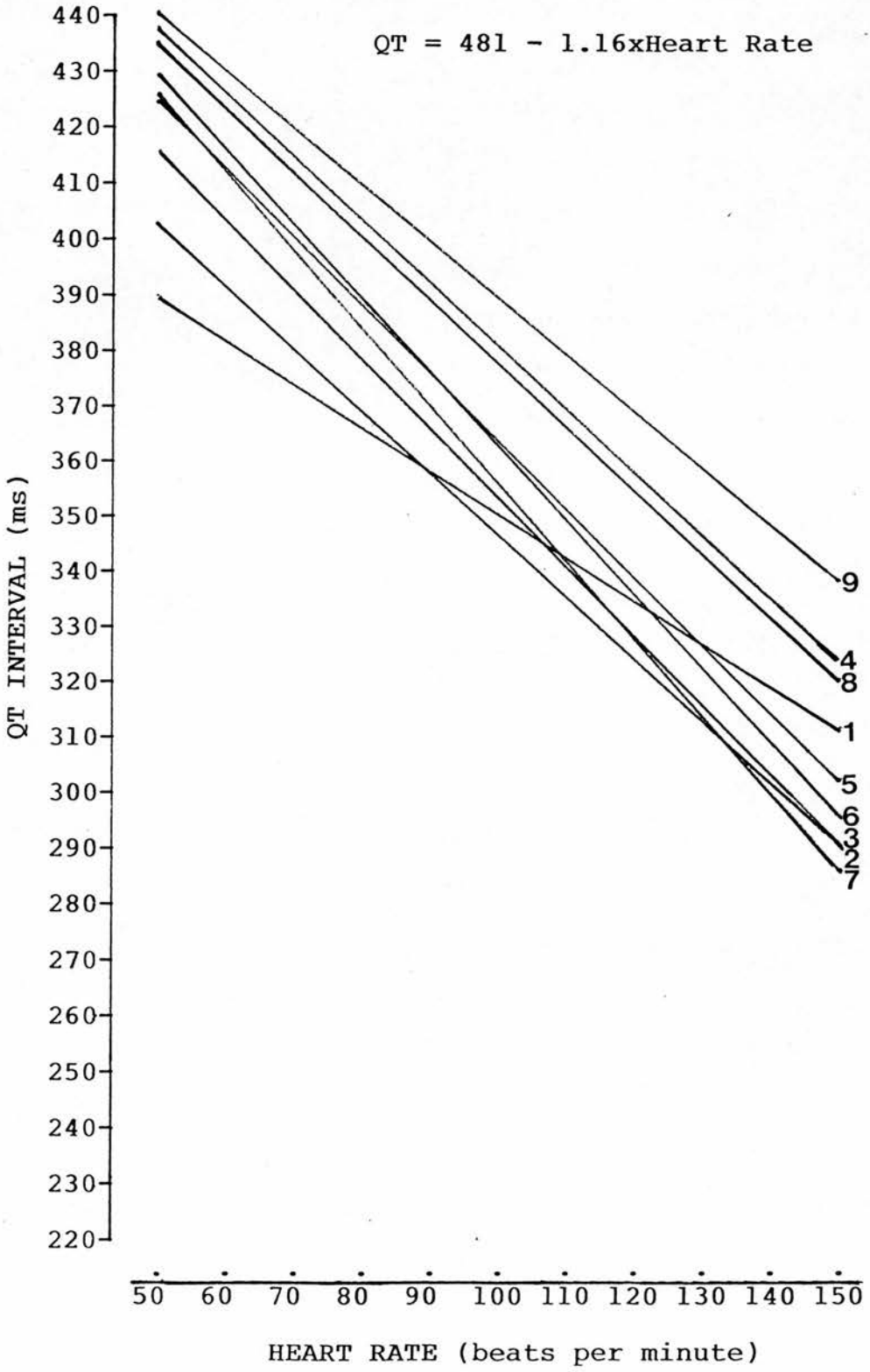


Figure 11b. Regression lines describing heart rate/QT interval relations in the 9 normal subjects during exercise, two hours after an oral dose of a 100 mg atenolol.

(ii) The Effect of Acute Beta Adrenergic Receptor Blockade on the Heart Rate/QT Interval Relation During Exercise in Normal Subjects:

The effect of acute beta adrenergic receptor blockade on the heart rate/QT interval relation during exercise was further investigated in a group of 9 normal volunteers.

QT interval values determined at various heart rates recorded during exercise, before and after an oral dose of a 100 mg atenolol are shown in Table XIV and the corresponding linear regression equations describing the heart rate/QT interval relations in individual subjects are compared in Table XV.

The slopes of the regression equation after acute beta blockade were reduced in every subject, (for the group, $p<0.01$). The finding is further illustrated by comparing the slopes of the regression equations describing the heart rate/QT interval relation for the group, before and after atenolol; Pre-Beta Adrenergic Receptor Blockade:
QT Interval (ms) = 493 - 1.58 x Heart Rate (bpm) and
Post-Beta adrenergic Receptor Blockade:
QT Interval (ms) = 481 - 1.165 x Heart Rate (bpm).

Acute beta adrenergic receptor blockade resulted in QT interval prologation which was more evident at higher

compared with QT interval values obtained in subjects who were not on any medication (A - section B and A´ - section H-ii).

Similarly, the slope of the linear regression equation describing the relation between heart rate and QT interval for the group, [QT Interval (ms) = 520 - 1.71 x Heart Rate (bpm)], in patients on chronic beta adrenergic receptor blockade was not significantly different from control subjects A and A´, as illustrated in Figure 12.

(iv) Comparison of Resting and Exercise Heart Rate/QT Interval Relations and the Effect of Acute and Chronic Beta Adrenergic Receptor Blockade on the Heart Rate/QT Interval and Heart Rate/QTc Interval Relations:

(a) Heart Rate/QT Interval:

The slopes of the regression equations expressing the paced-atrial rate/QT interval relation at rest (section E-i, Table IX), were significantly ($p<0.002$) less than the slopes of the linear regression equations describing the heart rate/QT interval relation during exercise (section B, Table IV).

By comparison, there was no significant difference ($p>0.1$) between the slopes of the paced-atrial rate/QT interval regression equations at rest and the slopes of the exercise heart rate/QT interval regression equations after acute beta adrenergic receptor blockade (as shown in Figure 12 and by the comparison of Table IX with Table XV).

(b) QTc Interval:

QTc interval which is based on Bazett's formula and which corrects the measured QT interval for an arbitary heart rate of 60 beats per minute should remain constant under all circumstances - at rest, during exercise and after beta adrenergic receptor blockade, if heart rate alone

accounts for differences in the duration of the QT interval. This was not observed to be the case.

QTc, during exercise in the controls A and A´, increased progressively to reach a maximum at a heart rate of 100 to 110 beats per minute (Figures 13a and 14), and thereafter, with increasing heart rates, QTc became progressively small.

By comparison, QTc continued to increase beyond heart rates of 100 beats per minute after acute beta adrenergic receptor blockade, as shown in Figure 13b. Hence acute beta adrenergic receptor blockade significantly increased QTc at a heart rate of 120 beats per minute (Figure 14).

In contrast to these findings, QTc interval relation in patients on long term atenolol therapy did not continue to increase beyond heart rates of 110 beats per minute and the heart rate/QTc interval relation behaved similarly to that in patients who were not on any medication, such as controls A and A´ (Figure 14).

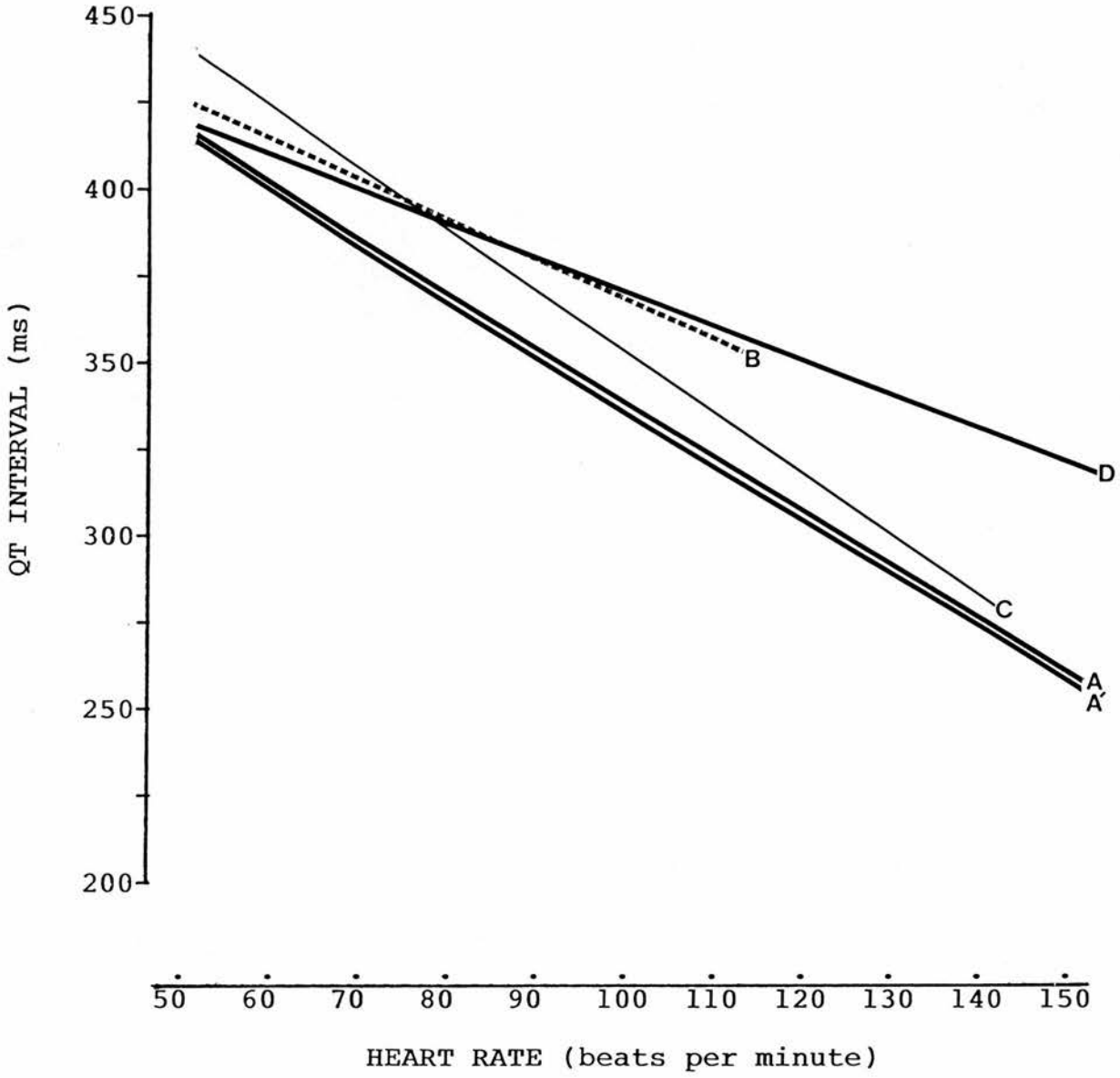


Figure 12. Comparison of linear regression lines, describing the heart rate/QT interval relations during exercise (A) in 14 normal subjects, (A´) in 9 subjects before and (B) two hours after an oral dose of a 100 mg atenolol, and (C) in 16 patients who had taken a 100 mg atenolol daily for more than three months and (D) at rest during atrial pacing in 11 patients.

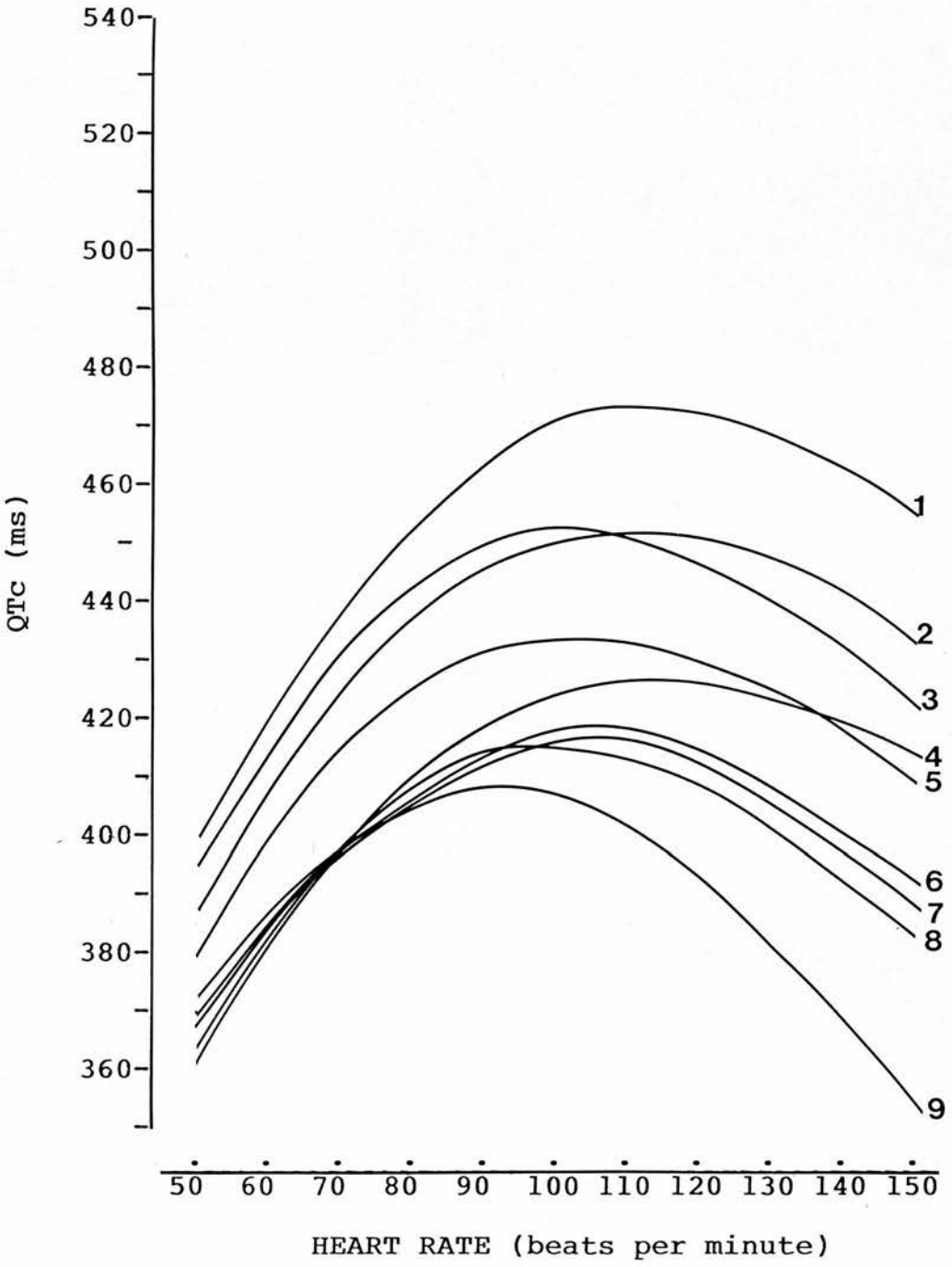


Figure 13a. QTc changes with increasing heart rates during exercise, in nine subjects, before beta adrenergic receptor blockade.

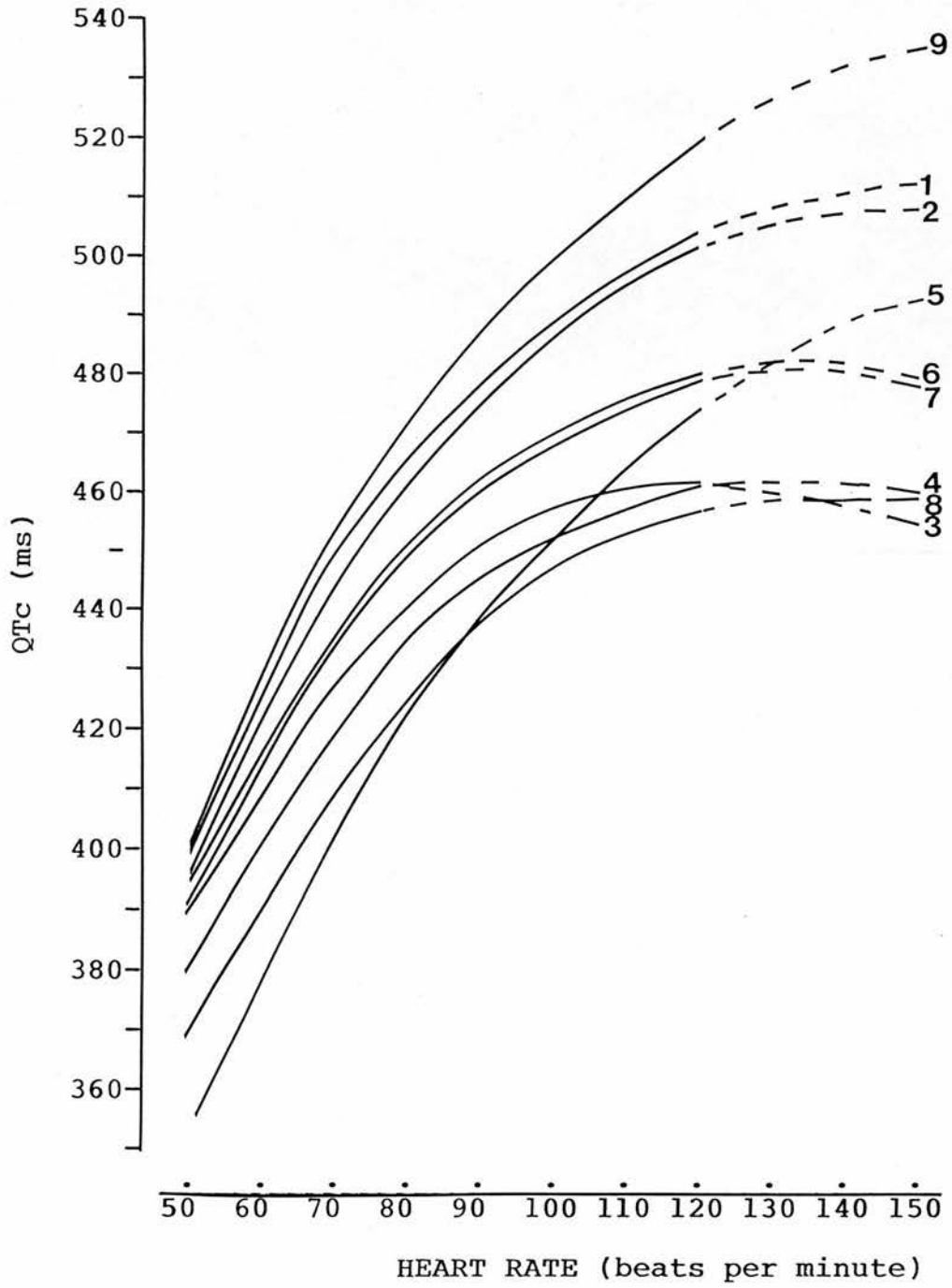


Figure 13b. QTc changes with increasing heart rates during exercise in nine subjects, two hours after an oral dose of 100 mg atenolol.

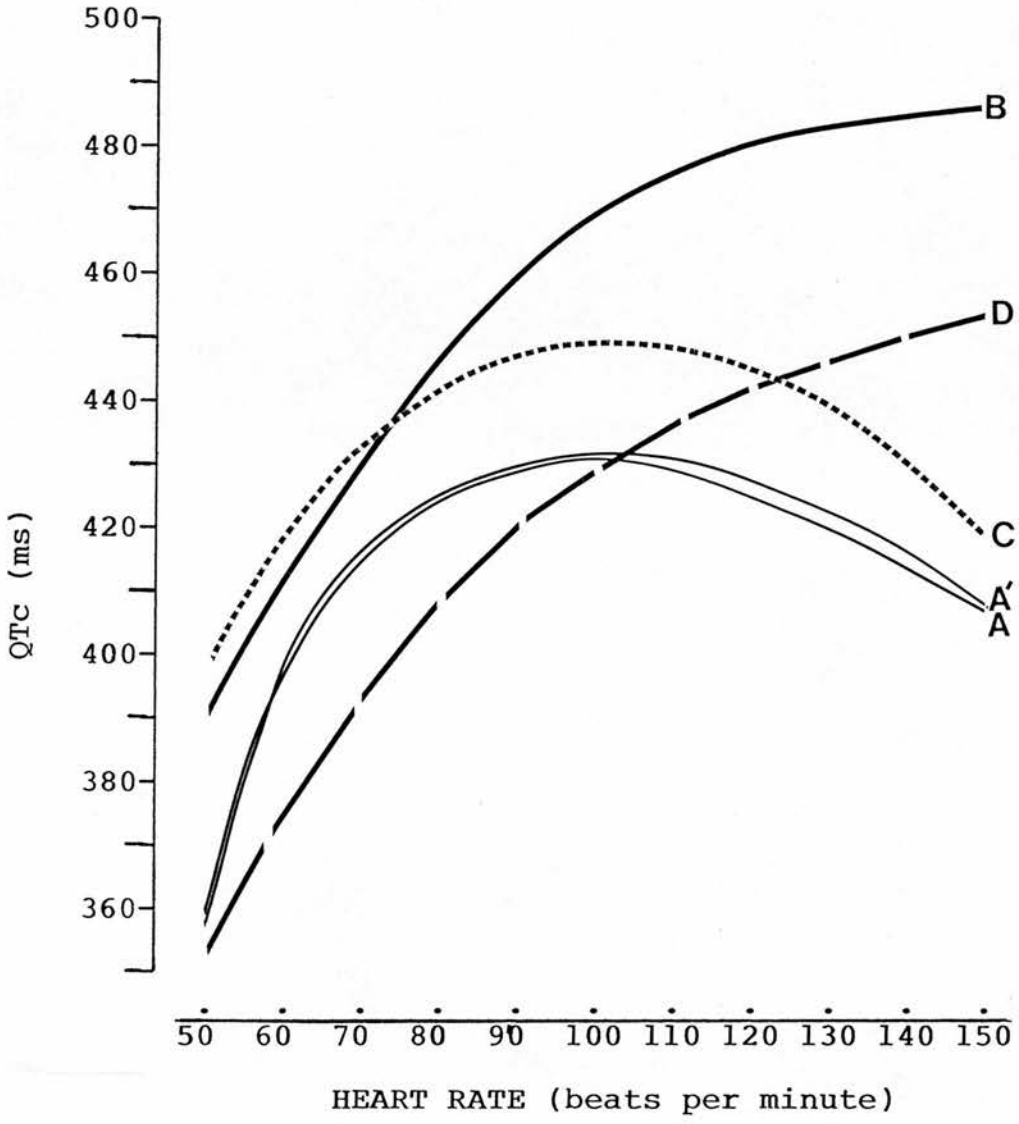


Figure 14. Comparison of mean QTc changes with increasing heart rates during exercise in (A) 14 normal subjects, (A´) 9 normal subjects before and (B) two hours after an oral dose of 100 mg atenolol, (C) 16 patients who had taken a 100 mg atenolol daily for more than three months and (D) during atrial pacing at rest.

I-i Paced-Ventricular Rate/QT Interval/Ventricular Effective Refractory Period Relations:

Changes in the duration of ventricular effective refractory period (VERP) reflect local events, whilst corresponding changes in the QT interval indicate more global myocardial events. The duration of both intervals is affected by heart rate and it has been the practice in the literature to report on the class III activity of a drug based on measurements made at a single pacing rate. This section explores the relation between these variables over a range of paced-ventricular rates.

QT interval and VERP values obtained at various paced-ventricular rates in 10 patients are shown in Table XVIII.

In individual subjects, a negative correlation existed between the paced-ventricular rate and the QT interval, and between paced-ventricular rate and VERP as shown in Table XIX and Figure 15. As would therefore be expected, a positive correlation also existed between VERP and the QT interval (Table XIX and Figure 16). The paced-ventricular rate/QT interval, paced-ventricular rate/VERP and VERP/QT interval relations differed significantly from patient to patient (Table XIX).

In 13/14 patients, the QT interval contracted more than VERP for a given increase in the ventricular pacing rate, as shown by the slopes of the respective regression

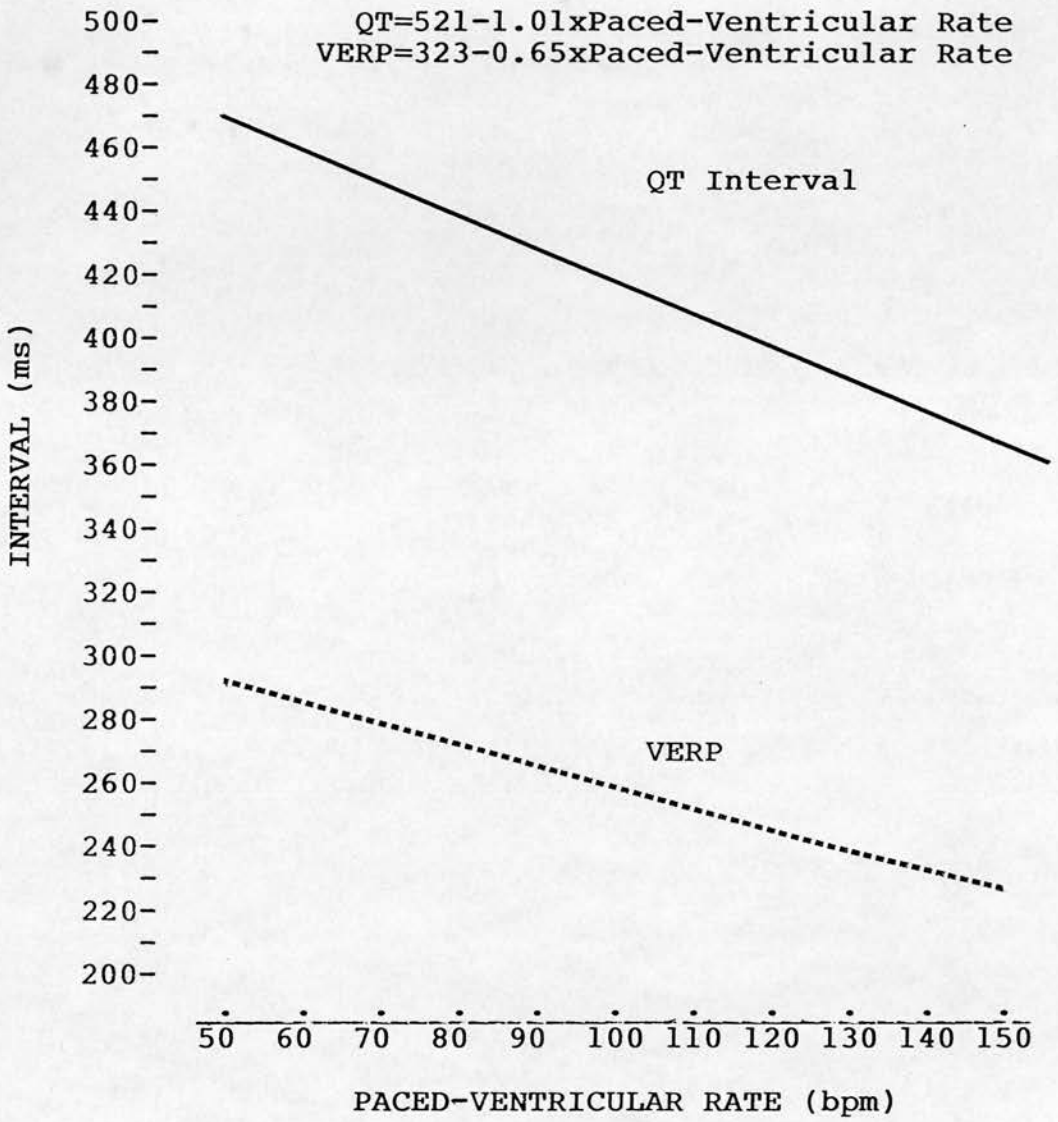


Figure 15. Linear regression lines describing the paced-ventricular rate/QT interval (solid lines) and paced ventricular rate/VERP (broken lines), in the same group of subjects.

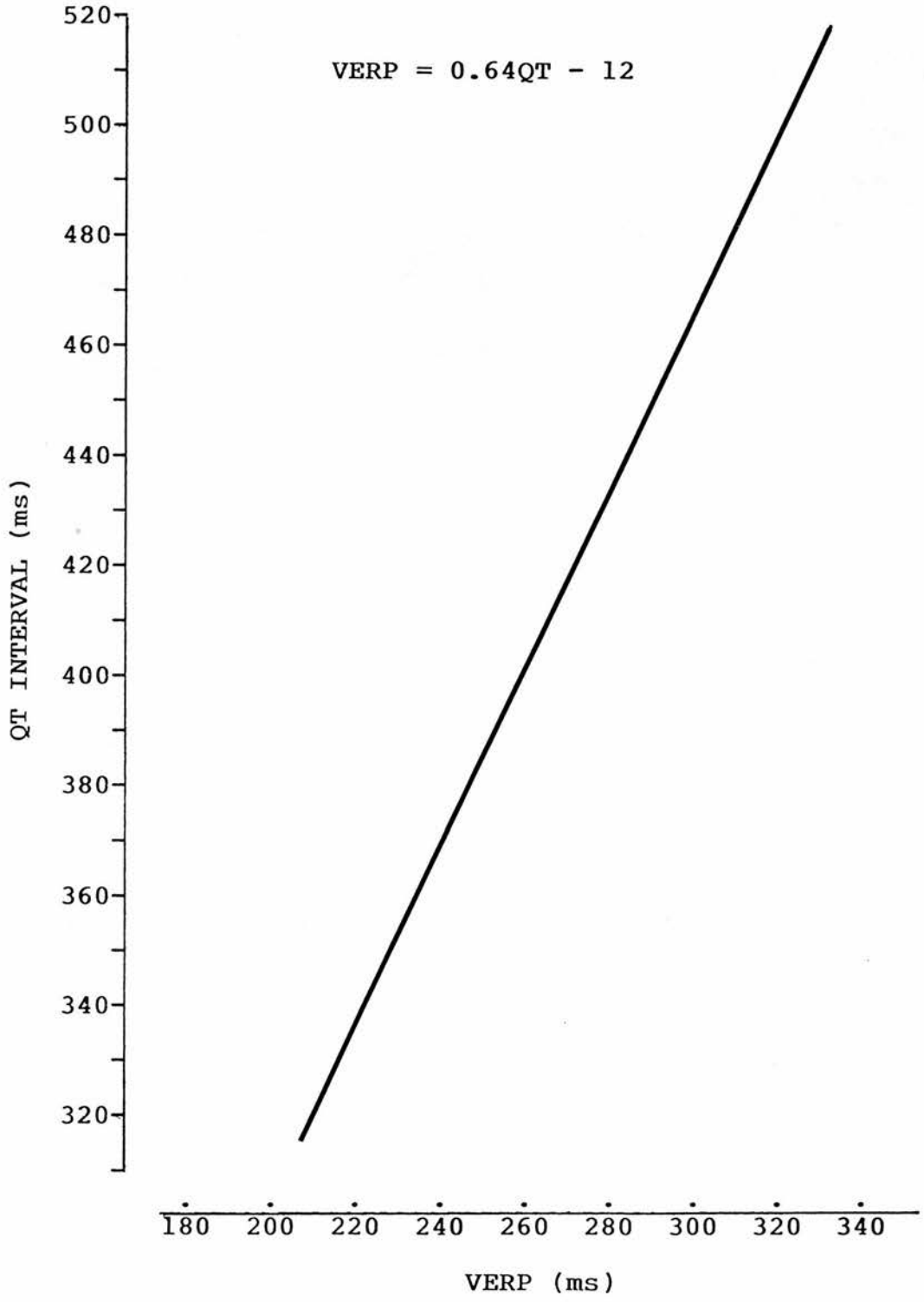


Figure 16. Ventricular effective refractory period (VERP)/QT interval relation.

equations shown in Table XIX.

The overall relations between heart rate and QT interval and VERP and VERP and QT interval were expressed by the following regression equations; QT Interval (ms) 521 - 1.01 x Paced-ventricular Rate (bpm), r = -0.90, VERP (ms) = 323 - 0.65 x Paced-Ventricular Rate (bpm), r = -0.79 and VERP (ms) = 0.64 x QT (ms) - 12.

These regression equations suggest that for a QT interval shortening of 100 ms at rest, VERP reduced by 52 ms.

There was no change in the ratio VERP:QT interval between ventricular paced rates of 60 to 120 beats per minute as shown in Table XX.

I-ii The Effect of Amiodarone on the Paced-Ventricular Rate/VERP/QT Interval Relations:

Antiarrhythmic drugs with class III activity such as amiodarone may prolong both the QT interval and VERP. There may however be quantitative difference between them in terms of their effect on the heart rate/VERP/QT interval relations.

Pre-treatment, maximal post-treatment, VERP and QT interval values in 10 patients are shown in Table XXI. Amiodarone significantly increased the duration of the QT interval from 420 $\pm$ 34 ms to 481 $\pm$ 55 ms and VERP from 250 $\pm$ 23 ms to 323 $\pm$ 62 ms, (mean $\pm$ 1 S.D.), at paced-ventricular rate of 120 beats per minute.

In contrast to the effect of heart rate, VERP changes with

amiodarone were greater than the corresponding changes in QT interval in half of the patients.

Consequently, the ratio of changes in the duration of VERP to changes in the duration of the QT interval was equal to 1.2 (Table XX).

This is also reflected in the finding that the ratio of VERP to QT interval increased from 250 ms/420 ms or 0.595, pre-treatment, to 323 ms/481 ms or 0.672 with amiodarone therapy.

(I-iii) The Effect of Sotalol on the Paced-Ventricular Rate/VERP/QT Interval Relations:

The effect of sotalol, a beta blocker with class III effect, on the heart rate/VERP/QT interval relations is compared with the effect of amiodarone on the same relations.

QT interval and VERP values measured at a ventricular pacing rate of 120 beats per minute are detailed in Tables XXIIa and XXIIb respectively.

At the same ventricular pacing rate, sotalol caused a smaller increase in the duration of the QT interval VERP. The QT interval increased from 398 $\pm$ 29 ms to 427 $\pm$ 29 ms (mean $\pm$ 1 S.D.) or by 29 ms and VERP increased from 214 $\pm$ 13 ms to 242 $\pm$ 22 ms (mean $\pm$ 1 S.D.) or by 27 ms.

As the QT interval and VERP were prolonged almost to the same extent a small but significant increase occurred in the ratio of VERP to QT interval, as shown in Table XX.

Table II. Intra-observer error: QT interval values estimated on two separate occasions (X and Y).

	QT Interval Estimate (ms)				
No.	1st (X)	2nd (Y)	No.	1st(X)	2nd (Y)
1.	405	415	2.	420	420
3.	425	420	4.	382	385
5.	415	410	6.	362	360
7.	350	352	8.	332	330
9.	330	335	10.	350	340
11.	336	345	12.	340	350
13.	340	345	14.	412	415
15.	412	420	16.	415	422
17.	415	420	18.	425	426
19.	420	422	20.	450	450
21.	455	450	22.	445	440
23.	380	390	24.	420	422
25.	390	388	26.	396	395
27.	380	395	28.	380	395
29.	390	390	30.	345	345
31.	350	350	32.	332	335
33.	335	330	34.	365	365
35.	378	376	36.	485	395
37.	410	403	38.	402	400
39.	420	420	40.	425	420

Table III. QT interval measurements at different heart rates recorded during exercise and in the immediate post-exercise period in patients who were not on any medication.

Subject	Heart Rate (bpm)	QT Interval (ms)	Subject	Heart Rate (bpm)	QT Interval (ms)
1.	82	350	2.	73	375
	94	335		83	370
	120	290		107	345
	125	300		110	310
	136	280		116	310
	143	270		120	325
	150	260		125	285
	110	315		136	275
	100	330		150	255
	100	335		160	240
				170	230
2.	83	370	3.	88	350
	107	345		85	355
	110	310		91	350
	116	310		103	330
	120	325		103	325
	125	285		94	345
	136	275		111	310
	150	255		107	300
	160	240		115	295
	170	230		125	285
				130	275
				146	280
				158	250

Table III continued:

Subject	Heart Rate (bpm)	QT Interval (ms)
4.	75	370
	75	365
	94	350
	100	320
	110	300
	120	285
	130	270
	130	260
	150	240
	167	220
7.	83	355
	86	340
	115	295
	120	295
	125	280
	128	270
	136	253
	145	250
	150	240
	162	235
	176	225
	188	210
5.	97	350
	100	340
	125	325
	130	320
	136	290
	141	270
	155	255
6.	98	300
	75	335
	76	345
	71	355
	120	305
	120	285
	125	280
	150	250
	94	340
9.	111	320
	120	300
	125	300
	125	280
	136	272
	143	265

Table III continued:

Subject	Heart Rate (bpm)	QT Interval (ms)
8.	88	360
	88	360
	92	340
	94	325
	104	305
	107	305
	130	275
	120	320
	120	312
	122	312
	130	308
	140	280
11.	75	385
	75	370
	96	370
	107	345
	107	330
	120	315
	125	305
	125	295
	142	275
	150	270
	167	252
	60	410
10.	83	360
	94	320
	94	340
	107	330
	107	320
	115	310
	111	300
	125	280
	136	280
	158	240
	162	232
	158	240
	150	240
	83	372
12.	70	390
	64	410
	107	360
	115	335
	120	320
	136	280
	125	320

Table III continued:

Subject	Heart Rate (bpm)	QT Interval (ms)	Subject	Heart Rate (bpm)	QT Interval (ms)
13.	68	400	14.	125	305
	88	380		123	306
	100	360		130	300
	97	360		132	292
	103	355		150	270
	122	345		150	265
	123	305		117	285
	130	315		94	350
	136	300		79	385
	130	290		111	330
				115	325
				115	315

Table IV. Comparison of the coefficients of correlation of 4 regression equations describing the heart rate/QT relation during exercise.

	Regression Equation				
Patient	Linear	Exponential	Logarithmic	Power Curve	p
1.	-0.9876*	-0.9866	-0.9827	-0.9287	<0.001
2.	-0.9769*	-0.9768	-0.9654	-0.9563	<0.001
3.	-0.9553	-0.9613	-0.9680	-0.9702*	<0.001
4.	-0.9872	-0.9921*	-0.9888	-0.9847	<0.001
5.	-0.9464*	-0.9378	-0.9278	-0.9168	<0.01
6.	-0.9453	-0.9462*	-0.9358	-0.9320	<0.001
7.	-0.9848	-0.9931	-0.9952*	-0.9939	<0.001
8.	-0.9282	-0.9588*	-0.9476	-0.9588	<0.01
9.	-0.9450	-0.9472	-0.9491	-0.9504*	<0.01
10.	-0.9793	-0.9832*	-0.9808	-0.9788	<0.001
11.	-0.9825	-0.9836*	-0.9739	-0.9654	<0.001
12.	-0.9680*	-0.9548	-0.9490	-0.9318	<0.01
13.	-0.9533	-0.9533	-0.9600*	-0.9531	<0.001
14.	-0.9449*	-0.9340	-0.9312	-0.9168	<0.001
mean	-0.9629	-0.9649*	-0.9396	-0.9526	
± 1 S.D.	±0.0203	±0.0205	±0.0768	±0.0247	

* = r value of regression equation which describes the best curve fit.

Table V. QT intervals determined after prolonged bed rest at various heart rates.

	Heart Rate (bpm)	QT Interval (ms)		Heart Rate (bpm)	QT Interval (ms)
A.	72	376	C.	64	402
	66	376		88	347
	78	369		73	377
	81	368		67	388
	78	379		72	369
	77	367		85	364
	87	345		74	351
	56	428		79	364
	62	407		74	354
	71	384		81	382
B.	64	380	D.	57	393
	83	344		65	387
	66	375		69	379
	85	359		58	395
	80	364		67	382
	66	387		80	364
	64	427		79	361
	83	361		76	350
	68	393		70	367
	66	382		74	367
	79	363		69	371

Table V continued:

	Heart Rate (bpm)	QT Interval (ms)	Heart Rate (bpm)	QT Interval (ms)
E.	65	393	74	367
	63	397	69	371
	70	378	70	376
	75	357	72	365
	78	366	69	388
	66	375	68	374
	64	389	65	382
	66	386	70	390
	69	369	70	376
	65	400	77	376
	59	402	65	389
	71	374		
F.	71	355	76	355
	78	340	72	360
	76	345	71	360
	69	365	70	345
	73	356	69	360
	77	360	78	340
	70	370	68	375
	65	380	67	375
	71	370		

Table V continued:

	Heart Rate (bpm)	QT Interval (ms)		Heart Rate (bpm)	QT Interval (ms)
G.	58	403	H.	57	401
	62	385		58	403
	66	353		66	391
	72	356		67	385
	73	363		69	382
	80	345		76	352
	74	363		80	363
	78	362		70	370
	80	355		71	371
	61	339		74	369
I.	65	404	J.	61	415
	85	345		69	398
	73	374		73	390
	66	386		76	387
	74	360		71	396
	58	410		79	378
	62	402		65	410
	68	380		65	400
	63	395		65	405
	72	370		66	405

Table VI. Mean ± 1 S.D. heart rate and QT intervals measured in 10 subjects during prolonged bed rest.

Subject	Heart Rate (bpm)	QT Interval (ms)
1.	73±10	380±22
2.	73±9	376±22
3.	74±10	375±24
4.	69±6	376±12
5.	68±6	382±14
6.	72±4	358±12
7.	70±8	362±19
8.	69±7	379±16
9.	69±8	383±21
10.	69±6	398±11
All patients	71±2	377±11

Table VII. Mean QT intervals and heart rates recorded on the two occasions during sleep in 12 subjects.

Subject	Heart Rate (bpm)	QT Interval (ms)
1.	56	420
	64	427
2.	65	420
	70	415
3.	70	410
	60	410
4.	75	376
	83	372
5.	63	390
	70	380
6.	70	374
	62	435
7.	68	390
	74	370
8.	75	400
	70	400
9.	65	395
	68	395
10.	58	400
	62	398
11.	65	390
	67	395
12.	67	398
	71	395
Mean ± 1 S.D.	67 ± 6	398 ± 17

Table VIII. Regression equations describing the heart rate/QT interval relation during exercise in individual subjects.

