INDIRECT ASSESSMENT OF SINUS NODE FUNCTION IN MAN

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SUMMARY

Current tests of sinus node function in man lack sufficient sensitivity and specificity to be of use in patients with equivocal sinus node function. This study was performed with the aim of closely re-examining, in man, these tests of sinus node function, looking particularly at the phenomenon of overdrive suppression of the sinus node and at the post-pacing sequence, in order to improve objective assessment using intracardiac electrophysiology study. The study group consisted of 22 subjects with normal sinus node function, 35 subjects with the sick sinus syndrome, and 123 subjects who failed to meet strict pre-study criteria for either of the former subgroups. The major initial finding was that the majority of sequences following overdrive atrial pacing in each of the three groups of patients followed a typical pattern of a maximally prolonged first post-pacing interval, and progressive but decreasing reduction in subsequent intervals.
The first post-pacing interval, unlike the other post-pacing intervals, contained a component of sinoatrial conduction. Such sequences were observed i) at all rates of pacing tested (60 to 200 beats per minute), ii) with pacing from the high right atrium and from the coronary sinus, iii) both before and after cardiac vagal blockade with atropine and "total" cardiac autonomic blockade with atropine and propranolol, and iv) with pacing duration from one beat to one minute. Particularly in patients with sinus node dysfunction, secondary cycle length prolongations were observed. The extent of suppression of the sinus node as measured by the first post-pacing interval, increased with increase in the rate of pacing only in patients with sinus node dysfunction.

The typical post-pacing sequences were suitable for fitting to a mathematical model of overdrive suppression of the sinus node, which had been developed at the time of the initial part of this study by Dr. A. Helfgott.
Application of this model allowed computation of indices of both sinoatrial conduction and of sinus node automaticity, the mean values of many such indices being significantly greater in patients with sinus node dysfunction. In subjects with normal sinus node function, computed indices of both sinoatrial conduction and of automaticity showed little or no change with different pacing rate, site, or duration of pacing. In contrast, in subjects with the sick sinus syndrome, with higher pacing rates and with longer duration of pacing, computed indices of sinoatrial conduction and of automaticity increased. Application of these new indices for the first time clearly separated sinoatrial conduction from sinoatrial automaticity, and has the potential for better discrimination of normal and abnormal sinus node function by intracardiac electrophysiology study.
DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

[Signature]

William F. Heddle
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The work to be presented was performed by me while a member of a research group, consisting principally of Dr. A. M. Tonkin, Dr. A. Helfgott, and myself. The major contributions of the other members of this group must be fully acknowledged, in particular the original contribution of Dr. Helfgott in development of the mathematical model to be described.
In addition I wish to acknowledge the assistance of Lyn Bartlett, R.N., both in the catheterisation laboratory and with preparation of figures. Last, but in no way least, I wish to acknowledge the unfailing support and encouragement of my wife.
Chapter I

INTRODUCTION

A) HISTORY

The development of our current understanding of the electrical events in the mammalian heart has occurred predominantly in the last 140 years, with four clear stages.

First, the ability to record electrical activity of the heart in animals was developed in the 1840's with the observations of Mateucci (1842) and Kölliker and Müller (1855). The experiments of William Gaskell (1883) on influences on the electrical activity of the heart of the tortoise will be commented upon later, but were the first studies of the behaviour of the primary and subsidiary pacemakers of the heart. Many other workers also studied the electrical behaviour of the heart in experimental animals (Marey, 1881; Engelmann, 1878, 1892, 1896; Cushny and Matthews, 1897). Study of cardiac electrical activity in man was not undertaken until this century. However, many remarkable observations on heart rhythm were made in the absence of recordings of such activity. For example, Mackenzie (1902) published the first description of sinoatrial exit block, and Wenckebach (1904) his observations on atrioventricular block on the basis of pulse wave recordings.
Second, Waller (1887) first recorded cardiac electrical activity in man. However, the major advance was the application by Einthoven (1903, 1909) of the string galvanometer to the recording of the surface electrocardiogram in man. Following this, there was rapid development and understanding of the clinical usefulness of the electrocardiogram (Lewis, 1920), with, later, some brilliant deductions being made about the nature of arrhythmias on the basis of surface electrocardiographic (ECG) recordings.

It is interesting to note that from animal experimentation, Wenckebach (1903) had studied the responses of the sinus node to induced atrial extrastimuli (discussed further in Chapter VI), before the classic description of the anatomy of the sinus node in vertebrate hearts by Keith and Flack in 1907. In this paper, the authors stated: "It therefore appears to us that the sino-auricular "block" cannot be due to an anatomical lesion of a narrow bridge of fibres, but must arise from the depression, probably of vagal origin, of the muscular tissue in this region". In retrospect, these observations appear very far sighted.

The third important development was the application of micro-electrode techniques to study the membrane potentials of individual cardiac cells (Draper and Weidmann, 1951; West, 1955). These techniques have now provided an experimental understanding of many of the electrical mechanisms of both arrhythmias and pacemaker activity (Hoffman and Cranefield, 1960; Brooks and Lu, 1972; Cranefield, 1975; Bonke, 1968, 1978; Noble, 1979).
Finally, the techniques for intracardiac electrical studies in man have led to further understanding of the electrical events in the heart. Three important landmarks made this possible. First, Alanis et al. (1958) recorded the electrical activity of the His bundle in the dog. Second, Puech and coworkers used transvenous electrode catheters to record the electrical activity of the His bundle in man (Giraud et al., 1960). Third, Damato's group, working initially with dogs, and then with man (Scherlag et al., 1968, 1969), developed a simple and reproducible method of recording His bundle electrical activity. To the present time, the major clinical contributions of these techniques have been in the diagnosis and management of tachyarrhythmias (Wellens, 1971; Krikler and Goodwin, 1975; Josephson and Seides, 1979), and in determining the need for permanent cardiac pacing by localisation of the level of atrioventricular block to above or below the bundle of His (Puech, 1975).
In contrast, despite initial optimism, the contribution of intracardiac recording and pacing techniques to investigation of bradyarrhythmias associated with sinus node dysfunction, has not been as useful.

B) BACKGROUND

The historical evaluation of patients who present with dizzy spells (presyncope) and/or syncope is frequently difficult. The differential diagnosis includes transient cerebral ischaemia, epileptiform seizures, and hypotension, which may in turn relate to postural change, drug effects (particularly of antianginal, hypotensive, and antidepressant agents), and reduced cardiac output due to mechanical and electrical problems. Such abnormalities may frequently coexist. For example, the combination of a relative sinus bradycardia, inadequate postural reflex change, and impaired cerebral artery autoregulation together would be much more likely to lead to symptoms than one of the above alone.
The most readily correctable of the above are adverse drug effects and cardiac bradyarrhythmias, hence the accurate diagnosis and correction of these problems are clinically important. The cardiac arrhythmias which may be responsible for a reduced cardiac output and hence symptoms include:

1) Complete or intermittent high degree atrioventricular block

2) Tachyarrhythmias, both ventricular and supraventricular, causing symptoms through rate effects, and/or loss of atrioventricular sequence, particularly in patients with associated myocardial disease.

3) Sick sinus syndrome (Ferrer, 1968; Rubenstein et al., 1972; Moss and Davis 1974; Kerr et al., 1981) where both brady- and tachy-arrhythmias may be responsible for the symptoms.
C) SICK SINUS SYNDROME

a) Clinical Features

The majority of patients with the syndrome are elderly, although it is occasionally observed in the young, with familial forms having been described (Caralis and Varghese, 1976).

The major symptoms of the sick sinus syndrome are syncope, presyncope, and palpitations. Other symptoms are lethargy, dyspnoea, and angina, and those associated with systemic embolism (Ferrer, 1968; Rubenstein et al., 1972; Moss and Davis, 1974; Grant et al., 1979a). The electrocardiographic abnormalities are, marked and/or inappropriate sinus bradycardia, sinoatrial block, sinus arrest, atrial tachyarrhythmias, particularly atrial flutter and fibrillation, and atrioventricular conduction disturbances (Ferrer, 1968; Rosen et al., 1971). The electrocardiographic differentiation between sinus arrest and sinoatrial exit block is made using the length of the pause. If the interval is a multiple of the resting cycle length, it is considered to be sinoatrial exit block. If it is neither the above, nor follows a typical sequence of sinoatrial Wenckebach, it is considered to be "sinus arrest". Care must be taken to differentiate both sinoatrial exit block and sinus arrest from pauses related to non-conducted premature
atrial beats. Prolonged asystole may also be seen in the sick sinus syndrome after cardioversion for atrial fibrillation. The bradyarrhythmias probably result from either impaired impulse formation (automaticity) or impaired sinoatrial conduction (Strauss et al., 1976).
One variant of the syndrome is the "brady-tachy syndrome" (Short, 1954; Moss and Davis, 1974), with alternation between brady- and tachy-arrhythmias. The bradyarrhythmias are on the basis of sinus node dysfunction, and the tachyarrhythmias (usually atrial flutter or fibrillation) on the basis of associated atrial disease. The symptoms in these patients may develop during either or both the bradycardias and the tachycardias, leading to problems with management. However, the major cause of syncope in this group has been found to be prolonged asystole following abrupt cessation of a paroxysm of supraventricular tachycardia (Moss and Davis, 1974).