Patient	REGRESSION EQUATIONS			
	Linear	Exponential	Logarithmic	Power Curve
	$QT = a - b.HR$	$ae^{-b.HR}$	$a - b\ln.HR$	$a.HR^{-b}$
1.	$464 - 1.3589.HR$	$513e^{-0.0019.HR}$	$1038 - 356\ln.HR$	$3378.HR^{-0.5077}$
2.	$500 - 1.6132.HR$	$579e^{-0.0024.HR}$	$1185 - 425\ln.HR$	$5609.HR^{-0.6139}$
3.	$473 - 1.4406.HR$	$527e^{-0.0021.HR}$	$1112 - 392\ln.HR$	$4275.HR^{-0.5583}$
4.	$494 - 1.7038.HR$	$575e^{-0.0025.HR}$	$1200 - 441\ln.HR$	$6253.HR^{-0.6400}$
5.	$534 - 1.7788.HR$	$526e^{-0.0020.HR}$	$1136 - 507\ln.HR$	$8003.HR^{-O.6988}$
6.	$438 - 1.2325.HR$	$438e^{-0.0018.HR}$	$1250 - 460\ln.HR$	$2060.HR^{-0.4120}$
7.	$455 - 1.3590.HR$	$521e^{-0.0021.HR}$	$1120 - 521\ln.HR$	$5638.HR^{-0.6210}$
8.	$526 - 2.0186.HR$	$612e^{-0.0028.HR}$	$1336 - 507\ln.HR$	$8003.HR^{-0.6988}$
9.	$512 - 1.7628.HR$	$623e^{-0.0026.HR}$	$1371 - 515\ln.HR$	$11947.HR^{-0.9504}$
10.	$489 - 1.5951.HR$	$568e^{-0.0024.HR}$	$1206 - 439\ln.HR$	$6564.HR^{-0.9808}$
11.	$497 - 1.5125.HR$	$546e^{-0.0020.HR}$	$1061 - 361\ln.HR$	$3039.HR^{-0.9654}$
12.	$508 - 1.5548.HR$	$547e^{-0.0019.HR}$	$1000 - 327\ln.HR$	$2223.HR^{-0.9318}$
13.	$503 - 1.6000.HR$	$566e^{-0.0022.HR}$	$1180 - 419\ln.HR$	$4631.HR^{-0.5666}$
14.	$517 - 1.6034.HR$	$567e^{-0.0020.HR}$	$1090 - 368\ln.HR$	$2927.HR^{-0.4643}$

Table IX. Linear regression equations describing the heart rate/QT interval relations during atrial and ventricular pacing at rest, and for the same group of patients.

Patient	Atrial Pacing		Ventricular Pacing	
	QT1 = a1 - b1 xAR	r	QT2 = a2 - b2 xVR	r
1.	417 - 1.13 xAR	0.97	483 - 0.91 xVR	0.98
2.	406 - 1.08 xAR	0.98	516 - 1.13 xVR	0.98
3.	426 - 1.04 xAR	0.99	517 - 0.99 xVR	0.99
4.	443 - 1.08 xAR	0.99	526 - 1.03 xVR	0.98
5.	455 - 1.15 xAR	0.98	524 - 0.94 xVR	0.97
6.	443 - 0.99 xAR	0.99	527 - 1.06 xVR	0.99
7.	460 - 1.11 xAR	0.98	523 - 1.01 xVR	0.98
8.	454 - 0.95 xAR	0.98	568 - 1.14 xVR	0.99
9.	445 - 1.02 xAR	0.98	523 - 1.01 xVR	0.95
10.	422 - 0.90 xAR	0.97	737 - 1.14 xVR	0.99
11.	398 - 0.55 xAR	0.93	460 - 0.58 xVR	0.94

AR = Paced-atrial rate; VR = Paced-ventricular rate and r = Correlation coefficient of linear regression equations.

Table X. QT intervals recorded during exercise, at various atrial rates (AR) and heart rates (HR) during fixed-rate (VOO) and atrial synchronized (VAT) ventricular pacing modes.

	Pacing Mode			
	VOO		VAT	
Patient	AR	QT	HR	QT
1.	94	420	85	415
	100	418	99	400
	105	414	98	382
	106	410	102	373
	108	400	103	390
	115	396	106	363
	115	388	108	382
	129	385	118	360
	143	380	119	353
	146	370	123	350
			124	347
			128	344
2.	94	450	89	430
	92	450	92	426
	96	433	94	410
	100	439	94	410
	103	420	96	405
	107	422	97	398
	115	410	106	392
	118	410	107	385
	120	405	112	366
	129	400	120	365
	125	402	118	380
	117	412	110	395
	111	432	105	395
	101	436	98	420
	96	440	94	415
	92	430	81	440
3.	102	410	123	388
	102	410	128	370
	107	415	122	375
	127	413	132	350
	154	405	138	343
4.	93	420	92	410
	94	420	114	400
	158	395	119	380
	180	396	123	360
	170	390	135	338

Table X continued:

	VOO		VAT			VOO		VAT	
	AR	QT	HR	QT		AR	QT	HR	QT
	162	385	136	340		176	385	146	323
	139	405	152	345		178	380	150	315
	118	425	153	330				161	310
	115	430	157	335				172	300
	115	435	101	410				170	307
	107	445	142	337				147	336
			128	347				123	370
			130	370				112	390
			118	380				112	400
			114	390				106	400
5.	87	395	73	385	6.	94	495	82	470
	123	386	107	350		138	463	108	432
	130	378	111	325		139	455	114	402
	135	375	114	315		148	440	115	400
	150	360	122	310		152	432	137	370
	159	340	125	296		122	435	88	412
	161	335	130	288		99	460	81	460
			140	282		95	480	78	474
			150	275		87	495	79	483
			159	270		86	490	79	485
7.	64	510	67	490	8.	114	400	100	345
	86	505	85	485		118	390	115	322
	93	500	88	475		122	385	120	310
	97	498	96	463		123	381	118	320
	100	480	97	446		129	373	120	310
	105	473	101	426		138	368	130	305
	113	460	104	428		139	360	136	282
			109	400		144	355	136	282
			113	390				138	275

Table X continued:

	VOO		VAT			VOO		VAT	
	AR	QT	HR	QT		AR	QT	HR	QT
9.	72	404	71	413	10.	103	438	99	420
	95	392	94	380		126	425	109	400
	97	385	93	370		133	420	111	380
	102	380	94	368		138	406	122	350
	108	380	94	355		137	398	121	350
	111	375	95	355		143	405	127	335
	114	375	100	352		147	395	129	340
	113	372	106	345		148	388	133	328
	122	370	108	330		158	370	138	320
	128	370	119	323		165	365	141	310
	136	367	127	308		172	355	146	290
	143	356	138	300					
			139	295					
11.	112	400	114	330	12.	107	410	115	345
	134	382	125	318		132	404	121	334
	135	385	129	316		146	400	127	337
	135	375	127	316		157	390	123	330
	140	372	130	314		160	380	127	322
	147	374	132	306		165	370	136	315
	146	370	134	304					
	154	363	139	302					
	159	355	141	300					
			144	293					
			147	290					
			151	270					
			155	265					
			165	260					

Table X continued:

	VOO		VAT	
	AR	QT	AR	QT
13.	87	460	88	405
	100	423	103	390
	111	425	105	388
	117	430	107	376
	120	416	109	375
	128	400	113	365
	130	390	115	360
			120	350
			124	340
14.	118	402	112	352
	128	397	125	334
	131	380	125	326
	133	387	125	315
	136	387	131	305
	140	384	133	293
	140	373	136	287
	146	365	138	282
	148	358	143	275
	151	352	147	273
	162	350	151	261
15.	86	413	79	385
	114	396	112	340
	115	383	111	341
	115	382	117	325
	136	374	132	315
	146	375	129	310
	145	360	137	300
	161	355	159	293
			165	282
			167	272
16.	106	422	95	390
	115	412	107	372
	117	415	107	363
	118	410	107	363
	122	405	111	360
	123	400	112	353
	125	404	114	343
	125	397	115	340
	126	400	119	350
			122	340

Table X continued:

	VOO		VAT	
	AR	QT	HR	QT
17.	104	460	78	475
	115	445	106	415
	117	440	112	402
	117	445	97	400
	125	436	111	390
	130	430	110	400
	130	430	113	388
	131	430	113	383
	137	425	116	380
	139	415	120	365
			121	356
			127	352
			132	348
18.	70	420	77	420
	97	415	86	405
	107	415	87	400
	122	400	88	390
	130	395	97	380
	128	395	100	375
	140	390	100	375
	154	372	111	355
	167	365	128	330
			143	310
			146	310
19.	120	440	112	405
	146	415	119	395
	158	395	132	353
	167	398	144	340
	167	380	145	330
	168	390	150	330
20.	69	458	57	450
	92	440	80	420
	93	435	80	422
	92	425	82	403
	102	422	96	390
	113	413	96	390
	114	420	111	360
	130	402	116	340
	136	392	116	350
	143	390	134	330
	158	380	134	330
			138	315
			143	305

Table X continued:

	VOO		VAT			VOO		VAT	
	AR	QT	HR	QT		AR	QT	HR	QT
21.	99	435	84	400	22.	115	425	88	410
	134	432	116	365		133	420	122	380
	140	430	128	350		140	415	125	360
	143	425	135	340		143	415	125	350
	150	410	135	340		150	410	130	330
	154	406	135	340		152	400	134	335
	158	405	138	330		156	392	132	325
			142	325		160	390	141	325
			147	312		165	375	148	315
			150	315		171	373	150	312
			157	305					
23.	100	450	103	400	24.	88	435	70	425
	105	433	103	398		123	435	103	390
	122	432	110	390		130	425	103	390
	125	425	111	395		140	425	111	367
	128	425	115	390		143	415	122	340
	130	415	120	365		154	410	129	326
	128	430	125	355		158	400	137	315
			125	362				143	305
			127	360					
			125	365					
			125	360					
			129	355					
			136	345					

Units: Atrial and heart rate = beats per minute and QT interval = ms.

Table XI. Exercise atrial rate/QT interval and paced-ventricular rate/QT interval relations, in individual patients, during fixed-rate, 70 beats per minute (VOO) and atrial synchronized (VAT) ventricular modes, respectively.

Patient No.	VOO Mode $QT_1 = a_1 - b_1$ x Atrial Rate	r	VAT Mode $QT_2 = a_2 - b_2$ x Heart Rate	r	b1/b2x100
1.	540-0.92xAtrial Rate	0.95	550-1.64xHeart Rate	0.94	56%
2.	583-1.45x ,,	0.92	598-1.94x ,,	0.93	74%
3.	487-0.57x ,,	0.72	545-1.41x ,,	0.91	40%
4.	456-0.39x ,,	0.95	563-1.43x ,,	0.97	25%
5.	477-0.81x ,,	0.91	486-1.43x ,,	0.96	57%
6.	555-0.78x ,,	0.85	612-1.80x ,,	0.92	43%
7.	585-1.02x ,,	0.87	668-2.34x ,,	0.93	43%
8.	554-1.38x ,,	0.98	511-1.65x ,,	0.96	84%
9.	445-0.61x ,,	0.96	518-1.64x ,,	0.96	37%
10.	591-1.35x ,,	0.96	676-2.63x ,,	0.98	51%
11.	503-0.91x ,,	0.98	510-1.53x ,,	0.97	59%
12.	482-0.62x ,,	0.89	536-1.66x ,,	0.93	37%
13.	576-1.38x ,,	0.89	559-1.72x ,,	0.89	80%
14.	568-1.38x ,,	0.94	626-2.45x ,,	0.97	56%
15.	473-0.73x ,,	0.96	470-1.17x ,,	0.98	62%
16.	555-1.24x ,,	0.95	574-1.96x ,,	0.95	63%
17.	575-1.12x ,,	0.96	651-2.34x ,,	0.95	48%
18.	472-0.61x ,,	0.96	535-1.58x ,,	0.99	39%
19.	565-1.04x ,,	0.94	629-2.01x ,,	0.97	52%
20.	514-0.87x ,,	0.98	499-1.16x ,,	0.81	75%
21.	493-0.52x ,,	0.80	518-1.35x ,,	0.99	38%
22.	555-1.04x ,,	0.93	552-1.60x ,,	0.93	65%
23.	532-0.87x ,,	0.85	589-1.81x ,,	0.96	48%
24.	483-0.47x ,,	0.85	554-1.73x ,,	0.98	27%

r= coefficient of correlation for the linear regression equations.

Table XII. Comparison of linear regression equations describing atrial rate/QT interval and heart rate/QT interval relations during fixed-rate, 70 beats per minute (VOO) and atrial synchronized (VAT) pacing modes, respectively, determined during exercise tests, performed on two occasions.

	First Occasion					
	VOO		VAT			
Patient	$QT_1 = a_1 - b_1 . AR$	r	$QT_2 = a_2 - b_2 . HR$	r	$b_1/b_2 \times 100$	$(Sy_1)(Sy_2)$
1.	548 - 1.18AR	0.88	572 - 1.93HR	0.84	61%	(4)(6)
2.	486 - 0.88AR	0.96	504 - 1.33HR	0.81	66%	(4)(5)
3.	484 - 0.65AR	0.65	528 - 1.38HR	0.96	47%	(7)(3)
4.	473 - 0.78AR	0.79	484 - 1.43HR	0.97	55%	(6)(3)
5.	456 - 0.39AR	0.94	559 - 1.56HR	0.94	25%	(8)(6)
6.	487 - 0.81AR	0.93	487 - 1.39HR	0.95	58%	(5)(5)
7.	482 - 0.88AR	0.74	545 - 1.80HR	0.98	45%	(7)(4)
8.	493 - 0.52AR	0.64	518 - 1.35HR	0.98	38%	(10)(6)
9.	576 - 1.38AR	0.79	559 - 1.72HR	0.95	80%	(9)(4)
10.	699 - 2.13AR	0.80	701 - 2.72HR	0.89	78%	(5)(7)
11.	503 - 0.91AR	0.93	510 - 1.53HR	0.95	59%	(3)(5)

Table XII continued:

	Second Occasion					
	VOO		VAT			
Patient	$QT_3=a_3 - b_3.AR$	r	$QT_4=a_4 - b_4.HR$	r	$b_3/b_4 \times 100$	$(Sy_3)(Sy_4)$
1.	568 - 1.48AR	0.67	671 - 2.88HR	0.85	51%	(5)(6)
2.	470 - 0.68AR	0.90	535 - 1.58HR	0.99	38%	(5)(6)
3.	456 - 0.38AR	0.69	547 - 1.41HR	0.85	27%	(5)(7)
4.	488 - 0.61AR	0.89	541 - 1.55HR	0.96	39%	(8)(7)
5.	509 - 0.93AR	0.85	475 - 1.21HR	0.94	77%	(9)(6)
6.	523 - 1.15AR	0.96	504 - 1.59HR	0.92	72%	(3)(6)
7.	591 - 1.35AR	0.92	676 - 2.63HR	0.97	51%	(7)(6)
8.	486 - 0.55AR	0.74	511 - 1.28HR	0.97	43%	(5)(4)
9.	582 - 1.90AR	0.88	654 - 3.02HR	0.65	63%	(3)(20)
10.	520 - 1.05AR	0.89	489 - 2.11HR	0.90	50%	(4)(5)
11	621 - 1.38AR	0.83	632 - 2.19HR	0.91	59%	(9)(8)

Sy= Standard error of the mean; r= correlation coefficient; AR= Atrial rate
HR= Heart Rate.

Table XIII. Atrial rate (AR), heart rate (HR)/QT interval relations in 3 patients with exercise during atrial synchronized (VAT) and fixed-rate (VOO) ventricular pacing modes, before and 2 hours after an oral dose of a 100 mg atenolol.

Patient	QT(A)	QT(B)	QT(C)	QT(D)
1.	587 - 2.33HR	577 - 1.82AR	537 - 1.53HR	510 + 0.04AR
2.	632 - 2.10HR	603 - 1.36AR	510 - 0.71HR	486 - 0.27AR
3.	414 - 1.43HR	435 - 0.80AR	437 - 0.75AR	420 + 0.06AR

QT(A)=VAT - atenolol; QT(B)=VOO - atenolol; QT(C)=VAT+atenolol; QT(D)=VOO+atenolol.

Table XIV. QT intervals in normal subjects, measured at various heart rates during exercise tests, performed before and two hours after an oral dose of a 100 mg atenolol.

	Before Atenolol		After Atenolol	
	Heart Rate	QT Interval	Heart Rate	QT Interval
Subject	(bpm)	(ms)	(bpm)	(ms)
R.M.	107	345	54	390
Male	73	375	65	375
Aet. 27	83	370	90	370
	120	325	64	375
	110	310	75	370
	116	310	74	370
	125	285	100	350
	136	275	107	350
	150	255	120	335
	160	240	120	330
	170	230	125	330
B.C.	88	350	66	380
Male	85	355	66	380
Aet. 27	91	350	78	385
	103	325	74	385
	103	330	85	350
	94	345	85	370
	111	310	80	360
	107	300	97	365
	115	295	100	350
	103	330	107	325
	107	305	107	335
	115	295	100	340

Table XIV continued:

Subject	Heart Rate (bpm)	QT Interval (ms)	Heart Rate (bpm)	QT Interval (ms)
	125	285	120	332
	130	275	122	315
	146	260	132	310
	158	250	136	310
	63	390		
A.O.M.	82	350	68	390
Male	94	335	83	372
Aet. 31	103	330	94	365
	120	290	97	336
	125	300	106	345
	136	280	103	355
	143	270	106	345
	150	260	115	330
	110	315	118	325
	100	330	77	385
	100	335	78	375
B.H.	68	400	50	440
Male	88	380	50	430
Aet. 18	100	360	62	435
	97	360	75	420
	103	355	81	400
	122	345	83	390
	123	305	85	400
	130	315	91	370
	136	300	100	350
	130	290	115	360
			125	360
			100	360
			109	370

Table XIV continued:

Subject	Heart Rate (bpm)	QT Interval (ms)	Heart Rate (bpm)	QT Interval (ms)
C.P.M.	83	360	58	415
Male	94	320	83	395
Aet. 22	94	340	73	395
	107	330	88	380
	115	310	92	375
	111	300	103	355
	125	280	115	340
	136	280	88	380
	158	240	83	372
	158	240		
	158	240		
	158	225		
	162	232		
	150	240		
C.W.	86	356	61	415
Female	90	355	64	410
Aet. 34	100	320	86	390
	107	305	97	370
	116	290	91	375
	120	282	75	385
	125	265	107	350
	150	250	68	395
	167	230		

Table XIV continued:

Subject	Heart Rate (bpm)	QT Interval (ms)	Heart Rate (bpm)	QT Interval (ms)
S.	75	385	59	410
Male	75	400	67	410
Aet. 26	96	370	83	390
	107	345	94	370
	107	330	91	365
	120	315	107	355
	125	305	130	315
	142	275	81	380
	150	270	81	375
	167	252	91	365
	70	410		
R.B.	79	385	55	435
Male	111	330	46	435
Aet. 27	115	325	82	405
	115	315	87	390
	125	305	100	370
	123	306	104	375
	130	300	120	355
	132	292		
	150	270		
	150	265		
L.F.	75	370	55	435
Male	82	352	62	425
Aet. 33	90	334	74	415
	96	320	83	413
	105	301	95	397
	115	284	111	383
	130	260	120	361
	150	215		
	165	207		

Table XV. Comparison of linear regression equations describing the heart rate/QT interval relation in normal subjects, during exercise before and two hours after an oral dose of a 100 mg atenolol.

	Before Atenolol		After Atenolol	
Subject	$QT = a_1 - b_{SU} \times$ Heart Rate	r	$QT = a_2 - b_2 \times$ Heart Rate	r
R.M.	QT=500-1.61xHeart Rate	0.97	QT=430-0.79xHeart Rate	0.97
B.C.	QT=482-1.59xHeart Rate	0.96	QT=458-1.12xHeart Rate	0.94
A.O.M.	QT=466-1.37xHeart Rate	0.98	QT=479-1.26xHeart Rate	0.98
B.H.	QT=514-1.50xHeart Rate	0.95	QT=496-1.15xHeart Rate	0.95
C.W.	QT=476-1.53xHeart Rate	0.95	QT=485-1.22xHeart Rate	0.95
C.P.M.	QT=480-1.55xHeart Rate	0.97	QT=497-1.35xHeart Rate	0.97
S.	QT=515-1.64xHeart Rate	0.98	QT=496-1.40xHeart Rate	0.97
R.B.	QT=500-1.50xHeart Rate	0.95	QT=493-1.15xHeart Rate	0.99
L.F.	QT=501-1.85xHeart Rate	0.99	QT=493-1.03xHeart Rate	0.98

r=coefficient of correlation; units: QT interval (ms), Heart Rate (bpm).

Table XVI. QT intervals determined at various heart rates during exercise, in patients who had taken a 100 mg atenolol daily for more than three months.

Subject	Heart Rate	QT	Subject	Heart Rate	QT
1.	51	435	2.	44	490
	54	440		57	475
	57	435		56	460
	88	365		70	440
	75	385		76	420
	5	412		82	430
	5	415			
3.	50	400	4.	83	355
	55	405		97	350
	58	400		107	345
	60	400		125	300
	64	388		128	300
	83	368		130	286
	83	365		136	280
	91	354		142	270
				100	355
				91	345
5.	54	430	6.	50	400
	62	420		65	400
	111	390		81	380
	88	365		86	365
	94	360		92	345
	88	375		105	340
	75	386		109	328
	67	380		122	318
	64	405		125	318
	59	420		128	295
				139	285
				143	280

Table XVI continued:

Subject	Heart Rate	QT	Subject	Heart Rate	QT
7.	52	420	8.	53	405
	78	400		56	390
	94	360		81	375
	105	320		81	365
	74	370		88	350
	65	390		97	350
	65	380		62	395
				59	410
				103	335
				107	330
				115	320
9.	60	440	10.	61	410
	71	400		97	345
	86	385		70	380
	94	355		75	365
	103	325		103	335
	77	395		111	310
				100	315
				115	300
11.	55	395	12.	54	395
	94	365		81	390
	97	345		86	370
	94	325		98	350
	107	340		107	330
	120	310		130	280
	111	295			

Table XVI continued:

Subject	Heart Rate	QT	Subject	Heart Rate	QT
13.	59	425	14.	54	440
	61	410		54	435
	77	400		56	430
	84	375		65	410
	100	380		68	400
	55	450		80	385
	88	365			
	83	387			
	79	400			
15.	54	440	16.	75	378
	54	435		59	430
	56	430		60	420
	65	410		77	360
	68	400		73	370
	80	385		83	392
	88	365		86	360
	83	387		60	410
	79	400		58	410

Units: Heart rate (bpm) and QT interval (ms).

Table XVII. Linear Regression equations describing the heart rate/QT interval relation during exercise in individual patients who had taken a 100 mg atenolol daily for more than three months.

	Regression Equation	
Patient	QT(ms) = a - b x Heart Rate (bpm)	r
1.	528 - 1.87 x Heart Rate	0.95
2.	471 - 1.26 x Heart Rate	0.97
3.	568 - 1.81 x Heart Rate	0.94
4.	500 - 1.59 x Heart Rate	0.97
5.	461 - 0.88 x Heart Rate	0.98
6.	592 - 1.39 x Heart Rate	0.95
7.	496 - 1.56 x Heart Rate	0.97
8.	480 - 1.39 x Heart Rate	0.97
9.	586 - 2.48 x Heart Rate	0.96
10.	472 - 2.04 x Heart Rate	0.95
11.	475 - 1.40 x Heart Rate	0.94
12.	534 - 1.84 x Heart Rate	0.98
13.	534 - 2.02 x Heart Rate	0.97
14.	585 - 2.47 x Heart Rate	0.95
15.	524 - 1.82 x Heart Rate	0.97
16.	510 - 1.42 x Heart Rate	0.98

Table XVIII. QT intervals and ventricular effective refractory periods (VERP), measured at various paced-ventricular rates (VR) in subjects who were not on any medication.

Subject	VR	QT	VERP	Subject	VR	QT	VERP
1.	55	520		2.	77	475	273
	60	510	308		84	435	267
	71	498	305		97	425	257
	86	485	303		109	400	236
	100	465	292		115	386	231
	115	450	281		130	375	219
	143	425	259		143	355	214
	150	430	249				
3.	80	395	238	4.	69	415	
	86	390	230		83	405	227
	92	395			97	415	223
	94	390	233		120	398	213
	107	375			135	380	215
	115	370	231		150	370	207
	125	355			158	365	213
	130	360	225				
	143	350					
	162	330					
	150	340	215				
5.	46	515	334	6.	144	362	231
	60	505	335		76	425	
	75	495	337		97	405	
	84	470	336		107	405	
	97	440	325		129	370	
	107	435	312		150	350	230
	118	405	303		71	430	260
	130	400	295		94	412	248
	146	390	281		110	395	245
					125	380	240
7.	75	460	260				
	85	435	260	8.	120	400	230
	100	420	240		70	450	260
	111	410	230		75	450	280
	120	400	230		88	440	240
	130	400	220		102	420	240
	143	380	220		114	405	240
	154	375			118	390	
	164	350	200		128	395	220
					148	380	220
					167	345	190

Table XVIII continued:

	VR	QT	VERP
9.	82	382	280
	91	415	263
	98	375	
	109	370	
	113	365	242
	59	445	309
	130	345	225
	150	325	217
	150	340	
	54	430	
	54	425	305
12.	81	400	277
	83	420	
	94	405	
	103	400	
	110	380	
	115	390	262
	125	375	
	133	360	242
	136	355	
	143	350	238
	77	440	281
	79	428	
14.	103	408	
	113	395	247
	123	380	
	133	370	
	140	360	
	98	410	255
	128	385	237
	74	435	266
	88	420	
10.	71	465	
	98	450	250
	109	440	230
	120	430	230
	133	415	220
	146	390	220
	162	360	205
	86	455	265
11.	39	500	
	40	485	320
	71	475	295
	81	470	287
	84	460	
	100	450	267
	113	450	261
	120	410	251
	146	387	229
	158	370	229
	30	510	320
13.	98	455	254
	109	450	246
	118	440	236
	128	430	226
	150	420	216
	81	462	265

Units: QT interval and VERP (ms); VR (bpm).

Table XIX. Comparison of the linear regression equations describing the paced-ventricular rate/QT interval, paced-ventricular rate/effective ventricular refractory period (VERP) and QT interval/VERP relations.

Patient	QT= a - b(HR)	r	VERP= a - b (HR)	r	VERP = a + b (QT)
1.	569 - 0.98HR	.94	354 - 0.67HR	.93	-30 + 0.67QT
2.	586 - 1.65HR	.94	346 - 0.96HR	.97	5 + 0.58QT
3.	464 - 0.82HR	.95	257 - 0.26HR	.97	108 + 0.32QT
4.	460 - 0.58HR	.89	242 - 0.23HR	1.00	60 + 0.40QT
5.	587 - 1.42HR	.97	374 - 0.58HR	.98	-132 + 0.41QT
6.	502 - 0.98HR	.98	285 - 0.37HR	.99	96 + 0.38QT
7.	531 - 1.06HR	.98	344 - 0.68HR	.99	7 + 0.64QT
8.	528 - 1.07HR	.98	318 - 0.73HR	.96	-41 + 0.68QT
9.	490 - 1.08HR	.97	362 - 1.02HR	.89	-102 + 0.95QT
10.	555 - 1.12HR	.94	318 - 0.71HR	.86	-34 + 0.63QT
11.	542 - 1.02HR	.95	348 - 0.78HR	.86	-66 + 0.76QT
12.	515 - 1.15HR	.96	331 - 0.65HR	.96	40 + 0.57QT
13.	517 - 0.65HR	.98	325 - 0.75HR	.97	-272 + 1.15QT
14.	476 - 0.74HR	.91	306 - 0.53HR	.96	-44 + 0.72QT

Units: QT interval and VERP (ms).

Table XX. Comparison of ventricular effective refractory period (VERP) and QT interval changes induced by heart rate, sotalol and amiodarone.

		VERP/QT	δVERP/ δQT
No treatment	Paced-Rate 60 bpm	284/460 = 0.617	
	Paced-Rate 120 bpm	245/440 = 0.613	0.646
Sotalol	Pre-Treatment (Paced-rate: 120 bpm)	214/398 = 0.538	
	Post-Treatment (Paced-rate: 120 bpm)	242/427 = 0.567	0.966
Amiodarone	Pre-Treatment (Paced-rate: 120 bpm)	250/420 = 0.595	
	Post-Treatment (Paced-rate: 120 bpm)	323/481 = 0.672	1.20

Table XXI. Amiodarone-induced ventricular effective refractory period (VERP) and QT interval changes, determined at a paced-ventricular rate of 120 bats per minute.

	Pre-Treatment		Post-Treatment			
Patient	VERP1	QT1	VERP2	QT2	VERP2-VERP1	QT2-QT1
1.	255	425	295	460	40	35
2.	280	433	390	460	110	27
3.	240	430	265	460	25	30
4.	240	360	430	625	190	265
5.	205	400	225	430	20	30
6.	260	420	355	480	95	60
7.	265	435	315	475	50	40
8.	278	480	298	490	20	10
9.	240	440	370	500	130	60
10.	235	380	290	430	55	50
Mean	250	420	323	481	74	61
± 1 S.D.	23	34	62	55	56	73

Units: QT interval and VERP (ms).

Table XXIIa. Sotalol-induced QT interval changes determined at a paced-ventricular rate of 120 beats per minute.

	Before Infusion	After Infusion
	QT Interval (ms)	QT Interval (ms)
B.	370	410
Y.	395	425
C.	415	440
C.	445	470
Y.	445	480
K.	385	390
R.	400	410
H.	375	390
N.	405	425
B.	365	405
K.	430	460
H.	360	430
C.	385	410

Table XXIIb. Sotalol-induced changes in ventricular effective refractory period (VERP) determined at a paced-ventricular rate of 120 beats per minute.

Patient	Ventricular Refractory Period (ms)		A Minus B
	Before Infusion (A)	After infusion (B)	
B.	190	230	40
Y.	210	240	30
C.	210	240	30
C.	220	250	30
Y.	260	280	20
K	230	230	0
R.	210	220	1
H.	200	230	30
N.	240	260	20
B.	180	210	20
K.	220	250	30
H.	190	240	50
C.	220	260	40

CHAPTER IV CONCLUSIONS AND DISCUSSION OF THE FIRST PART OF THE THESIS

The duration of the QT interval may be affected by heart rate or by autonomic nervous system activity. QT intervals were measured after prolonged bed rest and during sleep to reduce the level of sympathetic nervous system activity. Despite this, it was not possible to define a 'normal' resting QT interval because of significant patient variation. The QT interval varied between 358 $\pm$ 12 ms and 398 $\pm$ 11 ms, (mean $\pm$1 S.D.), at rest. The emphasis in the remaining part of the thesis has therefore been to describe QT interval changes over a range of heart rates rather than to determine whether isolated QT interval estimations were normal or otherwise.

Within the range of heart rates obtained during exercise, the heart rate/QT interval relation is only slightly curvilinear and although best described by an exponential regression equation, the relation is more conveniently and almost equally well expressed by a linear regression equation. Linear regression equations have recently been used by Rickards et al. (1979), Ackras et al. (1980) and Rickards and Norman, (1981), to describe the heart rate/QT interval relation.

The overall relation between heart rate and QT interval changes during exercise was hence given by the following

linear regression equation;

QT interval (ms) = 493 - 1.57 x heart rate (bpm).

QT interval changes were less impressive where these were brought about by an alteration in heart rate alone, such as atrial pacing at rest. In comparison to the exercise heart rate/QT interval relation, the heart rate/QT interval relation during atrial pacing at rest in a group of 11 patients was described by the following linear regression equation:

QT interval (ms) = 465 - 0.98 x paced-atrial rate (bpm).

Although intra-ventricular conduction is abnormal during ventricular pacing and the QRS complexes are consequently broad, almost identical QT interval changes occurred during atrial and ventricular pacing at rest in the same group of patients. For the group, the relation between ventricular pacing rate and the QT interval was expressed by the following regression equation;

QT interval (ms) = 537 - 0.99 xpaced-ventricular rate (bpm).

It therefore seemed valid to derive parallel information from ventricularly-paced groups of patients.

An important observation is that the QT interval exhibited hysteresis in relation to rate. This is particularly relevant to the estimation of QT intervals during pacing at rest. Although most of the changes in QT interval in response to an alteration in pacing rate were complete by 45 seconds, it is recommended that at QT interval estimations should be made only after at least two minutes of pacing

at a certain heart rate. It suggests that comparisons of rate/QT interval relations that are based on data which include QT intervals measured at a fixed-heart rate after a length of time and QT intervals obtained during rapid changes in heart rate should be interpreted with caution. It also has important implications for the QT responsive TX pacemaker. As described in the second part of the thesis, this pacing system senses the T wave of paced-ventricular complexes and alters heart rate in relation to changes in the duration of the interval between the stimulus and the T wave (Stim.-T interval). This system can thus provide measurements of this interval at rest at various programmed heart rates and the relation between heart rate and this interval at rest, derived in this way, has been used to programme values which affect the quality of rate response. The conclusion from this finding affecting the QT interval implies that the Stim.-T interval measurements may also be subject to hystereisis and thus Stim.-T interval measurements performed at rest after a certain length of time may not be directly relevant to the performance of the pacemaker during exercise and therefore may not prove useful in its programming.

The QT interval shortened with exercise during fixed-rate ventricular pacing at 70 beats per minute. This finding, together with the observation that QT interval changes during pacing at rest were less than those occurring during

exercise, indicated that factors other than heart rate played a major part in determining the duration of the QT interval.

Comparison of the slopes of the linear regression equations describing the heart rate/QT interval relation during prolonged bed rest with the less steep slopes obtained during pacing at rest also suggested that where heart rate changes were brought about by the autonomic nervous system activity QT interval changes were more marked. That the exercise-induced QT interval changes during fixed-rate ventricular pacing correlated well with the independent atrial rate was regarded as further evidence of the involvement of the autonomic nervous system in the determination of the changes in QT interval.

The atrial synchronized ventricular (VAT) pacemaker model provided the opportunity to compare, on a within-patient basis, QT interval shortening during fixed-rate ventricular pacing with that occurring during VAT pacing mode which permits theere the ventricular rate to alter in response to changes in sinus rate. Two important findings emerged from these studies. Firstly, by comparing the slopes of regression equations describing the atrial rate/QT interval relation during fixed-rate ventricular (only factors unrelated to heart rate, namely autonomic nervous sytem activity may act on the QT interval) and VAT (both heart rate and autonomic nervous system activity may act on the QT interval) pacing modes, factors unrelated to heart rate were found to account for as much as 52 $\pm$ 16% of

the QT interval changes during exercise; QT interval (ms) during VAT pacing was equal to: 564 - 1.75 x atrial rate (bpm) and QT interval (ms) during fixed-rate ventricular pacing at 70 beats per minute was equal to: 526 - 0.92 x atrial rate (bpm). Secondly, by similarly comparing the slopes of paired regression equations during exercise in these two pacing modes it was concluded that the contribution of heart rate to QT interval changes was subject to significant patient variation. For example, the contribution of heart rate to QT interval changes varied from 20% to 75% from one patient to another and 23% to 75% in the same subject from one occasion to the next. Examination of the heart rate/QT interval relation during exercise in subjects with normal electrocardiograms and also studies involving atrial and ventricular pacing at rest, confirmed that the heart rate/QT interval relation did exhibit significant subject variation.

The reasons for this patient variation are unclear. Ventricular myocardium may be affected by neurotransmitters from activation of the left and right stellate sympathetic nerves and vagus nerve, circulating catecholamines as well as by the intrisic action of heart rate. In the varying combinations and interactions of these factors may be found part of the explanation for the observed patient variation. Other explanations may include differences in the axis of ventricular depolarization and sensitivity of the sinus node to autonomic nervous system activity.

Whatever the explanation, however, this inter-patient and intra-patient variation which affects the heart rate/QT interval relation has important implications for the use of the QT interval as a biosensor to determine the pacing rate. Programming of the QT-responsive pacemaker may have to be carefully tailored to individual heart rate/QT interval characteristics and, more seriously, the same change in the duration of the QT interval may result in different pacing rates at various times in the same patient. This aspect of the performance of the rate responsive (TX) pacing system is examined in part II of the thesis. It is as yet undetermined how rapidly the heart rate/QT interval relation varies in individual subjects and whether it is affected by diurnal variation. These facts may be highly relevant to the programming of this pacing system, if it is confirmed that the heart rate/Stim.-T interval relation behaves similarly to the heart rate/QT interval relation.

At rest, heart rate changes are largely mediated through variations in vagal activity. During the initial stages of an exercise test, withdrawal of vagal inhibition also makes a significant contribution to the augmentation in sinus rate. During the later stages of an exercise test, sympathetic activity accounts for most of the increase in heart rate. The fact that QT interval changes which occurred during exercise with fixed-rate ventricular pacing, in patients with implanted atrial synchronized ventricular pacing systems, were virtually abolished by atenolol, suggests that the sympathetic nervous system

was primarily responsible for the autonomic contribution to the exercise-induced QT interval shortening.

This observation was further examined by testing the effect of atenolol on the heart rate/QT interval relation during exercise in normal subjects. Acute beta adrenergic receptor blockade reduced significantly the slope of the heart rate/QT interval relation: pre-beta adrenergic receptor blockade,

QT interval (ms) = 493 - 1.58 x heart rate (bpm), and

post-beta adrenergic receptor blockade,

QT interval (ms) = 481 - 1.16 x heart rate (bpm).

In contrast to this observation, the slopes of the heart rate/QT regression equations describing the heart rate/QT interval relation during exercise in patients on chronic atenolol therapy were not significantly different from the slopes of the linear regression equation in subjects who were not on any medication,

QT interval (ms) = 520 - 1.71 x heart rate (bpm). Thus the heart rate/QT interval relation in patients on beta adrenergic receptor blocker therapy appears to change after an unspecified interval of time and approximate the heart rate/QT interval relation in subjects who are not on any mediacation. This work supports the findings of Rickards and Norman (1981) and Vaughan Williams (1980a, 1981 and 1982) and suggests that whilst acute beta adrenergic blockade may severely blunt or even abolish rate response in patients with TX pacing system, adequate rate response may yet be achieved

in patients on chronic atenolol therapy.

The data which accumulated in these studies permitted examination of Bazett's QTc - measured QT interval, corrected for heart rate, under different conditions. QTc during exercise increased to maximal values around 100 to 110 beats per minute and thereafter decreased. Following acute beta adrenergic blockade, QTc continued to prolong beyond heart rates of 100 beats per minute. Chronic beta adrenergic blockade increased the QTc values, but restored the heart rate/QTc relation. The QTc was therefore not deemed to be a useful correction factor, as it neither provided for constant values during pacing at rest, nor when heart rate was altered by exercise, nor in the presence of acute beta adrenergic receptor blockade. It is therefore recommended that the practice of reporting observations based on QT intervals determined at a single heart rate (such as the QTc - QT corrected for an arbitary heart rate of 60 beats per minute) after a therapeutic manoeouvre should be abandoned and instead efforts should be made to characterize the effects on the heart rate/QT interval relation, in individual subjects, over a wide a range of heart rates.

Ventricular effective refractory period/QT interval relation was examined as a possible means of relating local events affecting ventricular depolarization to more global myocardial changes. As with the QT interval, the

ventricular effective refractory period (VERP) was found to vary inversely with the paced-ventricular rate; VERP (ms) = 323 - 0.65 x paced-ventricular rate (bpm). However, the effect of heart rate on VERP was less than on the QT interval; QT interval (ms) = 521 - 1.01 x paced ventricular rate (bpm).

As with the heart rate/QT interval relation, the heart rate/VERP relation also varied significantly from patient to patient.

Amiodarone and sotalol both increased substantially the QT interval and VERP. With amiodarone, however, in half of the patients VERP prolongation was greater than the corresponding increase in the QT interval and thus the VERP/QT interval ratio was altered, whilst with sotalol VERP and QT interval prolongation occurred to the same extent.

PART TWO

ADVANTAGES OF PHYSIOLOGICAL PACING,

THE PACED-VENTRICULAR RATE/STIMULUS-T INTERVAL RELATION

AND THE PERFORMANCE OF THE

RATE RESPONSIVE (TX) PACING SYSTEM

CHAPTER V INTRODUCTION:

Physiological or Adaptive Pacing:

Ventricular demand (VVI) is the most commonly used pacing mode. Approximately ninety per cent of all pacing systems implanted worldwide are of this type (Feruglio and Steinback, 1983). They are relatively inexpensive, reliable and effective in eliminating Stokes Adams attacks due to bradycardia and most patients with very low heart rate report an improvement in their symptoms and level of activities.

Fixed-rate ventricular pacing at an arbitary rate of 70 beats per minute however may be associated with deleterious haemodynamic effects and curtails the ability of patients to improve their cardiac output to meet increased physiological demand . Consequently, some patients continue to complain of dizziness, fatigue and dyspnoea.

A number of pacemakers are now available which are designed to improve cardiac output and be more responsive to the physiological needs of the patient. As no pacemaker can be said to be truly 'physiological' the term 'adaptive' has also been adopted in this thesis to describe these pacing systems.

These include:

(1) Pacing systems which only maintain the natural sequence of cardiac chamber activation e.g. fixed-rate

atrial (AOO), atrial demand (AAI), atrial-triggered (AAT), and atrio-ventricular sequential (DVI) pacemakers.

(2) Pacing systems which achieve both the natural sequence of atrio-ventricular activation and permit a chronotropic response to exercise e.g VAT, VDD (atrial synchronized ventricular demand) and DDD (universal). These pacemakers sense P waves via an atrial electrode which triggers ventricular activation via a second electrode after an interval of time which approximates to the normal PR interval.

(3) Pacing systems which sense changes in a physiological parameter and hence provide for a chronotropic response to increased metabolic demands but without atrioventricular synchrony.
Atrial electrical activity may still be used to indicate physiological needs. The RS4/SRT pacemaker (Cardiac Pacemakers Inc.) uses a single specially designed transvenous tripolar lead to sense p waves in the right atrium and pace the right ventricle: pairs of orthogonal 'floating' atrial electrodes are located at 10, 13 or 16 cm from the electrode tip, and are used for bipolar atrial sensing but not atrial stimulation. The ventricular pacing rate automatically varies between 63 and 115 beats per minute as a function of change in atrial (p wave) activity (Goldreyer et al., 1981). Significant

improvements in patient exercise performance have been described in the rate responsive mode (Goicolea de Oro et al., 1985). The lead is technically more difficult to implant because of its relative thickness and rate response may be unreliable due to respiratory-induced changes in the position of the sensor in the right atrium.