For an abnormally functioning sinus node to cause symptoms (the sick sinus syndrome), not only the sinus node, but also the subsidiary pacemakers usually either fail or have a markedly reduced rate when the primary pacemaker, the sinus node, fails. Another point which must be emphasised is that the electrocardiographic abnormalities may be paroxysmal and infrequent, making clinical diagnosis difficult.
The coexistence of slow sinus node and fast atrial rhythms may not become overt until the use of a drug to control or prevent the atrial tachyarrhythmias, such as digitalis, beta-blockers or verapamil, which suppresses not only the atrioventricular node, but also the sinus node (Margolis et al., 1975; Breithardt et al., 1978). In such patients, the tachyarrhythmia may cause symptoms prior to the drug, and the bradyarrhythmias after. Other drugs, such as disopyramide and lithium have also been shown to precipitate the syndrome (Wellens et al., 1975; Strauss et al., 1978a).
b) Pathology
To the present time, the pathology associated with the syndrome has been found to be multifactorial, with many disease processes that affect the atrium producing sinus node dysfunction (Hudson, 1960; James, 1977; Théry et al., 1977). Despite the frequent association of sinus bradycardias with acute myocardial infarction (James, 1968), the development of persistent abnormalities of sinus node function of sufficient severity to require permanent pacing is very uncommon in this situation (Hatle et al., 1976). This may relate to the rich blood supply to the sinus node, with anastomoses usually present between the sinus node artery and other arteries with origins from the parent or the opposite coronary artery (Kennel and Titus, 1972). In addition, extracoronary arterial anastomoses are often present.

The histological findings in the sick sinus syndrome have usually been a non-specific decrease in the number of pacemaker cells and increased fibrosis of the sinus node, with associated muscle damage, in the right atrium (Hudson, 1960; James, 1977; Théry et al., 1977).
c) Non-Invasive Assessment

It is preferable to be able to make the diagnosis of the sick sinus syndrome with investigations which do not require cardiac catheterisation or drug administration. In addition to the standard twelve lead electrocardiogram, which may show the characteristic features mentioned but which frequently is normal, prolonged ambulatory (Holter) monitoring is the most useful procedure. However, Brodsky et al., (1977) demonstrated marked bradyarrhythmias during Holter monitoring in fifty male volunteer students without heart disease. They found a mean minimum heart rate of 53 +/- 6 beats per minute (mean +/- one standard deviation) and 43 +/- 5 beats per minute during waking and sleeping hours respectively. In addition, they observed maximal pauses of 1.36 +/- 0.16 seconds (mean +/- one standard deviation) and 1.62 +/- 0.20 seconds during waking and sleeping hours respectively, fourteen subjects having sinus pauses of more than 1.75 seconds. The same group has recently reported similar findings in young females without heart disease (Sobotka et al., 1981).

Despite this, prolonged monitoring allows correlation of symptoms and electrocardiographic abnormalities, and when this occurs, produces clear indications as to further management (Hinkle et al., 1969; Crook et al., 1973; Reiffel et al., 1977).
Other non-invasive tests have been proposed, including the heart rate response to exercise (Holden et al., 1976; Abbott et al., 1977), and to the Valsalva manoeuvre (Mandel et al., 1972; Dighton et al., 1974, 1975). However, these tests have not gained wide clinical acceptance.

d) Invasive Assessment

In a large number of patients presenting with symptoms suggestive of the sick sinus syndrome, non-invasive investigation fails to provide a clear diagnosis. In these patients, the response of the sinus node to atrial pacing is used to assess sinus node function. Following 30 seconds or more of overdrive atrial pacing, the "sinus node recovery time" as measured by the interval from the last paced atrial beat until the first spontaneous sinus beat, has been proposed to ostensibly assess sinus node automaticity (Mandel et al., 1971; Narula et al., 1972). In addition, the responses to induced premature atrial stimuli (Strauss et al., 1973) or short periods (eight beats) of fixed rate atrial pacing (Narula et al., 1978) have been proposed to assess sinoatrial conduction.
The initial highly enthusiastic reports (Mandel et al., 1971; Narula et al., 1972) on the value of such methods in detection of sinus node dysfunction were followed by clear demonstration that the conventional testing and measures often failed to detect patients who subsequently had proven sick sinus syndrome responsive to permanent pacing (Gupta et al., 1974; Scheinman et al., 1976).

Recently, the Columbia University group, on the basis of observations made initially in animal experiments (Cramer et al., 1977, 1978) has described an electrode catheter technique to directly measure sinoatrial conduction time in man (Reiffel et al., 1980).

In addition to responses of the sinus node to atrial pacing, abnormal heart rate responses to intravenous administration of atropine (Rosen et al., 1971; Mandel et al., 1972; Ferrer, 1973), isoprenaline (Rubinstein et al., 1972; Mandel et al., 1973), and atropine and propranolol together (Frick et al., 1976; Jordan et al., 1978; Desai et al., 1981) have been used to assess sinus node function. When atropine (in doses of 1 to 2 mg or 0.04 mg/kg body weight) is administered, the heart rate is normally expected to increase to above 90 beats per minute. The normal response to isoprenaline has not yet been defined, due to marked variation in dose/response curves between individuals.
The heart rate after blocking doses of atropine and propranolol (0.04 mg/kg and 0.20 mg/kg body weight respectively), the "intrinsic heart rate" (Jose and Collison, 1970), can be predicted on the basis of age, and intrinsic heart rates falling more than two standard deviations below the predicted rate are suggestive for the sick sinus syndrome. These tests are now usually performed in conjunction with the atrial pacing studies discussed above.
e) **Treatment**

Treatment consists of withdrawal of any offending drugs, use of appropriate drugs to control atrial tachyarrhythmias, and for severe symptoms associated with bradyarrhythmias, the implantation of permanent demand pacemakers (Conde et al., 1973; Chokshi et al., 1973; Härtel and Talvensaari, 1975). This condition is now one of the most common indications for permanent pacemaker implantation (Kaplan, 1978), although there is no evidence to the present time that this influences the prognosis (Gann et al., 1979; Shaw et al., 1980).
D) OBJECTIVES

The aim of the studies to be described in this thesis was to examine both non-invasive and invasive techniques for testing of sinus node function in man, searching for more specific and sensitive markers of sinus node dysfunction. The study was based on 250 consecutive intracardiac electrophysiology studies in which I personally participated, performed at Flinders Medical Centre in the period January 1979 until March 1981 inclusive.
CHAPTER II

METHODS

A) PATIENT SELECTION

Patients were classified before electrophysiology study into three groups on the basis of history, clinical examination, standard twelve lead electrocardiogram, prolonged electrocardiographic monitoring, either in hospital in a continuously monitored bed, or by 24 hour ambulatory (Holter) monitoring:

i) Normal
   
a) No history of syncope or presyncope.
   
b) No history or electrocardiographic evidence of coronary artery disease.
   
c) No ECG evidence of sinus bradycardia (less than 60 beats per minute), sinus arrest, sinoatrial exit block, atrial flutter or fibrillation (an exception was made if the latter was associated with an accessory atrioventricular connection or AV nodal bypass).
ii) **Sick Sinus Syndrome**

   a) History of syncope or presyncope

   b) ECG evidence of sinus bradycardia (marked and inappropriate), and/or sinus arrest, and/or sinoatrial exit block.

   c) Symptoms of palpitations and ECG evidence of atrial flutter or fibrillation may have been present but were considered insufficient alone to allow the diagnosis and also not necessary for the diagnosis.
iii) Intermediate
   a) All criteria for i) "Normal" or ii) "Sick Sinus Syndrome" not fully satisfied.

Of the 180 patients having sinus node function assessed at electrophysiology study, 22 satisfied the criteria for a), 35 for b), and the remaining 123 were classified as c).

B) NON-INVASIVE INVESTIGATION

i) Electrocardiographic Monitoring

All patients had, in addition to multiple 12 lead resting electrocardiograms, either prolonged ambulatory monitoring or continuous monitoring within hospital, performed prior to electrophysiology study.

The heart rate responses to exercise were only assessed where exercise associated or precipitated symptoms were present.
ii) **Valsalva Manoeuvre**

At the time of intracardiac electrophysiology study, Valsalva manoeuvres were performed. The patient was supine with slight neck flexion. A large calibrated bottle containing coloured fluid, with zero on scale adjusted for the height of the patient, was used to quantify the oropharyngeal pressure developed by the patient during the Valsalva manoeuvre (Figure II-1). The bottle was positioned so that the scale was clearly visible to the patient. A small air leak was deliberately placed in the air containing plastic tube between the patient and the bottle to prevent undetected closure of the glottis.

After a rest period of at least a minute during which recordings of cycle length were made, the patient, having previously had trial efforts to become familiar with the procedure, performed sequential, multiple, and graded Valsalva manoeuvres. The patient supported for a minimum of two trials each pressure of 10 cm, 20 cm, and 30 cm of H2O for a minimum of 20 and (usually) a maximum of 30 seconds. Continuous recordings of cycle length were made before, during, and for at least 30 seconds after completion of the strain phase. Details of the data analysis will be presented in Chapter VII.
Figure II-1

photograph of "Valsalva" bottle, showing scale, and three-way tap for creation of leak on patient side (see text for further explanation).
iii) Carotid Sinus Massage

This manoeuvre was performed in selected patients, when on clinical grounds, a possible diagnosis of carotid sinus hypersensitivity was considered.

After determination of resting cycle length, verification of the presence of bilateral carotid pulses, and the absence of any carotid artery bruits, repeated right, and then left carotid sinus massage was performed for periods of 5 seconds. Continuous recording of cycle length, and intermittent recording of systolic and diastolic blood pressure was made before, during, and after carotid sinus massage. Trials were repeated at least twice on each side, to attempt to compensate in part for the phasic nature of the response to carotid sinus massage (Eckberg, 1976). The criteria for an abnormal response will be discussed in Chapter VII.

C) INTRACARDIAC ELECTROPHYSIOLOGY STUDY

Following the obtaining of informed consent, intracardiac electrophysiology study was performed in the fasting, non-sedated state, according to a protocol approved by the Clinical Research Ethics Committee of Flinders Medical Centre.
The studies were all performed in a catheter laboratory (equipped to Class A electrical standard), exclusively used for electrophysiology study. Attention was directed toward maintaining an environment which minimised patient anxiety during the study.

1) Catheter Placement

Using aseptic technique and local anaesthesia, 6F tripolar and quadripolar electrode catheters (USCI Inc) were inserted percutaneously via the right and/or left femoral veins, and advanced under fluoroscopic control to the tricuspid ring and high right atrium respectively. Usually a 6F bipolar electrode catheter was inserted via the left femoral vein and advanced to the right ventricular apex. In the study of suspected reentrant atrioventricular tachyarrhythmias, a 6F quadripolar electrode catheter was inserted via a left median antecubital venotomy and positioned in the coronary sinus for recording and stimulation of left atrial electrical activity, the catheter being advanced to within 1 cm of the left heart border in the anteroposterior projection.
ii) Drugs

All cardioactive drugs were routinely ceased at least five elimination half-lives prior to the study. Those few patients in whom antiarrhythmic drugs had to be continued for refractory malignant tachyarrhythmias were excluded from this study.

In 4% of patients, usually adolescents or young adults, either oral or intravenous diazepam was given in small doses before or at the start of the procedure. Heparin 5000 units intravenously was routinely given on completion of catheter placement, except when specifically contraindicated or when the patient was fully anticoagulated.

Administration of atropine and propranolol to achieve cardiac autonomic blockade will be fully discussed in Chapter VII.
iii) Recording

Intracardiac electrograms were obtained by filtering out frequencies below 50 Hz and above 500 Hz. Recordings of both surface ECG and catheter electrograms were made on a 6-channel direct writing recorder (Elema Mingograph Model 62), at paper speed of 100 mm/sec, using one of two programmes. The first recorded ECG leads I, II, V1, and high right atrial, proximal and distal His bundle catheter electrograms, and the second, ECG leads I, V1, and high right atrial, distal His bundle, and both proximal and distal coronary sinus catheter electrograms.

The His bundle electrogram was recorded by the tripolar electrode catheter positioned across the tricuspid ring using standard technique (Scherlag et al., 1969).

iv) Stimulation

Stimulation of adjacent electrode pairs was achieved by use of a Devices Neurolog isolated stimulator, using a rectangular pulse at approximately twice diastolic threshold and 2 msec in duration. The stimulator allowed both fixed rate cardiac pacing at variable rates, and introduction of atrial premature beats during sinus rhythm or following pacing.
For high right atrial stimulation, the distal pair of the quadripolar electrode catheter sited in the high right atrium was used. If right hemi-diaphragmatic stimulation or failure to capture occurred, the catheter was repositioned until the problem was overcome. Because of this problem of hemi-diaphragmatic stimulation with higher currents from the high right atrial pacing site, the effect of change of stimulus current on sinus node function was not studied.

For left atrial stimulation the distal pair of the quadripolar electrode catheter sited in the distal coronary sinus was selected.

v) Protocol

The electrophysiology study was performed to a standard protocol (Appendix A). The assessment of specialised cardiac conducting tissue other than the sinus node will only be discussed where relevant to this thesis.
A rest period of ten minutes was allowed following catheter insertion. Provocative testing then commenced with overdrive right atrial pacing (and in some patients coronary sinus pacing), using routinely pacing for one minute intervals, and recording for two minutes before the next pacing trial was commenced. Multiple (five) trials were performed at each pacing rate tested (see Chapters III and V). When continuous 1:1 atrial capture was not achieved, or when the first post-pacing beat was an atrial or ventricular ectopic beat, the pacing trial was considered invalid, and repeated after waiting two minutes. Then sinoatrial conduction time was assessed using the methods described by Strauss (1973) and Narula (1978). These methods will be discussed in detail in Chapter VI.

Programmed introduction of single and paired atrial and ventricular premature beats scanning diastole following eight fixed rate paced beats, and incremental atrial and ventricular pacing were used to assess atrioventricular node and His-Purkinje function and to screen for reentrant arrhythmias (Damato et al., 1969; Wit et al., 1970; Wellens, 1971).
After autonomic reflex interventions (Valsalva, carotid sinus massage), atropine and subsequently propranolol were administered and the above pacing procedures repeated.

D) ANALYSIS OF DATA

Recorded intervals were measured and plotted using a Hewlett Packard Model 9874A digitiser, coupled to a Model 9825A calculator and a Model 9872A plotter. Basic analysis involved digitising the intervals between consecutive initial rapid components of the high right atrial electrogram signals (Figure II-2).

The mathematical analyses which will be described in this thesis required high precision in the measured data. Accordingly consideration of the errors and limitations of the measuring techniques used is important.

E) ERRORS IN MEASUREMENT OF DATA

The errors involved in data analysis can be classified into illegitimate (operator mistakes, which can be completely corrected by performing the operation again correctly), and legitimate (those which are due to physical limitations of the recording and measuring equipment) (Bevington, 1969).
Figure II-2

Recordings of electrocardiographic lead V1 and high right atrial electrogram ("HRA") during both the last two of a series of atrial paced beats, and the subsequent sinus cycles. On visual inspection, the last paced and the first spontaneous atrial electrograms are seen to have different morphologies, preventing identification of equivalent points on these two electrograms. This creates an error in measurement of this interval, even when measured by the digitising cursor (shown placed on the first spontaneous atrial electrogram). The point recorded by the digitiser is that at the centre of the circle (placement guided by use of two perpendicular lines on the cursor, one of which is placed here on the isoelectric line).
Legitimate errors can be considered either random or systematic. Random errors are determined by the precision of the recording and digitising process and cannot be reduced except by improvements in the measuring equipment. Examples of random errors in this study included:

i) Chart speed variability of +/- 1%: this error was greater for the first five seconds of paper transport, hence the recorder needed to be running at the chosen recording speed for at least five seconds before the cessation of overdrive pacing.

ii) Intra-observer variability: a randomly chosen sequence was personally digitised ten times on each of two occasions. The mean standard deviation of the measurement of a given interval was found to be +/- 1 msec.

iii) Inter-observer variability: the same sequence was then digitised (blind) by three different trained observers. The error between observers was found to be +/- 2 msec.

Systematic errors include those which reproducibly result from faulty calibration of equipment or observer bias. An estimate of such errors can be made from analysis of the experimental conditions and techniques.
The systematic errors encountered in this study were:

i) Failure to reposition the digitising cursor after each interval. If this was not done, the error in the given beat changed sign in the subsequent beat.

ii) Inability to define identical points on the last paced and the first post-pacing electrogram (Figure II-2) due to their different morphology, giving an error of +/- 5 msec in this interval.

F) STATISTICAL METHODS

Comparison of paired variables was performed using the paired t-test. For two comparable groups of unpaired data, both with normal distribution, an unpaired t-test was used. Chi-squared test was used to compare the incidence of phenomena in different groups. For more than two groups of data, comparisons were performed using analysis of variance. For all these tests, a p level < .05 was considered significant.

Goodness of fit of data to the mathematical model was assessed by use of the multiple correlation coefficient $R^2$. 
CHAPTER III

THE SINUS NODE AND OVERDRIVE SUPPRESSION

A) INTRODUCTION

Gaskell (1883), was the first to observe the phenomenon of overdrive suppression, which is a property shared by all cardiac cells exhibiting spontaneous automaticity. The same phenomenon was observed following single atrial premature beats by Engelmann (1896) and by Cushny and Matthews (1897). It can be defined as the temporary suppression that follows cessation of artificial stimulation of the cell at a rate faster than its own. Detailed experiments have been undertaken to elucidate the mechanism (Amory and West, 1962; Lange 1965; Lu et al., 1965; Vassalle, 1970; Browning et al., 1979; Kodama et al., 1980; Steinbeck et al., 1980), which appears to differ between sinus node and Purkinje cells (Vassalle, 1977).

B) CLINICAL APPLICATION

In 1971, the initial recovery interval of the sinus node following overdrive atrial pacing was proposed as an index of sinus node automaticity (Mandel et al., 1971; Rosen et al., 1971; Narula et al., 1972). Called the "sinus node recovery time", it can be defined as the interval from cessation of atrial pacing to the first spontaneous sinus node activity, measured either by the interval from the last paced P wave (or stimulus) to the first spontaneous P wave, or from the last paced high right atrial electrogram (or stimulus), to the first spontaneous high right atrial electrogram.
Since then, many groups have studied the clinical value of this parameter in assessing sinus node dysfunction. Table III-1 summarises the methods and results in a number of these studies, selected to show differences in methods and results. The clinical features of the control groups have differed markedly, particularly with respect to age and associated cardiac disease. Subjects on digitalis or with coronary artery disease have been included in some studies. Pacing rates, duration, and rest period between trials have differed. All this has made both valid comparisons between different studies and definition of the normal range of the sinus node recovery time difficult. Marked variation in resting cycle length within and between individuals led Narula to propose the subtraction of the mean of ten cycles pre-pacing from the sinus node recovery time to give the "corrected sinus node recovery time" (Narula et al., 1972) (Table III-1). Other groups (Mandell et al., 1972; Kulbertus et al., 1975; Benditt et al., 1976) have shown a linear relationship between the sinus node recovery time and the pre-pacing cycle length, and have proposed correction for cycle length using linear formulae.

Attention to the post-pacing sequence rather than the first post-pacing interval alone has been cursory, with the exception of a few studies. Delius and Wirtzfeld (1976) proposed consideration of the "entire sinus node recovery time", which they defined as
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<th>REFERENCE</th>
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<th>RANGE (years)</th>
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<th>POST-PACING INTERVAL (sec)</th>
<th>MEASURE</th>
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<td>15-78</td>
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<td>-</td>
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<td>120</td>
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LEGEND: "n" = number of patients studied; "PPCL" = pre-pacing cycle length; "POST-PACING INTERVAL" = time from termination of pacing to resumption of pacing for next trial; "-" = not stated in publication; "SNRT" and "SNRTmax" = sinus node recovery time and maximal sinus node recovery time respectively; "CSRT" and "CSRTmax" = corrected sinus node recovery time and maximal corrected sinus node recovery time respectively; "SR" = sinus rhythm; results of pre-pacing cycle length, sinus node recovery time, corrected sinus node recovery time expressed as mean ± one standard deviation.
the total post-stimulation period until return of pre-stimulus sinus rate. The Duke University group looked at the post-pacing sequence in more detail (Strauss et al., 1976; Benditt et al., 1976). They determined 95% confidence limits for the first ten post-pacing intervals from a control group, so that points falling outside these limits, which they called "secondary pauses", were considered an index of sinus node dysfunction.