Approximately 50 per cent of all patients now undergoing pacemaker implant may not be suitable for adaptive pacing systems which rely on atrial electrical activity for their input due to sinus node dysfunction or presence of atrial arrhythmias (Rickards and Donaldson, 1983). There has therefore been a search for independent indicators of physiological demand.

The first such device was the pH triggered pacemaker (Cammilli et al., 1977, 1979, 1982 and 1983). This pacemaker utilized a pH sensing element which detected changes in venous blood pH and allowed the ventricular pacing rate to vary between 65 to 110 beats per minute. Wirtzfeld et al., (1982, 1983 and 1984), described a rate responsive pacing system based on measurement of mixed venous O_2 saturation. In 10 patients, they recorded increases in cardiac output as a result of a rise in pacing rate, in response to a fall in mixed venous O_2 saturation. The application of this principle has been limited by the time course of the O_2 saturation changes. Even under steady exercise conditions it takes 1 to 3

minutes for O_2 saturation to reach a steady value which is proportional to the degree of exercise.

Rossi et al. (1984) have reported initial successes with a pacing system (manufactured by Biotec) in which the pacing rate is driven between upper and lower bounds by a respiratory rate sensor. The respiratory rate is measured by means of an auxiliary lead placed subcutaneously, through the mid-sternum line, in the pectoral region on the side opposite to the pulse generator. The respiratory rate is detected by means of changes in electrical impedence between the pulse generator and the auxiliary lead. Among the problems reported with this system have been dislocation of the auxiliary lead and inability in some patients to obtain an optimum relation between the respiratory rate and the pacing rate. This relation may also be affected by respiratory disease. Despite these problems the system has been successfully used to provide AAI and rate responsive capability in patients with sinus node dysfunction.

A pacemaker made by Medtronic (Humen et al., 1983 and 1984) has recently been described which is sensitive to muscle noise. A good relation between muscle noise and heart rate has been demonstrated and the system responds well to moderate and vigorous exercise but not so well to light exercise and not at all to emotional stress. The main concern has been the triggering of the device by environmental noise, such as travelling in a motor

car (Ryden et al., 1984).

The TX-pacemaker, using a conventional lead, alters the ventricular pacing rate in response to changes in the QT-interval [or more accurately Stimulus artefact-to-T wave interval (Rickards and Norman, 1981)].
Other biosensors which have also been considered include central venous blood temperature (Griffin et al., 1983, Laczkovics, 1984, Jolgran et al., 1984), right atrial pressure (Cohen, 1984), and stroke volume (Neumann et al., 1985).

The increasing availability of different types of pacemakers makes it important to establish if adaptive pacing is of practical value to patients and if so which aspect of adaptive pacing contributes most to improved exercise performance.
This section addresses itself to these problems and investigates the performance of the rate responsive TX pacing system in the light of these considerations and in particular, the observations made in the first part of this thesis relating to the heart rate/QT interval relation.

Aims of Study:

The aims of the study were to

A.

Investigate the advantages if any, conferred by adaptive pacing as compared with fixed-rate ventricular pacing at 70 beats per minute by:

(i) Recording changes in haemodynamic indices at the time of pacemaker implantation, in patients with heart block, as the cardiac rhythm changed from second or third degree atrio-ventricular block at a slow intrinsic ventricular rate to ventricular pacing at 70 beats per minute, and finally to atrial synchronized ventricular pacing mode.

(ii) Comparing exercise performance during atrial synchronized ventricular pacing with fixed-rate ventricular pacing at a rate of 70 beats per minute.

(iii) Determining whether the magnitude of changes in haemodynamic indices recorded in the cardiac laboratory could predict which patients would benefit most from adaptive pacing.

(iv) Establishing whether improvement in exercise performance, if any, attributable to physiological pacing, was maintained with the passage of time.

B.

Determine which aspect of atrial synchronized ventricular pacing (maintenance of proper sequence of cardiac chamber activation or rate response without atrio-ventricular synchrony response) contributed most to improved exercise performance.

C.

Assess whether the findings of the above studies are borne out by the results of studies in patients with implanted rate responsive TX pacemaker. The following investigations were to be undertaken in patients with the TX pacing system:

(i) Compare exercise performance (a) during fixed-rate ventricular pacing with atrial synchronized ventricular pacing pre-pacemaker implantation and (b) following pacemaker implantation, exercise performance during rate responsive (TX) pacing mode with fixed-rate ventricular pacing mode.

(ii) Determine (a) the ability of the TX pacing system to sense T waves.

(b) The effect of changes in pacing rate on T wave amplitude.

(c) The effect of chronic T wave sensing changes, if any, on the paced-rate/Stim.-T interval relation and rate changes during exercise.

(iii) Ascertain the paced-ventricular rate/Stim.-T interval relation and determine whether this relation behaved similarly to the heart rate/QT interval relation, in that it was subject to significant patient variation.

(iv) Assess rate responses during exercise and by Holter monitoring.

(v) Assess the reliability of the Stim.-T interval as a biosensor and the effect of changes in programmable indices - T wave sensitivity, slope and T wave sensing window on rate changes during exercise.

(vi) Consider the best method for programming the pacemaker.

CHAPTER VI PATIENTS AND METHODS:

A. Comparison of Resting Haemodynamic Indices and Exercise Performance During Atrial Synchronized and Asynchronous Ventricular Pacing:

This study involved thirty-five patients who underwent implantation with atrial synchronized ventricular (Cordis 208A or 308A) pacemakers for chronic symptomatic atrioventricular block. The clinical details of the patients are shown in Table XXIII. The two patients with second degree atrioventricular block became rapidly pacemaker dependent on institution of temporary ventricular pacing. The criteria for exclusion were the presence of sinus node disease, atrial flutter or fibrillation, or inability to cope with exercise on the treadmill due to impaired cerebral or locomotor function. Informed consent was obtained in all patients.

Haemodynamic Measurements:

Resting haemodynamic measurements were performed in 28 out of 35 patients.

Cardiac indices measured were: cardiac output and pulmonary arterial pressure, using a thermodilution catheter inserted percutaneously via the femoral vein and systemic arterial pressures by percutaneous needle

puncture of the femoral artery.
Recordings were made (where possible) during spontaneous rhythm, asynchronous ventricular pacing at 70 beats per minute (bpm) and atrial synchronized ventricular pacing.

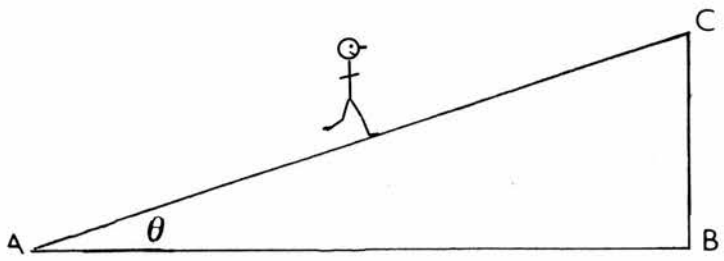
Treadmill Exercise Tests and Assessment of Exercise Performance :

A total of 67 pairs of exercise tests (during VAT and VOO pacing modes) were performed in the 35 patients.
Exercise testing was performed on a motor driven treadmill using the Bruce protocol (Bruce, 1971).
Pacing modes were chosen randomly with at least 30 minutes interval between the tests. Each test was observed by two physicians. One was responsible for the selection of the pacing mode used first, for continuous electrocardiographic monitoring and for measuring the systolic blood pressure by sphygmomanometer during the last 15 seconds of each stage of the exercise protocol. He also indicated that the exercise should be terminated only if a potentially dangerous arrhythmia or hypotension occurred. The second physician supervised the patient during exercise and encouraged the patient to his/her symptom-limited maximum effort. Neither this physician nor the patient was aware of the pacing mode.
The following recordings were made: (a) symptoms resulting in termination of exercise (angina, dyspnoea, exhaustion,

leg fatigue or lightheadedness) (b) presence of ventricular tachycardia (defined as 3 or more consecutive ventricular complexes, occurring at a rate of greater than 120 beats per minute) and frequent ventricular premature complexes (VPCs, defined as ventricular premature complexes occuring at a frequency of 5 or more beats per minute) (c) duration of exercise (d) systolic blood pressure at the start of the exercise, at the end of each stage of the exercise protocol and immediately after the cessation of exercise (hypotension was defined as a fall in systolic arterial pressure of 10 mmHg or more) and (e) atrial rate at 3-minute intervals during exercise and symptoms experienced during exercise.

Changes in haemodynamic indices recorded at the time of pacemaker implantation were correlated with average changes in exercise performance on changing from fixed-rate, 70 bpm, ventricular pacing to atrial synchronized ventricular pacing mode.

Exercise performance was calculated either (a) as the total distance walked on the treadmill (estimated from the speed of the treadmill during each stage of the Bruce protocol and the duration of the exercise test) or (b) as the sum of work done during each stage of the Bruce protocol.



It was assumed that work done on the treadmill on walking an incline AC was equivalent to the sum of work done on walking along AB against frictional force and along BC against gravity.

Hence work done during each stage could be expressed as follows:

$$p \times V \times \frac{3}{60} \times (\text{cosine}\,\theta + \text{sine}\,\theta)$$

where p= weight of patient; V= velocity of the treadmill and θ = angle of incline of the treadmill.

A change in work done during VAT pacing mode, was also expressed as a percentage of the work done during VOO pacing mode:

$$\frac{\text{Total Work during VAT - Total work during VOO}}{\text{Work during VOO}} \times 100\ (\%)$$

B. Atrial Synchronized Ventricular Pacing - Contribution of Chronotropic Response to Improved Exercise Performance:

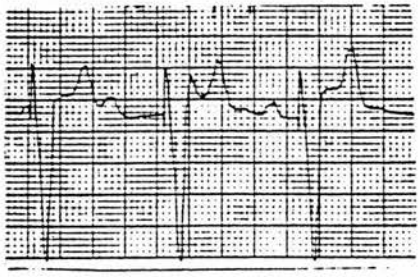
Fourteen patients with atrial synchronized ventricular pacemakers (Cordis model 308A), implanted for chronic idiopathic atrioventricular block, were studied. The clinical details of the patients are shown in Table XXIV. Exercise testing on a motor driven treadmill, using the Bruce protocol, was performed on all patients in 3 different pacing modes, selected in a random order (Table XXV), (a) atrial synchronized ventricular (VAT) pacing, (b) chest wall triggered ventricular (V-CWS-T) pacing; and (c) fixed-rate ventricular (VOO) pacing at 70 beats per minute (Figure 17).

Chest Wall Stimulation Triggered Ventricular (V-CWS-T) Pacing Mode:

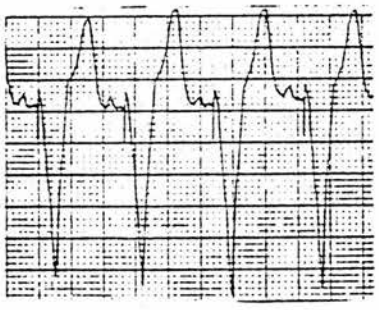
A chronotropic response to exercise, similar to the patient's atrial rate but without atrioventricular synchrony was achieved using chest wall stimulation (CWS). This was carried out using two electrodes connected to a temporary pacing box, one (positive) applied directly to the skin over the implanted pacemaker and another (negative) to the third intercostal space, at the left sternal edge. With the implanted pacemaker programmed to VAT mode, chest wall stimuli rather than P waves triggered

E.C.G. recorded during three exercise tests in a patient

1. Asynchronous Ventricular Pacing (VOO):



2. Atrial Synchronised Ventricular Pacing (VAT):



3. Pacemaker Programmed to VAT Mode but Driven by Chest Wall Stimulation (V-CWS-T):

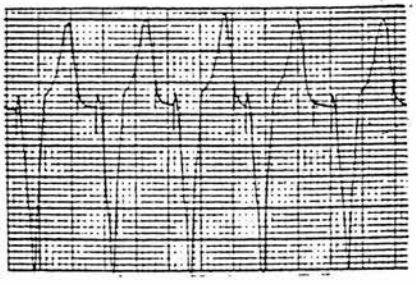


Figure 17. Exercise electrocardiograms during fixed-ventricular rate (VOO, 70 beats per minute), atrial synchronised ventricular (VAT) and chest wall stimulation triggered ventricular (V-CWS-T) pacing modes.

ventricular activity. The implanted pacemaker was thereby driven externally at rates which were kept fractionally above the independent atrial rate. The atrial rate was measured at 20 second intervals from the electrocardiogram. The Marquette CASE TM Computer Assisted System for Exercise (Marquette Electronics, Milwaukee, Wisconsin, U.S.A.) minimized baseline electrocardiographic fluctuations and hence facilitated measurement of atrial rate during exercise. Care was taken to ensure atrioventricular asynchrony by continuously monitoring the electrocardiogram, frequently checking the electrocardiographic recordings and altering the pacing rate accordingly.

C. Studies on the TX Pacing Systems:

The TX pacing system was evaluated in 14 patients (9 patients had a TX pacemaker implanted at the Western General Hospital and Royal infirmary, Edinburgh and 5 patients at Wythenshawe Hospital, Manchester). The clinical details of the patients are shown in Table XXVI. The indications for pacing were symptomatic, stable third degree atrioventricular block in thirteen patients and sinus bradycardia in one patient.

The patient with sinus bradycardia had satisfactory atrio-ventricular conduction (A-V Wenchebach developed with atrial pacing at 160 beats per minute) and had previously received a permanent atrial demand pacing system but had continued to suffer exertional syncope despite normal pacemaker function. During treadmill exercise tests he developed lightheadedness and ataxia associated with hypotension, presumably on the basis of exercise-induced vasodilatation and absence of an adequate atrial rate response. Prior to TX pacemaker implantation, he was fitted with a temporary ventricular pacing system and re-exercised in two pacing modes: (i) ventricular demand pacing at 80 bpm and (ii) where the pacing rate was progressively increased in the first minute of exercise to 120 bpm. His exercise performance improved by 80 per cent with the provision of rate increase and his blood pressure rose during exercise (it fell when the heart rate was

maintained at 80 beats per minute). He did have evidence of intermittent ventriculo-atrial conduction at rest. This was however not associated with any untoward effects and disappeared during exercise. The evidence therefore suggested that he would benefit from a rate responsive pacemaker

Comparison of Exercise Performance During TX, VAT and Fixed Rate Ventricular Pacing Modes:

Temporary atrial and ventricular leads (Cordis) were inserted in 8 patients pre-operatively and connected to a Cordis 308A atrial synchronised generator adapted for external use. The patients were exercised on the treadmill using the Bruce protocol or a modified version, in a double blind manner, during VAT and VOO (70 beats per minute) modes, chosen randomly.

Two weeks after pacemaker implantation, the generator was programmed to TX mode. Twelve of the 14 patients were exercised, during rate responsive (TX) and ventricular demand (VVI), 70 bpm, pacing modes, selected randomly. The exercise protocol followed was identical in any pair of exercise tests.

Stimulus-T Interval Measurements:

The Stim.-T interval was measured at rest and in the supine position in increments or decrements of 10 beats per minute, at paced-ventricular rates of between 40 bpm

and 120 bpm on 75 occasions in 12 patients.
The Stim.-T measurements were made 2 minutes after altering the paced-ventricular rate to permit the Stim.-T interval to the adapt to the new heart rate.
The paced-ventricular rate/Stim.-T interval relation was studied before and after exercise tests and at different programmed T wave amplitudes.
The paced-ventricular rate/Stim.-T interval relation was examined to determine the regression equation which provided the best curve fit.

Comparison of Heart rate/QT Relation Derived from the Surface Electrocardiogram with Heart Rate/Stim.-T Interval Relation:

On 15 occasions the electrocardiogram was recorded at a paper speed of 50 mm per second and at twice magnification, immediately following measurement of the Stim.-T interval at each paced-ventricular rate. In this way, the paced-ventricular rate/Stim.-T interval relation, derived from values displayed by the HP-85 computer, was compared with the ventricular rate/QT interval relations obtained from measurements made from the surface electrocardiogram. Two paced-ventricular rate/QT interval relations were studied based on (a) QT interval durations calculated from the pacing artefact to the apex of the T wave of the paced-ventricular complex, 'Stim.-T(Apex)' and

(b) from the pacing artefact to the terminal portion of the QT interval of the ventricular complex, 'Stim.-T(SE)'.

Holter Monitoring:

Rate responses were also studied by 24 hour Holter monitoring. Twenty-four hour Holter monitoring was recorded on 18 occasions in 9 patients.

Description of the TX Pacing Systems Implanted:

The TX pacing systems which were implanted included the TX1, TX2 and the newer Quintech model (3 patients).

(a) The TX1 Pulse Generator:

The system uses a conventional unipolar pacing electrode with a pacemaker capable of sensing the timing of the evoked T wave that follows ventricular depolarization. The pacemaker is sometimes referred to as QT-responsive but should be more correctly called rate responsive, Stimulus-T responsive or TX pacing system.
The TX1 (Vitatron medical diagnostic pulse generator; Vitatron Medical BV, The Netherlands) is lithium powered and microprocessor based (RCA 1802) with a bit serial I/O that permits full transcutaneous programmability through radiofrequency coupling via a programmer head to an external microcomputer (Hewlett-Packard HP-85) containing the monitor programme in its operational memory. This permits analysis and programming of all conventional and

T wave tracking, pacing, and sensing variables. Algorithms simulating normal physiological response alter the paced rate in response to relative changes in the interval between the stimulus and the T wave; a decrease in this interval causes an increase in the rate and vice versa. The sensivity or slope of the system to the changes in the interval (from 0.5 to 5 bpm per ms) and the slow exponential drift back to the basic rate (nulling) (from 35 to 125 bpm per hour) are programmed non-invasively 1 to 2 weeks after implantation and tailored individually to produce steady increases in rate (with a maximal rate of change set at 30 bpm per minute) to reach a preset upper rate over 6 to 12 minutes and then to gradually decrease to the basic pacing rate. In case of malfunction of the T wave tracking mode the pacemaker can revert to a standard ventricular inhibited (programmable VVI) fixed-rate ventricular pacing mode.

(b) TX2 Pulse Generator:

In the course of the study, implanted TX1 pacing systems were externally programmed to TX2. In the TX2 pacemaker the software is updated in such a way that the TX mode will function in cases where the pacemaker is inhibited by spontaneous rhythm. This 'tracking' property is of particular value in patients who accelerate their spontaneous rate and thereby switch off the rate responsive mode. This is most likely to occur in patients

with congenital atrio-ventricular block. Whenever the pacemaker is inhibited in this way, it will gradually decrease its escape interval (steps of 6.4 ms) until the pacing rate is above the spontaneous rate. A pacing pulse will then be released and, if capture follows, the Stim.-T interval will be measured. On the basis of this measured Stim.-T interval the pacemaker will increase the paced-ventricular rate or slow down again and allow the spontaneous rhythm to prevail. When employing this mode it is appreciated that, in cases where spontaneous rhythm is adequate, the electrocardiographic recording may show a mixture of fusion and pseudofusion complexes.
With this model, T wave amplitude is no longer displayed. Instead the HP-85 computer will show the percentage of T waves sensed at each programmed T wave sensitivity.

The Quintech TX Pulse Generator:

This latest TX model incorporates the tracking mechanism as well as hardware change which involves the design of a completely new filtering unit for T wave sensing, in the expectation that this will overcome the problem of T wave sensing which arises in some patients with TX1 and TX2 models.
The pacemaker also has an antitachycardiac mode. There is no available experience of this and its discussion is outside the scope of the present study.

Programmmable Indices:

T Wave Sensing:

In order to be sensed, T waves must (a) have an amplitude greater than 0.5 mV, (b) possess a relatively fast ´down-sloping´ (6 mV per ms) and (c) fall within the "T wave sensing window" (Figure 18).

It has recently become possible to test how well the TX pacing system senses the T waves of paced-ventricular complexes at operation using an external device which incorporates the Quintech TX sensing system. This device indicates whether T wave sensing is good, indifferent, or poor.

The quality of T wave sensing may be tested at rest using the HP-85 computer. When the pacemaker has been programmed to the TX mode, it is reassuring to observe that the duration of the displayed Stim.-T interval varies inversely with the programmed pacing rate. Additionally, the TX2 and Quintech models indicate the number of T waves sensed (expressed as a percentage of heart rate). This value should ideally remain at 100 percent throughout the range of heart rate. It falls during inadequate T wave sensing and when ventricular pacing is inhibited by spontaneous cardiac activity. A special ´beep´ has been incorporated that will be heard each time a T wave is sensed.

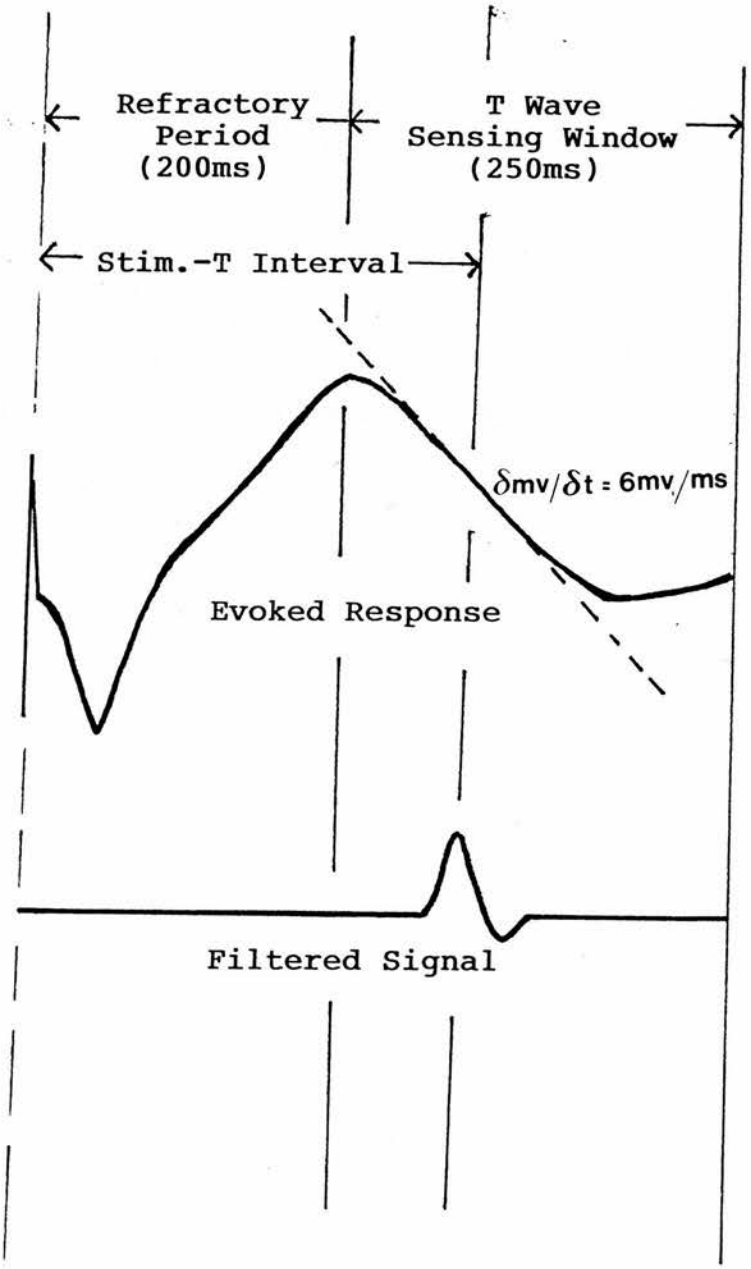


Figure 18. Diagramatic representation of the 'evoked response', Stim.-T interval and the T wave sensing window.

T wave Amplitude and Sensitivity:

T wave sensitivity is programmable from 0.5 mV through to 5.0 mV with the TX2 and Quintech models (0.5 mV to 3.0 mV with TX1) in steps of 1 mV.

The effect of pacing rate on T wave amplitude was recorded at rest in 9 patients with the TX1 pacing system.

The effect of different T wave sensitivity settings on (a) the paced-ventricular rate/Stim.-T interval relation at rest was studied in 8 patients (recordings made at the same clinic attendance) and (b) heart rate changes during exercise in 3 patients.

T Wave Sensing Window:

After delivery of a pacing impulse the pacemaker is refractory to all incoming signals during a blanking period of 200 ms. Thereafter, a T wave sensing window, which is programmable to 450 ms (calculated from the pacing impulse), is set out. During this interval T waves are sensed and timed (Figure 18). At the end of the T wave sensing window, QRS sensing is enabled. The effect of altering T wave sensing window on paced-ventricular rate changes during exercise was studied on different days or on the same day but with at least one hour of rest in between exercise tests.

Slope:

The slope defines the sensitivity of the TX pacemaker to changes in the Stim.-T interval. It is programmable from 0.5 to 2.7 beats per minute per millisecond change in the Stim.-T interval.

It has been recommended (Ursula Gebhardt-Seehausen, 1985 and De Jongste et al., 1985), that the slope to be programmed-in should be derived from the recorded change in the Stim.-T interval (δ Stim.-T) from a given alteration in the paced- rate (δ Paced-Rate):

Slope = δ Paced-Rate/ δ Stim.-T interval.

The ability of this method to provide suitable slopes was tested by determining the correlation between slopes predicted by linear regression equations describing the paced-ventricular rate/Stim.-T interval relations at rest with programmed slopes arrived at by trial and error, which resulted in satisfactory rate changes during exercise, all other programmable indices remaining unaltered. This exercise was performed twice in each of 10 patients.

Upper Rate Limit:

The maximum programmable upper rate limit with TX "ON" is between 123 and 142 beats per minute. The pacemaker algorithms are such that the exact value of the upper rate limit that can be programmed-in is affected to a small degree by duration of the T wave sensing window.

CHAPTER VII RESULTS

A. ADVANTAGES OF ATRIAL SYNCHRONIZED VENTRICULAR PACING MODE COMPARED WITH FIXED-RATE VENTRICULAR PACING MODE

Resting Haemodynamic Studies:

There was a significant improvement in cardiac output and mean arterial pressure on changing from atrioventricular block at patients´ intrinsic rate to asynchronous ventricular pacing at 70 beats per minute with a further improvement on programming to atrial synchronized ventricular pacing (Table XXVII).

No significant corresponding changes were observed in mean pulmonary arterial or pulmonary diastolic pressures (Table XXVII).

Heart Rate and Arterial Systolic Pressure Changes During Exercise:

There was a significantly greater increase in systolic pressure with each stage of the Bruce protocol and during the immediate post-exercise period during atrial synchronized ventricular pacing mode as compared with asynchronous ventricular pacing at 70 beats per minute, as shown in Figure 19.

Hypotension was an important limiting factor in 11 patients during asynchronous ventricular pacing, but

occurred in only 3 of the same patients (less pronounced in 2 patients) during atrial synchronized ventricular pacing mode (Figure 20).

There were smaller increases in atrial rate with atrial synchronized ventricular pacing compared with asynchronous ventricular pacing mode for each exercise stage, as shown in Figure 19.

Improvement in Exercise Performance Attributable to Atrial Synchronized Ventricular Pacing Mode:

Exercise performance during atrial synchronized ventricular pacing mode was better in 59/67 paired exercise tests and in 30/35 patients. This amounted to more than 33 percent increase in work done in 23/35 patients and 50 percent or more in 14/35 patients. The mean ($\pm$ 1 S.D.) improvement in exercise performance in the 35 patients was 45 ($\pm$ 39) per cent, range: -12 percent to +160 percent (Figure 21).

In 20 patients who had two sets of exercise tests, the improvement in exercise performance with atrial synchronized ventricular pacing increased from a mean of 18 percent to 48 percent with the passage of time, the interval between the two tests was 5 $\pm$ 2 weeks (mean $\pm$ 1 S.D.) and the range was 2 to 12 weeks as shown in Figure 22.

Calculation of the total distances walked on the treadmill on the two occasions, in this group of patients showed that by comparison, exercise performance during asynchronous ventricular pacing had changed little during the same period of time (Figure 23).

Frequency of Factors Limiting Exercise Performance in the Two Pacing Modes (VOO And VAT):

Exercise-induced ventricular arrhythmias, hypotension, lightheadedness and angina occurred more frequently during asynchronous ventricular pacing mode (Figure 20). Exercise during atrial synchronized ventricular pacing mode was associated with fewer untoward effects, being limited most commonly by exhaustion, leg fatigue and dyspnoea, symptoms which occurred as frequently and with the same or greater severity (indicated by the patient) during fixed-rate ventricular pacing, despite the shorter distances walked in this pacing mode.

Comparison of Changes in Haemodynamic Indices with Improvement in Exercise Performance:

There was no correlation between the magnitude of changes in resting haemodynamic indices and improvement in exercise performance due to atrial synchronized ventricular pacing mode in the 28/35 patients for whom both sets of data were available (Figures 24 to 27).

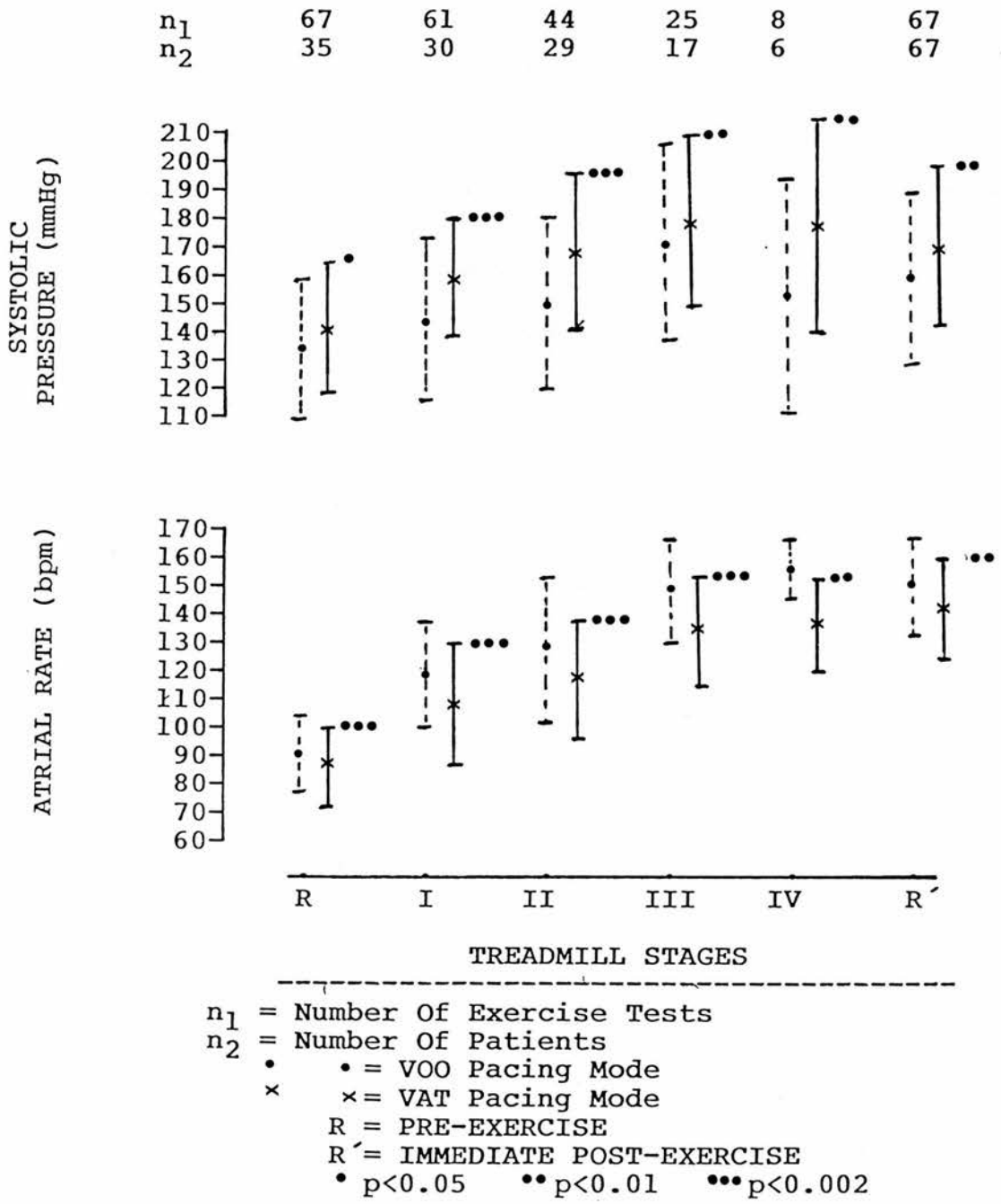


Figure 19. Exercise-induced atrial rate and systolic arterial pressure responses during fixed rate (VOO) and atrial synchronized (VAT) ventricular pacing modes.

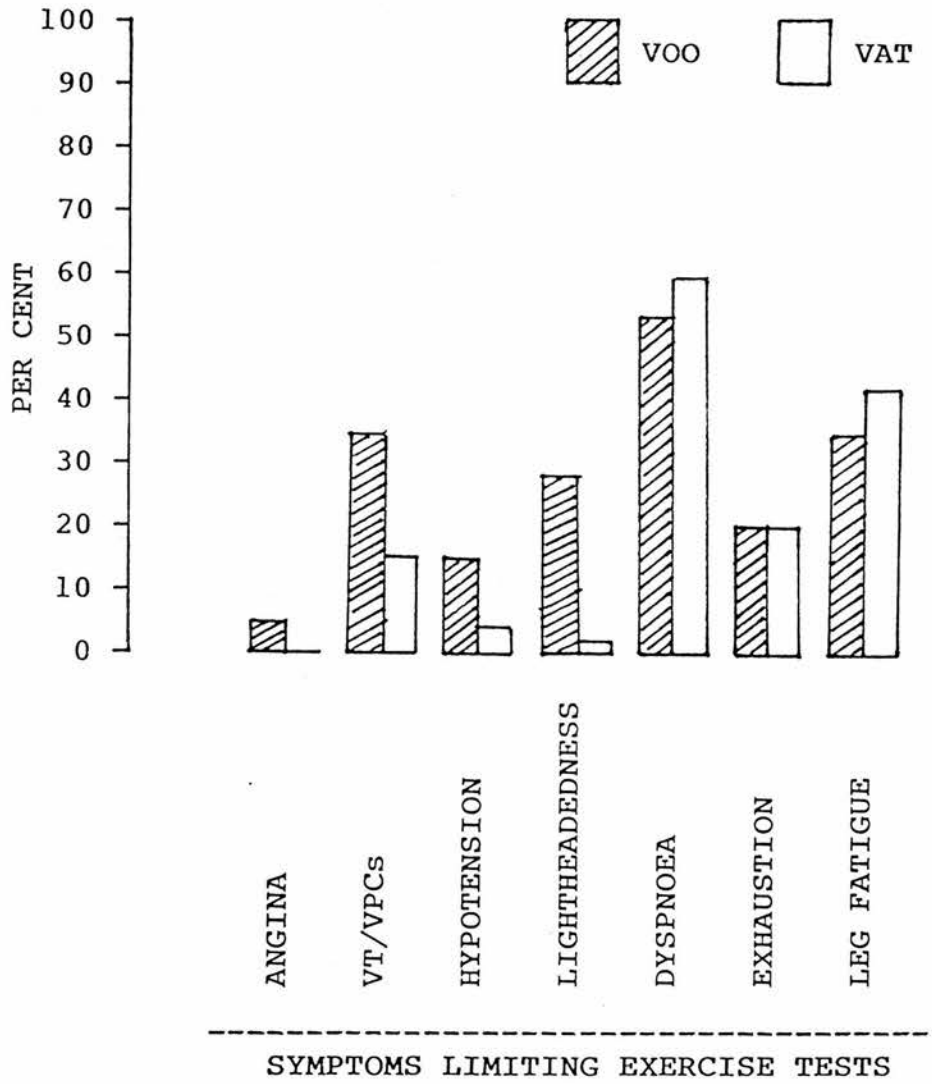


Figure 20. Frequency of symptoms limiting exercise performance during fixed-rate (VOO) and atrial synchronized (VAT) ventricular pacing modes.

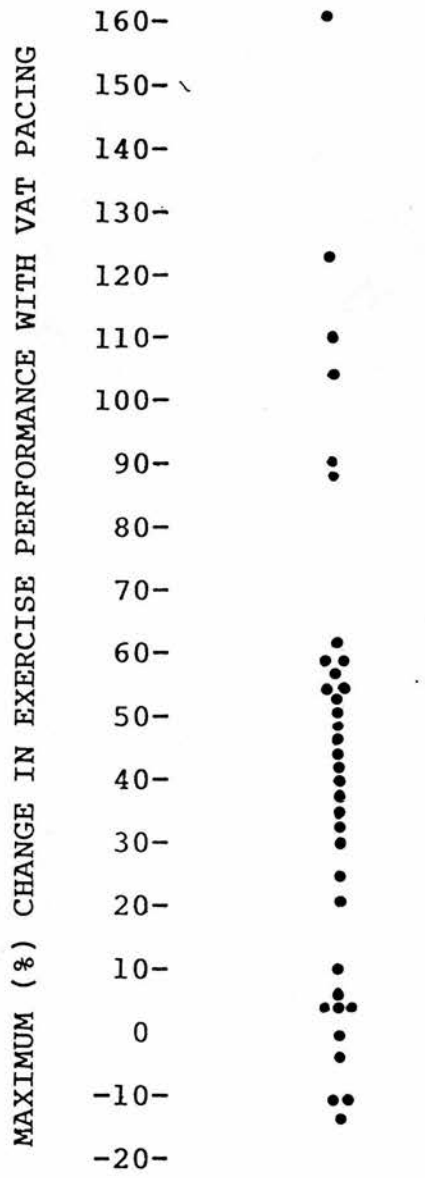


Figure 21. Maximum improvement in exercise performance during atrial synchronized ventricular (VAT) pacing mode (expressed as per cent of exercise performance during fixed-rate ventricular pacing mode). Individual data and mean $\pm$1 SD for the group.

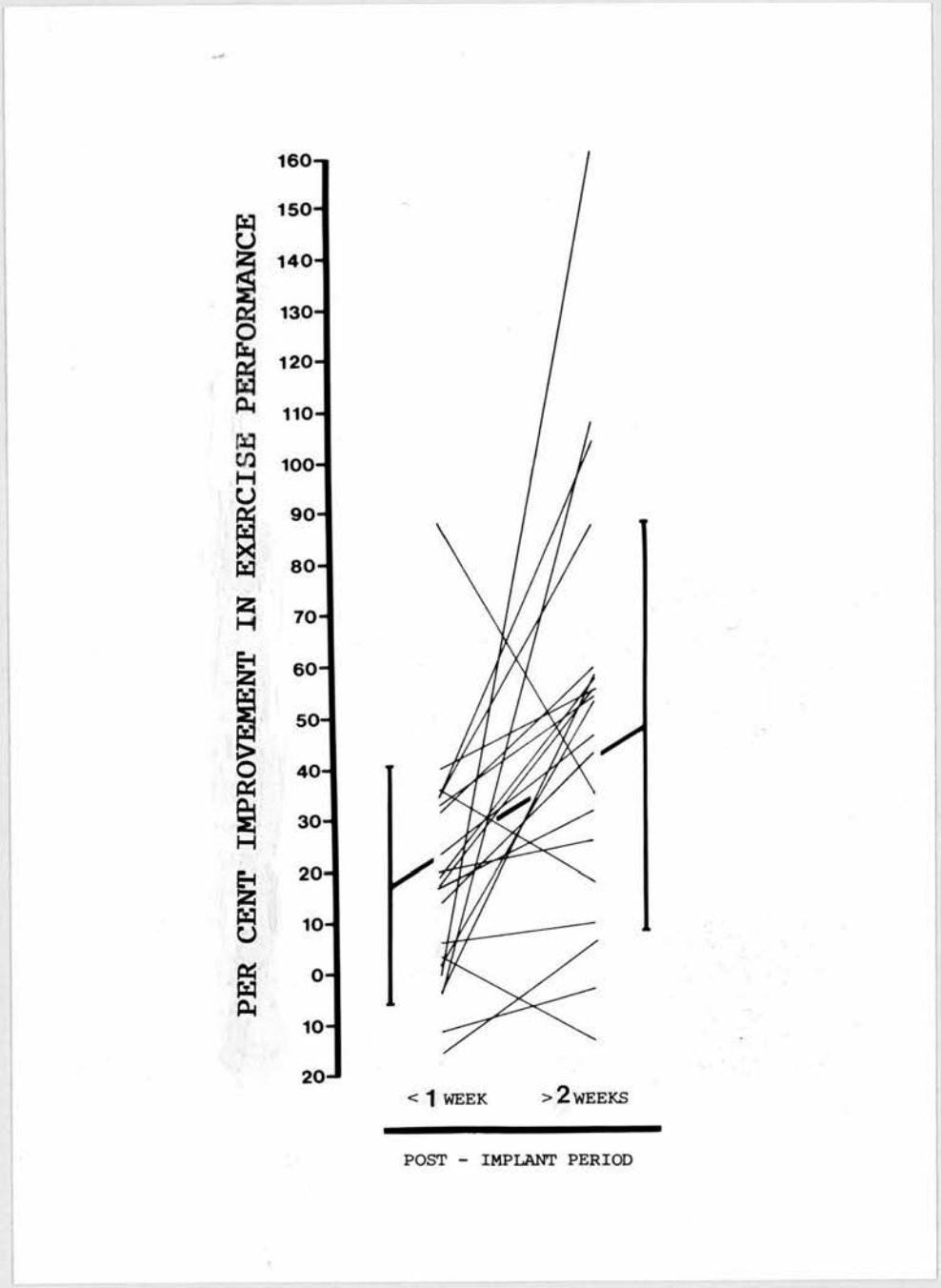


Figure 22. Comparison of changes in exercise performance due to VAT pacing mode in 20 patients who had two sets of exercise tests, separated by several weeks.
Individual data and mean $\pm$1 SD for the sets of exercise tests.