It is paradoxical that the first post-pacing interval has been used to measure either sinoatrial automaticity when following thirty or more seconds of pacing, or, as will be discussed in Chapter VI, sinoatrial conduction if the pacing was for less than nine beats.

With the aim of improving understanding of these tests and resolving this paradox, not only the first post-pacing intervals, but also the post-pacing sequences were studied.

C) METHODS

One hundred and eighty patients had sinus node function assessed by electrophysiology study as described in Chapter II. The classification into patients with normal sinus node function (to be referred to as "normal"), with sick sinus syndrome, and with "intermediate" sinus node function has been described in Chapter II.
In the last group, only the morphology of the post-pacing sequences was studied in detail.

Overdrive high right atrial pacing for one minute was performed at both 100 and 130 beats per minute (bpm) in each patient. Two minutes elapsed before recommencing the next of the five pacing trials at each rate. If all pacing stimuli were not followed, or an atrial or ventricular ectopic beat was the first post-pacing beat, the trial was considered invalid; nevertheless, two minutes was always allowed before recommencing pacing. All other trials, including those with non-sinus node escape rhythms and with atrial and ventricular ectopics after the first post-pacing beat, were considered valid for study of the morphology of the post-pacing sequence. Only trials in which the first post-pacing beat showed P wave morphology and intra-atrial electrogram profile consistent with a sinus node origin were used to calculate the sinus node recovery time. For a given patient with multiple pacing trials at each rate, conventional indices (the sinus node recovery time and the corrected sinus node recovery time) were expressed as both the mean and the maximum value at the specified rate.

Indices of sinus node function will be expressed as the group mean +/- one standard deviation.
D) RESULTS

i) Clinical Features

The clinical and electrocardiographic features of the patients with normal sinus node function and with the sick sinus syndrome are shown in Tables III-2 and III-3 respectively. The mean age was significantly greater in those with the sick sinus syndrome (70.8 years compared to 41.4 years in the patients with normal sinus node function; p < .001).

The thirty-five patients with the sick sinus syndrome could be further subdivided on the basis of documented electrocardiographic abnormalities into those with:

a) sinoatrial exit block (seven patients); characteristic electrocardiograms are shown in Figures III-1 and III-2,

b) brady- and tachy-arrhythmias (twelve patients); in four of these patients prolonged pauses were documented on termination of paroxysms of atrial fibrillation (Figure III-3),

c) sinus or junctional bradycardia without documented sinoatrial exit block or atrial tachyarrhythmias (sixteen patients),
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LEGEND:  "F" = female, "M" = male; "EAVNC" = enhanced atrioventricular nodal conduction; "AVNT" = atrioventricular nodal reentrant tachycardia; "AAVC" = accessory atrioventricular connection (* in all but this patient anterograde preexcitation was present); "VT" = ventricular tachycardia (idiopathic); "DCD" = distal conduction disease; "N" = normal; "RBBB", "LBBB" = complete right and left bundle branch block respectively; "LEFT" and "RIGHT" = left and right axis deviation respectively of the mean QRS vector in the frontal plane. Age is given in years, cycle length and PR interval in milliseconds.
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<th>PR (msec)</th>
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**LEGEND:** "M" = male; "F" = female; "CL" = cycle length; "P wave" = P wave duration; "PR" = PR interval; "N" = normal; "RBBB" = right bundle branch block; "IVCD" = generalised intraventricular conduction defect; "Infarct" = pattern of old myocardial infarction; "LBBB" = left bundle branch block; "Ind." = indeterminate; "AF" = atrial fibrillation; "SB" = sinus bradycardia; "JB" = junctional bradycardia; "SA" = sinus arrest; "SAEB" = sinoatrial exit block.
Figure III-1

Electrocardiographic recording of Lead II showing 2:1 sinoatrial exit block, the pause (1400 msec) being double the preceding cycle length (700 msec).
Figure III-2

Electrocardiographic recording, at 25 mm/sec chart speed, of lead II showing 2:1 sinoatrial exit block. In contrast to Figure III-1, junctional escape beats are seen, but with abnormally long coupling, suggesting the presence of impaired function of both the sinus node and the subsidiary pacemakers, as is frequently seen in the sick sinus syndrome.
Figure III-3

Electrocardiographic recording, at 25 mm/sec chart speed, of lead II from a patient with the "brady-tachy syndrome" showing prolonged pauses on termination of two consecutive episodes of paroxysmal atrial fibrillation. The second episode was observed to be associated with syncope.
Twenty patients (57%) of the thirty-five with the sick sinus syndrome had additional evidence of either impaired atrio-ventricular nodal function, with a Wenckebach threshold less than 130 beats per minute, or impaired distal conduction manifest by complete right or left bundle branch block pattern.

In the patients with the sick sinus syndrome, the mean P wave duration, 126 +/- 17 msec, was significantly greater than in patients with normal sinus node function (106 +/- 22 msec; p < .0005)
The final diagnoses in the patients with normal sinus node function were atrioventricular nodal tachycardia in seven, enhanced atrioventricular nodal conduction in four, accessory atrioventricular connection (either concealed or overt) in four, ventricular tachycardia in two, mitral valve prolapse in one, distal conduction disease localised to the His bundle in one, and hyperventilation in one.

To the present time, nine patients in the intermediate group have had permanent pacemaker implantation for symptomatic sinus node bradyarrhythmias.

ii) Conventional Indices

a) cycle length

The mean pre-pacing cycle lengths in the patients with normal sinus node function and with the sick sinus syndrome were significantly different (p < 10^-6), being 787 +/- 144 msec (mean +/- one standard deviation) and 1030 +/- 180 msec, respectively.
To assess variation of resting cycle length (mean over one minute), it was measured in seventeen unselected patients, ten minutes after the study commenced (866 +/- 187 msec), and again ten minutes after catheter insertion (899 +/- 158 msec) (difference not significant). Both these measurements preceded any pacing of the heart.
b) sinus node recovery time

Mean values of both the sinus node recovery time and the maximal sinus node recovery time are presented in Table III-4. At the pacing rate of 100 bpm beats per minute, the sinus node recovery time was significantly greater in the patients with the sick sinus syndrome, being 1412 +/- 469 msec (mean +/- one standard deviation) compared to 1064 +/- 180 msec in the patients with normal sinus node function (p < .005). At the same pacing rate, the maximal sinus node recovery time was 1106 +/- 173 msec in normals and 1668 +/- 770 msec in the sick sinus syndrome. The distribution of values in those with sinus node dysfunction was skewed. If very long post-pacing intervals were excluded (those more than double the pre-pacing cycle length), the mean value of the maximal sinus node recovery time was 1447 +/- 179 msec, significantly greater than in normals (p < 10^-7).

At the pacing rate of 130 bpm, the sinus node recovery time was significantly greater in the patients with the sick sinus syndrome (1520 +/- 656 msec), compared to the patients with normal sinus node function (972 +/- 209 msec; p < .001). At this rate, the maximum sinus node recovery time in the patients with sick sinus syndrome (1792 +/- 821 msec) was also significantly greater than in the patients with normal sinus node function (1034 +/- 226 msec; p < .001).
<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>SICK SINUS SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparing Cycle Length</strong></td>
<td>787 ± 144</td>
<td>1030 ± 180</td>
</tr>
<tr>
<td><strong>PACING RATE 100 bpm (19)</strong></td>
<td>(35)</td>
<td></td>
</tr>
<tr>
<td>SNRT</td>
<td>1064 ± 180</td>
<td>1412 ± 469</td>
</tr>
<tr>
<td>SNRTmax</td>
<td>1106 ± 173</td>
<td>1668 ± 770*</td>
</tr>
<tr>
<td>CSRT</td>
<td>243 ± 108</td>
<td>504 ± 477</td>
</tr>
<tr>
<td>CSRTmax</td>
<td>291 ± 108</td>
<td>649 ± 736**</td>
</tr>
<tr>
<td><strong>PACING RATE 130 bpm (17)</strong></td>
<td>(34)</td>
<td></td>
</tr>
<tr>
<td>SNRT</td>
<td>972 ± 209</td>
<td>1520 ± 656</td>
</tr>
<tr>
<td>SNRTmax</td>
<td>1034 ± 226</td>
<td>1792 ± 821***</td>
</tr>
<tr>
<td>CSRT</td>
<td>231 ± 109</td>
<td>586 ± 696</td>
</tr>
<tr>
<td>CSRTmax</td>
<td>289 ± 125</td>
<td>772 ± 825****</td>
</tr>
</tbody>
</table>

When values over twice resting cycle length excluded,
* = 1447 ± 179
** = 432 ± 165
*** = 1442 ± 297
**** = 403 ± 259

**LEGEND:** "bpm" = beats per minute; "SNRT" = sinus node recovery time; "SNRTmax" = maximal sinus node recovery time; "CSRT" = corrected sinus node recovery time; "CSRTmax" = maximal corrected sinus node recovery time; numbers in parentheses "( )" represent number of patients studied. All indices are in units of milliseconds and are expressed as mean ± one standard deviation.
Within each group, the differences between the maximal sinus node recovery times at the two pacing rates were not significant. Note should be made of the trend of the sinus node recovery time, with increase of the pacing rate from 100 to 130 bpm, to decrease \(0.1 > p > 0.05\) in the patients with normal sinus node function, compared to no change \(p = \text{ns}\) in the patients with the sick sinus syndrome. (The effect of pacing rate on the sinus node recovery time will be examined more closely in Chapter V).
c) corrected sinus node recovery time