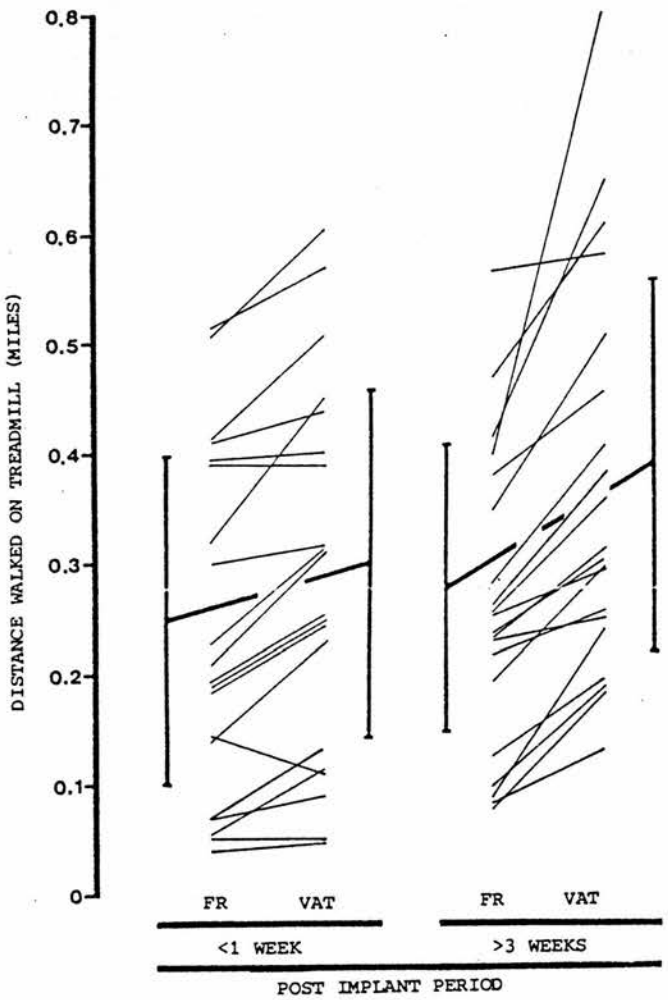


Figure 23. Comparison of distances walked during fixed-rate (VOO) and atrial synchronized (VAT) ventricular pacing modes, in 20 patients who had two sets of exercise tests separated by several weeks.

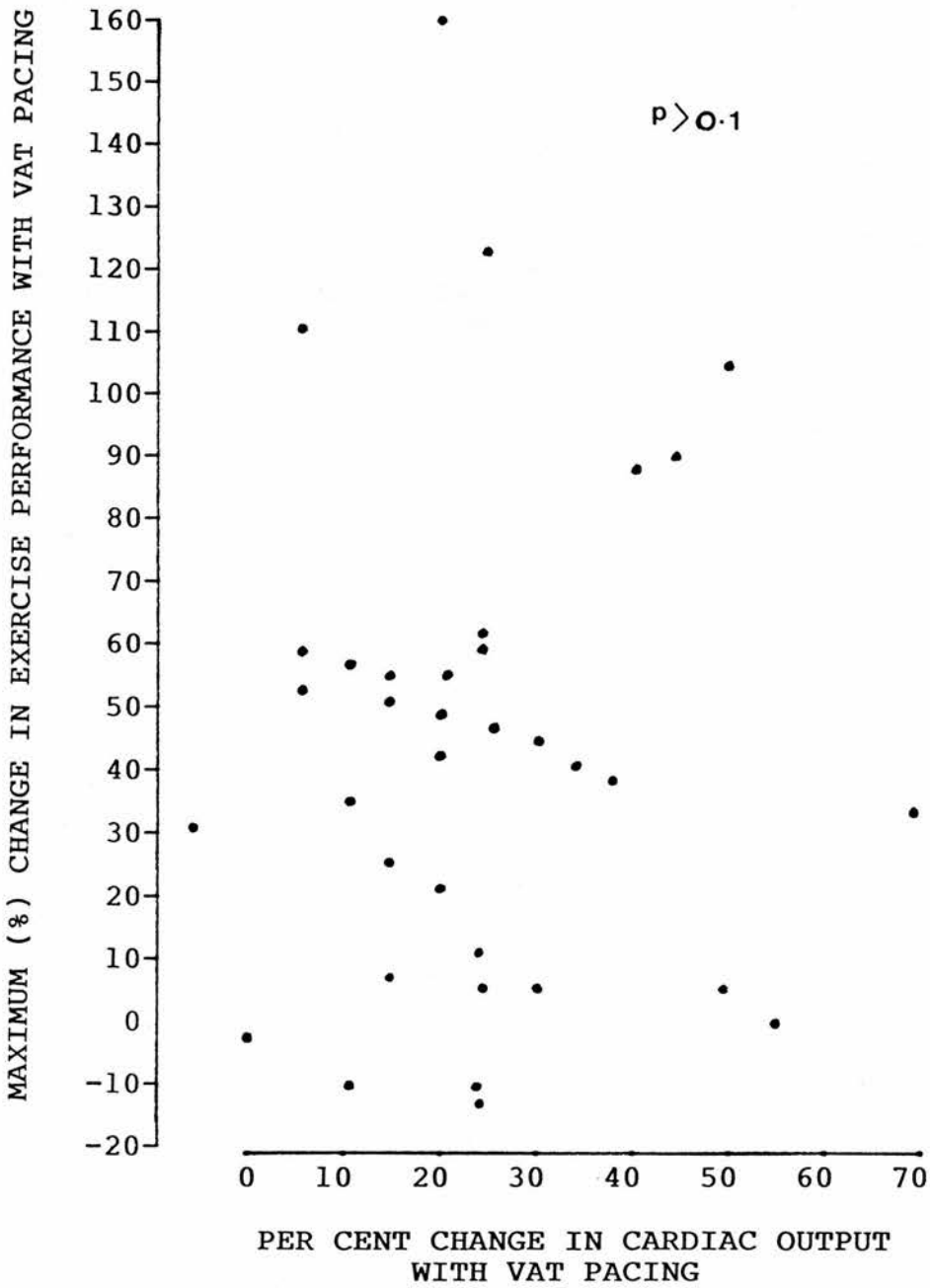


Figure 24. Correlation of changes in cardiac output recorded at pacemaker implantation, with changes in exercise performance due to atrial synchronized ventricular pacing mode.

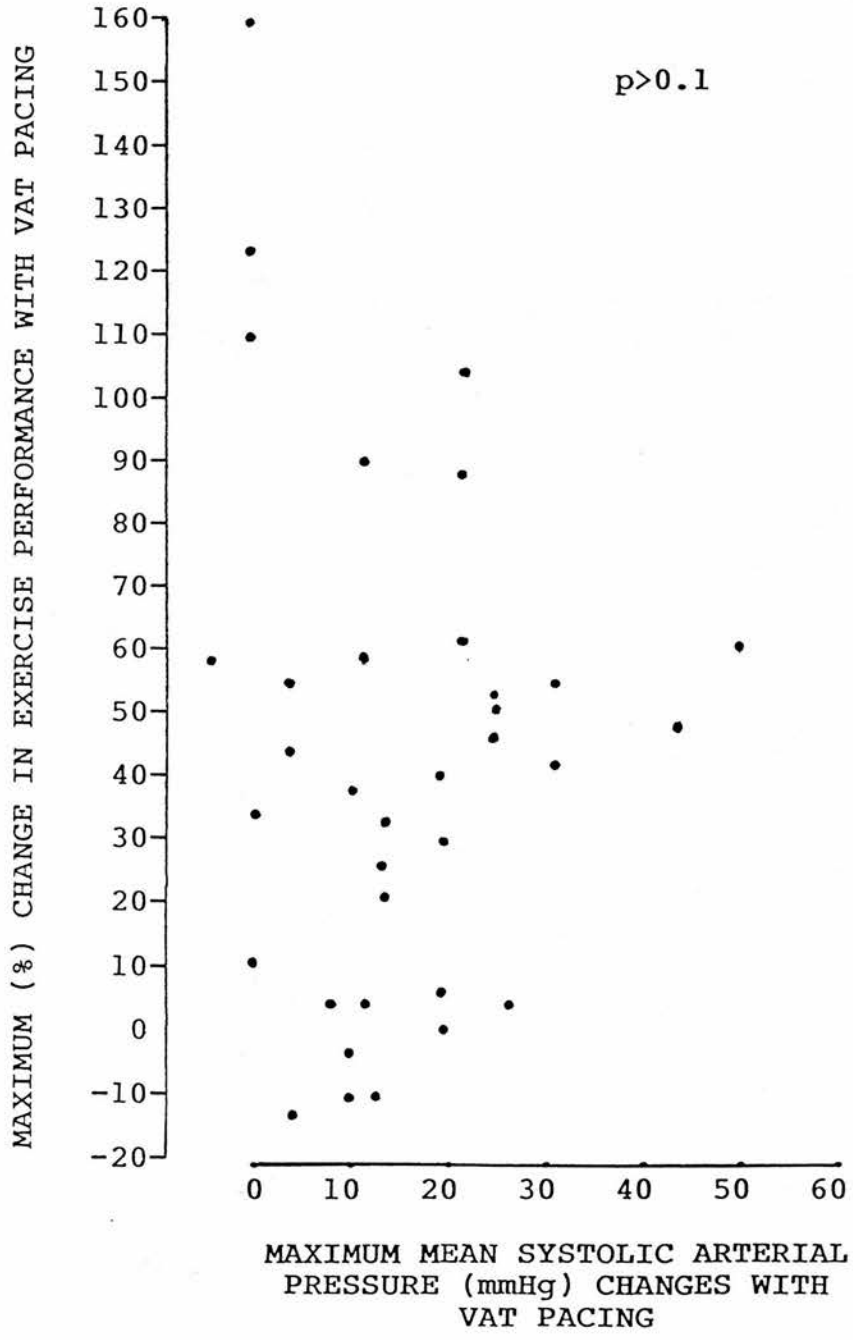


Figure 25. Correlation of changes in mean systolic arterial pressure recorded at rest with changes in exercise performance due to atrial synchronized ventricular pacing mode.

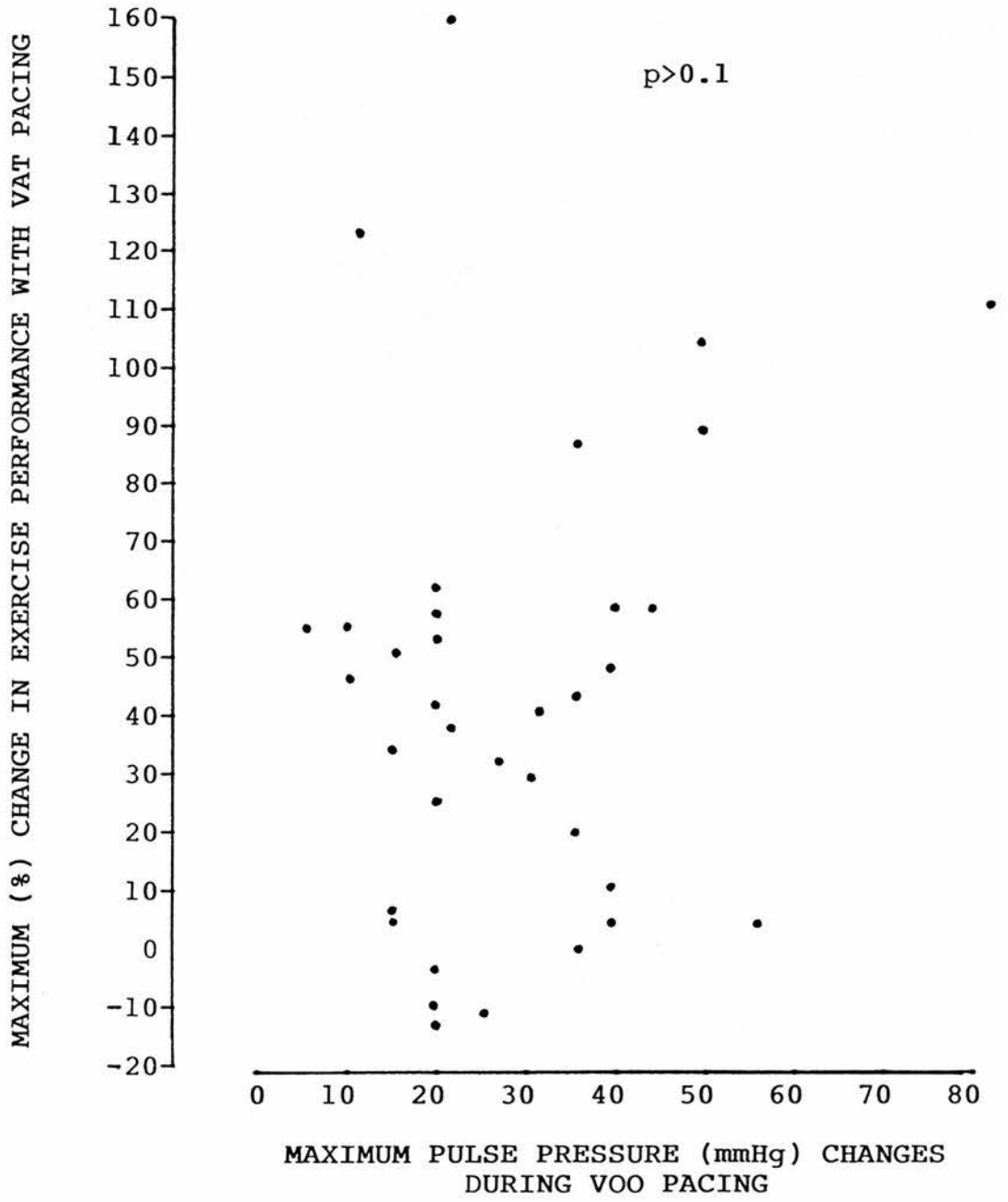


Figure 26. Correlation of changes in arterial pulse pressure during fixed-rate, 70 beat per minute (VOO) pacing recorded at rest, with changes in exercise performance due to atrial synchronized ventricular pacing mode.

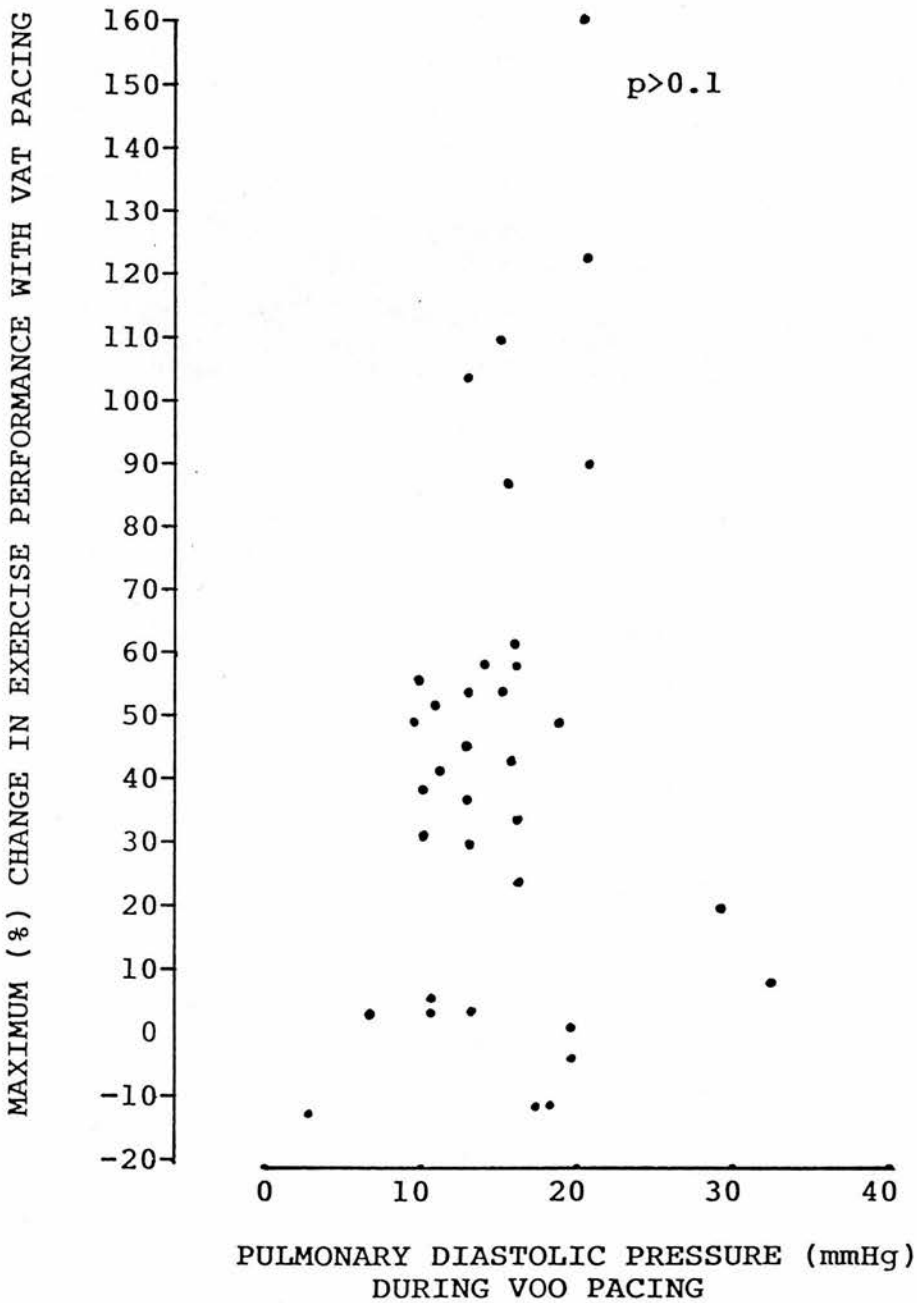


Figure 27. Correlation of pulmonary diastolic pressures recorded during fixed-rate, 70 beats per minute (VOO) pacing mode at rest, with changes in exercise performance due to atrial synchronized ventricular pacing mode.

B. ATRIAL SYNCHRONIZED VENTRICULAR PACING: CONTRIBUTION OF CHRONOTRPIC RESPONSE TO IMPROVEMENT IN EXERCISE PERFORMANCE

Comparison of Exercise Performance During Atrial Synchronized (VAT), Chest Wall Stimulation Triggered (V-CWS-T) And Fixed Rate Ventricular Pacing Modes:
The rate of chest wall stimulation throughout exercise during V-CWS-T was 2.5 $\pm$ 3 (mean $\pm$ 1 SD) pulses per minute higher than the corresponding atrial rate. This represented only a fraction of the total heart rate changes recorded during exercise.

Exercise performance was significantly improved during V-CWS-T and VAT modes as compared with that during VOO mode (Tables XXVIII and Figures 28 and 29). Exercise performance during V-CWS-T mode, however, was similar to that during VAT mode (Table XXIX and Figures 28 and 29).

Atrial rates were higher (Figure 30), and systolic arterial pressures lower (Figure 31) during VOO mode as compared with V-CWS-T and VAT modes, for each stage of the Bruce protocol and during the immediate post-exercise period. There were no corresponding significant differences between atrial rates during V-CWS-T and VAT modes.

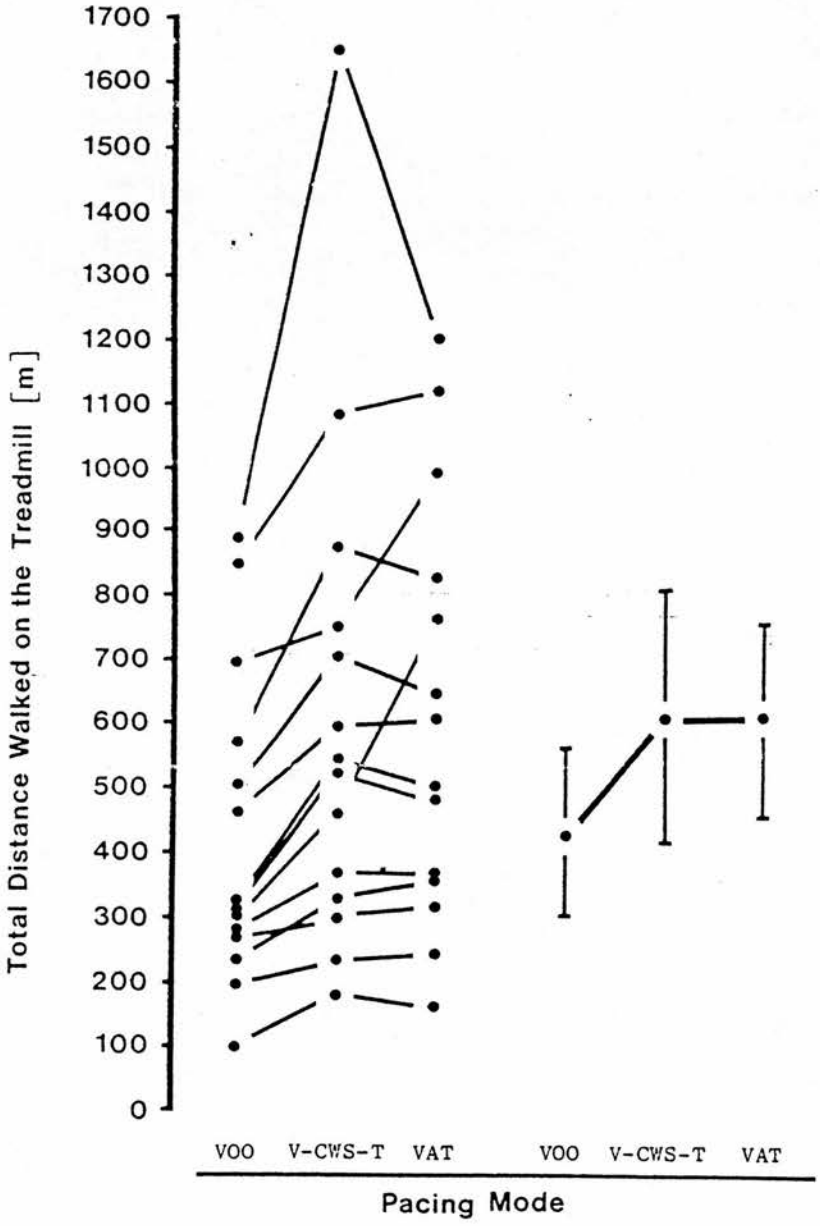


Figure 28. Comparison of total distances walked during fixed-rate, 70 beats per minute (VOO), atrial synchronized (VAT) and chest wall stimulation triggered (V-CWS-T) ventricular pacing modes.

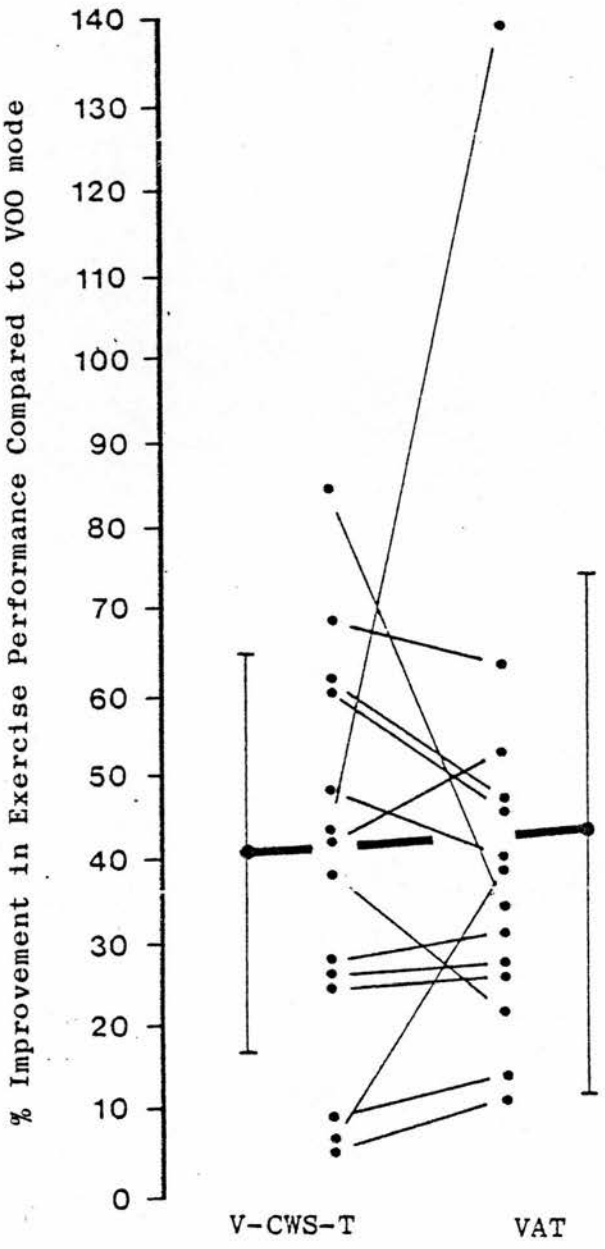


Figure 29 . Comparison of exercise performance during atrial synchronized (VAT) and chest wall stimulation triggered (V-CWS-T) pacing modes, (expressed as per cent of exercise performance during fixed-rate ventricular pacing mode).

Arterial systolic pressures were on average higher during V-CWS-T than VAT mode (Figure 31), but the heart rates were slightly higher (mean $\pm$ 1 SD; 4 $\pm$ 3, beats per minute) in V-CWS-T pacing mode.

The frequency of parameters limiting exercise duration is shown in Figure 32. Lightheadedness, postural hypotension, and premature ventricular complexes complicated VOO mode more frequently than V-CWS-T and VAT modes. Symptomatically the patients did equally well in the latter two pacing modes.

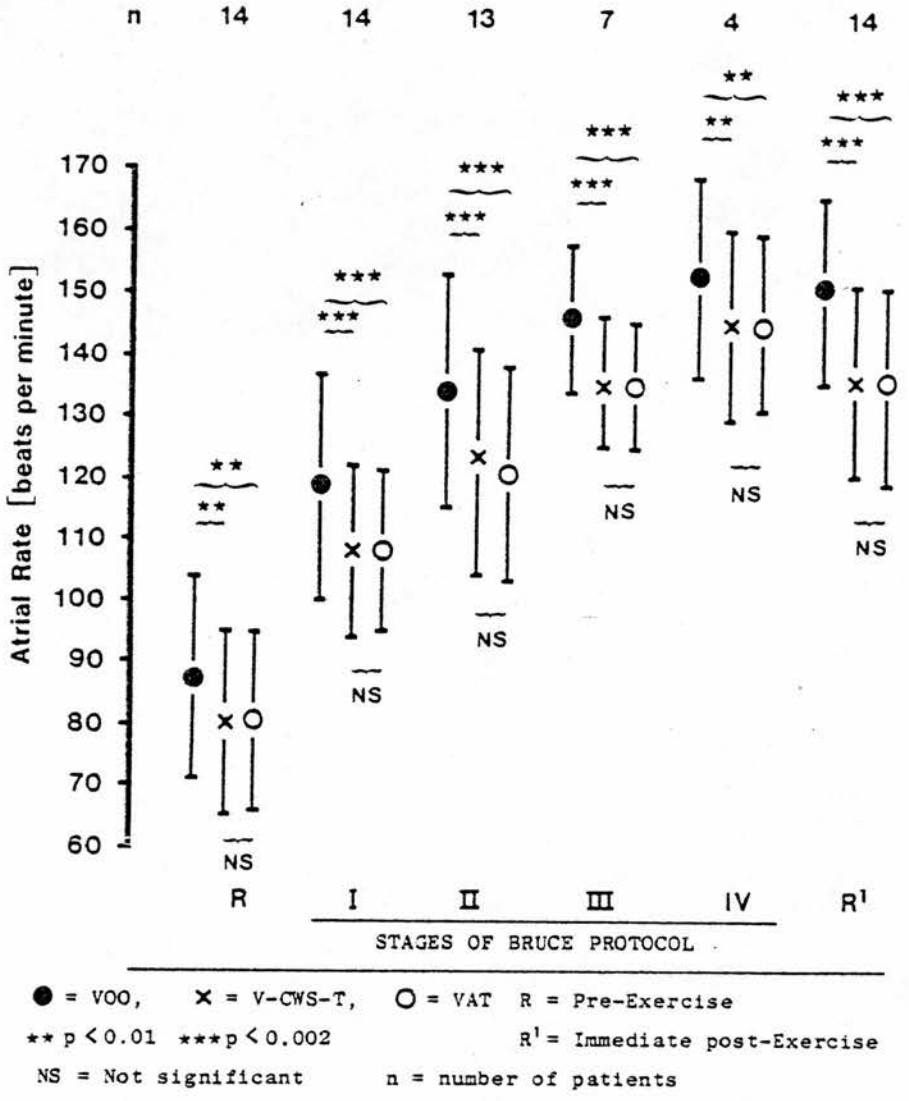


Figure 30. Atrial rate responses to exercise during fixed-rate (VOO), atrial synchronized (VAT) and chest wall stimulation triggered (V-CWS-T) pacing modes.

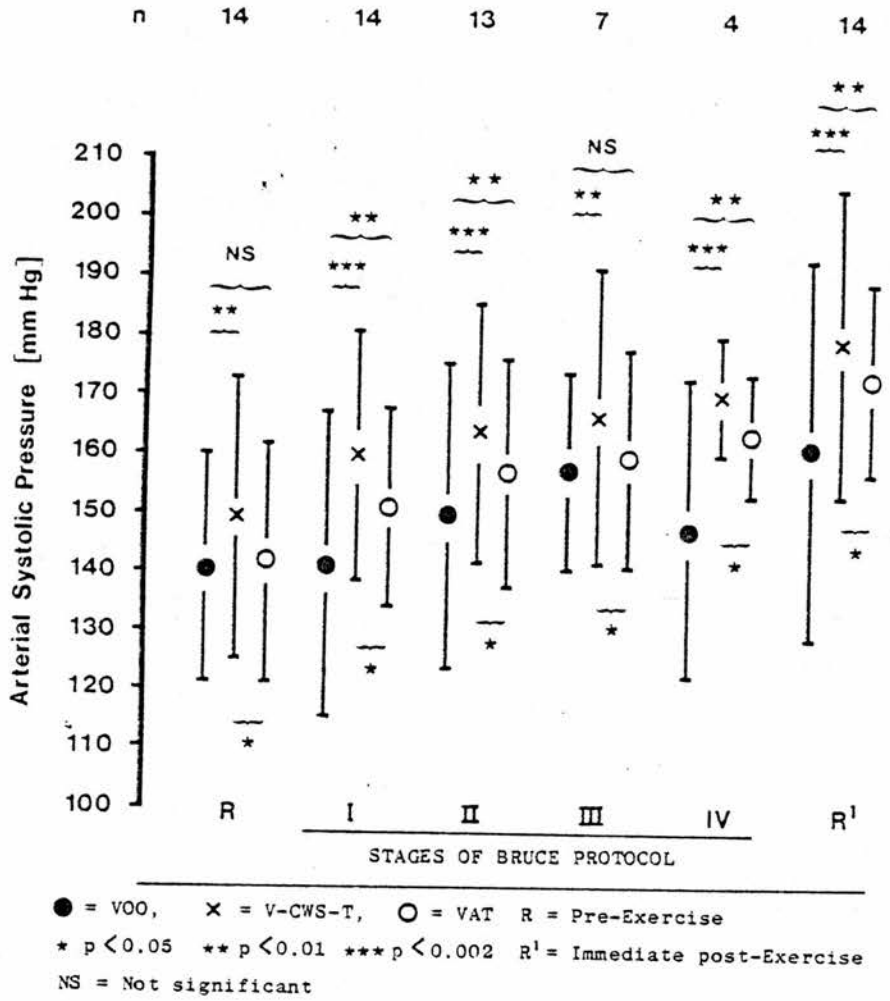


Figure 31. Systolic arterial pressure responses to exercise during fixed-rate (VOO), atrial synchronized (VAT) and chest wall stimulation triggered (V-CWS-T) pacing modes.

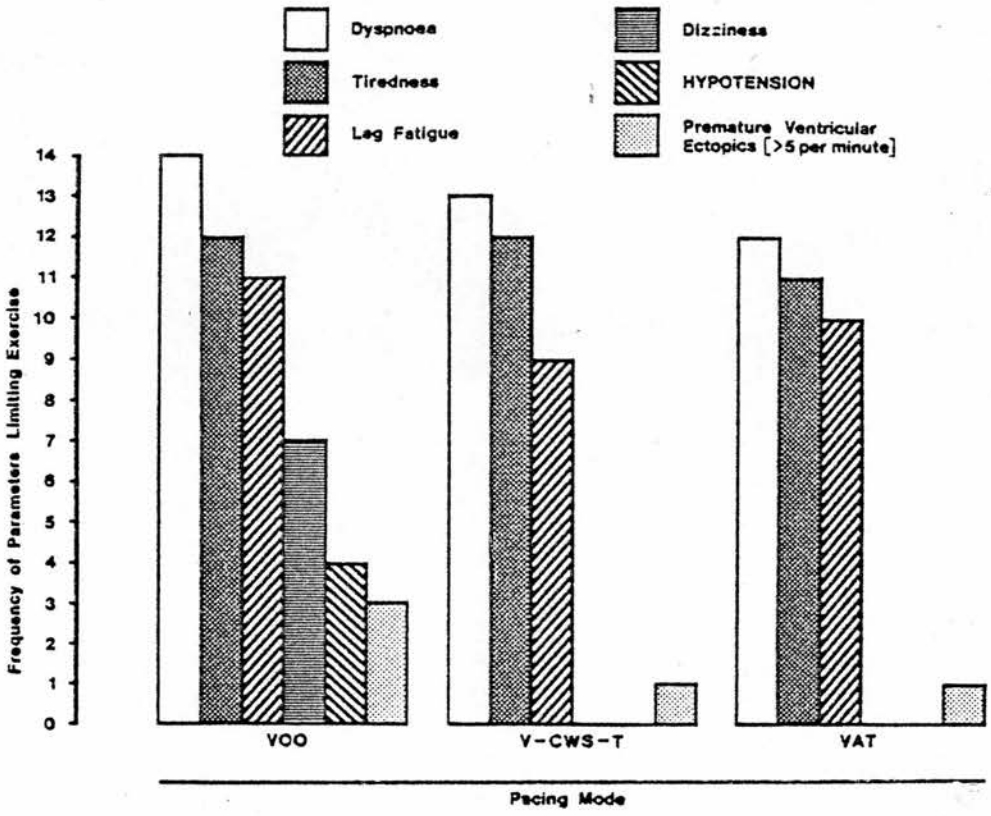


Figure 32. Frequency of symptoms limiting duration of exercise tests during fixed-rate (VOO), atrial synchronized (VAT) and chest wall stimulation triggered (V-CWS-T) pacing modes.

C. STUDIES INVOLVING THE TX PACING SYSTEMS

(i) Comparison of Exercise Performance During Fixed-Rate Ventricular (VOO and VVI), Atrial Synchronized Ventricular (VAT) And Rate Responsive (TX) Pacing Modes:

VAT Mode Versus VOO Mode:

The total distances walked on the treadmill during atrial synchronized ventricular pacing mode were significantly ($p<0.01$) greater than those achieved during fixed-rate ventricular pacing at 70 beats per minute pacing mode, (Figure 33);

Mean $\pm$ 1 S.D. distance during VOO mode:
468 $\pm$ 279 yards (range, 183 to 937 yards).

Mean $\pm$ 1 S.D. distance during VAT mode:
689 $\pm$ 384 yards (range, 261 to 1356 yards).

The ventricular rate at maximal exercise during atrial synchronized ventricular pacing mode was 148 $\pm$ 15 beats per minute (mean $\pm$ 1 S.D.).

Rate Responsive (TX) Mode Versus
Ventricular Demand Mode:

The total distances walked on the treadmill during TX and VVI, 70 beats per minute, pacing modes are shown in Figure 33;

Mean ± 1 S.D. distance walked during the VVI mode:
539 ± 387 yards (range, 33 to 1329 yards).

Mean ± 1 S.D. distance walked during the TX mode:
750 ± 435 yards (range, 99 to 1490 yards).

Exercise performance during the rate responsive mode was significantly ($p<0.002$) greater than that during ventricular demand pacing at 70 beats per minute. The ventricular rate at maximal exercise during TX pacing mode was 124 ± 9 beats per minute (mean ± 1 S.D.).

The tracking mode was observed on one occasion in a patient with congenital heart block whose spontaneous heart rate accelerated with exercise (Figure 34).

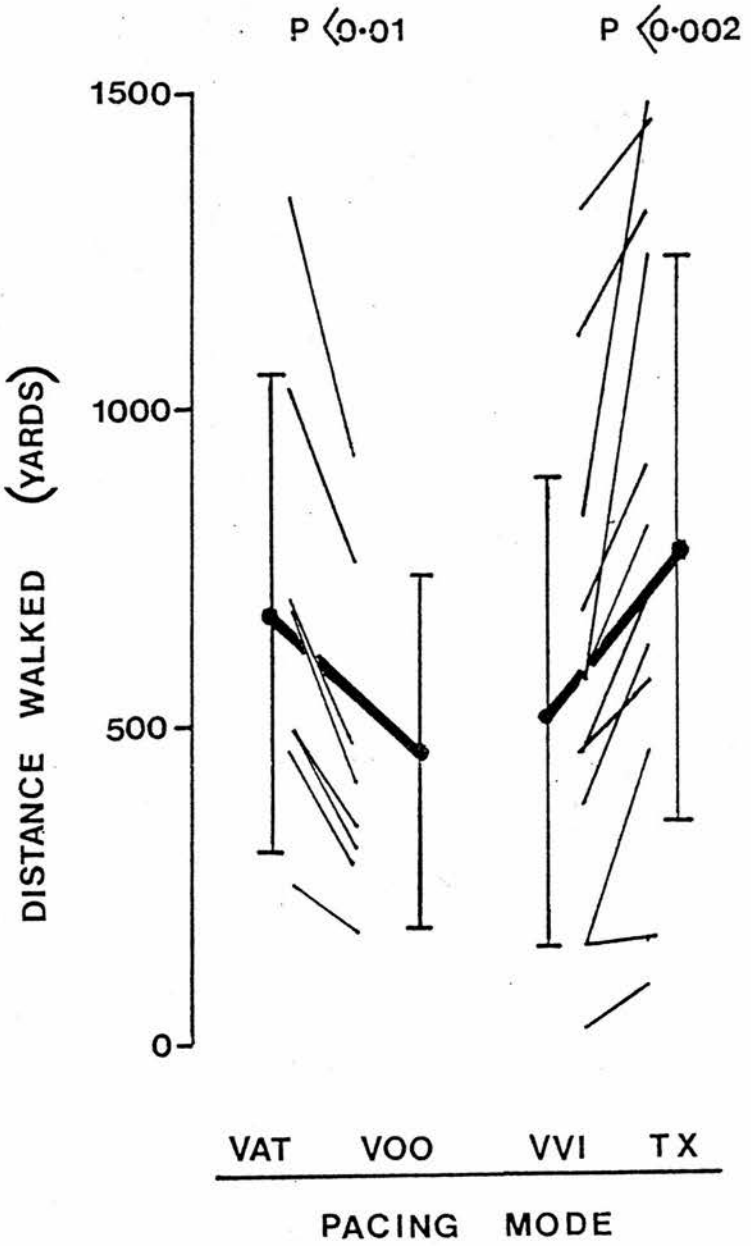


Figure 33. Comparison of exercise performance during fixed-rate (VOO) and atrial synchronized (VAT) pacing modes pre-pacemaker implantation and exercise performance during VAT and rate responsive (TX) pacing modes following TX pacemaker implantation.

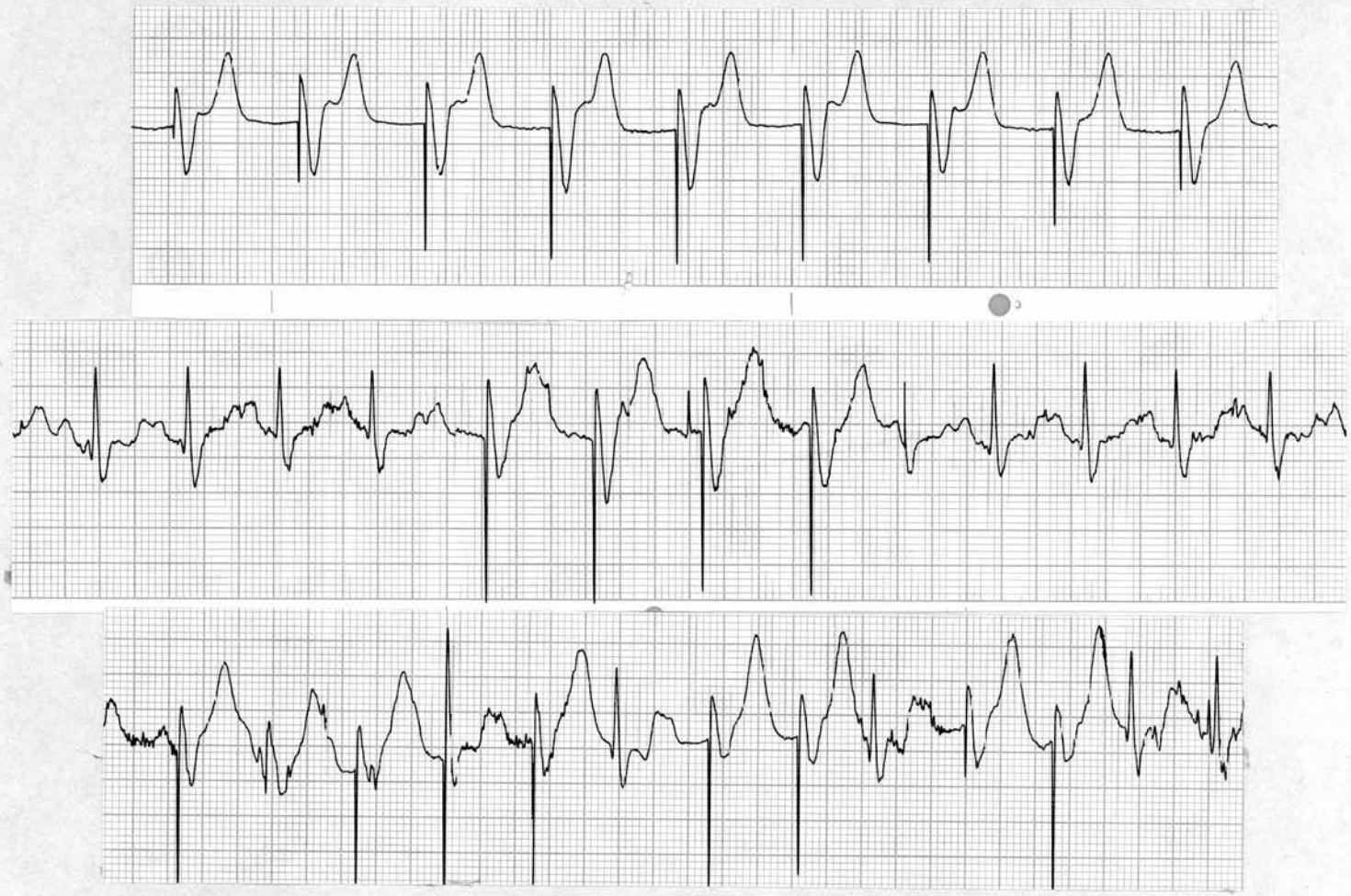


Figure 34. TX pacemaker performing in the ´tracking´ mode in a patient with congenital heart block whose spontaneous rate accelerated with exercise.

(ii) Performance of the TX Pacemaker as Assessed by Holter-Monitoring:

The rate changes during 24 hours of Holter monitoring are illustrated in Figures 35 to 38.

The rate remained appropriately low during periods of inactivity such as sleep and accelerated during periods of increased activity.

On 2 occasions in the same patient however, the rate accelerated during the night without the patient reporting any increased activity (Figure 36). It remained uncertain whether these episodes represented inappropriate rate responses or were related to dreaming or activity for which the patient had no recollection. The patient however did not complain of palpitations or any other form of discomfort and the pacemaker programme was therefore left unaltered.

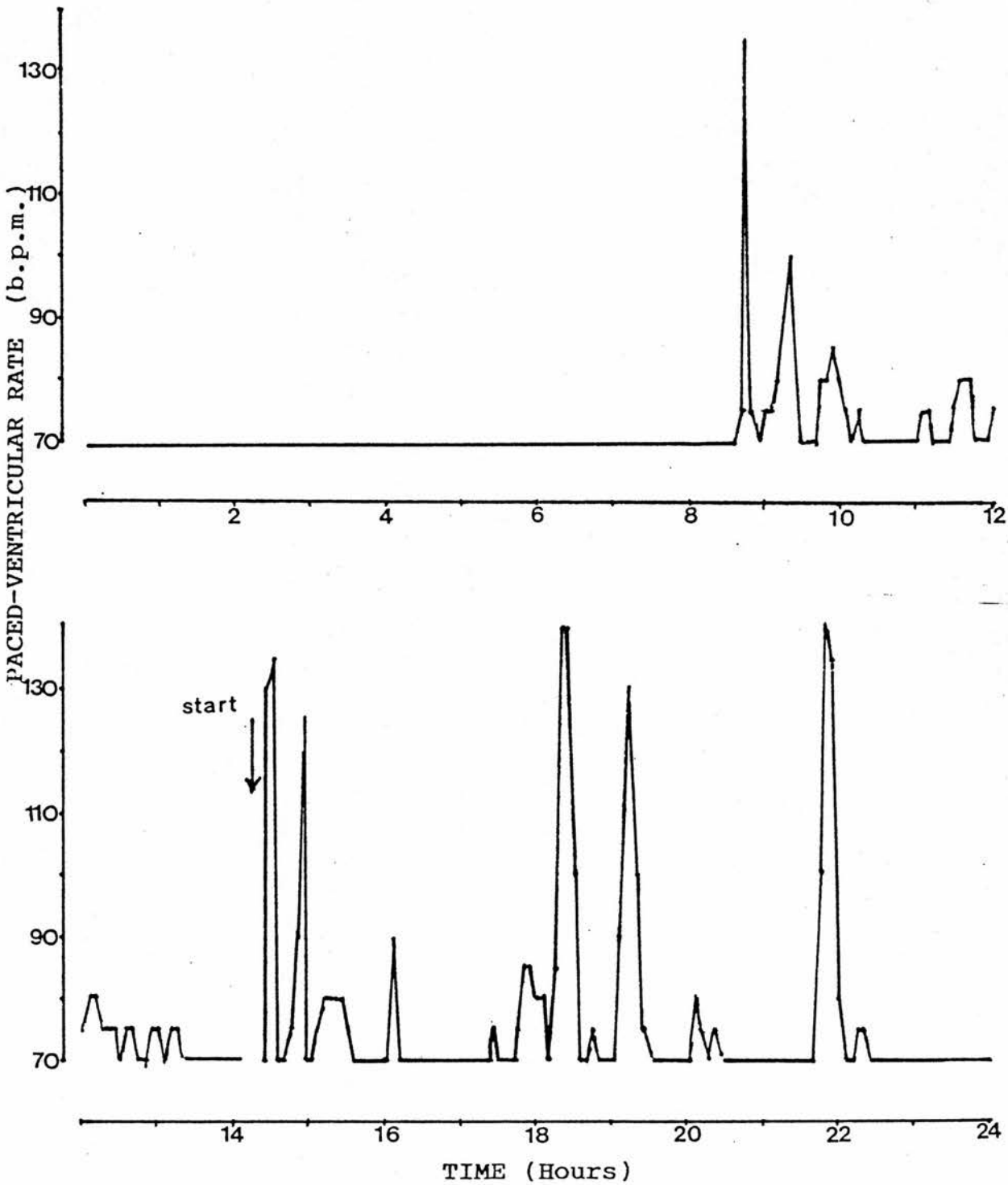


Figure 35. Example of 24 hour Holter recording in a patient (A) programmed to TX pacing mode.

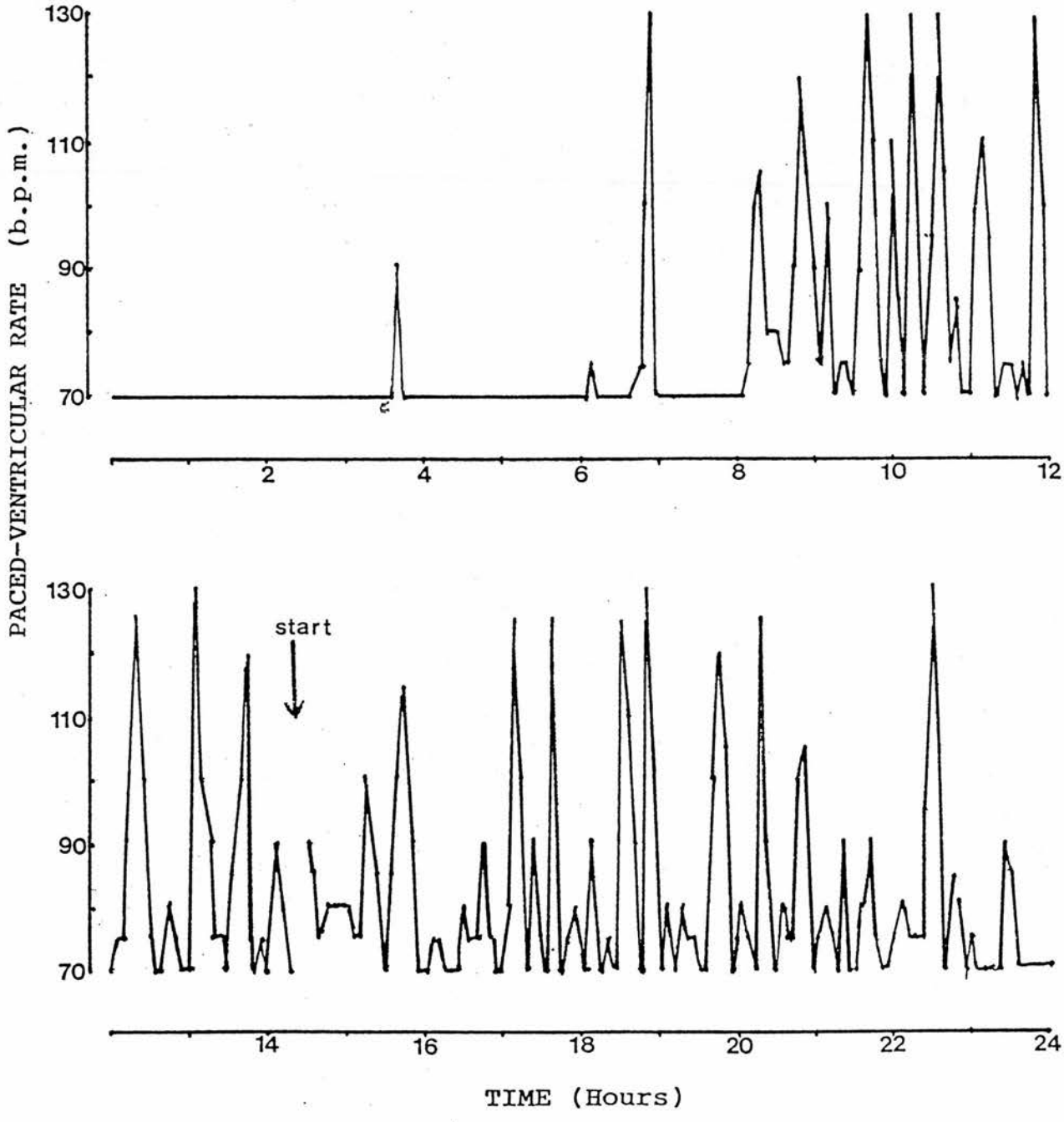


Figure 36. Example of 24 hour Holter recording in a patient (B) programmed to TX pacing mode.

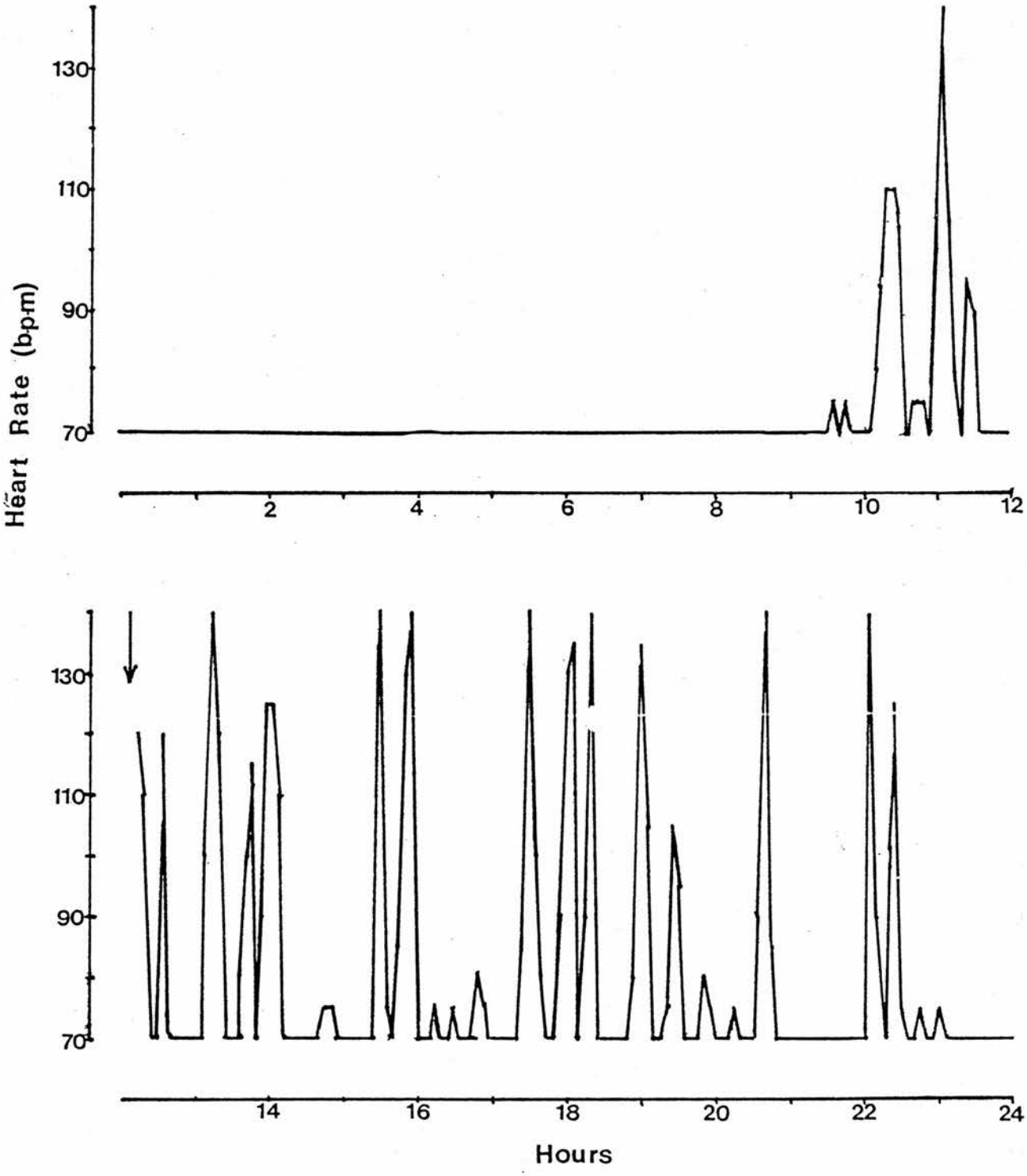


Figure 37. Example of 24 hour Holter monitoring in a patient (C) programmed to TX pacing mode.

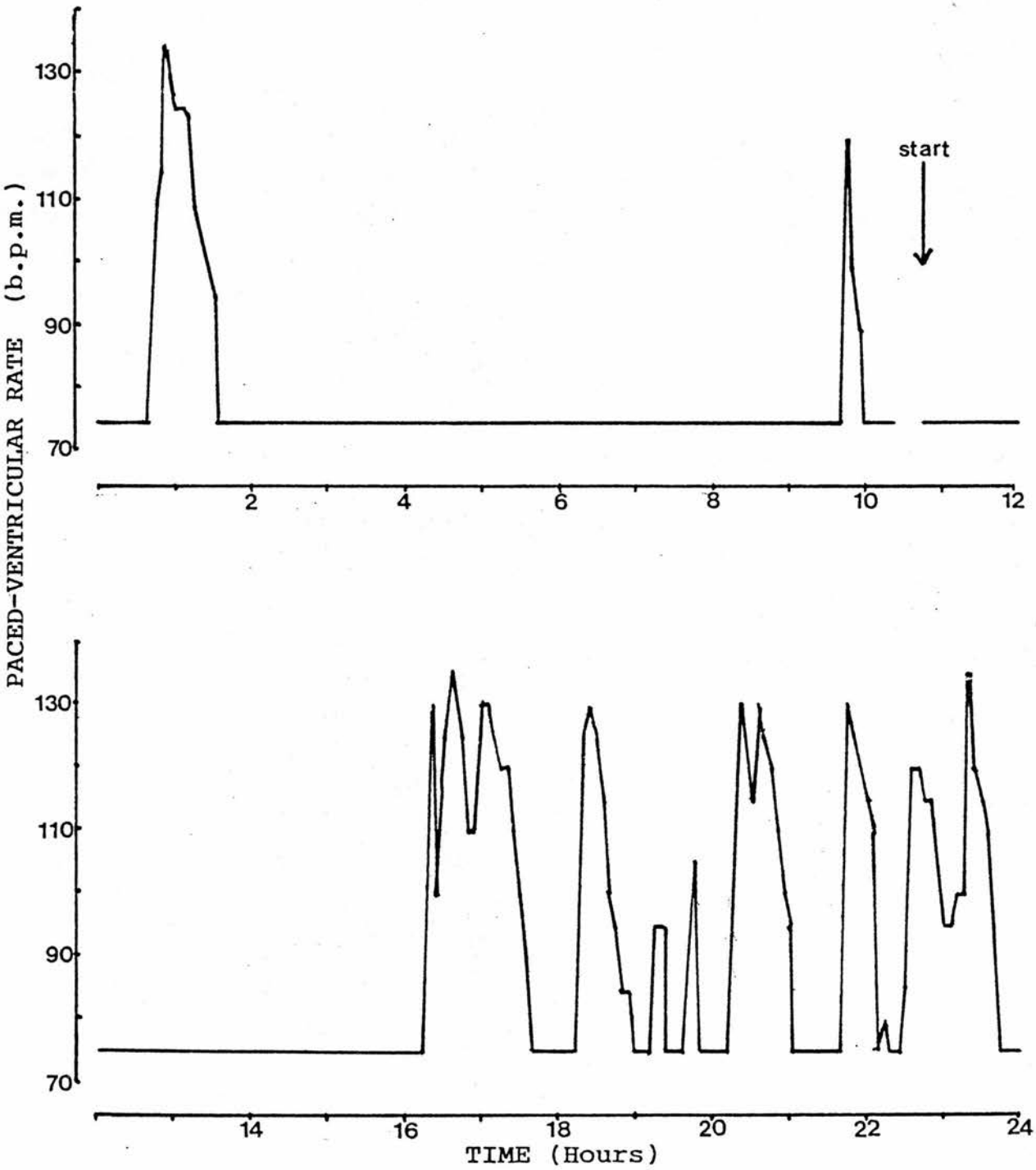


Figure 38. Example of 24 hour Holter monitoring in a patient (C) programmed to TX pacing mode.

(iii) The Paced-Ventricular Rate/Stim.-T Interval Relation - Curve Fitting:

The Stim.-T intervals obtained at rest for each paced-ventricular rate on each occasion are shown in Table XXX.

A very close correlation existed between the paced-heart rate and the Stim.-T interval for each occasion that this relation was examined.

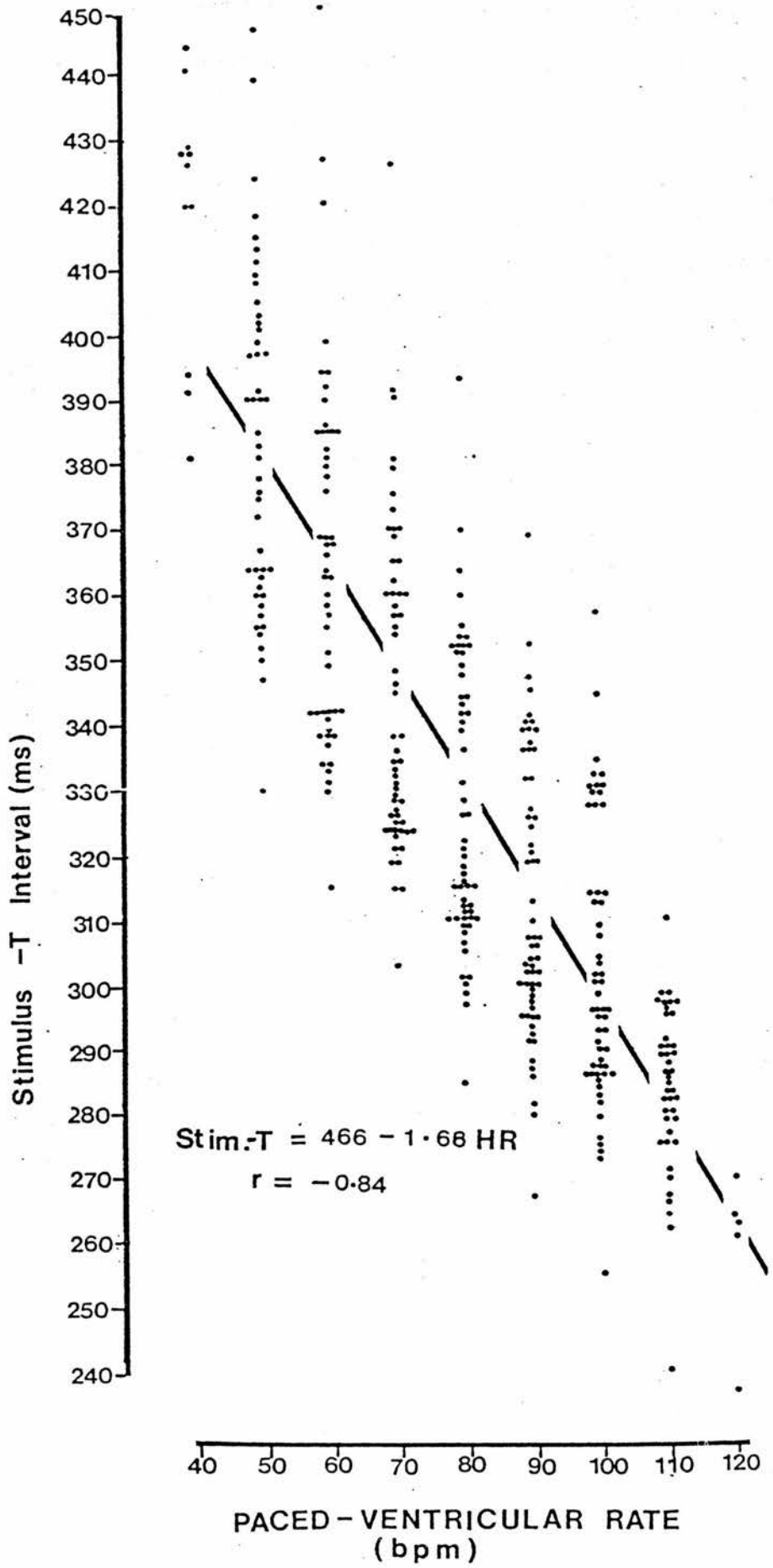
The correlation coefficients of exponential, logarithmic and power curve, regression equations on 24 separate occasions are compared in Table XXXI. The differences between the various correlations of coefficients were small. The best fit however was provided by the power curve regression equation on 14 occasions, logarithmic equation on 7 occasions and exponential equation on 2 occasions. On 2 occasions, power curve and logarithmic regression equations provided jointly the best curve fit. At each heart rate, there was a marked variation in Stim.-T interval (Figure 39).

For the group a linear regression equation described the rate/Stim.-T interval relation equally well: (Figure 39)

Stim.-T Interval (ms) = 466 - 1.68 x Paced-Rate(bpm),

$r = -0.84$.

Figure 39. Paced-ventricular rate/Stim.-T relation at rest.


450
440
430
420
410
400
390
380
370
360
350
340
330
320
310
300
290
280
270
260
250
240
Stimulus -T Interval (ms)
Stim.-T = 466 - 1·68 HR
r = -0·84
40
50
60
70
80
90
100
110
120
PACED - VENTRICULAR RATE
(bpm)

(iv) The Paced-Ventricular Rate/Stim.-T Interval Relation - Inter-Patient and Intra-Patient Variation:

The paced-rate/Stim.-T interval relation was subject to significant inter-patient (Figure 40) and intra-patient (Figure 41) variation.

Consequently, the regression equations describing the paced-rate/Stim.-T interval, predict that a given change in the Stim.-T interval would be produced by different heart rates. For example, a 100 ms reduction in the Stim.-T interval is predicted to occur as the result of an increase in heart rate from 70 to 109 beats per minute in patient 6 compared with 70 to 203 beats per minute in patient 11 and 70 to 130 beats per minute in patient 4 on one occasion and 70 to 180 beats per minute on another occasion (Figure 42).

This finding further indicates that the workloads which are necessary to trigger the sensor and to achieve the upper rate limit will vary from patient to patient and in the same patient from one occasion to another.

This was observed in practice in 3 patients who underwent exercise testing on more than one occasion using identical exercise protocols and programmed settings.

Figure 43, 44 and 45 show that the onset of rate response and the time taken to achieve the upper rate limit varied on different occasions in the same patient, despite identical programmed parameters and similar atrial rate responses (and hence presumbably comparable states of autonomic nervous system activity).

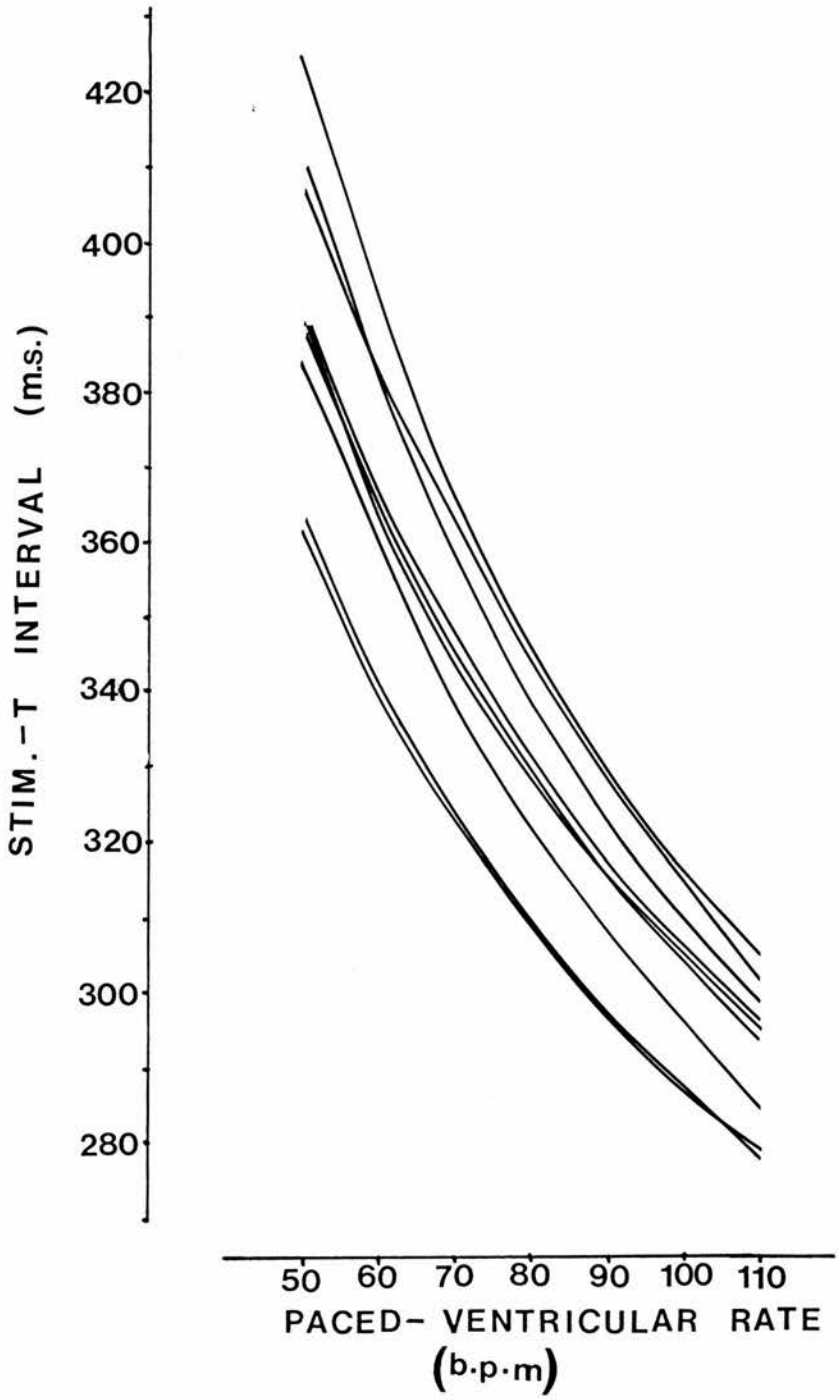
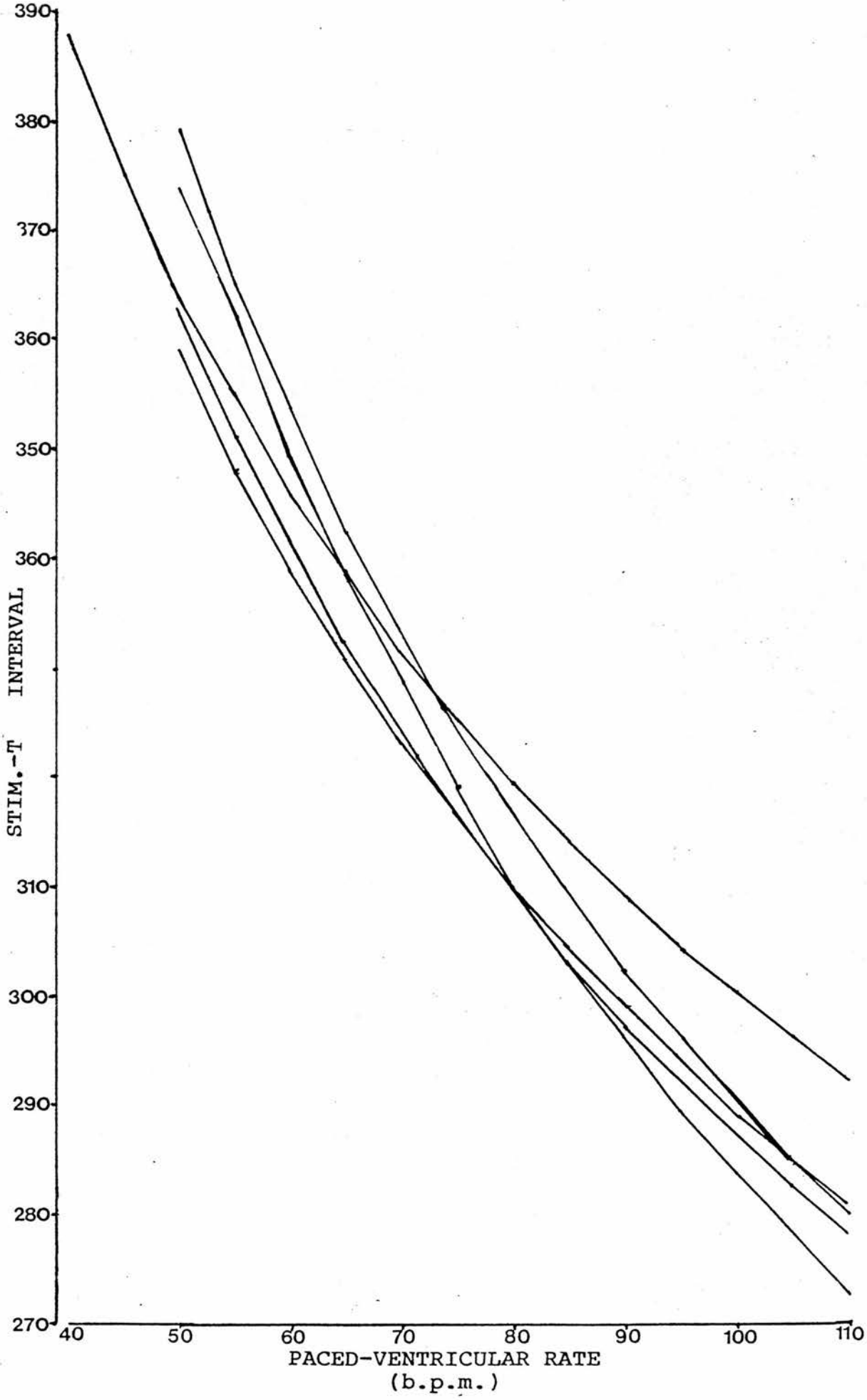


Figure 40. Regression lines describing the paced-ventricular rate/Stim.-T interval relation in 9 patients.

Figure 41. Heart rate/Stim.-T relation on 5 separate occasions in the same patient.

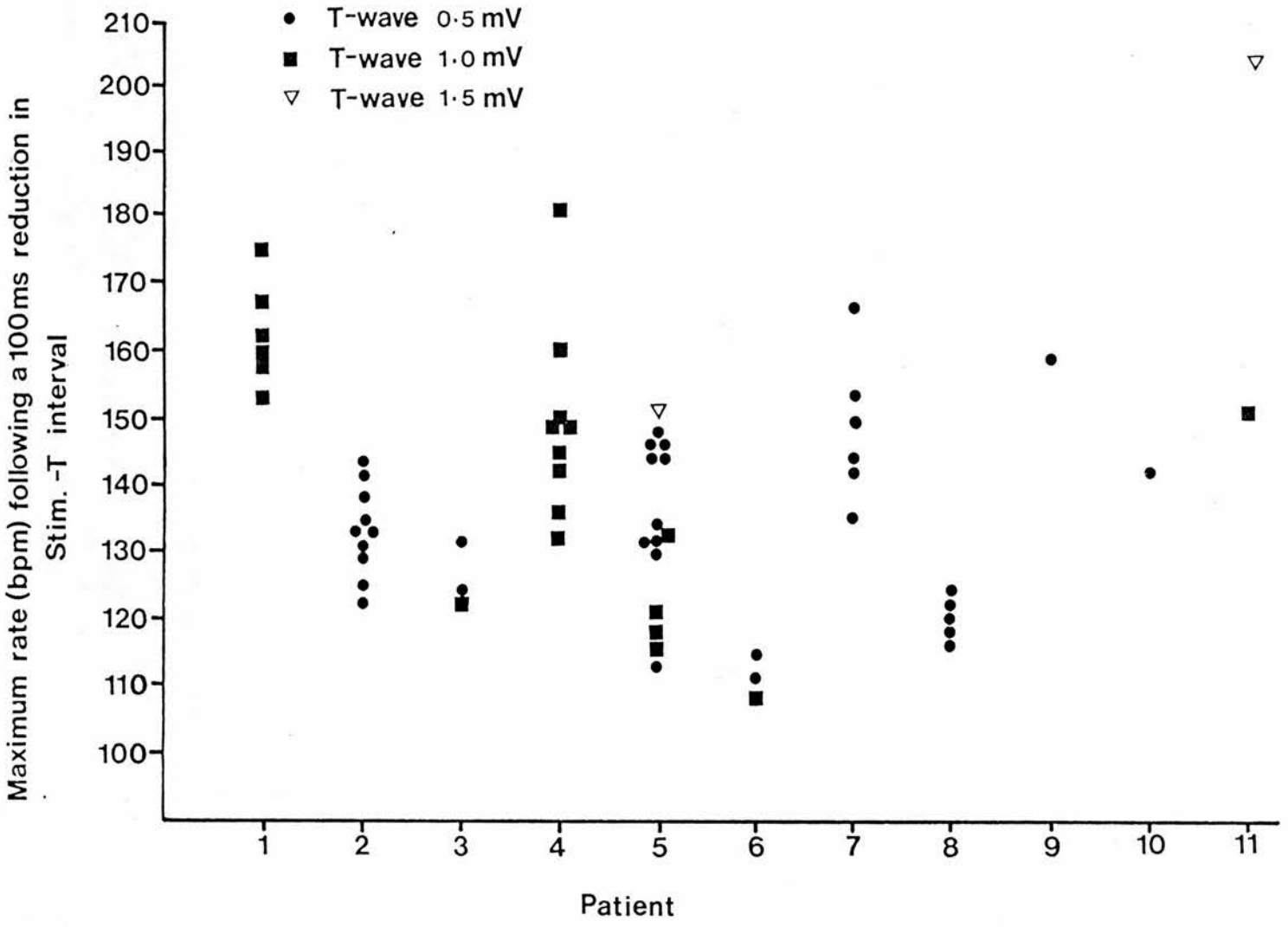

390
380
370
360
350
360
310
300
290
280
270
STIM.-T INTERVAL
40
50
60
70
80
90
100
110
PACED-VENTRICULAR RATE
(b.p.m.)

(v) Comparison of Paced-Ventricular Rate/Stim.-T, Paced-Ventricular Rate/Stim.-T(Apex) and Paced-Ventricular Rate/Stim.-T(SE) Relations:

The results of the comparison between the paced-ventricular rate/Stim.-T relation, derived from values provided by the computer, and the paced-ventricular rate /Stim.-T(apex) and paced-ventricular rate/Stim.-T(SE) relations derived from surface electrocardiogram are shown in Table XXXII.

1. T waves were sensed just short of the Stim.-T(Apex) in 3/5 patients and in one patient the Stim.-T and the Stim.-T(Apex) were very similar.
2. In 11/15 cases the slopes of the regression equations describing the heart rate/Stim.-T and the heart rate/Stim.-T(Apex) were also very similar, because of the proximity of the Stim.-T intervals to the corresponding Stim.-T(Apex) intervals.
3. There was no agreement between the slopes of the heart rate/Stim.-T(SE) regression equations and those of the heart rate/Stim.-T and heart rate/Stim.-T(Apex) equations in 12/15 cases. The slopes of the heart rate/Stim.-T(SE) equations in these patients were steeper than those describing the heart rate/Stim.-T and heart rate/Stim.-T(Apex) relations.

Fig.42. Predicted heart rates following a 100 ms reduction in Stim.-T interval.



(vi) Effect of Changes in Certain Programmable Parameters on the Performance of the TX Pacemaker:

(A) T Wave Sensing:

Sensing problems arose in 3 patients. In one patient with a Quintech model (J. Mc.), this was overcome by reducing the pacemaker output from 5.0 V to 2.5 V, presumably through a reduction in the afterpotential. In a second patient spontaneous recovery of T wave sensing occurred 5 months following pacemaker implantation. In the remaining patient T wave sensing has remained unsatisfactory.

In the last patient to undergo pacemaker implantation the ability of the TX pacing system to sense T waves was tested successfully during operation using an external device which incorporated the pacemaker's sensing circuit.

(B) Changes in T Wave Amplitude:

There was a progressive increase in the amplitude of the sensed T wave with increasing paced-ventricular rate (Figure 46).

(C) T Wave Sensitivity:

Although T wave sensitivity was programmable between 0.5 mV to 5.0 mV in intervals of 0.5 mV, in 12/13 patients T waves were only satisfactorily sensed and displayed at

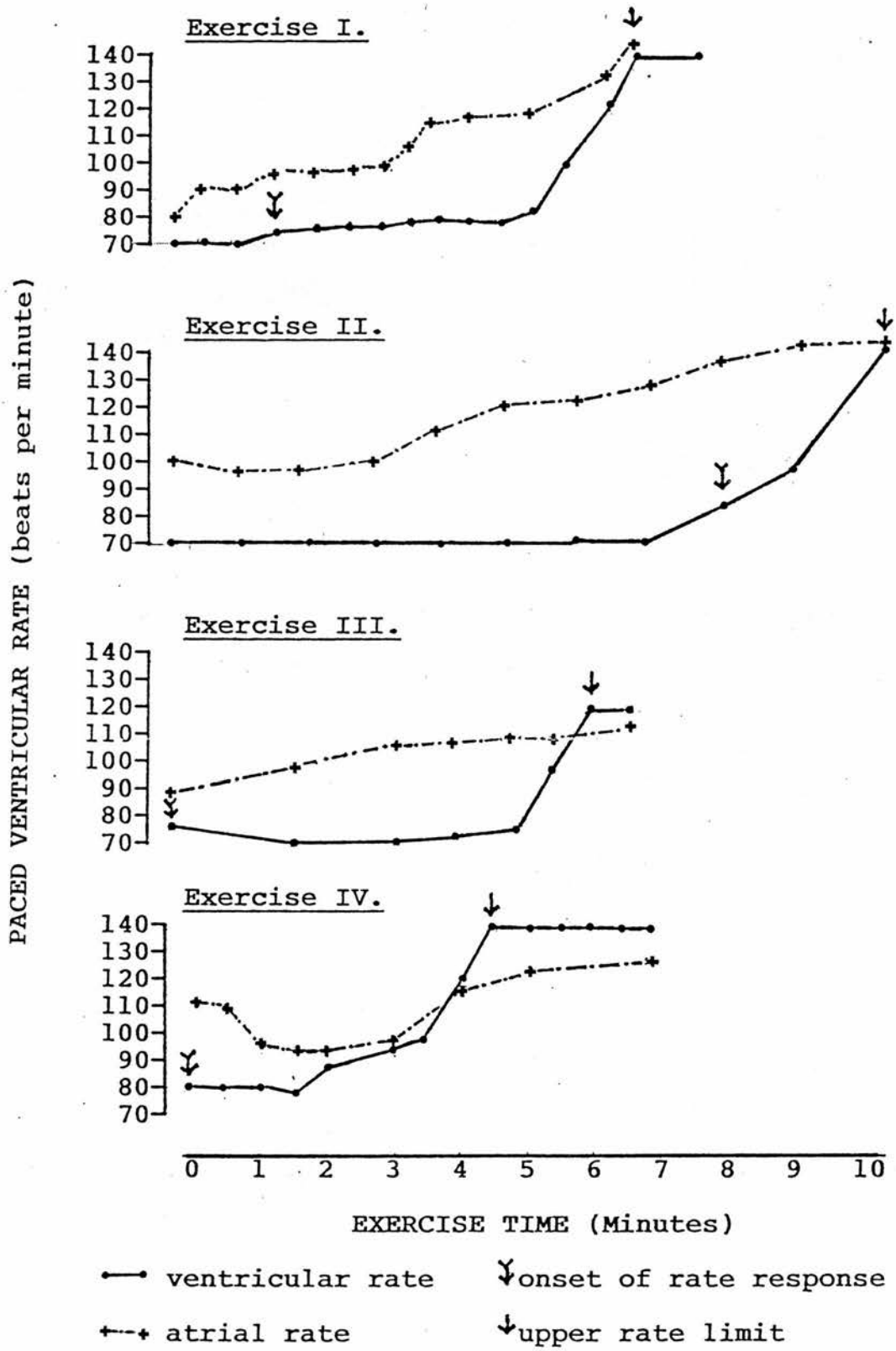


Figure 43. Atrial and paced-ventricular rates during exercise on 4 separate occasions in a patient whose programmed parameters were unaltered.