The corrected sinus node recovery time and the maximal corrected sinus node recovery time were both significantly greater in the patients with the sick sinus syndrome (Table III-4). After pacing at 100 bpm, the corrected sinus node recovery time was 243 +/- 108 msec in the patients with normal sinus node function and 504 +/- 477 msec in the patients with the sick sinus syndrome (p < .025). At the same pacing rate, the maximal corrected sinus node recovery time was 291 +/- 108 msec and 649 +/- 736 msec in patients with normal sinus node function and with the sick sinus syndrome respectively (p < .025). When the very long post-pacing intervals were excluded, the mean value was 432 +/- 165 msec in the sick sinus syndrome (p < .001 compared to normals).
After pacing at 130 bpm, the corrected sinus node recovery time was 231 +/- 109 msec in the patients with normal sinus node function, and 586 +/- 696 msec in the patients with the sick sinus syndrome ($p < .025$). At this pacing rate, the maximal corrected sinus node recovery time was 289 +/- 125 msec in normals, and 772 +/- 825 msec in the sick sinus syndrome ($p < .025$).
iii) Post-Pacing Sequences

a) normals

In the 22 patients with normal sinus node function, after multiple trials of pacing for one minute duration at 100 and 130 bpm, the following initial post-pacing sequences were observed, and an arbitrary classification developed. Excluding thirteen trials where junctional, or ectopic atrial or ventricular beats occurred, 131 of 136 trials (96%) showed maximally prolonged first post-pacing cycle length and progressive decrease of subsequent cycle lengths (Figure III-4). Figure III-5A shows a typical decaying post-pacing sequence, with cycle length plotted against post-pacing beat number. Figure III-5B shows the initial sequence on an expanded scale. In 25 (18.4%) of these trials, the minimum value was reached before the fifth post-pacing interval, while in the rest (106, 77.6%) at or after the fifth interval. This decaying sequence will be referred to as "Type 1" (Figure III-6, top panel).
Figure III-4

Electrocardiographic recording of a typical sequence following termination of right atrial pacing ("RAP") for one minute at cycle length of 600 msec (100 beats per minute), with maximally prolonged first post-pacing interval (cycle length 1480 msec) and progressive decrease until the seventh interval (cycle length 1115 msec).
Figure III-5A

Plot of post-pacing cycle length of beat j ("PPCLj") on the ordinate against beat number ("j") following overdrive high right atrial pacing for one minute at 100 beats per minute in a patient with normal sinus node function. The typical initial post-pacing sequence and subsequent cycle length fluctuations are shown.
Figure III-5B

Initial twenty cycles of the plot of Figure III-5A on an expanded scale, showing initial maximum interval, and progressive decrease to a minimum at the seventh interval. "T_∞" represents an asymptotic cycle length toward which the initial seven cycles tend (this concept is further discussed in Chapter IV).
Figure III-6

Diagrammatic representation of three types of post-pacing sequences observed in normals. In each panel, pre-pacing cycle length ("PRE PACING"), right atrial pacing for one minute ("RAP"), and post-pacing cycle length are represented. The latter is plotted against the post-pacing beat number ("BEAT NUMBER"). In the top panel, "TYPE 1", the first post-pacing cycle length is maximally prolonged, with decrease to a minimum, usually before the tenth cycle length. In the middle panel, "TYPE 2", the second post-pacing cycle length has the minimum value, with increase over the next five to ten cycle lengths. In the bottom panel, "TYPE 3", the first post-pacing cycle length is lengthened, the others unaffected by the pacing. (See text for further discussion).
NORMAL RESPONSE OF SINUS NODE TO ATRIAL PACING

PRE PACING

RAP

TYPE 1

CYCLE LENGTH

TYPE 2

BEAT NUMBER

TYPE 3
In the only other type of sequence seen in this group (in only five (3.7%) trials), a minimum occurred at the second interval with progressive (but decreasing) increase in subsequent cycles (Figure III-6, middle panel, "Type 2" sequence).

Although not seen in these trials, one other type of post-pacing sequence was seen in patients with normal sinus node function both during Narula conduction time estimation (Chapter VI) and after atropine (Chapter VII), and is included here for completeness. As shown in Figure III-6 (bottom panel, "Type 3") the post-pacing sequences consisted of a prolonged first interval, and subsequent cycles behaving as for pre-pacing. This usually occurred when the pacing cycle length and pre-pacing cycle length were within fifty milliseconds.
b) sick sinus syndrome

Some major differences were observed following overdrive pacing at 100 and 130 bpm in the 35 patients with the sick sinus syndrome compared to the patients with normal sinus node function. After exclusion of sequences with ectopic beats, of 309 sequences, 124 (40%) were "Type 1", as already described for patients with normal sinus node function. Of these, 21 had initial minimum value at the third or fourth interval, and 103 at or after the fifth interval. However, 74 (24%) sequences were like Type 1 except for a short first post-pacing interval (Figures III-7, and III-8, top panel, "Type 1 Secondary Pause") and the second interval having the maximum value.
Figure III-7

Electrocardiographic recordings in a patient with the sick sinus syndrome, of initial post-pacing events in consecutive trials of overdrive right atrial pacing ("RAP") at cycle length of 600 msec (100 beats per minute). Panel A shows progressive decrease in cycle length after maximally prolonged first post-pacing cycle length (1480 msec). Panel B shows a short first post-pacing cycle length (1065 msec), maximal second cycle length (1335 msec), and then progressive decrease of subsequent intervals (see text for further discussion).
Figure III-6

Diagrammatic representation of three types of secondary cycle length prolongation post-pacing ("Secondary Pauses"), in the same format as Figure III-6. Post-pacing cycle length ("CYCLE LENGTH") is plotted against post-pacing beat number ("BEAT NUMBER"). The sequence shown in the top panel ("Type 1" secondary pause) is equivalent to that shown in Figure III-7, Panel B, and consists of a short first post-pacing cycle length, a maximum second postpacing cycle length, and progressive decrease in subsequent cycles. The middle panel ("Type 2" secondary pause) shows a sequence with minimum first post-pacing cycle length, and progressive (but decreasing) increase until maximum value at or after the third cycle, after which maximum a decrease in cycle length is again seen. The sequence shown in the bottom panel ("Type 3" secondary pause) is equivalent to that to be shown in Figure III-9, with initial post-pacing cycle lengths being near multiples of the subsequent minimum cycle length ("a"). Note that the first is represented as being greater than an exact multiple. Refer to text for further explanation.
SECONDARY PAUSES

TYPE 1

PRE PACING  RAP

TYPE 2

CYCLE LENGTH

TYPE 3

BEAT NUMBER
Twenty-two sequences (7%) showed the initial minimum value at the first or second interval. In seventeen of these, the second post-pacing interval had the minimum value, as for Type 2 sequences in normals (Figure III-6, middle panel). However, in five sequences, the first post-pacing interval had the minimum value and the initial maximum value was not seen until the third to tenth post-pacing cycle (Figure III-8, middle panel, "Type 2 Secondary Pause").

The third type of sequence seen, in 58 (18%) of the sequences, was one of long post-pacing intervals, most of which were nearly exact multiples of the pre-pacing and subsequent post-pacing cycle length (Figure III-8, bottom panel, "Type 3 Secondary Pause"). Figure III-9 shows a typical electrocardiogram recorded with such a sequence. The first interval was usually more than an exact multiple of the pre-pacing/post-pacing cycle length. This type of sequence was typically observed in those seven patients with previously observed sinoatrial exit block on pre-study electrocardiograms (as in Figures III-1, III-2).
Figure III-9
Electrocardiographic recording of lead II showing prolonged secondary pauses following termination of right atrial pacing at 130 beats per minute (pacing cycle length 460 msec). Note that the second to fifth cycle lengths are near multiples of the subsequent minimum cycle length. The first cycle length is greater than an exact multiple (more than four times) the subsequent minimum cycle length.
Following atrial pacing at 100 bpm, such sequences were seen in six of these seven patients, and after pacing at 130 bpm, in all seven and in three additional patients, two with sinus bradycardia, and in one with the bradycardia-tachycardia syndrome.

Variation in P wave morphology, in the initial post-pacing beats, but without clear change in atrial activation sequence as recorded by the intracavitary electrograms, was observed in 2/149 sequences in patients with normal sinus node function, and significantly more frequently (in 25/331 sequences) in patients with the sick sinus syndrome (p < .01; Chi-squared test). When sequences containing such changes were plotted, there were usually discontinuities associated with the change in P wave morphology (Figures III-10, and III-11).
Figure III-10

Electrocardiographic recording of lead II showing the last five paced beats of one minute of overdrive atrial pacing at 100 beats per minute (chart speed faster than 25 mm/sec), and initial postpacing beats. The arrows point to the different P wave morphology of the first two post-pacing beats compared to subsequent beats.
Figure III-11

Plot of post-pacing cycle length ("PPCLj") on the ordinate against post-pacing beat number ("BEAT NUMBER j") following one minute of overdrive atrial pacing at 100 beats per minute. Illustrated is the discontinuity in sequence associated with change in P wave morphology as illustrated in Figure III-10. The most likely explanation for this change is a pacemaker shift, either within the sinus node or to a subsidiary atrial site.
c) intermediate group

Post-pacing sequences were analysed in eighty patients in the intermediate group (Table III-5). At pacing rate of 100 bpm, 221 (62%) of 356 trials had maximally prolonged first post-pacing interval, with initial minimum value characteristically reached at the seventh interval (Figure III-6, top panel, "Type 1" sequence). In 199 of the 221 sequences of this type, the minimum value was reached after the fourth interval, and in only 22 was it reached at the third or fourth post-pacing interval.

In 26 sequences after pacing at 100 bpm, the first post-pacing interval was short, with a maximally prolonged second interval (Figure III-8, top panel, "Type 1 Secondary Pause"). "Type 2" sequences (Figure III-6, middle panel) were observed in 21 pacing trials at this rate.
<table>
<thead>
<tr>
<th>pacing rate (bpm)</th>
<th>100</th>
<th>130</th>
<th>100 and 130</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean initial minimum beat number</td>
<td>6.75*</td>
<td>5.08*</td>
<td>-</td>
</tr>
</tbody>
</table>

Type 1 sequence
- a) minimum after T4 | 199 | 95 | 294 |
- b) minimum T3 or T4 | 22 | 34 | 56 |
- a) + b) | 221 | 129 | 350 |
Type 2 sequence | 21 | 47 | 68 |
Type 3 sequence | 0 | 1 | 1 |

Type 1 secondary pause | 26 | 18 | 44 |
Type 2 secondary pause | 3 | 8 | 11 |
Type 3 secondary pause | 1 | 5 | 6 |

Escape rhythms | 10 | 4 | 14 |
Ectopic beats | 36 | 40 | 76 |
Variable P morphology | 34 | 32 | 66 |
Unclassifiable (scatter) | 4 | 3 | 7 |

Total number of sequences | 356 | 287 | 643 |

**LEGEND:** For arbitrary classification of types of sequences and "secondary pauses" refer to Figures III-6, III-8 and to text. "T3" and "T4" represent third and fourth post-pacing cycle lengths respectively. * significantly different (p < 10^-5).
At the pacing rate of 130 bpm, "Type 1" sequences (Figure III-6, top panel), with a maximally prolonged first post-pacing interval and progressive decay thereafter, were most commonly seen (129 (45%) of 287 trials). Again, the majority of these sequences (95% of the 129) reached the minimum value after the fourth post-pacing interval, although the mean beat number (5.08) of the initial minimum interval was significantly less than at 100 bpm (6.75; p < 10^-6).

"Type 2" sequences (Figure III-6, middle panel), with a prolonged first interval, a minimum second interval, and subsequent increase, were seen in 16% of trials at 130 bpm.

Sequences which rose from a minimal first interval (Figure III-8, "Type 2 Secondary Pause") were observed uncommonly, in 3 trials at 100 bpm and in 8 trials at 130 bpm.

In six trials (in three patients), prolonged and unexpected secondary pauses were seen, in one patient being as long as 3.9 seconds.
Variation in P wave morphology and atrial electrogram morphology, without a change in atrial activation sequence (as assessed by intracavitary electrogram recordings), was observed in 66/643 sequences in this group of patients.

E) DISCUSSION

The conventional indices, the cycle length, the sinus node recovery time, the corrected and the maximum corrected sinus node recovery time, were similar to those previously noted in other studies (Mandel et al., 1971; Narula et al., 1972; Dhingra et al., 1973; Gupta et al., 1974; Kulbertus et al., 1975; Okimoto et al., 1976; Scheirman et al., 1976; Breithardt et al., 1977) (Table III-1). These measures appear capable of distinguishing grossly abnormal sinus node dysfunction, but also show overlap of the values observed in patients with the sick sinus syndrome with the values observed in patients with normal sinus node function. The specificity and sensitivity of these tests will be addressed further in Chapter VIII.
The sequences ("Type 1") which were most commonly observed in patients with normal and intermediate sinus node function, and frequently in patients with the sick sinus syndrome will be studied in detail in Chapter IV. The possible basis for the "Type 2 sequence" observed in normals will be discussed below with the "Type 2 Secondary Pause" observed in patients with the sick sinus syndrome. The "Type 3" sequences observed in patients with normal sinus node function will be discussed in more detail in Chapters IV and VI. In brief, these sequences were considered to be due to failure of atrial pacing to capture the sinus node (isorhythmic sinoatrial dissociation).

From studying the form of the initial post-pacing sequences, valuable information can be obtained which suggests sinus node dysfunction. The abnormal post-pacing sequences observed in patients with the sick sinus syndrome will now be discussed.
i) Secondary Pauses

a) "Type 1 Secondary Pause"

"Type 1" secondary pauses (Figure III-8) in particular, with first post-pacing cycle length less than a maximally prolonged second, are probably due to atriosinus entrance block of the last paced beat (Ticzon et al., 1975, Strauss et al., 1976; Steinbeck et al., 1980; Kerr and Strauss, 1981), and were not seen in the patients with normal sinus node function. In the intermediate group, such sequences were seen in 6% and 16% of trials at 100 and 130 bpm respectively, the significance of which requires further study. It can be stated however, that the presence of such sequences at a pacing rate of 100 bpm must raise a suspicion of sinus node dysfunction.

Figure III-12 illustrates in ladder diagram form the postulated events with Type 1 secondary pauses. The major assumption is that all pacing stimuli although capturing the atrium, do not fully enter and "capture" the sinus node. Recent experimental work in animals strongly supports this assumption (Steinbeck et al., 1980). It has been believed that this particularly applies to high rates of pacing (> 150 bpm or < 400 msec pacing cycle length) in man, as maximum post-pacing suppression in normals has been seen below this pacing rate (Mandel et al., 1971).
Figure III-12
Ladder diagram with sinus node, perinodal, and atrial electrical activity, and high right atrial electrogram recording ("HRA"), illustrating a simple theoretical explanation for post-pacing sequences with short first post-pacing cycle length, maximally prolonged second cycle length, and progressive decrease in subsequent cycle lengths. Panel A shows the "normal" situation with 1:1 atriosinus conduction during pacing. With 2:1 second degree atriosinus block, the duration of the first post-pacing cycle length depends on whether it was the final paced stimulus (Panel B – longest first post-pacing cycle length) or the second to last paced stimulus (Panel C – short first post-pacing cycle length) that last captured the sinus node (see text for discussion). The dotted arrow in Panel C represents the possibility of partial electrical influence of the last paced stimulus on the sinus node (see Chapter IV for further discussion).
Figure III-12 panel A represents the situation if all paced beats capture the sinus node. Panels B and C represent the simplest hypothetical situation of incomplete capture, with alternate paced beats capturing. They show how the length of the first post-pacing interval depends on whether the last paced beat enters the sinus node. If so (panel B), the post-pacing sequence shows no secondary pause, and is similar to the sequence if all paced beats had captured the sinus node. However, if the second to last paced beat captures the sinus node and the last does not (panel C), the first post-pacing interval is shorter than the second. Recent experimental work with single induced premature stimuli in rabbits has shown that when there is failure of complete capture, often there is partial depolarisation (Kerr et al., 1980), possibly due to either decremental conduction or electrotonic interaction (Bonke et al., 1971), which may lead to some delay of the next sinus impulse. More detailed study of such post-pacing sequences (see Chapter IV) suggests that this may also apply in man, even at low pacing rates if there is sinus node dysfunction.
b) "Type 2 Secondary Pause"

Sequences which rose before the fifth post-pacing interval appeared to be of two distinct forms. "Type 1" sequences (Figure III-6, top panel) with maximally prolonged first post-pacing interval and subsequent decrease occasionally reached the minimum value before the fifth interval. This was seen more frequently at shorter pacing cycle lengths and may have related to either rapid vagal reflexes or events intrinsic to the sinus node. The alternative form of sequence rising before the fifth post-pacing interval had a minimum value at the first or second post-pacing interval (Figure III-8, "Type 2 Secondary Pause", and Figure III-6, "Type 2 sequence" respectively), and increasing intervals until a maximum was reached between the fourth and tenth post-pacing interval. In animal experimental studies (Kodama et al., 1980), such sequences have been associated with an initially increased phase 4 slope (or "overdrive acceleration") following overdrive pacing at cycle lengths close to the pre-pacing cycle length. In such experiments, this response has been much less frequently observed than the characteristic initial depression of phase 4 slope.
In normal patients, with this type of sequence, the first post-pacing interval was still the longest or differed little from the subsequent maximum interval. In some patients with the sick sinus syndrome and with intermediate sinus node function, the first interval was the shortest. Although speculative, this may possibly have been due to atriosinus entrance block, giving both a low effective rate of pacing of the sinus node (and hence acceleration), and atriosinus entrance block of the last paced impulse (that is, a combination of "Type 2" sequence and a "Type 1 secondary pause"). In its extreme form, this may include complete atriosinus block with electrotonic interaction causing acceleration of sinus node activity. (Electrotonic interactions in the presence of failure of conduction have been demonstrated in experimental preparations for both ventricular pacemaker cells (Jalife and Moe, 1979), and for the sinus node with single premature atrial beats (Bonke et al., 1971; Miller and Strauss, 1974)). The low incidence of such sequences which progressively rise after a minimum at the first post-pacing interval (0% in normals, 1.7% in the intermediate group, and 1.5% in the sick sinus syndrome), makes assessment of their meaning with regard to normality of sinus node function difficult.
c) "Type 3 Secondary Pauses"

Secondary pauses with marked prolongation of cycle length (Figure III-8, "Type 3 Secondary Pause"), appear highly specific for sinus node dysfunction, but are usually seen in patients who have clearly abnormal sinus node function on clinical criteria. Long secondary pauses were observed in three patients in the intermediate group, in whom on subsequent electrophysiology testing with cardiac vagal and cardiac autonomic blockade, normal responses were observed, suggesting that high vagal tone rather than intrinsic sinus node dysfunction was responsible. It must be stressed that pauses which were near or exact multiples of the resting cycle length were only observed in the sick sinus syndrome. The mechanism of such secondary pauses is disputed. The simple and obvious explanation is complete failure of sinus node impulses to penetrate the (abnormal) perinodal cells (Strauss et al., 1976). Figure III-13 shows this in ladder diagram form, with sinus node impulse generation at the expected time, but intermittent failure to penetrate the perinodal tissue.
Figure III-13

Ladder diagram illustrating the simplest theoretical explanation for prolonged post-pacing pauses that are multiples of the pre-pacing cycle length. Sinus node ("SAN"), perinodal, and atrial electrical activity are represented, together with high right atrial electrogram recordings ("HRA"). Following termination of atrial stimulation ("S"), the first, second, and fourth spontaneous sinus node impulses (represented by solid circles) fail to conduct to the atrium because of sinoatrial exit block.
Alternatively, subthreshold sinus node waves but absent sinus node action potentials have been observed in animal experiments at the time of absent atrial activity (Steinbeck and Lüderitz, 1976).