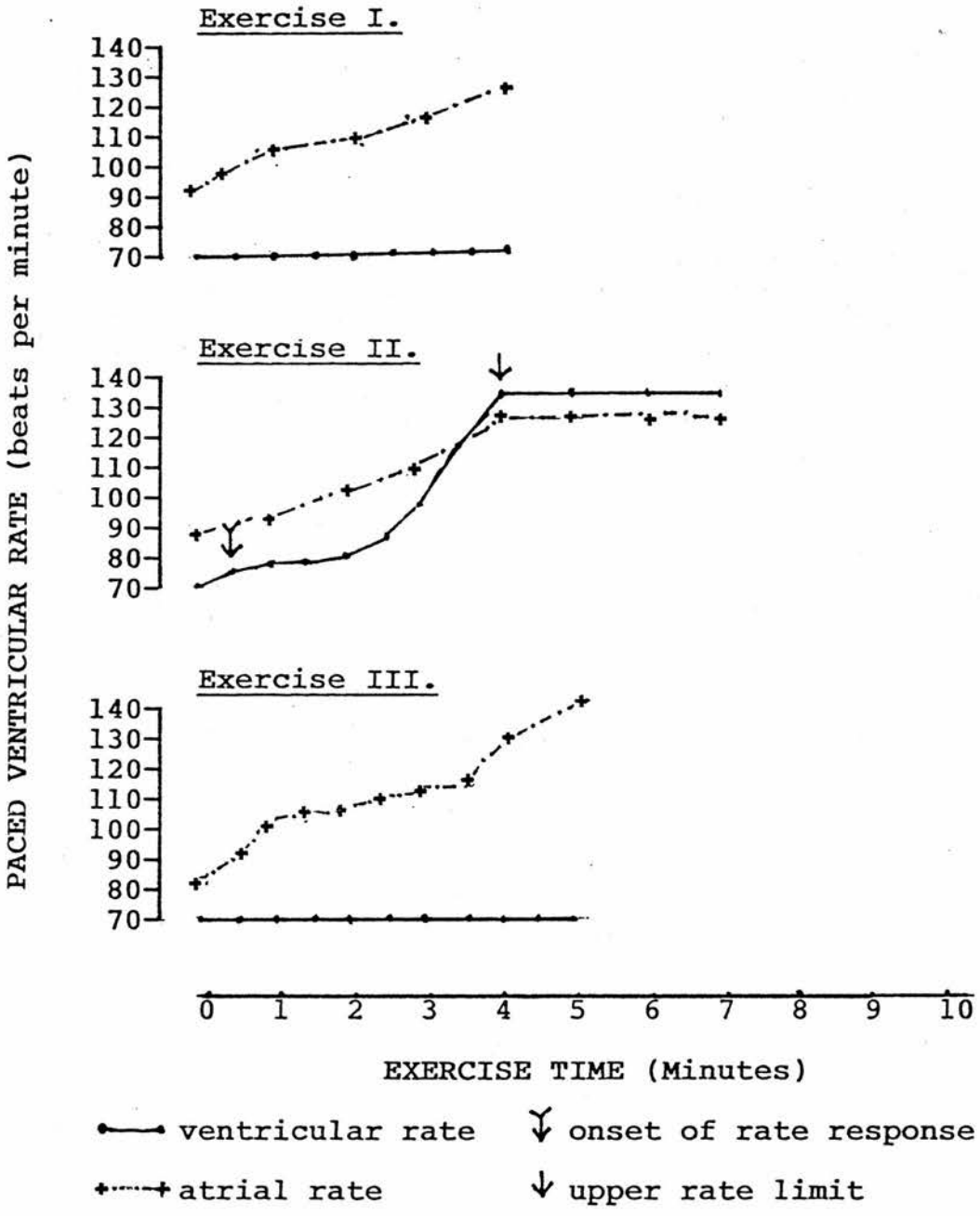


Figure 44. Atrial and paced-ventricular rates during exercise on 3 separate occasions in a patient whose programmed parameters were unaltered.

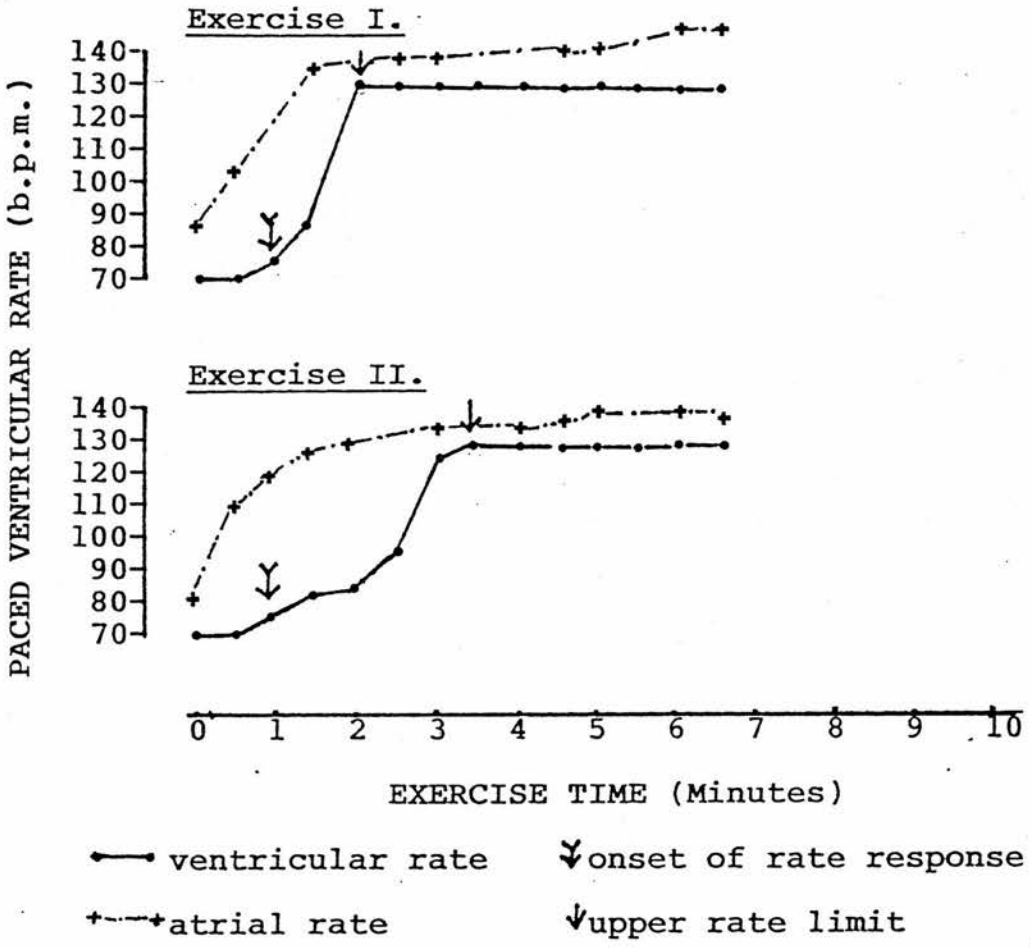


Figure 45. Atrial and paced-ventricular rates during exercise on two separate occasions in a patient whose programmed parameters were unaltered.

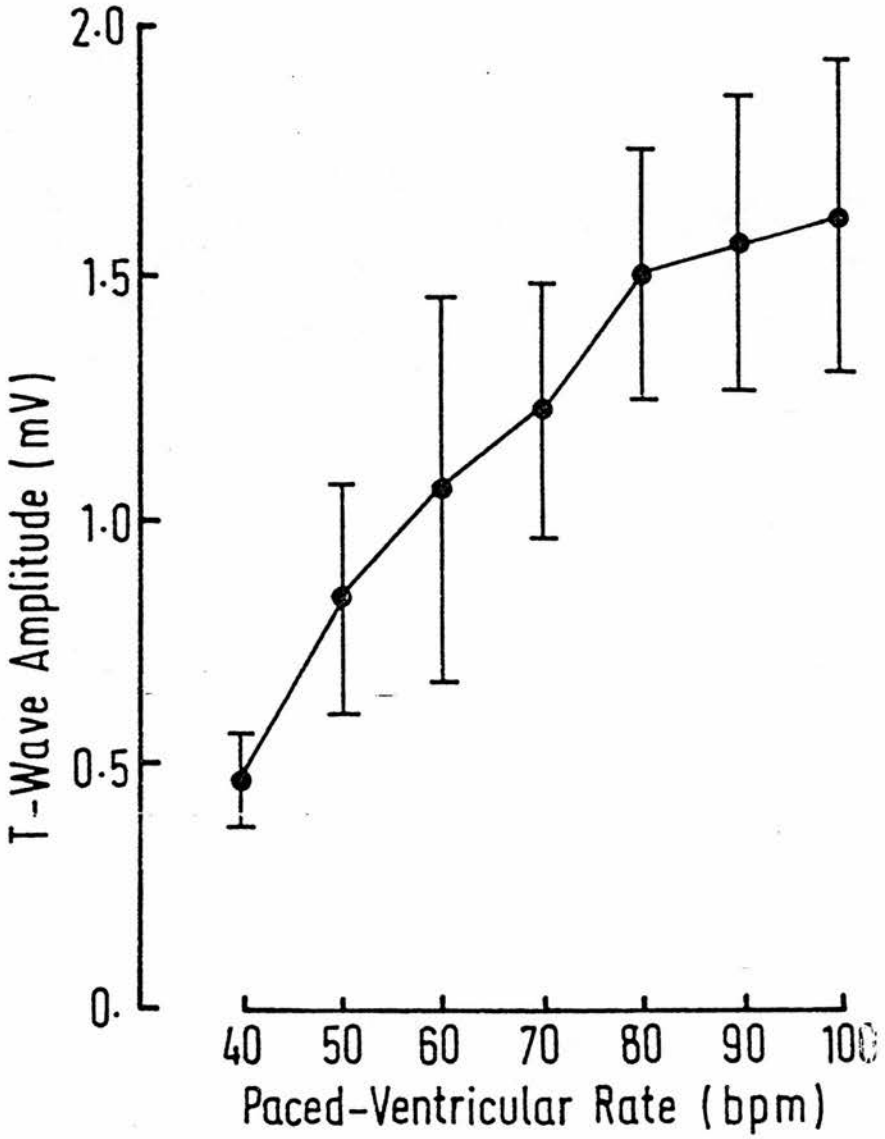


Figure 46. Changes in T wave amplitude with increasing paced-ventricular rate recorded in patients with implanted TX1 pacemaker.

rest using the HP-85, over a paced-ventricular rate of 40 to 110 bpm by programming to T wave sensitivities of 1.5 mV or less.

The quality of T wave sensing was affected by the programmed paced-ventricular rate. T wave sensing was usually less satisfactory at extremes of a heart rate range.

(D) Chronic Changes in T Wave Sensing:

Changes in T wave sensing with the passage of time were not formally tested in the immediate post-operative period as most of our patients were switched on to a TX mode after two weeks.

Satisfactory T wave sensing probably occurs earlier than this in some patients. In one patient (M.D.) with a Quintech generator, no T wave sensing occured at a T wave sensitivity of 1.0 mV and a variable T wave sensing at a programmed T wave sensitivity of 0.5 mV, 7 days following pacemaker insertion. The quality of T wave sensing improved in the subsequent week:

Pacemaker implant
Date - 300384

Paced-Rate (bpm)	50	60	70	80	90	100
Date - 060484 %T waves sensed	Nil	0-50	80	97-100	100	95-100
Date - 130484 %T waves sensed	30-80	100	100	99-100	100	100

T wave sensing was also observed to deteriorate in some patients. For example, patient H.B. lost T wave sensing over all paced heart rates (50 to 120 bpm), 8 months after pacemaker implantation at a programmed T wave amplitude of 1.0 mV. Adequate T wave sensing however was restored by programming to a T wave sensitivity of 0.5 mV.

(E) Effect of T Wave Sensitivity on the Heart Rate/Stim.-T Interval Relation:

Altering the T wave sensitivity affected:

(i) The paced-ventricular rate/Stim.-T interval relation, (Figures 47, 48 and 49) and

(ii) The rate of onset of rate response and time taken to attain the upper rate limit (Figures 50 and 51).

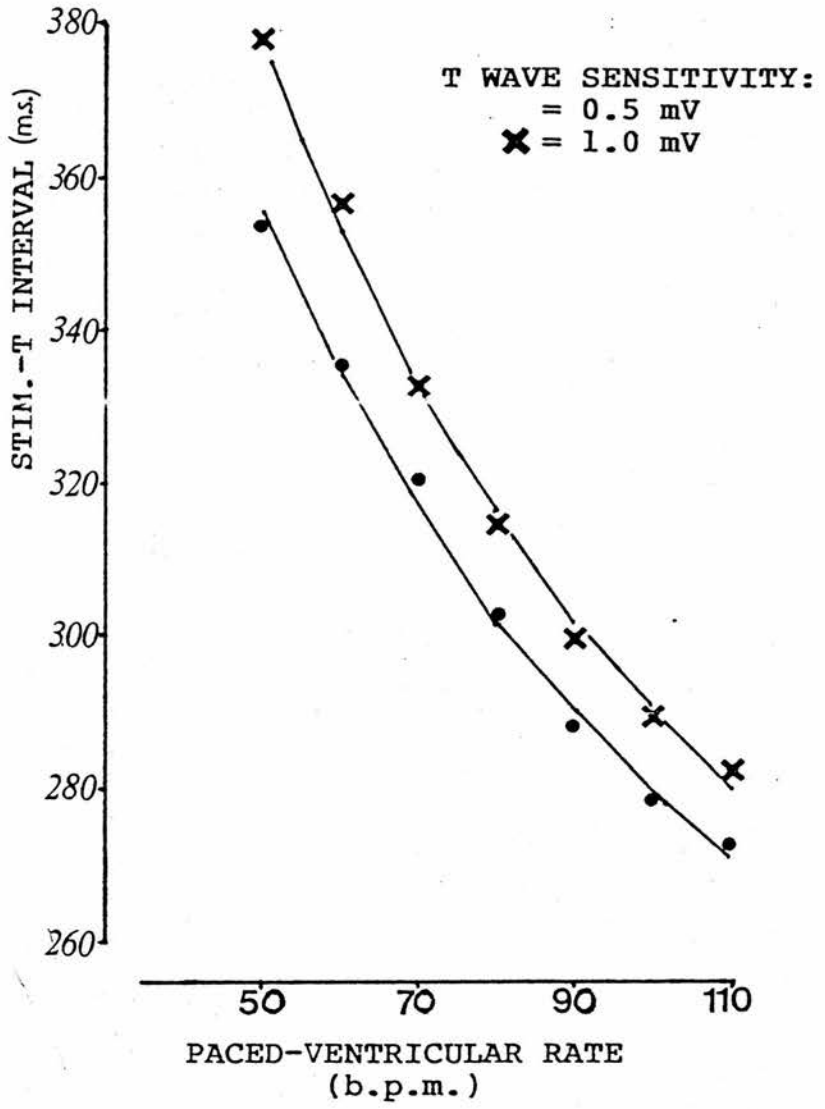


Figure 49. Paced-ventricular rate/Stim.-T interval relation derived at two different T wave sensitivities in a patient (C).

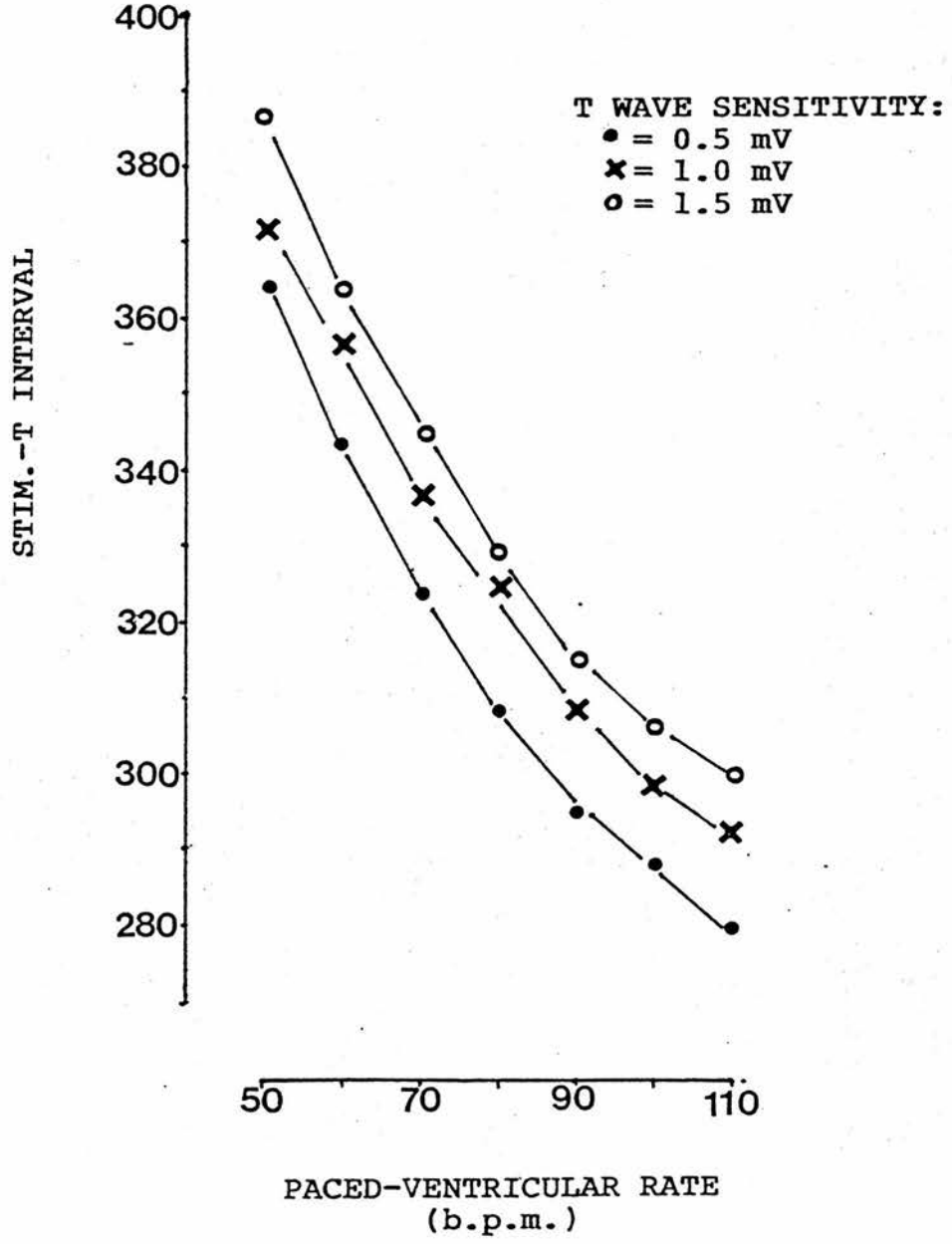


Figure 47. Paced-ventricular rate/Stim.-T interval relation derived at 3 different T wave sensitivities in a patient (A).

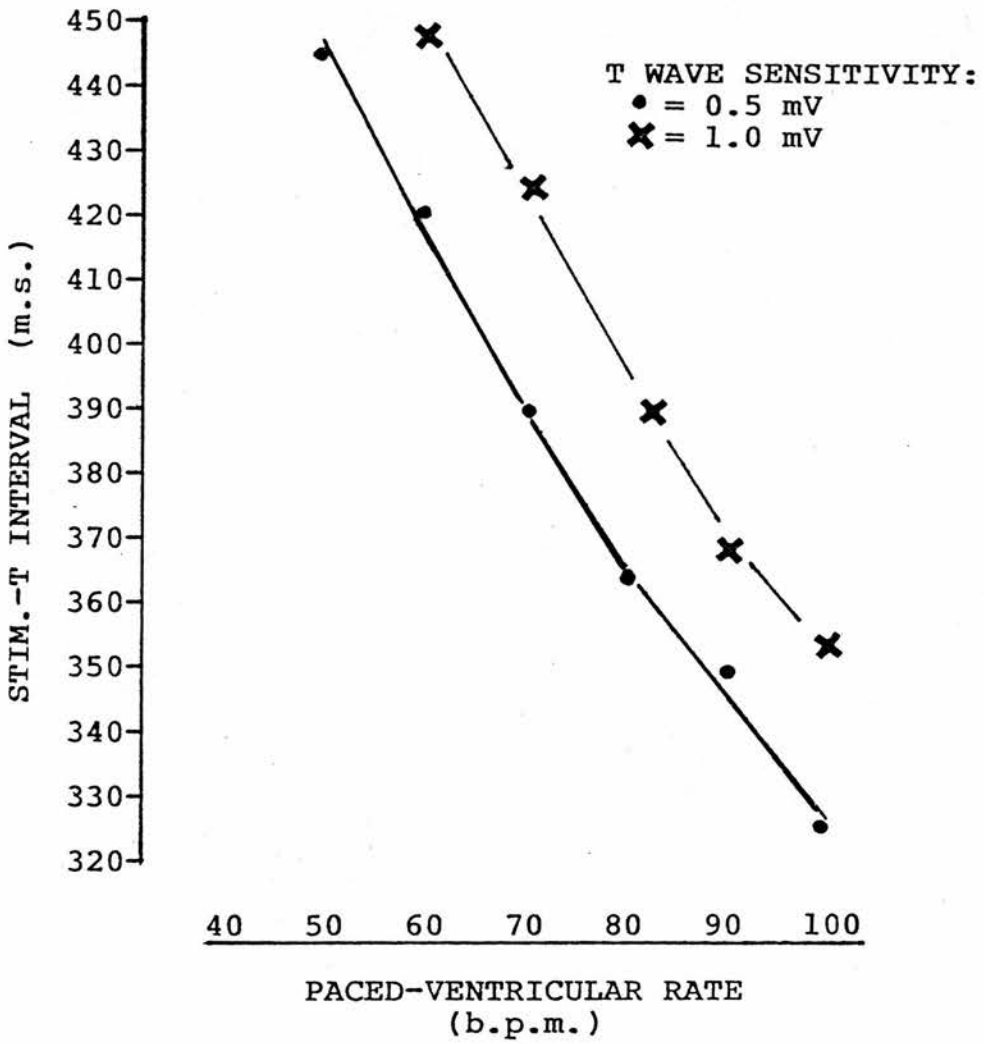


Figure 48. Paced-ventricular rate/Stim.-T interval relation derived at two different T wave sensitivities in a patient (B).

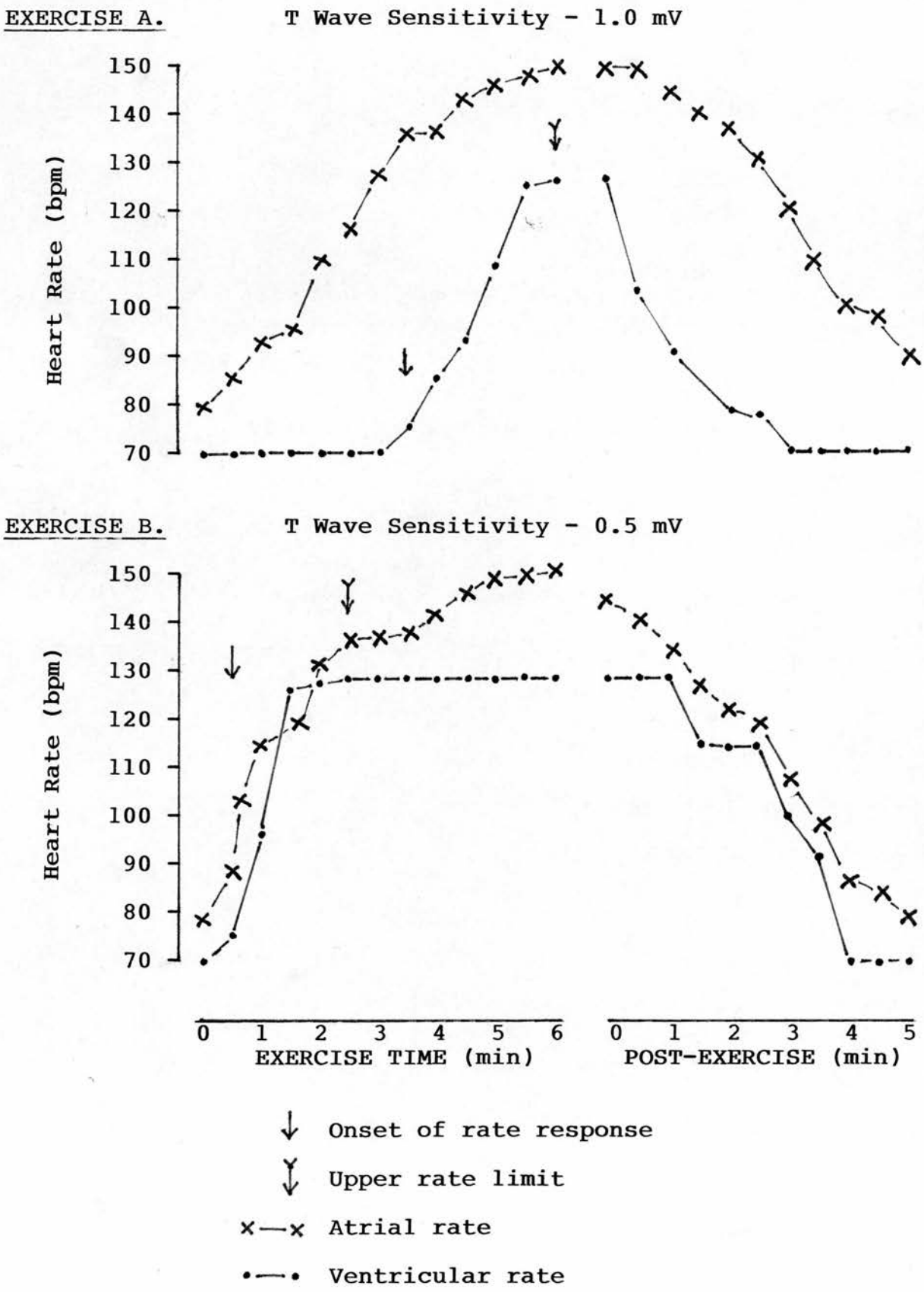


Figure 50. The effect of two differing T wave sensitivities on the paced-ventricular rate responses during identical exercise tests in a patient (A) in whom all other programmed parameters were unaltered.

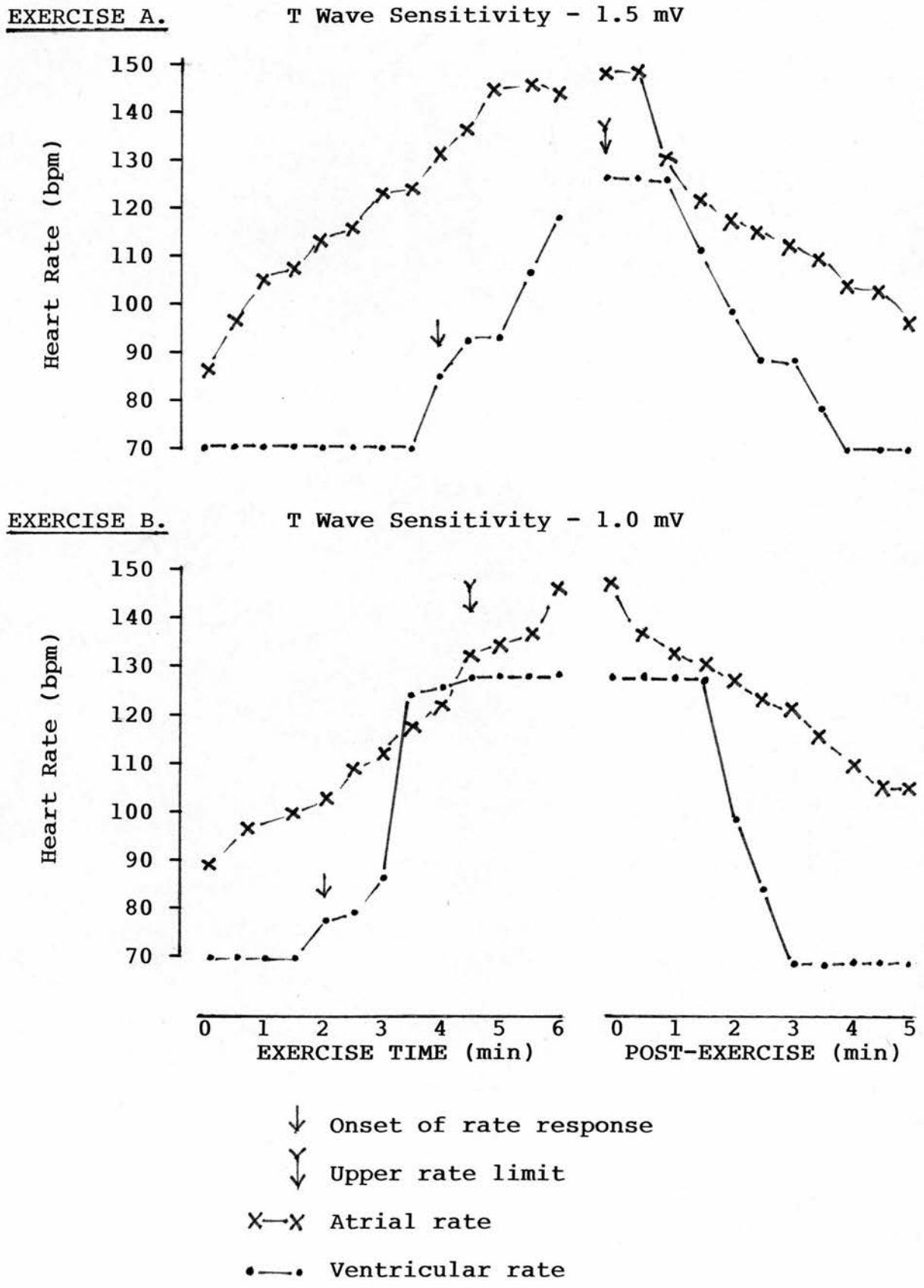


Figure 51. The effect of two differing T wave sensitivities on the paced-ventricular rate responses during identical exercise tests in a patient (B) in whom all other programmed parameters were unaltered.

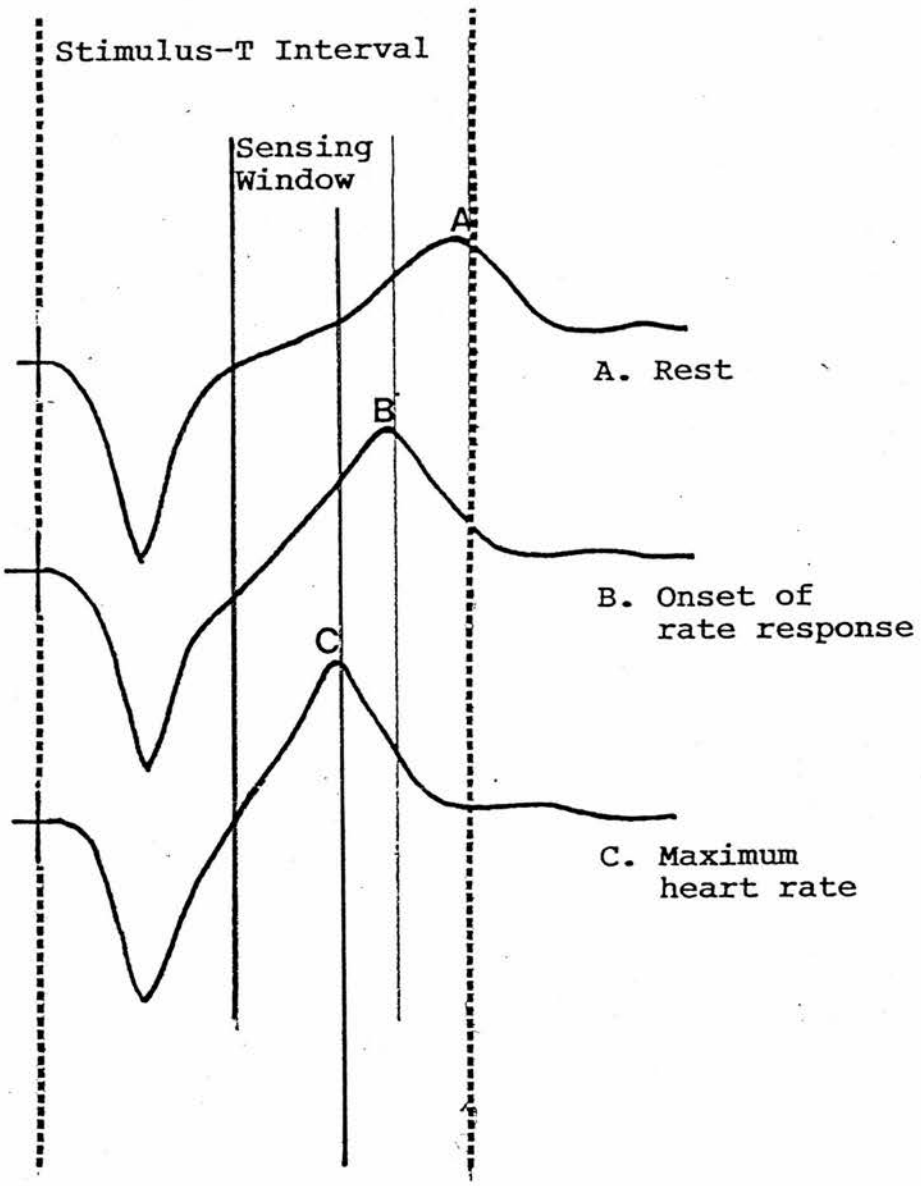


Figure 52. The varying relation of the Stim.-T interval to the T wave sensing window during exercise.

(F) T Wave Sensing Window:

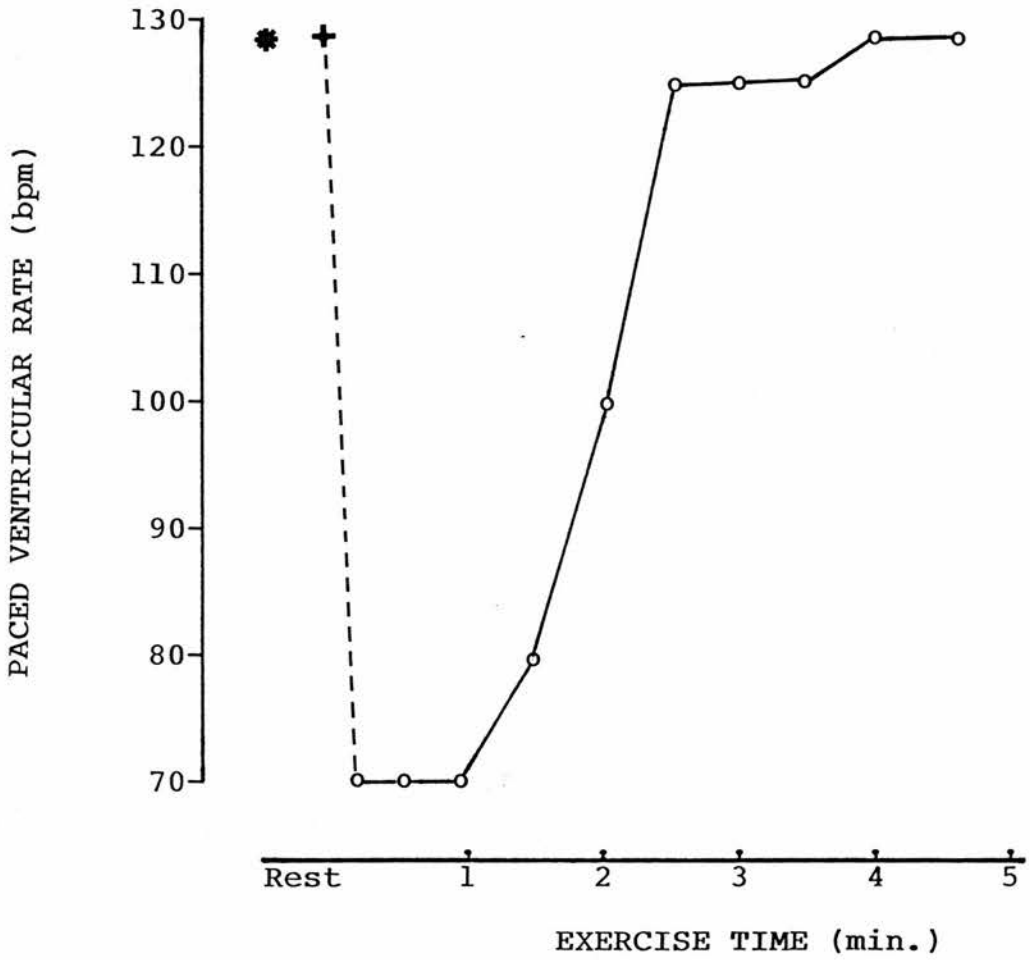
The upper limit of the T wave sensing window was initially set at a value equal to the Stim.-T interval at paced-ventricular rate of 70 bpm at rest plus an additional 20 ms ('fudge factor').

With experience it became clear that when the T wave sensing window was set too wide, i.e. equal to or greater than the Stim.-T interval, rate response often occurred at rest with the pacing rate frequently reaching the programmmed upper rate limit (Figures 52 and 53). Conversely, when the T wave sensing window was inappropriately short, the Stim.-T interval would not shorten sufficiently during exercise to permit a rate response (Figure 54).

Rate response would then occur occasionally in the recovery period (as illustrated in Figure 55) as the Stim.-T continued to shorten both due to the presence of high levels of sympathetic activity, as indicated by the high atrial rates, and because of the delay which is necessary for the Stim.-T interval to adapt fully to changes in heart rate.

When the sensing window was appropriately shorter than the Stim.-T interval, rate response would occur during exercise, after an interval of time which depended on the 'Stim.-T interval - sensing window' difference.

Figure 53. The effect of slope and T wave sensing window on paced-ventricular rates in a patient: Rate response occurred at rest and heart rate accelerated to the upper rate limit, at a programmed slope of 1.6 bpm/ms and a T wave sensing window of 400 ms (measured Stim.-T interval at 70 bpm was 350ms) response to exercise: Rate response at rest overcome by reducing the sensing window; The heart rate remained high despite halving the slope; Rate response was abolished by reducing the sensing window by 50ms with satisfactory rate changes during exercise thereafter.



✱=slope: 1.6 bpm/ms ; sensing window: 200-400 ms
✚=slope: 0.8 bpm/ms ; sensing window: 200-400 ms
o =slope: 0.8 bpm/ms ; sensing window: 200-350 ms

Subsequently, the maximum heart rate and the time taken to achieve it would be determined by the programmed slope, the upper rate limit and the extent to which the Stim.-T interval shortened i.e.

´the T wave sensing window´ - ´Stim.-T interval´ difference.

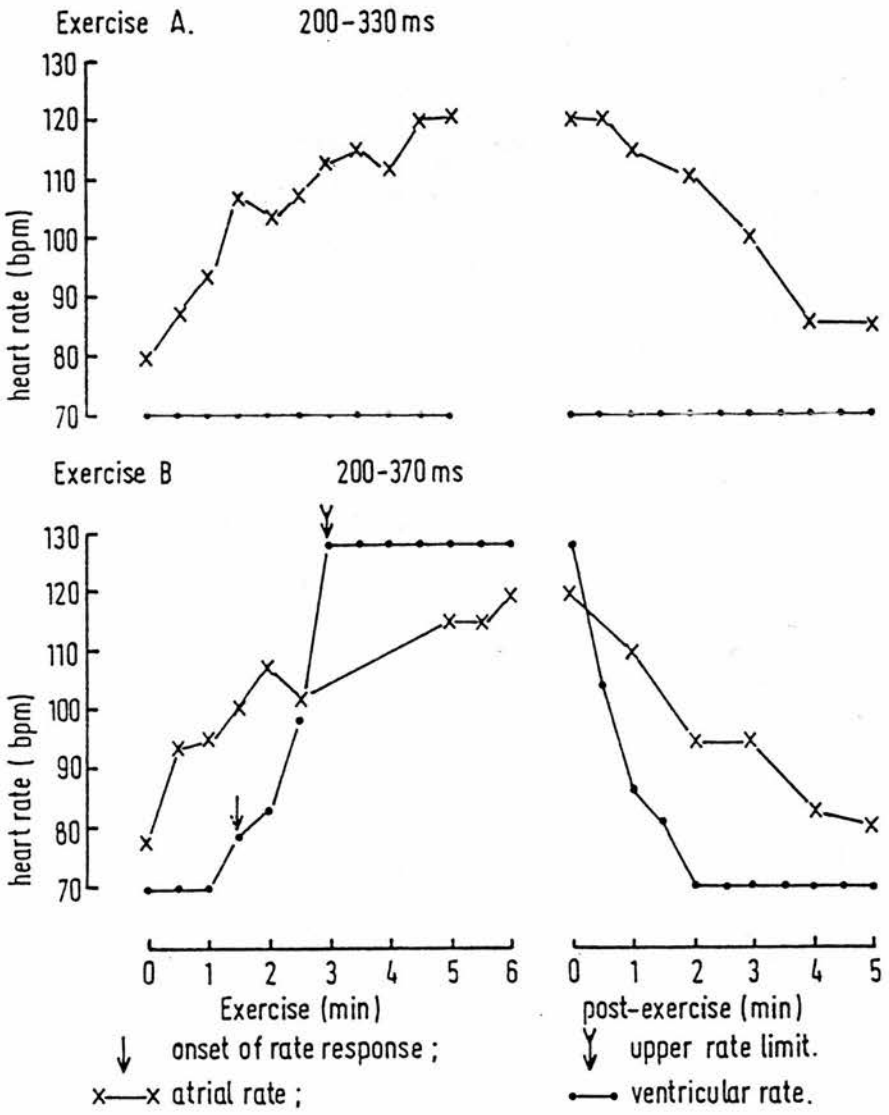


Figure 54. Absence of rate response to exercise due to inappropriately short T wave sensing window (Exercise A), overcome by increasing the T wave sensing by 40ms (Exercise B).

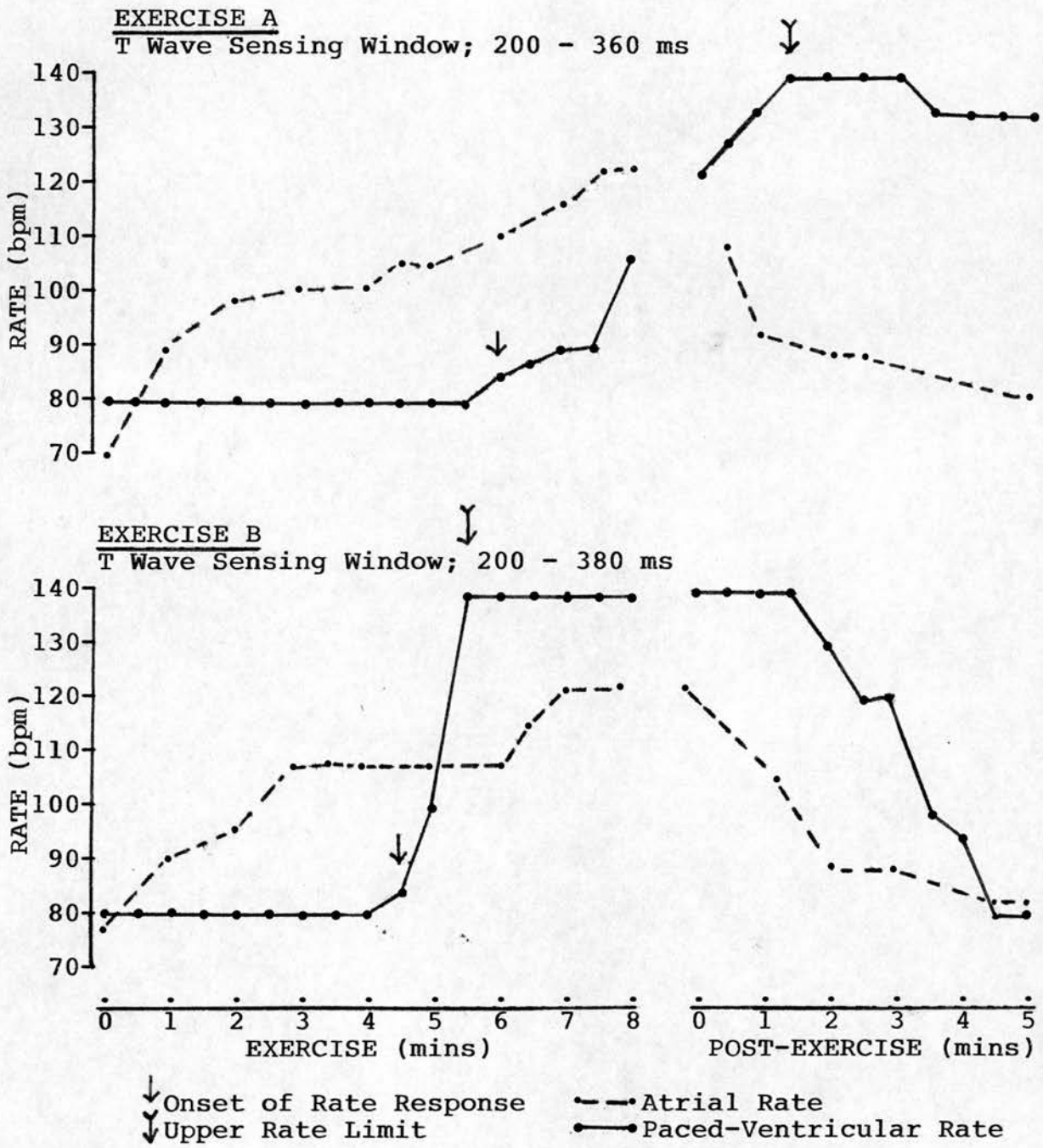


Figure 55. Rate response occurring late with the upper rate limit achieved in the recovery period of an exercise test (Exercise A), overcome by increasing the T wave sensing window by 20 ms (Exercise B).