Which of these postulated mechanisms applies to these long pauses seen in humans with the sick sinus syndrome remains speculative, but may be answered by direct recording of sinus node action potentials by catheter techniques (Reiffel et al., 1980).
ii) P wave Morphology Variation

Steinbeck and Läderitz (1977) have previously observed change in P wave morphology, associated with change in atrial electrogram morphology, but without change in atrial activation sequence as assessed by intracavitary recordings. The possible explanations for these P wave changes are:

a) Minor pacemaker shifts within the primary pacemaker region of the sinus node, but sufficient to cause different exit from the sinus node and hence different atrial activation sequence, as postulated on the basis of previous experimental observations by Steinbeck and Läderitz (1977).

b) Major pacemaker shifts to a subsidiary pacemaker area, with marked difference in the initial site of atrial activation (this situation could include the presence of sinoatrial exit block from the primary pacemaker area).
c) Block in specialised intra-atrial conduction pathways (Pick and Langendorf, 1979)

d) Different atrial geometry in the initial post-pacing beats leading to different apparent atrial activation sequence.

In this study, the incidence of such changes in P wave morphology was found to be significantly higher in patients with the sick sinus syndrome compared to patients with normal sinus node function.
Finally, and most importantly, are the typical "Type 1" (Figure III-6, top panel) post-pacing sequences, with initial maximum value, and progressive decrease in subsequent cycles to reach a minimum usually between the fifth and tenth cycles. If trials with ectopic beats, escape rhythms, secondary pauses, and variable P wave morphology were excluded, these sequences were present in 80% of trials in patients with normal sinus node function, in 47% of trials in patients with the sick sinus syndrome, and in 63% of trials in patients with intermediate sinus node function. Further detailed study of such typical sequences appeared to be the most promising approach to improvement of sinus node function assessment, and will be discussed in the following chapters.
CHAPTER IV

MATHEMATICAL MODEL OF SINUS NODE RECOVERY FOLLOWING OVERDRIVE SUPPRESSION

As 95% of post-pacing sequences in normals follow the same pattern of decrease, with minimum value reached in 80% after the fifth post-pacing interval, such sequences were studied in more detail. Mathematical modelling of this sequence was a major original contribution of Dr. A. Helfgott (see Appendix B).

A) EXPERIMENTAL BACKGROUND

West and coworkers performed the first studies looking in detail at the mechanisms of overdrive suppression of the sinus node, using isolated rabbit atrial preparations (Amory and West, 1962; Vincenzi and West, 1963). Using high frequency (up to 100 cps) stimulation, they observed both depression and acceleration following overdrive. The characteristic response consisted of a period of depressed activity followed by a late acceleration of pacemaker activity, usually observed 10-15 seconds after cessation of pacing.
Associated with the initial depression, they observed hyperpolarisation of the sinus node pacemaker cells, and flattened phase 4 (spontaneous depolarisation) slope. They then used pharmacological interventions and showed abolition of the initial suppression in the presence of atropine. In addition sympathetic interventions modified the response. It was known that the sinus node is richly innervated with both vagal and sympathetic neurones. They concluded that the release of neurotransmitters, namely acetylcholine and noradrenaline, by pacing was responsible for the chronotropic effects.
More recent experimentation has failed to clearly determine the cellular mechanisms of overdrive suppression of the sinus node, although the electrical events have been well described (Lu et al., 1965; Vassalle, 1977; Strauss et al., 1977; Kodama et al., 1980; Steinbeck et al., 1980). More recently, hypopolarisation of the membrane has been observed (Steinbeck et al., 1980; Kodama et al., 1980), but regardless of changes in maximum diastolic potential, decreased slope in phase 4 was present.

Postulated mechanisms at the cellular level include extracellular potassium accumulation, possibly due to acetylcholine release, activation of the electrogenic sodium pump, and change in membrane handling of calcium (Brooks and Lu, 1972; Vassalle, 1977; Kodama et al., 1980; Steinbeck et al., 1980).
B) MATHEMATICAL MODEL

A summary of the derivation of the model as described by Dr. Helfgott is given in Appendix B. In essence, if the electrical events associated with overdrive suppression are due to a single phenomenon, such as clearance of extracellular potassium (which has been shown to be cleared exponentially with a half-life of 3-5 seconds (Spear et al., 1979)), and the initial electrical events, (for the first five to ten beats) are dominated by the preceding overdrive, and assuming:

i) constant action potential duration,

ii) constant difference between maximum diastolic potential and threshold potential,

iii) capture and reset of the sinus node by all atrial paced beats, and

iv) absence of pacemaker shifts,
the prolongation of the initial post-pacing sinus node cycle lengths behaves as a decaying geometric progression:

\[ T_j = T_\infty + \Delta T_1 \cdot q^{(j-1)} \]

where \( j \) is the post pacing interval number, \( T_j \) the cycle length of post-pacing interval \( j \), \( T_\infty \) the asymptotic cycle length of the geometric progression, \( \Delta T_1 \) the first post-pacing cycle length prolongation, and \( q \) the common ratio of the geometric progression (\( \Delta T_1 > 0 \), \( 0 < q < 1 \), \( T_\infty > 0 \)) (Figure IV-1).

This model applies to intervals as theoretically measured directly from the sinus node pacemaker cell. However, if the post-pacing cycle length sequence is measured between consecutive high right atrial electrogram signals, assuming that anterograde conduction time is constant, then the sequence follows the above relation with the exception of the first post-pacing interval, which contains an additional interval of both retrograde and anterograde sinoatrial conduction (Figure IV-2). In this ladder diagram are represented sinus node ("SAN"), and high right atrial ("RA") electrical activity, and the electrograms recorded in the high right atrium. Following the termination of atrial pacing, the measured first post-pacing interval "T1" is the sum of the initial post-pacing sinus node automatic interval, "Ta", and atriosinus and sinoatrial conduction ("CTain" and "CTaout" respectively). Subsequent measured post-pacing intervals, "T2", "T3", to "T6", are equivalent to sinus node automatic intervals,
Figure IV-1

Schematic illustration of the mathematical model of the initial post-pacing sinus node sequence. Post-pacing cycle length is plotted on the ordinate against post-pacing beat number on the abscissa. The closed circles represent the measured intervals. The open circle represents the first post-pacing interval extrapolated from curve fitting analysis to the rest of the sequence. The initial sequence after the maximally prolonged first interval behaves as a decaying geometric progression of the initial post-pacing cycle length prolongation \( \Delta T_l \), with common ratio \( q \), toward an asymptotic cycle length \( T_\infty \). "SACT" represents the theoretical component of sinoatrial conduction in the first postpacing interval (see text and Figure IV-2 for further explanation). "Total SNRT" represents the time for decay to within 1% of \( T_\infty \).
\[ T_j = T_{\infty} + \Delta T_j \]

Diagram:
- Total SNRT
- Beat Number
- Post-Packing Cycle Length
- \( \Delta T_j \)
- SACT
Figure IV-2

Ladder diagram representing sinus node ("SAN"), and high right atrial ("RA") electrical activity, high right atrial electrogram recording ("A"), and electrode catheter used for both stimulation and recording ("SR"). Following the last of a series or even a single paced atrial beat, retrograde conduction ("CTain"), the sinus node automatic interval ("Ta"), and anterograde conduction time ("CTaout"), make up the first interval. If anterograde conduction time of subsequent beats is constant, the subsequent measured intervals "T2", "T3" etc., as recorded in the high right atrium, will be equal to the subsequent sinus node automatic intervals "Tb", "Tc", etc., and in contrast to the first interval, will not contain any component of sinoatrial conduction.
\[ T_1 = T_a + C_{T_{a_{in}}} + C_{T_{a_{out}}} \]

\[ T_1 = T_a + C_{T_{a_{in}}} + C_{T_{a_{out}}} \rightarrow T_{2_{1}} \quad T_{3_{1}} \quad T_{4_{1}} \quad T_{5_{1}} \quad T_{6_{1}} \]
"Tb","Tc" to "Tf" respectively. The assumptions that must be made added to the above i) to iv), if high right atrial signals, are used for measuring post-pacing cycle lengths, are:

i) constant anterograde sinoatrial conduction time,

ii) constant intra-atrial conduction time from the sinoatrial border to the recording catheter, and

iii) minimal time for intra-atrial as opposed to sinoatrial conduction.

Later these points will be further discussed, as they are probably not always valid and lead to problems in fitting the model, as subsequently tested by myself.
C) METHODS

The post-pacing sequences following one minute of overdrive right atrial pacing at 100 and 130 bpm in patients with normal and abnormal sinus node function, already presented in Chapter III, were further analysed in the following way.

Post-pacing sequences were fitted by computer to the mathematical model using non-linear least squares curve fitting techniques.

Based on the assumption that the first post-pacing interval contained an additional component of sinoatrial conduction, both into and out of the sinus node (Figure IV-2), the first interval, (T1) was excluded from the analysis, and a theoretical first post-pacing sinus node automatic interval extrapolated from the subsequent sequence. Ninety-five percent confidence limits were derived by computer from the fitted sequence and used to further test whether the first post-pacing interval belonged to the sequence. The difference between the measured and theoretical (extrapolated) first post-pacing interval was considered the computed sinoatrial conduction time ("SACTc"). In addition, indices of automaticity, q, the common ratio of the geometric progression, ΔT1 the first post-pacing cycle length prolongation, and T∞ the asymptotic cycle length, were computed.

Goodness of fit was assessed by the multiple correlation coefficient $R^2$. 