(G) Slope:

Estimating the slope from calculations based on paced-ventricular rate/Stim.-T interval relation at rest frequently resulted in inappropriate rate responses. A significant correlation did exist however, between calculated slopes and programmed slopes which were eventually discovered to provide satisfactory rate changes during exercise (Figure 56).

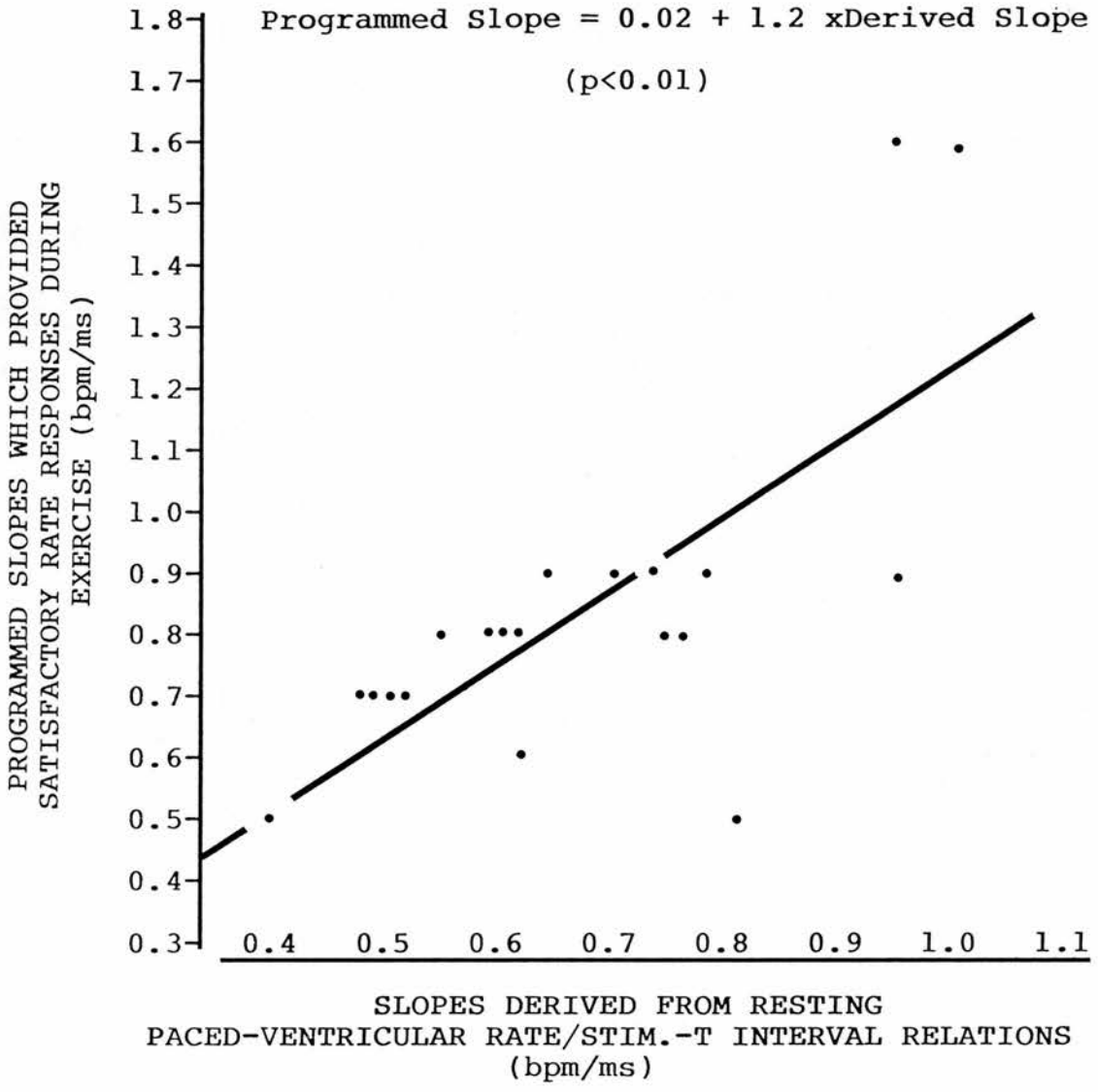


Figure 56. Correlation of slopes derived from resting paced-ventricular rate/Stim.-T interval relations and programmed slopes which provided satisfactory rate responses during treadmill exercise tests.

Table XXIII. Pre-operative clinical characteristics of patients who received atrial synchronized ventricular pacing systems.

		No. Of Patients
Age (years)	Mean; 62	35
	Range; 20-82	
Sex	Male	18
	Female	17
Rhythm	Chronic 2nd degree	
	A-V block (Mobitz II)	2
	Chronic complete A-V Block	33
Aetiology	Idiopathic	28
	Ischaemic heart disease	3
	Congenital	2
	Aortic valve surgery	1
	Cardiomyopathy	1

Table XXIV. Clinical characteristics of patients who underwent exercise tests in VOO, VAT and V-CWS-T pacing modes.

Patient	Sex	Age (yr)	Weight (kg)
1.	Female	76	61.8
2.	Male	60	70.0
3.	Male	63	98.6
4.	Female	76	59.6
5.	Male	70	71.0
6.	Male	73	78.0
7.	Male	70	68.0
8.	Male	71	72.7
9.	Male	62	76.4
10.	Female	67	60.0
11.	Female	72	57.0
12.	Male	73	70.0
13.	Male	51	111.4
14.	Male	78	50.9

Abbreviations:yr = years; kg = kilograms.

Table XXV. Pacing order in individual patients.

	Occasion		
Patient	1st	2nd	3rd
1.	VOO	VAT	V-CWS-T
2.	VOO	V-CWS-T	VAT
3.	V-CWS-T	VAT	VOO
4.	VAT	V-CWS-T	VOO
5.	VAT	V-CWS-T	VOO
6.	VAT	V-CWS-T	VOO
7.	VOO	VAT	V-CWS-T
8.	VOO	V-CWS-T	VAT
9.	V-CWS-T	VOO	VAT
10.	V-CWS-T	VOO	VAT
11.	VAT	V-CWS-T	VOO
12.	VAT	VOO	V-CWS-T
13.	V-CWS-T	VAT	VOO
14.	VOO	VAT	V-CWS-T

Abbreviations: VOO = fixed-rate ventricular pacing; VAT = atrial synchronized ventricular pacing; V-CWS-T = chest wall triggered ventricular pacing.

Table XXVI. Clinical characteristics of patients who received the rate responsive (TX) pacing system.

Patient	Sex	Age	Rhythm	Aetiology
1. I.M.	Male	42	3rd degree AV block	Congenital
2. J.M.	Female	70	,,	Idiopathic
3. H.B.	Male	72	,,	Idiopathic
4. J.C.	Mal	55	,,	Idiopathic
5. G.L.	Male	75	,,	Idiopathic
6. J.Mc.	Female	53	,,	Congenital
7. J.H.	Male	66	,,	Idiopathic
8. M.D.	Female	67	,,	His Bundle Ablation
9. J.B.	Male	17	,,	Congenital
10. S.M.	Female	24	,,	Congenital
11. J.C.	Female	51	,,	Idiopathic
12. E.S.	Male	58	,,	Idiopathic
13. W.S.	Male	60	,,	Idiopathic
14 W.T.	Male	66	sinus bradycardia	Idiopathic

Table XXVII. Haemodynamic indices at rest before pacemaker insertion (CHB) and during fixed-rate, 70 beats per minute (VOO) and atrial synchronized (VAT) ventricular pacing modes.

	Cardiac Output l/min			Mean aortic systolic pressure(mmHg)		
	CHB	VOO	VAT	CHB	VOO	VAT
Mean	2.9	3.7	4.5	100	105	115
± 1 SD	0.8	0.8	1.2	26	25	28
p		<0.01	<0.01		<0.01	<0.01

	Mean PA (mmHg)			PA diastolic pressure (mmHg)		
	CHB	VOO	VAT	CHB	VOO	VAT
Mean	18	20	19	15	16	16
± 1 SD	5	4	6	4	4	6
p		NS	NS		NS	NS

Abbreviations: PA=pulmonary arterial pressure, NS=not significant.

Table XXVIII. Comparison of total distances walked on the treadmill during fixed-rate (VOO), atrial synchronized (VAT) and chest wall stimuli triggered (V-CWS-T) ventricular pacing modes.

Pacing Mode	Distance (m) Mean + 1 SD (Range)		
VOO	436 ± 128 (98 to 894)	**	**
V-CWS-T	613 ± 198 (166 to 1652)	NS	
VAT	610 ± 152 (162 to 1204)		

** =p<0.001; NS= Not significant.

Table XXIX. Improvement in exercise performance during atrial synchronized (VAT) and chest wall stimuli triggered (V-CWS-T) ventricular pacing modes compared with fixed-rate ventricular (VOO) mode.

Pacing Mode	Mean + 1 S.D. (Range)	
V-CWS-T	40 ± 24 %	
	(5 to 85 %)	NS
VAT	44 ± 31 %	
	(12% to 140 %)	

Abbreviation: NS= Not significant.

Table XXX. Stim.-T intervals recorded at rest at various paced-ventricular rates in individual patients on separate occasions.

Patient	Date	Paced-Ventricular Rate (bpm)									
		40	50	60	70	80	90	100	110	120	
I.M.	071083		367	334	323	315	306	298	290		^^
	101083		360	342	328	315	303	295	286		^^
	131083		352	342	329	318	307	301	298		^^
	*131083		350	338	325	315	306	296	288		^
	*131083		355	338	326	316	304	296	289		^
	080384		345	339	321	309	297	287	276		^
J.M.	071083		364	342	324	310	295	286	282		^
	141083		383	360	338	321	307	295	288		^
	*141083		390	366	348	328	313	304	297		^
	111183		385	363	338	320	302	296	290		^
	*111183		381	364	346	331	319	300	295		^
	100284		390	369	345	326	310	301	297		^
	*100284		408	385	360	344	325	313	310		^
	130484		364	342	324	310	295	286	282		^
	110584		409	382	355	343	325	307	298		^
	*110584		418	394	373	352	331	313	297		^
	100585				342			303			^
H.B.	090983	382	361	355	336	326	307	298	288		^^
	300983		360	338	324	310	300	287	283		^^
	071083		364	342	324	310	295	286	282		^^
	021283	394	363	341	324	308	298	290	284		^^
	*021283		364	342	334	313	303	296	286		^^
	100284						293	290	275		^^
	270484		378	357	333	315	300	290	283		^^
	250584				326	311	299	284	275		^^
	250584				315	297	282	273	264		^
	*250584					299	287	275	266		^
	070684		358	337	319	301	286	274	262		^
	070684		376	349	331	310	295	286	271		^^
	100585				312			270			^
J.C.	181183		403	369	360	351	339	330			^
	*181183	428	397	385	376	352	336	329			^^
	*181183			392	369	355	341	330			^
	161283	429	399	376	357	342	339	327			^
	161283	420	390	368	365	353	340	332			^
	*161283	444	401	390	381	360	347	344			^
	240184	428	397	385	370	352	336	329			^
	*240184		403	369	360	351	339	330			^
	*100284	420	390	368	365	353	340	332			^
	100284	426	397	380	370	352	337	327			^
	270484	441	411	381	360	339	324	312			^^
	270484			363	357	342	336				^^^
	*270484		439	399	379	347	327	312	297		^^
	250584		413	386	362	344	320	308	296		^^
	*250584		424	394	370	349	331	313			^^
	100585				351			300			^^

Table XXX continued:

Patient	Date	Paced-Ventricular Rate (bpm)									
		40	50	60	70	80	90	100	110	120	
J.H.	110584		375	351	327	312	291	279	270	261	^
	110584		405	378	354	336	318	303	291		^^
	*110584		391	358	334	322	304	287	275		^
	010684		415	385	358	340	319	300			^^
G.L.	020384		347	331	325	306	296	288			^
	*160384		357	333	321	309	300	291			^
	300384	391	355	334	319	301	292	283	280		^
	*300384	381	354	330	315	300	291	282	285		^
	110584		372	342	332	311	302	293	287		^
	*110585				330	317	302	293	290		^
J.Mc.	030584		447	420	390	363	345	327			^
	*030584			427	391	370	352	334			^
	030584			450	426	393	369	357			^^
M.D.	060484			438	411	384	366	351			^
	060484			434	401	380	362	350			^
	130484		446	422	398	380	365	353			^
	130484			437	416	389	371	359			^
	180584		443	422	395	377	362	344			^
	080684		372	360	345	336	321	312	309		^
	*080684			361	346	351	322	313	302		^
	100585				348			306			^
	100585				369			324			^^
W.S.	020484				327	312	300	285	279	270	^
E.S.	020484		330	315	303	285	267	255	240	237	^
J.C.	020484				324	288	276	267	264		^^
	020484					280	286	295			^^^
J.T.	200585			364	343	324	309	295	288	280	^
	200585			371	356	336	324	309	298	292	^^
	200585			386	363	344	329	314	306	300	^^^

*= post-exercise data; ^= T wave, 0.5 mV; ^^= T wave, 1.0 mV; ^^^=T wave, 1.5 mV.

Table XXXI. Comparison of correlation coefficients of four regression equations describing the paced-ventricular rate/Stim.-T interval relation.

Patient	Occasion	Regression Equation (r^2)			
		Linear	Exponential	Logarithmic	Power
J.M.	1.	0.961	0.972	0.991	0.990
	2.	0.970	0.981	0.996	0.998
	3.	0.966	0.977	0.993	0.996
	4.	0.950	0.962	0.984	0.989
	5.	0.988	0.992	0.994	0.989
	6.	0.954	0.965	0.986	0.990
	7.	0.961	0.971	0.989	0.992
	8.	0.961	0.972	0.991	0.995
	9.	0.977	0.988	0.996	0.988
	10.	0.997	1.000	0.996	0.988
I.M.	1.	0.912	0.931	0.956	0.969
	2.	0.990	0.990	0.999	0.999
H.B.	1.	0.977	0.986	0.996	0.995
	2.	0.965	0.977	0.993	0.996
	3.	0.970	0.980	0.994	0.997
	4.	0.961	0.972	0.991	0.995
	5.	0.939	0.958	0.989	0.996
	6.	0.971	0.980	0.990	0.991
	7.	0.989	0.996	0.999	0.997
	8.	0.978	0.989	0.997	0.997
J.M.	1.	0.989	0.995	0.998	0.996
	2.	0.979	0.984	0.989	0.990
G.L.	1.	0.924	0.946	0.980	0.990
	2.	0.911	0.928	0.973	0.980

Table XXXII. Comparison of the paced-ventricular rate/Stim.-T relations derived from values provided by the computer and the heart rate/Stim.-T(Apex) and paced-ventricular rate/Stim.-T (SE) relations derived simultaneously from the surface electrocardiogram.

Patient	Date	Stim.-T (ms)	r	Stim.-T(Apex), (ms)	r	Stim.-T(SE) (ms)	r
1 IM	071083	410-1.14xRate	0.91	457-1.34xRate	0.97	588-1.53xRate	0.94
2 IM	131083	405-1.09xRate	0.98	424-1.17xRate	0.96	580-1.51xRate	0.96
3 IM	131083	399-1.03xRate	0.99	413-1.00xRate	0.97	557-1.27xRate	0.94
4 IM	131083	397-0.95xRate	0.97	423-0.93xRate	0.93	502-1.56xRate	0.95
5 IM	141083	416-1.12xRate	0.98	450-1.18xRate	0.89	637-1.92xRate	0.99
6 JM	141083	460-1.56xRate	0.97	471-1.49xRate	0.87	582-1.51xRat	0.95
7 JM	100284	486-1.69xRate	0.98	509-1.72xRate	0.98	606-1.63xRate	0.98
8 HB	090983	432-1.34xRate	0.99	430-1.36xRate	0.96	674-2.47xRate	0.96
9 HB	021283	422-1.28xRate	0.97	424-1.21xRate	0.95	611-2.17xRate	0.98
10 HB	100284	373-0.90xRate	0.94	410-1.10xRate	0.99	692-2.75xRate	0.82
11 JC	161283	482-1.64xRate	0.93	438-1.24xRate	0.99	612-1.89xRate	0.99
12 JC	100284	462-1.35xRate	0.93	431-1.06xRate	0.91	592-1.49xRate	0.96
13 JC	100284	481-1.59xRate	0.98	448-1.34xRate	0.95	531-1.09xRate	0.94
14 GL	020384	405-1.20xRate	0.98	423-1.26xRate	0.98	599-2.06xRate	0.94
15 GL	160384	413-1.26xRate	0.96	422-1.26xRate	0.97	565-1.74xRate	0.95

Units: Rate=beats per minute.

CHAPTER X DISCUSSION

Atrial synchronized ventricular pacing maintains the physiological sequence of cardiac chamber activation and permits a chronotropic response to exercise in patients with second or third degree atrio-ventricular block. It was first introduced by Center et al., in 1963. Since then, the haemodynamic advantages of this pacing mode compared to fixed-rate ventricular pacing have been well recognized. Atrio-ventricular sequential pacing has been shown to improve resting cardiac output (Center et al., 1963; Gilmore et al., 1963; Samet et al., 1965; Karlof, 1975; Hartzler et al., 1977 and Sutton et al., 1979), prevent pacemaker syndrome (Alicandri et al., 1978) and some arrhythmias (Heiman and Helwig, 1966; Zipes et al., 1968 and Berkovits et al., 1979).

The development of stable and reliable atrial leads, since the late 1970s, has brought about a rapid growth in the number of implanted dual chamber systems. However these pacing systems are more expensive than ventricular demand pacemakers and with few exceptions (Sowton et al., 1981; Cameron et al., 1981) require the insertion of two pacing leads. They can therefore be more time consuming to implant and programme and may be associated with an increased complication rate.

It is therefore important to ascertain whether physiological pacing does result in increased exercise performance - a measure of far greater practical importance to patients than resting haemodynamic indices. Few studies have examined this aspect of adaptive pacing. Kruse and Ryden (1981) published their observations on 16 patients who were exercised on a bicycle ergometer during atrial synchronous ventricular inhibited and ventricular demand pacing modes. They found that patients tolerated greater work loads in the former mode. The improvement in exercise performance was long-lasting (Kruse et al., 1982).

The results of a larger study are presented in this thesis, involving 35 patients with stable high degree atrio-ventricular block who received atrial synchronized ventricular pacemakers.

Twenty-eight patients underwent haemodynamic studies at the time of pacemaker implantation.

On average, resting cardiac output increased by 28 per cent as the cardiac rhythm changed from a slow spontaneous ventricular rate to ventricular pacing at 70 beats per minute. Atrial synchronized ventricular pacing resulted in further improvement of cardiac output by 22 per cent. There were small but significant corresponding increases in the mean systolic arterial pressure.

Exercise performance during atrial synchronized

ventricular pacing was compared with fixed-rate ventricular pacing at 70 beats per minute, in studies involving all 35 patients.

The importance of performing such studies as double-blind as possible cannot be overemphasized. The treadmill was chosen in preference to the bicycle ergometer as it is more akin to most patients' daily activities.

Most patients improved their exercise performance on changing from fixed ventricular pacing at a rate of 70 beats per minute to atrial synchronized ventricular pacing. This was substantial in the majority of patients amounting to 33 per cent or more in 23/35 patients.

In 20 patients who had two sets of exercise tests, average exercise performance increased from 18 per cent, recorded soon after institution of atrial synchronized ventricular pacing mode, to 48 per cent about five weeks later.

In addition, atrial synchronized ventricular pacing reduced the incidence of exercise-induced hypotension and lightheadedness and arrhythmias. Furthermore, the greater increases in blood pressure and lesser increases in atrial rate indicated that cardiac output during exercise was higher during this pacing mode.

An interesting observation was significantly higher atrial rates for each stage of the exercise protocol with fixed-rate ventricular pacing, indicating that this pacing mode was accompanied by a higher sympathetic activity. Additionally, the greater increases in systolic arterial

pressures during exercise with atrial synchronized ventricular pacing mode suggested that cardiac output during exercise was greater with this pacing mode.

These observations have subsequently been confirmed by others (Perrins et al., 1983 and Yee et al., 1984).

It has been suggested that ischaemic heart disease may be a contraindication to physiological pacing, as the increased heart rate may induce angina (Karloff, 1975). It is noteworthy in this context that three of our patients developed angina in fixed-rate ventricular pacing mode but not during atrial synchronized ventricular pacing mode, despite longer distances walked in the latter pacing mode. This finding of an increased tendency to develop angina during non-physiological pacing in patients with ischaemic heart disease may be explained by the presence of increased sympathetic nervous system activity.

As it may not be possible for economic reasons for all patients with complete heart block to receive atrial synchronized ventricular pacing systems, it would be convenient to have a simple method which identifies pre-operatively patients who would benefit most from this pacing mode.

Edhag et al. (1981) reported that variations in pulse pressure during fixed-rate ventricular pacing may indicate

patients who would benefit from physiological pacing. Reiter and Hindman (1982) have also described the existence of a good correlation between the percentage increase in pulse pressure by fortuitous atrial and ventricular synchrony (i.e. PR interval of 100 to 200 ms) during ventricular pacing, and the change in cardiac index achieved subsequently by atrioventricular sequential pacing. Unfortunately, we (Fananapazir et al., 1983b) could not find a correlation between changes in resting haemodynamic indices and the degree to which exercise performance improved with adaptive pacing. Pehrsson and Astrom (1983) have confirmed that aortic pressures at rest do not predict the magnitude of increase in cardiac output during exercise in atrial synchronized ventricular pacing mode. Others have also shown that age, sex, co-existing cardiac disease, heart size, systolic time intervals, echocardiographic data and resting haemodynamic findings do not separate groups of patients which would benefit from atrial synchronized ventricular pacing mode (Kruse and Ryden, 1981; Kruse et al., 1982 and Kristensson et al., 1983a).

Having established that atrial synchronized ventricular pacing was of practical value to most patients with a high degree of atrioventricular block, the studies were extended to examine the separate contributions of atrioventricular synchrony and chronotropic response to

improvement in exercise performance during atrial synchronized ventricular pacing mode, on a within-patient and double-blind basis. That heart rate was the more important factor was suggested by the observation that two patients with congenital heart block, who spontaneously increased their ventricular rates during exercise, did not benefit from physiological pacing (Fananapazir et al., 1983b).

To unravel the problem patients were exercised in three pacing modes: first, fixed-rate ventricular pacing at 70 beats per minute; second, atrial synchronized ventricular pacing mode where chest wall stimuli were used to provide a rate response in the absence of atrioventricular synchrony and third, atrial synchronized ventricular pacing mode. Exercise performance was significantly increased during the pacing modes which provided a chronotropic response to exercise compared with fixed-rate ventricular pacing mode. On average, exercise performance during asynchronous ventricular pacing, where heart rate was increased to approximate atrial rate, was similar to that during atrial synchronized ventricular pacing mode. Rate augmentation rather than proper sequence of atrio-ventricular contraction therefore accounted for most of the improvement in exercise performance which occurred during atrial synchronized ventricular pacing mode. (Fananapazir et al., 1983c)

This study supported the observations of Karloff (1975)

that at matched pacing rates of 120 beats per minute, almost identical work loads and cardiac outputs are achieved by atrial synchronized and fixed-rate ventricular pacing modes, and Knudson (1982) and MacCarter (1982) who reported that considerable increases in exercise performance and cardiac output could be achieved by appropriately increasing the asynchronous ventricular pacing rate in response to physical activity. Pehrson and Astrom, (1983) and more recently Kristensson et al., (1985), have also independently shown that the difference in exercise performance between fixed rate ventricular and atrial synchronized ventricular pacing modes is largely due to the capability to increase heart rate in the latter mode.

The contribution of heart rate and properly timed atrial systole to optimal cardiac output differs at rest from that during exercise. At rest, atrial contraction increases cardiac output by about 20 to 25 per cent (Braunwald and Fram, 1961, Samet et al., 1965 and Martin and Cobb, 1966) by augmenting stroke volume. The atrial contribution to resting cardiac output varies with heart rate (Samet et al. 1966) and depends on the state of the myocardium. It is reported to be of particular importance to patients with noncompliant ventricles (Snell et al., 1966; Chamberlain et al., 1970; Rahimtoola et al., 1975; Johnson and Daily, 1975). Heart rate, on the other hand,

may vary within wide limits at rest without haemodynamic consequences (Stein et al., 1966) as a result of compensatory changes in stroke volume.

It was originally thought that properly timed atrial contractions were more important in failing hearts than in those with normal hearts (Benchimol et al., 1965). However in failing hearts the left ventricular end-diastolic pressures are already high and with the heart operating at the flat end of Frank Starling's curve, the atria contribute relatively less to stroke volume (Greenberg et al., 1979).

Oxygen consumption during exercise may increase from 0.25 litres per minute to 3 to 4 litres per minute. This is achieved through enhanced oxygen extraction, redistribution of blood flow to muscles and most importantly, through an increase in cardiac output. This increased cardiac output is achieved largely through rate augmentation, especially in patients with diseased ventricles who have a limited capacity to improve stroke volume during exercise (Kelman, 1977). Increased venous return due to the pumping action of muscles and to deeper and more rapid breathing and increased random atrio-ventricular sequence further diminish the need for provision of properly timed atrial contraction during exercise by the pacing system.

These findings form a rational basis for pacing systems that respond to changes in an indicator of physiological

need by altering heart rate without atrio-ventricular synchrony and hence the interest in the rate responsive TX pacemaker. This pacing system relies on the principle that the QT interval shortens during exercise. Using a conventional ventricular lead it paces the right ventricle and senses the T wave of the evoked response. Changes in the Stimulus-to-sensed T wave (Stim.-T) interval indicate physiological needs, to which the pacemaker responds by altering the paced-ventricular rate (Rickards and Norman, 1981; Rickards et al., 1981; Rickards and Donaldson, 1983; Rickards et al., 1983).

Donaldson et al. (1983a-c) reported their experience with this pacemaker in 5 patients. Pharmacologically induced changes in rate were obtained soon after implantation of the pacemaker with administration of isoprenaline in boluses of 2 ug intravenously (the slope was set at 0.5 bpm per ms). Stim.-T interval shortening was documented by an HP-85 computer and increases in heart rate from electrocardiographic recordings. Exercise testing was performed in each patient during ventricular demand pacing at 70 beats per minute and rate responsive pacing (with a maximal rate set at 125 beats per minute). Cardiac output was measured in triplicate both at rest and at peak exercise with both modes of pacing by the thermodilution technique. Holter monitoring was also performed on the patients over periods of 24 hours.

With isoprenaline the maximal rate of 125 beats per minute

was achieved around three and a half minutes after infusion which then fell gradually over the next 6 minutes. The Stim.-T interval decreased from 340 ms to 320 ms after 2 minutes of isoprenaline infusion. There was a smooth and progressive rate response to exercise and a gradual return to the basic paced rate after activity stopped. Rate responsive pacing resulted in a 45 per cent increase in cardiac output when compared with fixed-rate ventricular pacing. Similarly, a 57 per cent increase in maximal exercise capacity was noted when rate responsive pacing was compared with conventional pacing at 70 beats per minute.

Comparison of exercise performances during TX rate responsive, atrial synchronized and fixed-rate ventricular pacing modes confirmed our previous finding that adaptive pacing significantly improved exercise performance largely through an increase in heart rate. Thus in this respect the TX pacing system compares favourably with pacemakers which combine atrio-ventricular synchrony with the ability to provide a chronotropic response to exercise.
The incidence of inadequate T wave sensing has been estimated to have been about 18 per cent (63/350 implanted units) with the TX1 but only 3.6 per cent (9/251 implanted units) with the introduction of the Quintech model (Vitatron Medical, October 1984).
T wave sensing may deteriorate with the passage of time.

Fortunately in our series a change in the programmed T wave sensitivity in most instances ensured adequate rate changes. Reprogramming T wave sensitivity however may upset the rate/Stim.-T interval relation and may require adjustments of the slope and T wave sensing window.
The amplitude of the sensed T wave was noted to increase with higher pacing rates. This may be explained by the observation that action potentials are longer in endocardial than in epicardial muscle (Moore et al., 1965). Gradients of endocardial-to-epicardial transmembrane action potential therefore exist which may determine the configuration of the T wave and which in turn may be affected by heart rate.
As the heart rate/Stim.-T interval relation depends in part on the T wave configuration and amplitude, this relation therefore probably changes constantly during exercise. This in turn may explain the finding that the heart rate/Stim.-T (dependent on T wave configuration) and heart rate/QT interval relations conform to different regression equations.

Additional problems with the TX pacing system which were identified included:

Firstly, the complexity of programming. (a) Several factors simultaneously affect the paced-ventricular rate/Stim.-T interval relation and hence the

quality of rate responsive to a given work load as judged by the onset of rate acceleration and the time interval taken to reach the programmed upper rate limit during an exercise test. These include the individual´s state of autonomic nervous system activity, changes in T wave sensing, programmed T wave sensitivity, T wave sensing window and lower and upper rate limits. (b) The HP-85 programmer is cumbersome, expensive and difficult to operate.

Secondly, assuming that a satisfactory programme is one that provides the patient with rate responses during periods of activity only, there is a great deal of uncertainty as to the best method which would determine such a programme. This study indicates that the suggestion (Ursula Gebhardt-Seehausen, 1985 and de Jongste et al., 1985) that this can be achieved by adjusting the programmed slope, based on the Stim.-T interval changes occurring at rest and in response to alterations in the pacing rate may not always provide appropriate slopes. There may be several reasons for this, namely (a) the paced-ventricular rate/Stim.-T interval relation is not linear but curvilinear, (b) the timing of rate changes are affected as much by the T wave sensing window as the programmed slope and (c) the factors affecting the Stim.-T interval at rest may be different to those operating during exercise: at rest, heart rate predominantly

determine the Stim.-T wave interval, whilst during exercise both heart rate and autonomic nervous system activity contribute to Stim.T interval changes. It is therefore not surprising that predicted slopes derived from resting heart rate/Stim.-T interval relations in many instances did not provide for satisfactory rate responses during exercise tests.

Thirdly, the reliability of the Stim.-T interval as a biosensor, and ultimately the performance of the TX pacemaker, is affected by the variable nature of the relation between heart rate and the Stim.-T interval, and in this respect the paced-ventricular rate/Stim.-T interval relation behaves very similarly to the heart rate/QT interval relation. The duration of the Stim.-T interval depends on the pacing rate as well as the state of autonomic nervous system activity. Hence in the interaction of heart rate, circulating catecholamines, vagal and left and right sympathetic nervous system activity and their variable contributions to Stim.-T changes may be found the explanation for the wide inter- and intra-patient variation exhibited by the paced-ventricular rate/Stim.-T interval relation. This patient variation is potentially the most serious limitation of this biosensor, as it indicates that not only will the programme have to be tailored to individual needs but that more seriously, the same programme may give

rise to unpredictable results. After achieving seemingly satisfactory rate responses through programming, inappropriate rate acceleration may occur at rest as a result of minimal Stim.-T interval shortening due to an increase in the slope of the heart rate/Stim.-T interval relation or alternatively vigorous exercise resulting in a large reduction in the Stim.-T interval, may result in ineffective rate acceleration due to a reduction in the slope of the heart rate/Stim.-T interval relation. Preliminary experience (Fananapazir et al., 1985a and 1985b) suggests that this does occur in practice in some patients.

Fourthly, programming difficulties are further compounded by the fact that after a stress test undertaken to determine the appropriateness or otherwise of a certain programmed parameter, the autonomic nervous system status of the patient and hence the heart rate/Stim.-T interval relation are automatically altered. It may therefore be necessary to test the effect of further changes in the programmed indices at a later date.

The following was found to be the quickest and most convenient method of obtaining a programme which provided for satisfactory rate responses during exercise but avoided inappropriate rate augmentation at rest: It relies on the principle that satisfactory results are

obtained if the pacing rate remains at the basal rate at rest and rises only during periods of exertion.
This can be achieved in most patients by maintaining the slope at about 0.6 beats per minute per millisecond change in the Stim.-T interval, and adjusting only the T wave sensing window.
The T wave sensing window set at a value 20 ms less than the Stim.-T interval, measured at the basal rate. Thus the risks of inappropriately high heart rates at rest are minimized. The duration of the T wave sensing window may then be refined further by evaluating the onset of rate response during exercise - the shorter the duration of the T wave sensing window in relation to the Stim.-T interval the greater is the likelihood that rate response will be delayed during exercise. The duration of the T wave sensing window is therefore so adjusted that rate response will occur after about one to two minutes of exercise and a heart rate of about 120 beats per minute is achieved smoothly after a further one to two minutes of exercise, with a smooth fall to the basic rate during the recovery period. Heart rates in excess of 120 beats per minute probably do not result in further improvements in exercise performance and may cause serious haemodynamic problems if they occur inappropriately at rest.

Fifthly, an important consideration is the large number of medications, myocardial conditions and metabolic states

that can affect the QT interval or the Stim.-T interval, either to shorten it or prolong it (Donaldson and Rickards, 1982). Any change in the Stim.-T interval would affect the heart rate/Stim.-T interval relation. It may be possible in some circumstances, such as with patients receiving amiodarone (Fananapazir et al., 1985b), to adjust the programmed sensing window and slope and maintain satisfactory rate responses. This may be impracticable in patients receiving drugs with much shorter half-life or more transient effect on the Stim.-T interval.

The effect of acute beta adrenoreceptor blocker therapy on the performance of the TX pacemaker may differ from that of chronic beta adrenoreceptor blocker therapy. Preliminary studies indicate that (as expected from the findings of the first part of this thesis) acute administration of a beta adrenoreceptor blocker will severely blunt or abolish rate response to exercise but that it may be possible to achieve satisfactory rate changes in patients on chronic beta adrenoreceptor blocker therapy (Fananapazir et al., 1985b). Further studies are necessary to confirm these findings.

Given these considerations and until further modifications of the TX pacing system, our findings suggest that patients with this pacing system should be followed up closely, as frequent reprogramming based on results of

exercise tests and Holter monitoring may be necessary to adjust for chronic changes in the Stim.-T interval and in the heart rate/Stim.-T relation and deterioration in T wave sensing, so as to ensure that the pacemaker continues to function optimally.

Rate adaptive pacing systems such as the TX pacemakers should also only be implanted in those patients in whom it has been clearly shown that the level of exercise performance is limited by a lack of rate augmentation. This can be assessed by exercising patients during fixed-rate ventricular pacing at 70 beats per minute and during ventricular pacing where the heart rate is progressively increased to 120 beats per minute, using a temporary ventricular lead and an external pacing system. The TX pacing system is hence not indicated in patients who are inactive and in whom the provision of atrio-ventricular synchrony may be more advantagous than high pacing rates.

Although the development of stable and reliable atrial leads since the end of the 1970´s has increased the popularity of dual chamber pacing systems, these also are not without their problems. Problems peculiar to these pacing systems include pacemaker mediated tachycardias (incidence reduced by the availability of long atrial refractory periods and post-ectopic increases of ventricular refractory period), sensing the atrial

stimulus via the ventricular channel ('cross talk'), myopotential oversensing via the atrial channel of unipolar systems (facilitated by the use of lower sensitivity values in the atrial channel but overcome by using bipolar atrial leads) and shortened service life due to the need to maintain atrial pacing (aggravated by high pacing thresholds in the atrium). Additionally, the various types of universal (DDD) pacing systems which are available differ importantly in the details of their programming facilities and there is also a growing complexity in the analysis of electrocardiographic recordings obtained with this kind of pacemaker. The response of a DDD pacemaker to the upper rate limit may be an important factor in determining exercise performance. Some pacing systems provide for a 2:1 atrioventricular response and others permit a Wenchebach-type ventricular response. The latter upper rate limit response ensures a less sudden fall in heart rate and is the one we favour as being least likely to be associated with exertional lightheadedness.

The advantages of the TX pacing system over universal (DDD) pacemakers are (a) the use of a single ventricular lead which facilitates pacemaker implantation and (b) its suitability in patients with atrial arrhythmias.

The TX pacing system is potentially capable of further

developments:

Programming could be simplified if the pacemaker design permits the system periodically and automatically to reset (a) the duration of the T wave sensing window- the pacemaker should probably adjust its T wave sensing window to a value about 20 ms less than the Stim.-T interval recorded at its programmed lower rate limit, and (b) slope - the pacemaker would increase its pacing rate to a value 10 to 20 beats per minute higher than the lower rate limit and reset its slope in response to the magnitude of sensed change in Stim.-T interval. However this solution presupposes that there is a direct and constant relation between slopes obtained in this way by the pacemaker and the heart rate/Stim.-T interval relation existing during periods of activity. The evidence is that such a relation probably exists but may not be sufficiently strong for it to be of practical value.

How frequently the pacemaker needs to adjust these parameters will depend on a better understanding of the diurnal changes in the duration of the Stim.-T interval and the heart rate/Stim.-T interval relation.

The Stim.-T interval could be used in conjunction with other biosensors to provide a more comprehensive indication of metabolic demand.

Patients with sinoatrial disease may not increase their heart rate adequately during exercise and in this group of patients current DDD pacing systems function mostly as an atrio-ventricular sequential pacing system and the exercise performance of the patient may remain limited. In this group of patients the TX principle could be used to advantage as it may be possible to have a pacing system which combines DDD functions with rate responsive capability. During periods of increased physiological need, the pacemaker would accelerate atrial rate via a second electrode, in response to changes in ventricular Stim.-T interval, whilst at the same time ensuring atrio-ventricular synchrony.

It is therefore envisaged that the TX pacemaker will continue to evolve rapidly and prove a most useful and satisfactory rate responsive pacing system.

REFERENCES

Abildskov J.A. (1976).
Adrenergic effects on the QT interval of the electrocardiogram.
Am Heart J 92: 210

Adams W. (1936).
The normal duration of the electrocardiographic ventricular complex.
J Clin Invest 15:335

Ahnve S., Lundman T., Shoaleh-var M. (1978).
The relationship between QT interval and ventricular arrhythmias in acute myocardial infarction.
Acta Med Scand 204:17

Ahnve S., Helmers C., Lundman T. (1980).
QTc intervals at discharge after myocardial infarction and long-term prognosis.
Acta Med Scand 208:55

Ahnve S., Helmers C., Lundman T., Rehngvist N., Sjögren A. (1980).
QTc intervals in acute myocardial infarction: First year prognostic implications.
Clin Cardiol 3:303

Ahnve S., Vallin H. (1982).
Influence of heart rate and inhibition of autonomic tone on the QT interval.
Circulation 65:435

Akhras F., Rickards A.F. (1980).
The relationship between QT interval and heart rate during physiological exercise and pacing.
Jap Heart J 22:345

Alicandri C., Fouad F.M., Tarazi R.C. (1978).
Three cases of hypotension and syncope with ventricular pacing.
Am J Cardiol 42:137

Anderson R.C. (1981).
Annotation: QT interval in sinus arrhythmia.
J Electrocardiol 4:407

Armitage P. (1971).
Statistical methods in medical research.
Blackwell Scientific Publications. Oxford and Edinburgh.

Ashman R. (1939).
Normal duration of the Q-T interval.
Proc Soc Exper Biol Med 40:150

Ashman R. (1942).
The normal duration of QT interval.
Am Heart J 23:522

Ashman R. (1942).
The normal duration of the QT interval.
Am Heart J 23:522

Ashman R., Hull E. (1945).
Essentials of electrocardiography.
New York, The MacMillan Company.

Bassingthwaighte J.B., Fry C.H., McGuigan J.A.S. (1976).
Relationship between internal calcium and outward current in mammalian ventricular muscle: a mechanism for the control of the action potential duration?
J Physiol 262:15

Bazett H.C. (1920).
An analysis of the time-relations of electrocardiogram.
Heart 7:353

Bekeit S.G., Ali A.A., Deglin S.M., Jain A.C. (1981).
Analysis of QT interval in patients with idiopathic mitral valve prolapse.
Chest 81:620

Benchimol A., Ellis J.G., Dimond E.G. (1965).
Haemodynamic consequences of atrial and ventricular pacing with normal and abnormal heart.
Am J Med 39:911

Bennett D.H. (1982).
Acute prolongation of myocardial refractoriness by sotalol.
Br Heart J 47:521

Berkowitz W.D., Wit A.L., Lau S.H., Steiner C., Damato A.N. (1969).
The effects of propranolol on cardiac conduction.
Circulation 40:855

Berkowitz B.V., Castellanous A., Dreifus L.S. (1979).
Double demand sequential pacing for the treatment and termination of paroxysmal re-entry tachycardia:
In: Proceedings of the VI World Symposium on Cardiac Pacing. Meere C. (Ed.). PaceSymp, Montreal.
Chapter 6-21

Bigger J.T.,Jr., Heissenbuttel R.H. (1969).
The use of procainamide and lidocaine in the treatment of cardiac arrhythmias.
Prog Cardiovasc Dis 11:515

Bigger J.T., Jr., Jaffe C.C. (1971).
The effect of bretylium on the electrophysiological properties of ventricular muscle and Purkinje fibers.
Am J Cardiol 27:82

Boudoulas H., Sohn Y.H., O´Neil W., Brown R., Weissler A.M. (1982).
The QT/QS2 Syndorme: A new mortality risk indication in coronary artery disease.
Am J Cardiol 50:1229

Boyett M.R., Jewell B.R. (1978).
A study of the factors responsible for rate-dependent shortening of the action potential duration in mammalian ventricular muscle.
J Physiol 285:359

Braunwald E.H., Fram C.J. (1961).
Studies on Starling´s law of heart: IV. Observations on the hemodynamic function of the left atrium in man.
Circulation 24:633

Brooks C.M., Hoffman B.F., Suckling E.E., Orias O. (1955).
In: Excitability of the heart. New York.
Grune and Stratton.

Browne K., Zipes D.P., Heger J.J., Prystowsky E.N. (1982).
Influence of the autonomic nervous system on the QT interval in man.
Am J Cardiol 50:1099

Bruce R.A. (1971).
Exercise testing in patients with coronary heart disease: principles and normal standards for evaluation.
Ann Clin Res 3:323

Burch G.E., Myers R., Ablidskov J.A. (1954).
A new electrocardiographic pattern observed in cerebrovascular accidents.
Circulation 9:719

Burgess M.J. (1982).
Ventricular repolarization and electrocardiographic T wave form and arrhythmia susceptibility.
In: Excitation and neural control of the heart.
Levy M.N. and Vassalle (Eds.).
American Physiological Society. Maryland pages 181-202.

Butrous G.S., Ward D.E., Nathan A.N., Camm A.J. (1984).
The dynamics of QT interval during valsalva manouver in normals and in long QT syndrome.
Eur Heart J 5(Abstr Suppl 1):651

Cabasson J., Peuch P., Mellet J.M., Guimond C., Bachy C., Sassine A. (1976).
Analyse des effet electrophysiologique de l´amiodarone par l´enrigistiement simultane des potentials d´action monophasiques et du faisceau de His.
Arch Mal Coeur 69:691

Cameron J.R., Chisholm A.W., Harrison A.W., Froggatt G.M. (1981).
In: Feruglio G.A. (ed.) Cardiac Pacing. Proceedings of the 2nd European Symposium on Cardiac Pacing.
pages 1091-1092

Cammilli L., Alcidi L., Papeschi G. (1977).
A new pacemaker autoregulating the rate of pacing in relation to metabolic needs.
In: Y Watanabe (Ed.) Cardiac Pacing. Proceedings of the Proceedings of the Vth International Symposium.
Amsterdam Excerpta Medica. page 414

Cammilli L., Green G.D., Ricci D. (1979).
pH-triggered pacemaker; design and clinical results.
In: Proceedings of the VI World Symposium on Cardiac Pacing. Meere C. (Ed.) PaceSymp. Montreal.
Chapter 19-8

Cammilli L., Alcidi L., Risani R. (1982).
Results, problems and perspectives in the autoregulating pacemaker.
PACE 3:3a65 (Astract).

Cammilli L. (1983).
Results, problems and perspectives in the autoregulating pacemaker.
PACE 6, 2:488

Candelon B., Diaz A., Wittkampf F. (1985).
Technical aspects of a rate responsive pacemaker.
The TX pulse generator.
In Francisco Perez Gomez (ed.) Cardiac Pacing
pages 822-825

Carmaliet E. (1982).
Electrophysiological effects of catecholamines in the heart.
In: Catecholamines in the non-ischaemic and ischaemic myocardium.
Riemersma and Oliver (eds.) Elsevier/North-Holland, Biomedical Press. pages 77-86

Castellanos A., Agha A.S., Befeler B., Castillo C.A., Berkovits B.V. (1973).
A study of arrival of excitation at selected ventricular

sites during human bundle branch block using close bipolar catheter electrodes.
Chest 63: 208

Castellanos A., Befeler B., Myerburg R.J., Castillo C.A., Agha A.S., Vagueira M.C. (1973). Functional properties of the ventricular muscle and distal conducting system during right ventricular stimulation with special reference to RBBB pattern in Vl, "supernormal intraventricular conduction", and physiological "gate".
Eur J Cardiol 1:41

Center S., Nathan D., Wu C.Y. (1963). The implantable synchronous pacer in the treatment of complete heart block.
J Thorac Cardiovasc Surg 46:744

Chamberlain D.A., Leinbach R.C., Vassaux C.E. (1970). Sequential atrioventricular pacing in heart block complicating acute myocardial infarction.
N Eng J Med 282:577

Charlier R. (1970). Cardiac actions in the dog of a new antagonist of adrenergic excitation which does not produce competitive

blockade of adrenoreceptors.
Br J Pharmacol 39:668

Cheer S.N., Li R.C. (1930).
Studies on the electrical systole ("Q-T interval") of the heart. I. The duration of the electrical systole in the Chinese.
Chinese J Physiol 4:191

Clements S.D., Hurst J.W. (1972).
Diagnostic value of electrocardiographic abnormalities observed in subjects accidentally exposed to cold.
Am J Cardiol 29:729

Cohen T.J. (1984).
A theoretical right atrial pressure feedback heart rate control system to restore physiological control in the rate limited heart.
PACE 7, 4:671

Coumel P., Lavalee P., Attuel P. (1978).
Amiodarena. In: Diagnostico tratamento de las arritmias Cardicas. Bayes A. and Cosin J. (Eds.), Barcelona, Ediociones Doyma S.A. page 678

Cowan J.C., Vaughan Williams E.M. (1977).
The effect of palmitate on intracellular potentials

recorded from Langendorff-perfused guinea-pig hearts in normoxia and hypoxia, and during perfusion at reduced rate of flow.
Journal of Molecular and Cellular Cardiology 9:327

Cowan J.C., Vaughan Williams E.M. (1980).
The effects of various fatty acids on action potential shortening during sequential periods of ischaemia and reperfusion.
Journal of Molecular and Cellular Cardiology 12:347

Crampton R.S. (1979).
Pre-eminence of the left stellate ganglion in the long Q-T Syndrome.
Circulation 59:769

Curry P.V.L. (1975).
Fundamentals of arrhythmias: modern methods of investigation. In: Krikler D.M., Goodwin J.F. (eds.)
London: WB Saunders, pages 39-80

Davidowski T.A., Wolf S. (1984).
The QT interval during reflex cardiovascular adaptation.
Circulation 69:22

de Hamptinne A. (1971).
The frequency dependence of outward current in frog auricular fibers. Pflugers Arch 329:322

de Jongste M.J.L., Nagelkerke D., Ebels T., Lie K.I. (1985).
Rate adaptive pacing using the QT interval.
In: Francisco Perez Gomez (ed.) Cardiac Pacing.
pages 841-856

Denes P., Wu D., Dhingra R. (1974).
The effects of cycle lengths on cardiac refractory periods in man.
Circulation 49:32

Donaldson R.M., Rickards A.F. (1982).
Evaluation of drug-induced changes in myocardial repolarization in man using the paced endocardial evoked response.
Br Heart J 48:381

Donaldson R.M., Rickards A.F. (1983)a.
The ventricular endocardial evoked response.
PACE 6:253

Donaldson R.M., Fox K., Rickards A.F. (1983)b.
Initial experience with a physiological, rate responsive pacemaker.
B M J 286:667

Donaldson R.M., Rickards A.F. (1983)c.
Rate responsive pacing using the evoked QT principle. A Physiological alternative to atrial synchronous pacemakers.
PACE 6:1344

Doroghazi R.M., Childers R. (1978).
Time-related changes in the Q-T interval in acute myocardial infarction; possible relation to local hypocalcaemia.
Am J Cardiol 41:684

Dreifus L.S., Ogawa S. (1977).
Quality of the ideal antiarrhytmic drug.
Am J Cardiol 39:466

Drury A.N. (1936)
The effective refractory period, full recovery time, premature response interval of ventricular muscle, in the intact unanaesthetised cat and rabbit.
Quat J Expt Physiol 26:181

Duchene-Marullaz P. (1973).
Effet de l´innervation cholinergique sur le coeur de mammifere. Le tonnes cardiomoderateur.
J Physiol Paris 66:373

Edhag O., Fagrell B., Freyschuss U. (1981).
Digital pulse volume in the evaluation of haemodynamic effects of cardiac pacing.
Clin Physiol 1:263

Edvardsson N., Hirsch I., Emanuelsson H., Ponten J., Olsson S.B. (1980).
Sotalol-induced delayed ventricular repolarization in man.
Eur Heart J 1:335

Edvardsson N., Olsson S.B. (1981).
Effects of acute and chronic beta-receptor blockade on ventricular repolarization in man.
Br Heart J 45:628

Elek S.R., Silver A.S., Tober J.N., Griffith G.C. (1953).
The QT interval in myocardial infarction and left ventricular hypertrophy.
Am Heart J 45:80

Elmsie-Smith D., Sladden G.E., Stirling G.R. (1959).
The significance of changes in the electrocardiogram in hypothermia.
Br Heart J 21:343

Fananapazir L., Bennett D.H., Faragher E.B. (1983)a.
Contribution of heart rate to QT interval shortening during exercise.
Eur Heart J 4:265

Fananapazir L., Srinivas V., Bennett D.H. (1983)b.
Comparison of resting hemodynamic indices and exercise performance during atrial synchronized and asynchronous ventricular pacing.
PACE 6:202

Fananapazir L., Bennett D.H., Monks P. (1983)c.
Atrial synchronized ventricular pacing: Contribution of the chronotropic response to improved exercise performance.
PACE 6:601

Fananapazir L., Srinivas V., Bennett D.H. (1984).
Onset of action and peak effect of oral and intravenous amiodarone on myocardial repolarization.
IBID 5:47

Fananapazir L., Rademaker M., Bennett D.H. (1985)a.
Performance of the rate responsive (TX) pacemaker.
In: Francisco Perez Gomez (ed.) Cardiac Pacing.
pages 833-846
Abstract: PACE 8:A-110

Fananapazir L., Rademaker M., Bennett D.H. (1985)b.
Reliability of the evoked response in determining the paced ventricular rate and performance of the rate responsive (TX) pacemaker.
PACE 8:701

Fenn G.K. (1922).
Studies in the variation of the length of the Q-R-S-T interval.
Arch Int Med 29:441

Feruglio G.A., Steinback K. (1983).
Pacing in the world today. World survey on cardiac pacing for the years 1979 to 1981.
In: Steinback K., Glogar D., Laszkovics A. (eds.) Proceedings of the VIIth World Symposium On Cardiac Pacing. Darnstadt, Steinkomff Verlag. pages 953-967

Fidelle J., Attuel P., Roumieux M.C., Coumel P. (1976).
L´utilisation de l´miodarone dans les troubles rythmiques graves et rebelles del´enfent. A propos de 50 cas.
Ann Cardiol Andeiol 25:385

Fields J.Z., Roeske W.R., Moskin E., Yamamura H.I. (1978).
Cardiac muscarinic cholinergic receptors.
L Biol Chem 253:3251

Fitzgerald J.D. (1969).
Perspectives in adrenergic beta-receptor blockade.
Clin Pharmacol Ther 10:292

Fozzard H.A. (1981).
Basic membrane mechanism of neurotransmitter effects in the heart.
In: Disturbances in neurogenic control of the circulation.
American Physiological Society. pages 177-203

Fridericia I.S. (1920).
Die Systolendaur im electrokardiogramm bei normalen menschen und bei herzkranken.
Acta Med Scand 53:469

Gardner R.M. Allen D.O. (1976).
Regulation of cyclic nucleotides levels and glycogen phosphorylase activity by acetyl choline and epinephrine in perfused rat hearts.
J Pharmacol Exp Ther 198:412

Gelles G.M. (1977).
Use of calcium inophores to determine the effects of intracellular calcium on the action potential of canine cardiac Purkinje fibers.
Circulation Res 6:368

Gettes L.S., Reuter H. (1974).
Slow recovery from inactivation of inward currents in mammalian myocardial fibers.
J Physiol 240:703

Geppert M.P. (1949).
Die intraindividuelle QT/-RR-relation in menschlichen electrokardiogramm. Arch Kreislaufforsch 15:64

Gilmore J.P., Sarnoff S.J., Mitchell (1963).
Synchronicity of ventricular conduction: Observations comparing haemodynamic effects of atrial and ventricular pacing.
Br Heart J 25:299

Goiccolea de Oro A., Wilhelmi Ayza J., Alvarez Morales, de la Llana R., Gutierrez Diez J.R., Gonzalez Alvarez. (1985).
Rate responsive pacing: Clinical experience.
In: Francisco Perez Gomez (ed.) Cardiac Pacing.
pages 776-780

Goldreyer B.N., Olive A.L., Leslie J., Cannonn D.S., Wyman M.G. (1981).
P synchronous pacing; A new orthogonal approach to P-wave sensing.
Am J Cardiol 47:434 (abstract)

Greenberg B., Chatterjee K., Parmley W., Werner J., Holly A. (1979).
The influence of left ventricular filling pressure on atrial contribution to cardiac output.
Am Heart J 98:742

Griffin J.C. (1983).
Central body temperature as a guide to optimal heart rate.
PACE 6, 2:498

Guss S.B., Kastor J.A., Scharf D.L., Josephson M.E. (1975).
Effects of rate, atropine and procainamide on human ventricular refractoriness.
Am J Cardiol 35:142

Guss S.B., Kastor J.A., Josephson M.E., Scharf D.L. (1976).
Human ventricular refractoriness. Effects of cycle length, pacing site and atropine.
Circulation 53:450

Han J. (1969).
Mechanisms of ventricular arrhythmias associated with myocardial infarction.
Am J Cardiol 24:800

Han J., Moe G.K. (1964).
Nonuniform recovery of excitability in ventricular muscle.
Circ Res 14:44

Hauswirth O., Noble D., Tsien R.W. (1972).
The dependence of plateau currents in cardiac Purkinje fibers on the interval between action potentials.
J Physiol 224:27

Hartzler G.O., Maloney J.D., Curtis J.J. (1977).
Hemodynamic benefits of atrio-ventricular sequential pacing after cardiac surgery.
Am J Cardiol 40:232

Haynes R.E., Hallstrom A.P., Cobb L.A. (1978).
Repolarization abnormalities in survivors of out-of-hospital ventricular fibrillation.
Circulation 57:654

Hegglin R., Holtzmann M. (1937).
Die klinsche Bedeutung der verlangerten Q-T distanz (systolendauer). Med 132:1

Heinman D.F., Helwig J. Jr. (1966).
Suppression of ventricular arrhythmia by transvenous intra-cardiac pacing.
JAMA 195:1972

Higgins C.G., Vatner S.F., Braunwald E. (1973).
Parasympathetic control of the heart.
Pharmacol Rev 25:120

Hirsch E.F. (1971).
The innervation of the veterbrate heart.
In: Springfield I.L.(ed.) page 80

Hodges M., Salero D., Erlien D. (1983).
Bazzett´s QT correction reviewed. Evidence that a linear QT correction for heart rate is better.
J Am Coll Cardiol 1:694 (abstract)

Hoffman B.F., Cranefield P.F. (1960).
In: Electrophysiology of the heart. New York.
McGraw-Hill, page 253.

Humen D.P. (1983).
A pacemaker which automatically increases its rate with physical activity.
In: Steinback (ed.) Proceedings of the VIIth World Congress on Cardiac Pacing. Darmstadt, Steinkomf Veralg. page 259

Humen D.P., Kostuk W.J., Klein G.J. (1984).
Activity sensed, rate responsive pacing; treadmill performance and haemodynamic characteristics.
(abstract) JACC 3, 2:508

Hunt R. (1899).
American Journal of Physiology, II,395

Isenberg G. (1977).
Cardiac Purkinje fibres. Resting, action and pacemaker potential under the influence of Ca^{++} as modified by intracellular injection techniques.
Pfluhers Arch 371:51

Isenberg G. (1977).
Cardiac Purkinje fibers. The slow inward current component under the influence of modified [Ca^{++}].
Pflugers Arch 371:61

Isner J.M., Sours H.A., Paris A.L., Ferrans V.J., Roberts W.C. (1979).
Sudden, unexpected death in avid dieters using the liquid-protein-modified-fast diet.
Circulation 60:1401

Isner J.M., Roberts W.C., Heynfield S.B., Yager J. (1985).
Anorexia nervosa and sudden death.
Ann Intern Med 102:49

Ito S., Surawicz B. (1981).
Effect of tetraethylammonium chloride on action potential in cardiac Purkinje fibers.
Am J Physiol 241:H139-44

Janse M.J., Van der Steen A.B.M., Van Dam R.T. (1969).
Refractory period of the dog´s ventricular myocardium following sudden changes in frequency.
Circ Res 24:51

Jervell A., Lange-Nielson F. (1957).
Congenital deaf mutism, functional heart disease with prolongation of the Q-T interval and sudden death.
Am Heart J 54:59

Johnson A.D., Daily P.O. (1975).
Hypertrophic subaortic stenosis complicated by high degree heart block: Successful treatment with atrial synchronous ventricular pacemaker.
Chest 67:491

Kaski J.C., Firotti L.A., Messtui H., Ruttzky B., Rosenbaum M.B. (1981).
Long-term management of sustained, recurrent, symptomatic ventricular tachycardia with amiodarone.
Circulation 64:273

Karlof I. (1975).
Haemodynamic effect of atrial triggered fixed rate pacing at rest and during exercise in complete block.
Acta Med Scand 197:195

Kastor J.A., Goldreyer B.N., Moore E.N., (1975).
Intraventricular conduction in man studied with an endocardial electrode catheter mapping technique.
Patients with normal QRS and right bundle branch block.
Circulation 32:786

Kelly H.B., Fay J.E., Laverty S.G. (1963).
Thioridazine hydrochloride (melleril) - its effects on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities.
Can Med Assoc J 89:546

Kelman, G.R. (1977).
In: Applied Cardiovascular Physiology.
(Second Edition). London. Buttersworth. page 170

Kent K.M., Epstein S.E., Cooper T., Jacobowitz D.M. (1974).
Cholinergic innervation of the canine and human ventricular system.
Circulation 50:948

Kline R., Morad M. (1976).
Potassium efflux and accumulation in heart muscle.
Biophys J 16:367

Knudson M., Amundson D.C., Mosharrafa M. (1982).
Haemodynamic demand pacing.
In: Barold S.S. and Mujica J. (eds.): The Third Decade of Cardiac Pacing. Futura page 249-264

Kralios F.A., Martin L., Burgess M.J., Miller K. (1975).
Local ventricular repolarization changes due to sympathetic nerve branch stimulation.
Am J Physiol 228:1621

Kramer B., Brucher R., Myer-Waarden K. (1984).
Bazett´s correction of the QT-interval in ECG: Is it reliable?
Eur Heart J 5(Abstr Suppl 1):649

Krasnoff S.O. (1950).
The duration of the Q-T interval in myocardial infarction.
Am Heart J 39:523

Krikler D.M., Curry P.V.L. (1976).
Torsade de pointes, an atypical ventricular tachycardia.
Br Heart J 38:117

Kristensson B-E., Arnman K., Ryden L. (1983)a.
Atrial synchronous ventricular pacing in ischaemic heart disease.
Acta Med Scand 214:295

Kristensson B-E., Arnman K., Smedgard P. (1983)b.
Physiological versus fixed-rate ventricular pacing. A double-blind cross-over study.
PACE 6(II):A-38

Kristensson B-E., Arnman K., Ryden L. (1985).
The haemodynamic importance of atrioventricular synchrony and rate increase at rest and during exercise.
Eur Heart J 6, 9:773

Kruse I., Ryden L. (1981).
Comparison of physical work capacity and systolic time intervals with ventricular inhibited and atrial

synchronous ventricular inhibited pacing.
Br Heart J 46:129

Kruse I., Arnman K., Conradson T-B. (1982).
A comparison of acute and long-term hemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing.
Circulation 65:846

Kuck K.H., Kunze K.P., Roewer N., Bleifeld (1984).
Sotalol-induced torsade de pointes.
Am Heart J 107:181.

Laczkovics A.(1984).
The central venous blood temperature as a guide to optimal pacing rate.
PACE 7:822

Lepeschkin E. (1951).
In: Modern electrocardiography. Volume I., Baltimore, Williams and Wilkins.

Lepeschkin E., Surawicz B. (1952).
The measurement of the QT interval of the electrocardiogram.
Circulation 6:378.

Levy M.N. (1976).
Parasympathetic control of the heart.
In: Neural regulation of the heart. Randall W.C. (ed.).
New York, Oxford. pages 97-129

Levy M.N., Martin P.J. (1979).
Neural control of the heart.
In: Handbook of physiology.
Section 2: The cardiovascular system.
Volume 1, Chapter 16:581

Lewis T., Drury A.N. (1926).
Revised views of the refractory period, in relation to drugs reputed to prolong it, and in relation to circus movement.
Heart 13:95

Lian C., Goblin V., Haraige (1934).
Diagnostic et valeur Semeeiologique de l´allognement et du raccourcissement de la systole ventriculair.
Press Med 42:787

Lish P.M., Weikel J.H., Dungan K.W. (1965).
Pharmacological and toxicological properties of two new B-adrenergic receptor antagonists.
J Pharmacol Exp Ther 149:161

Lombard W.P.L., Cope O.M. (1919).
Effect of heart rate on the length of the systoles and diastoles of the normal heart in the standing position.
Am J Physiol 49:139

Lorenzo J.G., Goicolea de Oro A., Rodriguez J., Botella S., Terol I., Wilhelmi M., Coma R., Diaz A. (1985).
Rate responsive multiprogrammable pacemaker controlled by the QT interval. Experience in 31 cases.
In: Francisco Perez Gomez (ed.) Cardiac Pacing.
pages 826-832

MacCarter D., Santini A., Giocoles A. (1982).
Improved exercise tolerance and arrhythmia protection with a new dual chambered rate responsive system.
Circulation 66:218 (Abstract).

Manion C.V., Whitsett T.L., Wilson M.F. (1980).
Applicability of correcting the QT interval for heart rate.
Am Heart J 99:678

Martin R.H., Cobb L.A. (1966).
Observations on the effect of atrial systole in man.
J Lab Clin Med 68:224

Martins J.B., Zipes D.P. (1980).
Vagal stimulation prolongs duration of repolarization in the left ventricle but not the anterior right ventricle of the dog.
Circulation 62, Suppl.III:175

Mayeda I (1934)
On time relations between systolic duration of heart and pulse rate.
Acta Scholae Med Univ Imp, Kioto 17:53

Meakins J. (1919).
Prolongation of the "S-T" interval of ventricular complex as shown by the electrocardiogram.
Arch Int Med 24:489

Meech R.W. (1976).
Intracellular calcium and the control of membrane permeability.
In: Calcium in biological systems; Symposium of the Society for Experimental Biology.
Cambridge University Press.

Mendez C., Gruhitz C.G., Moe G.K. (1956).
Influence of cycle length upon the refractory periods of auricles, ventricles and A-V node in the dog.
Am J Physiol 184:287

Miki Y. (1922).
Experimentelle und klinische untersuchungen uber die dauer des K-Ekg (Kammer-Electrokardiogramms).
Ztschr F D Ges Exper Med 27:323

Milne J.R., Camm A.J., Ward D.E., (1980).
Effect of intravenous propranolol on QT interval. A new method of assessment.
Br Heart J 43:1

Milne J.R., Camm A.J., Ward D.E., Spurrell R.A.J. (1982).
The ventricular paced QT interval: The effects of rate and exercise at a single paced ventricular rate.
PACE 5:352

Moore J.I., Swain H.H. (1960).
Sensitization to ventricular fibrillation.
II. Sensitization by amarine and congeners of U-0882.
J Pharmacol Exp Ther 128:253

Moore E.N., Preston J.B., Moe G.K. (1965).
Durations of transmembrane action potentials and functional refractory periods of canine false tendon and ventricular myocardium.
Cir Res 17:259

Morad M., Rolett E. (1972).
Relaxing effects of catecholamines on mammalian heart.
J Physiol 224:537

Moss A.J., McDonald J. (1971).
Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT syndrome.
N Eng J Med 285:903

Mugica J., Lazarus B., Beffet J., Catte M. (1972).
Pacemaker with automatic regulation to pacing threshold.
In: Proceedings of the IVth International Symposium on Cardiac Pacing.
(abstract) page 150

Munteaunu J., Wirtzfeld K., Stangl E., Alt K. (1985).
Is hemodynamic benefits of VDD pacing due to A-V synchrony or to rate response.
In: Francisco Perez Gomez (ed.): Cardiac Pacing
pages 893-897

Muscholl E. (1982).
Peripheral muscarinic control of norepinephrine release in the cardiovascular system.
In Levy M.N. and Vassale (eds.) Excitation and neural control of the heart.
American Physiological Society. Maryland. page 233

Nadamnee K., Hendrickson J.A., Kannan R., Singh B.N. (1982).
Antiarrhythmic efficacy and electrophysiologic actions of amiodarone in patients with life threatening ventricular arrhythmias. Potent suppression of spontaneously occurring tachyarrhythmias versus inconsistent abolition of induced ventricular tachycardia.
Am Heart J 103:950

Nathan A.W., Hellestrand, Bexton R.S., Ward D.E., Spurrell R.A.J., Camm A.J. (1982).
Electrophysiological effects of sotalol - just another beta blocker?
Br Heart J 47:515

Neumann G., Bakels N., Niedeau C. (1985).
Intracardiac impedence as stroke volume sensor.
In: Francisco Perez Gomez (ed.): Cardiac Pacing.
page 803-809

Neuvonen P.J., Elonen E. (1982).
Sotalol, prolonged Q-Tc interval, and tachyarrhythmia.
Lancet i:106 (abstract)

Noble D., Tsien R.W. (1965).
Outward membrane current activated in the plateau range of potentials in cardiac Purkinje fibers.
J Physiol (London) 200:205

Olsson S.B., Brorson L., Vernauskas E. (1973).
Class 3 antiarrhythmic action in man. Observations from monophasic action potential recordings and amiodarone treatment.
Br Heart J 35:1255

Palatini P., Sperti G., Maraglino G., Mos L., Pessina A.C., Palu C.D. (1984).
Prolonged QT interval and prevalence of ventricular dysrhythmias in professional athletes.
Eur Heart J 5(abstract Suppl 1):650

Patterson (1915).
Proc Roy Soc B, LXXXVIII, 371

Pehrsson S.K. (1983).
Influence of heart rate and atrioventricular synchronization on maximal work tolerance in patients treated with artificial pacemaker.
Acta Med Scand 214:311

Pehrsson S.K., Astrom H. (1983).
Left ventricular function after long-term treatment with ventricular inhibited pacing compared to atrial triggered ventricular pacing.
Acta Med Scand 214:295

Perrins E.J., Morely C.A., Chan S.L. (1983).
Randomized controlled trial of physiological and ventricular pacing.
Br Heart J 50:112

Petrovich L., Adyan Maya A., Dillman R., Alexander J. (1978).
Pituitary tumour, QT prolongation and ventricular arrhythmia.
Cardiovascular Diseases. Bull Texas Heart Inst 5:32

Pick A. (1957).
Digitalis and the electrocardiogram.
Circulation 15:603

Prystowsky E.N., Jackman W.M., Rinkenberger R.C., Heger J.J., Zipes D.P. (1981).
Effect of autonomic blockade on ventricular refractoriness and atrioventricular nodal conduction in man.
Circ Res 49:511

Quadbeck J., Reiter M. (1975).
Cardiac action potential and inotropic effect of noradrenaline and calcium.
Naun Schmied Arch Pharmacol 286:377

Quadbeck J., Reiter M. (1975).
Adrenoreceptors in cardiac ventricular muscle and changes in duration of action potential caused by noradrenaline and isoprenaline.
Naun Schmied Arch Pharmacol 288:403

**Rahimtoola S.H., Ehsani A., Sinno, M.Z (1975).
Left atrial transport function in myocardial infarction: Importance of its booster function.
Am J Med 59:686

Raine A.E.G., Pickering T.G. (1977).
Cardiovascular and sympathetic response to exercise after long-term beta-adrenergic blockade.
B M J 2:90

Rainey J.M., Pohl R.B., Bololikar S.G. (1982).
The QT interval in drug-free depressed patient.
J Clin Psychiatry 43:39

Reddy C.P., Gettes L.S. (1979).
Use of isoproterenol as an aid to electrical induction of chronic recurrent ventricular tachycardia.
Am J Cardiol 44:705

Reiter M.J., Hindman M.C. (1982).
Haemodynamic effects of acute atrioventricular sequential pacing in patients with left ventricular dysfunction.
Amer J Cardiol 49:687

Reuter H. (1973).
Time- and voltage-dependent contractile responses in mammalian cardiac muscle.
Eur J Cardiol 1:177

Reuter H. (1974).
Localization of beta-adrenergic receptors, and effect of noradrenaline and cyclic nucleotides on action potentials ionic currents and tension in mammalian cardiac muscle.
J Physiol. London. 242:429

Reuter H., Scholz H. (1976).
The regulation of the Ca conductance of cardiac muscle by adrenaline.
J Physiol. London. 264:49

Reynolds E.W., Vander Ark C.R. (1976).
Quinidine syncope and the delayed repolarization syndromes.
Mod Concepts Cardiovasc Dis 45:117

Rickards A.F., Akhras F., Baron D.W. (1979).
Effects of heart rate on QT interval.
In: Meere C. (ed.): Proceedings of the VI World Symposium on Cardiac Pacing. Montreal: Laplante and Langevin. 2:7 (abstract)

Rickards A.F., Norman J. (1981).
Relations between the QT interval and heart rate.
New design of physiological adatptive pacemaker.
Br Heart J 45:56

Rickards A.F., Norman J., Thalen H., Renirie, Wittkamp F. (1981).
The use of stimulus-T interval to determine the cardiac pacing rate.
Second European Symposium on Cardiac Pacing.
PACE 4:A-68 (abstract)

Rickards A.F., Donaldson R.M. (1983).
Rate responsive pacing using the Tx pacemaker.
Proceedings of the VIIth World Symposium on Cardiac Pacing.
PACE 6:A-12 (abstract)

Rickards A.F., Donaldson R.M., Thalen H.J.T. (1983).
The use of QT interval to determine pacing rate: Early clinical experience.
PACE 6:346

Romano C., Gemme G., Pongiglione R. (1963).
Aritme cardiache rare dell´eta pediatrica. II. Accessi syncopale per fibillazione ventriculare parisisstica.
Clinica Pediatrica 45:656

Rosenbaum M.B., Chiale P.A., Ryba D., Elizari M.V. (1974).
Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride.
Am J Cardiol 34:215

Rosenbaum M.B., Chiale P.A., Halpern M.S., Nau G.J., Przybylski J., Levi R.J., Lazzari J.O., Elizari M.V. (1976).
Clinical efficacy of amiodarone as an antiarrhythmic agent.
Am J Cardiol 38:934

Rossi P., Plicchi G., Canducci G.C., Rognoni G., Aina F. (1984).
Respiration as a reliable physiological sensor for controlling cardiac pacing rate.
Br Heart J 51:7

Roy P.R., Emanuel R., Hassan El Tayib M. (1976).
Hereditary prolongation of the QT interval. Genetic observations and management in three families with twelve affected members.
Am J Cardiol 37:237

Ryden L., Snedgard P., Kruse I., Anderson K. (1984).
Rate responsive pacing by means of activity sensing.
Stimcoeur 12:1181

Ryden L., Kristensson B-E. (1985).
In: Zipes D.P. and Jalife J (eds.) Cardiac electrophysiology and arrhythmias. Grunne and Stratton. pages 513-522.

Samet P., Bernstein W.H., Nathan D.A., Lopez A. (1965).
Atrial contribution to cardiac output in complete heart block.
Am J Cardiol 16:1

Samet P., Castillo C., Bernstein (1966).
Hemodynamic sequelae of atrial, ventricular and sequential atrioventricular pacing in cardiac patients.
Am Heart J 72:725

Sareli P., Lang R.M., Libhaber C., Segni E. Di.
Klein H.O., Dean H., David D., Kaplinsky (1984).
Giant negative T waves and marked QT prolongation:
A beningn condition of acute myocardial ischamia
occuring mainly in females.
Eur Heart J 8(Abstr Suppl 1):1575

Sarnoff S.J., Mitchell (1962).
The control of the function of the heart.
In: Handbook of Physiology. Circulation.
Hamilton W.F. (Ed.). Washington D.C.
An Physiol Soc 1:489

Schlomka G., Raab W. (1936).
Zur Bewertung der relativen Systolendauer; uber die
Abhangigkeit der relativen Systolendauer des Gesunder
vomlebensalter.
Ztschr Kreislaufforsch 28:673

Schlamowitz M.C. (1946).
An analysis of the time-relationships within the cardiac
cycle in the electrocardiogram of normal men. I.The
duration of the QT interval and its relationship to the
cycle length.
Am Heart J 31:329

Schmid P.G., Grief B.J., Lund D.D., Roskowski R. Jr. (1978).
Regional choline acetyl tranferase activity in the guinea pig heart.
Circ Res 42:657

Schwartz P.J., Periti M., Malliani A. (1975).
The long QT syndrome.
Am Heart J 89:3

Schwartz P.J., Wolf S. (1978).
Q-T prolongation as predictor of sudden death in patients with myocardial infarction.
Circulation 57:1074

Seides S.F., Josephson M.E., Batsford W.P., Weisfogel G.M., Lau S.H., Damato A.N. (1974).
The electrophsiology of propranolol in man.
Am Heart J 88:733

Sharma G.V.R., Kumar R., Molokhia F. (1920).
Oxygen cost of atrial and ventricular pacing in the intact dog.
Circulation 41 (Suppl III):285 (abstract)

Shipley R.A., Halloran (1936).
Four-lead electrocardiogram in 200 normal men and women.
Am Heart J 11:325

Siegel R., Cabeen W. Jr., Roberts W. (1981).
Prolonged QT interval ventricular tachycardia syndrome from massive rapid weight loss utilizing the liquid-protein - fast diet. Sudden death from sinus node ganglionitis.
Am Heart J 102:121

Simonson E., Cady L.D., Jr., Woodbury M. (1962).
The normal QT interval.
Am Heart J 63:747

Singh B.N., Vaughan Williams E.M. (1970).
The effect of amiodarone, a new antianginal drug on cardiac muscle.
Br J Pharmacol 39:657

Snell R.E., Luchsinger P.C., Shugol G.G. (1966).
The relationship between the timing of atrial systole on the useful work of the left ventricle in man.
Am Heart J 72:63

Sowton E., Crick J., Wainwright R.J. (1981).
The crown of thorns: A single pass electrode for physiologica; pacing.
In Feruglio G.A. (ed.) Cardiac Pacing. Proceedings of the 2nd European Symposium on Cardiac Pacing.
pages 1089-1092

Spear J.F., Moore E.N., Horowitz L.N. (1973).
Effect of current impulses delivered during the ventricular vulnerable period upon the ventricular fibrillation threshold.
Am J Cardiol 32:814

Staniforth D.H. (1983).
The QT interval and cycle length: The influence of atropine, hyoscine and exercise.
Br J Clin Pharmacol 16:615

Stein E., Damato A.N., Kosowsky B.D. (1966).
The relation of heart rate to cardiovascular dynamics: Pacing by atrial electrodes.
Circulation, 33:925

Stern S., Eisenburg S. (1969).
The effect of propranolol (Inderal) on the electrocardiogram of normal subjects.
Am Heart J 77:192

Strauss H.C., Bigger J.T., Jr., Hoffman B.F. (197)).
Electrophysiological and beta receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue.
Circ Res 26:661

Surawicz B., Mangiardi M.L. (1977).
Electrocardiogram in endocrine and metabolic disorders.
In: Rios J.C. (ed.) Clinical electrocardiographic correlations. Philedelphia. Davies F.A. page 243.

Sutton R., Citron P. (1979).
Electrophysiological and hemodynamic basis for sick sinus syndrome and atrioventricular block.
Br Heart J 41:600

Swartz M.B., Teicholtz L.E., Donoso E. (1977).
Mitral valve prolapse. A review of associated arrhythmias.
Am J Med 62:377

Tada M., Kirchberger M.A., Katz A.M. (1975).
Phosphorylation of a 22,000 dalton component in the cardiac sarcoplasmic reticulum by adenosine 3´-5´ monophosphate dependent protein kinase.
J Biol Chem 250:2640

Taylor G.J., Crampton R.S., Gibson R.S., (1981).
Prolonged QT interval at onset of acute myocardial infarction in predicting early phase ventricular tachycardia.
Am Heart J 102:16

Thalen H.J., Rickards A.F., Wittkampf F.H.M., Norman J., Nagelkerke D. (1981).
Evoked response sensing (ERS) as automatic control of the pacemaker output.
In: Proceedings of the Second European Symposium on Cardiac Pacing. PACE 4:A-68 (Abstract).

Ursula Gebhardt-Seehausen, (1985).
The rate responsive TX pacemaker.
Vitatext page 1-11.

Vaughan Williams E.M., Raine A.E.G., Cabrera A.A., Whyte J.M. (1975).
The effects of prolonged beta-adrenoreceptor blockade on heart weight and cardiac intracellular potentials in rabbit.
Cardiovasc Res 9:579

Vaughan Williams E.M. (1977).
Adaptations of the heart and sympathetic systems to prolonged adrenoreceptor blockade.
Proc R Soc Med, Suppl II:49

Vaughan Williams E.M., Hassan M.O., Floras J.S., Sleight P., Jones J.V. (1980).
Adaptation of hypertensives to treatment with cardioselective and non-selective beta-blockers. Absence of correlation between bradycardia and blood pressure control and reduction in slope of QT/RR relation.
Br Heart J 44:473

Vaughan Williams E.M. (1980)a.
Adaptations of heart rate and Q-T interval to prolonged beta-blockade in man. In The Clinical Impact of Beta-Adrenoreceptor Blockade. I:13-20. Proceedings of an international symposium. Berlin. Burley D.M.and Birdwood G.F.B. (Eds.). Published by CIBA Laboratories, Horsham, England. Page 13.

Vaughan Williams E.M. (1980)b.
Anti-arrhythmic action and the puzzle of Perhexilene.
London. Academic press. page 26

Vaughan Williams E.M. (1981).
Adaptation to prolonged interruption of sympathetic drive and protection against sudden death.
In: Catecholamines in the non-ischaemic and ischaemic myocardium. Proceedings of the Sixth Argenteuil Symposium held under the auspices of the Fondation Cardiologique. Princesse Liliane. Waterloo, Belgium. page 167.

Vaughan Williams E.M. (1982).
QT and action potential duration.
Br Heart J 47:513.

Vitatrin Medical. News. October 1984.
Vitatron U.K. Ltd. page 1

Waller. (1891).
Introduction to human physiology. page 53.

Ward O.C. (1964).
A new familial cardiac syndrome in children.
J Irish Med Assoc 54:103

Watanabe A.M., Besch H.R.,Jr. (1974).
Cyclic adenosine monophosphate modulation of slow calcium influx channels in guinea pig hearts.
Cir Res 35:316

Watanabe A.M., Hathaway D.R., Besch H.R.,Jr. (1978).
Mechanism of cholinergic antagonism of the effect of isoproternol on hearts from hypertrophied rats.
In: Recent advances in studies on cardiac structure and metabolism. Balinoni M.D. (ed.). University Pach Press. pages 423-499

Watanabe A.M., McConnaughey M.M., Strawbridge R.A., Fleming J.W. Jones L.R., Besch H.R J. (1978).
Muscarinic cholinergic receptor modulation of beta adrenergic receptor affinity for catecholamines.
J Biol Chem 253:4833

Waxman M.B., Wald R. (1977).
Termination of ventricular tachycardia by an increase in cardiac vagal drive.
Circulation 56:385

Weber J.W., Wyler F., Sidiropoulos D., (1972).
Arrhythmias due to psychoactive drugs.
Proc Assoc Eur Ped Cardiol 8:56

Weidmann S. (1956).
Shortening of the cardiac action potential due to a brief injection of KCl following onset of activity.
J Physiol 132:157

Weitz (1918).
Deutsch Archiv F Klin Med 77:325

Wellens H.J.J., Lie K.I., Bae F.W., Wesdorp J.C., Dohmen H.J., Duren D.R., Durrer D. (1976).
Effect of amiodarone in the Wolff-Parkinson-White Syndrome.
Am J Cardiol 38:189

Wheeler P.J., Puritz R., Ingram D.N., Chamberlain D.N. (1979).
Amiodarone in the treatment of refractory supraventricular and ventricular arrhytmias.
Postgrad Med J 55:1

Wiggers. (1917).
Archives of Internal Medicine 20:93

Wilson F.N., Johnson F.D., Hill I.G.W. (1935).
The form of the electrocardiogram in experimental myocardial infarction.
Am Heart J 12:523

Wirtzfeld A., Goedel-Meinen L., Block T. (1982).
Central venous oxygen saturation for the control of automatic rate responsive pacing.
PACE 5:829

Wirtzfeld A. (1983).
Mixed venous oxygen saturation for rate control of an implantable pacing system.
In: Proceedings of the VIIth World Symposium on Cardiac Pacing. pages 271-279

Wirtzfeld A., Heinze R., Stanzl K., Hoekstein K., Aet E., Liess H.D. (1984).
Regulation of pacing rate by variation of mixed venous oxygen saturation.
PACE 7:1257

Wit A.L., Fenoglio J.J., Hordof A.J., Reemtsma K. (1979).
Ultrastructure and transmembrane potentials of cardiac muscle in the human anterior mitral valve leaflet.
Circulation 59:1284

Yanowitz F., Preston J.B., Abildskov J.A. (1966).
Functional distribution of right and left stellate innervation to the ventricles: production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone.
Circ Res 18:416

Yee R., Benditt G., Kostuk W.J. (1984).
Comparative functional effects of chronic ventricular demand and atrial synchronous ventricular inhibited pacing. PACE 7:23

Zipes D.P., Festoff B., Schall S.F. (1968).
Treatment of ventricular arrythmias by permanent atrial pacemaker and cardiac sympathectomy.
Ann Int Med 68:591

Zipes D.P., Martins J.B., Ruffy R., Prystowsky E.N., Elharrar V., Gilmour R.F.,Jr. (1981).
Roles of autonomic innervation in the genesis of ventricular arrhythmias.
In: Disturbances in neurogenic control of the circulation American Physiological Society. Bethesda, Maryland.
Abboud F.M., Fozzard H.A., Gilmore J.P., Reis D.J. (Eds.)
The Williams and Wilkin Company, Baltimore, Maryland.
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