Page 79
a) **Criteria for Fitting Sequences**

The following criteria for selecting sequences for fitting were chosen:

i) Type 1 sequence, that is maximally prolonged first post-pacing cycle length ("T1") with subsequent decrease of cycle length (Figure III-6, top panel). Sequences where the second post-pacing cycle length ("T2") was maximally prolonged with subsequent decay (Type 1 secondary pause; Figure III-8, top panel) were also fitted, although a negative SACTc was always derived.

ii) Minimum value (excluding the first post-pacing interval "T1") reached after the fourth post-pacing cycle length. This related to a mathematical requirement for at least four data points, to be able to fit the curve with one or more degrees of freedom.

iii) Sequences with variation of P wave and high right atrial electrogram morphology (see Figures III-10, III-11) were excluded, even if the atrial activation sequence was as for normal sinus rhythm.

iv) No atrial, ventricular or atrioventricular junct-
ional beats, either escape or ectopic, within the first five post-pacing cycle lengths, regardless of the presence or absence of apparent sinus node reset by the escape or ectopic beat. If an ectopic beat occurred after the fifth cycle, the values up to but not including the ectopic interval were fitted.

v) With the exception of the latter situation, all post-pacing cycle lengths ("Tj") until the minimum value were fitted. If the next value was less than 10 msec greater, it was included if this order or beat-to-beat fluctuation had been present in the pre-pacing state.
vi) If the minimum occurred after the tenth post-pacing cycle length, both the full sequence to the minimum, and the first ten post-pacing cycle lengths were fitted. The data presented here will be those derived from fitting the first ten cycle lengths.

vii) In cases of doubt, the plot of the post-pacing sequences was used as a visual guide to the number of cycle lengths fitted.

b) Failure to Fit

The following criteria were used to define failure of fitting:

i) The computer programme "rejected" the sequence.

ii) The residual mean square value was greater than 1000.

iii) The computed values of q were < 0 or > 1, that is, outside the limits required by the model.

iv) The computed value of ΔT1 was negative.

v) The computed value of T∞ was negative.

vi) The computed value of SACTc was negative.
One exception to vi) was if the sequence was of "Type 1 secondary pause" (Figure III-8, top panel), with the first post-pacing cycle length less than the second, and, in addition, the computed \( SACT_c \) in absolute value was less than one pacing cycle length.
c) **Fitted Curves**

Figures IV-3 and IV-4 illustrate the types of curve the programme could fit to the data, and are included for mathematical interest. Only in curve A, Figure IV-3, was $0 < q < 1$ and $\Delta t_1 > 0$, that is, the other curves were considered failures to fit the model. In Figure IV-3, the curves B, C, D, were fitted if $q > 1$, or $\Delta t_1 < 0$. The oscillating curves in Figure IV-4 were fitted if $q < 0$.

The results of the computed indices in the patients with normal sinus node function, to be abbreviated as "normals", and in the patients with the sick sinus syndrome, to be abbreviated as "sick sinus syndrome", will be expressed as the mean $\pm$ one standard deviation. All the computed indices, with the exception of "$q"", the common ratio of the geometric progression, which is a dimensionless number, will be in units of milliseconds ("msec").
Figure IV-3

Plots of cycle length ('Tj') against post-pacing beat number ('j'), showing the curves fitted if the computer programme of the mathematical model generated q as a positive value. Only curve "A" (heavy black line) was considered successful fit to the model. In the other curves, "B", "C", and "D", either ΔT1 was negative, and/or q was > 1. "T∞" represents the asymptotic cycle length.
Fitted Curves: \( T_j = T_\infty + \Delta T_1 q^{j-1} \)
Figure IV-4

Plots of cycle length ("Tj") against beat number ('"j"') showing two ("E", "F") of the four oscillating curves fitted if the computer programme of the mathematical model generated q as a negative value.
D) RESULTS

In the patients with normal sinus node function, 104 of 149 sequences, and in those with the sick sinus syndrome, 167 of 331 sequences, were suitable for computation according to the above criteria (see Table IV-1). In all 22 patients with normal sinus node function, and in 28/35 patients with the sick sinus syndrome at least one sequence was suitable for computation. The most common reasons for sequences being unsuitable were minimum value before the fifth post-pacing interval, ectopic beats (in both "normals" and the "sick sinus syndrome"), and junctional escape beats and secondary pauses in the "sick sinus syndrome".

In 21/22 patients with normal sinus node function with sequences suitable for computation according to the above stated criteria, at least one sequence in each, and overall 85 of 104 sequences were successfully fitted. In all 28 patients with the sick sinus syndrome with sequences suitable for computation, at least one sequence in each, and overall in these 28 patients 140 of 167 sequences were successfully fitted. Figure IV-5 shows a computer plot of a fitted sequence with post-pacing cycle length ("PPBCLT T(J)") on the horizontal axis plotted against post-pacing beat number ("BEAT J") on the vertical axis. Measured intervals are plotted as circles, fitted intervals as stars. The difference between the measured and extrapolated first post-pacing interval is labelled "SACT", and the asymptotic cycle length "TINF". In
<table>
<thead>
<tr>
<th>TABLE IV-1</th>
<th>POST PACING SEQUENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORMAL</td>
</tr>
<tr>
<td>Pacing rate (bpm)</td>
<td></td>
</tr>
<tr>
<td>Type 1 sequence</td>
<td></td>
</tr>
<tr>
<td>a) minimum $T_3$</td>
<td>1</td>
</tr>
<tr>
<td>b) minimum $T_4$</td>
<td>8</td>
</tr>
<tr>
<td>c) minimum after $T_4$</td>
<td>55</td>
</tr>
<tr>
<td>a) + b) + c)</td>
<td>64</td>
</tr>
<tr>
<td>Type 2 sequence</td>
<td>1</td>
</tr>
<tr>
<td>Type 3 sequence</td>
<td>-</td>
</tr>
<tr>
<td>Type 1 secondary pause</td>
<td>-</td>
</tr>
<tr>
<td>Type 2 secondary pause</td>
<td>-</td>
</tr>
<tr>
<td>Type 3 secondary pause</td>
<td>-</td>
</tr>
<tr>
<td>Junctional rhythm</td>
<td>-</td>
</tr>
<tr>
<td>Ectopic beats</td>
<td>6</td>
</tr>
<tr>
<td>Variable P wave*</td>
<td>-</td>
</tr>
<tr>
<td>Total sequences</td>
<td>71</td>
</tr>
</tbody>
</table>

| Suitable for computation | 55 | 49 | 104 | 99 | 68 | 167 |
| Fitted | 44 | 41 | 85  | 89 | 51 | 140 |

**LEGEND:** "bpm" = beats per minute; "$T_3$", "$T_4$", represent third and fourth post-pacing cycle lengths respectively. * some sequences are classified twice in this table, in particular as Type 1 sequences and as variable P wave morphology. Hence "total sequences" is not the same as the sum of the columns. For further description of the arbitrary classification of types of sequences and "secondary pauses" refer to Figures III-6, III-8, and to text.
Figure IV-5

Computer plot of post-pacing sequence fitted to the mathematical model. Post-pacing cycle length ("PPBCLT T(J)"") (in milliseconds) is plotted on the horizontal axis against the post-pacing beat number ("J") on the vertical axis. The measured values (circles) and the fitted values (stars) coincide if within 10 milliseconds. The difference between the measured first post-pacing interval and the extrapolated first post-pacing interval, the computed sinoatrial conduction time is labelled "SACT". The asymptotic cycle length of the geometric progression is labelled "TINF".
over 95% of sequences fitted in patients with normal sinus node function, the multiple correlation coefficient $R^2$ was $> 0.98$, and the measured first post-pacing interval was found to be above approximate 95% confidence limits extrapolated from the subsequent sequence (chi-squared test, $p < .001$) (Helfgott et al., 1981).
The mean results in individual patients for computed indices were calculated. The pooled mean of each index for each group after overdrive pacing at rates of 100 and 130 bpm is shown in Table IV-2. For comparison, the mean and maximal sinus node recovery times at 100 and 130 bpm from the same patients are shown.

a) Computed Indices - Pacing Rate 100 beats per minute

The common ratio of the geometric progression, $q$, was $0.632 \pm 0.123$ (mean $\pm$ one standard deviation) in the patients with normal sinus node function, and significantly higher ($p < 0.005$) at $0.720 \pm 0.092$ in the patients with the sick sinus syndrome (see Table IV-2).

$\Delta T_1$ was $232 \pm 134$ msec in the "normals" and $250 \pm 123$ msec in the "sick sinus syndrome" (difference not significant).

The asymptotic cycle length, $T_\infty$, showed the most marked difference between the "normals" and the "sick sinus syndrome", being $736 \pm 0.79$ msec, and $931 \pm 162$ msec respectively ($p < 10^{-4}$).

The computed sinoatrial conduction time, SACTc, was $92 \pm 53$ msec in the "normals", and $185 \pm 116$ msec in the "sick sinus syndrome" ($p < .005$).
### TABLE IV-2

**COMPUTED INDICES OF SINUS NODE FUNCTION**

#### A. PACING RATE 100 BEATS PER MINUTE

<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>SICK SINUS SYNDROME</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(17)</td>
<td>(28)</td>
<td></td>
</tr>
<tr>
<td>SNRT (msec)</td>
<td>1064 ± 152</td>
<td>1286 ± 167</td>
<td>&lt;10^{-4}</td>
</tr>
<tr>
<td>SNRTmax (msec)</td>
<td>1109 ± 147</td>
<td>1447 ± 179</td>
<td>&lt;10^{-7}</td>
</tr>
<tr>
<td>q</td>
<td>.632 ± 123</td>
<td>.720 ± 092</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>ΔT₁ (msec)</td>
<td>232 ± 134</td>
<td>250 ± 123</td>
<td>n.s.</td>
</tr>
<tr>
<td>T∞ (msec)</td>
<td>736 ± 79</td>
<td>931 ± 162</td>
<td>&lt;10^{-4}</td>
</tr>
<tr>
<td>SACTc (msec)</td>
<td>92 ± 53</td>
<td>185 ± 116</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

#### B. PACING RATE 130 BEATS PER MINUTE

<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>SICK SINUS SYNDROME</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(14)</td>
<td>(21)</td>
<td></td>
</tr>
<tr>
<td>SNRT (msec)</td>
<td>968 ± 215</td>
<td>1268 ± 225</td>
<td>&lt;10^{-4}</td>
</tr>
<tr>
<td>SNRTmax (msec)</td>
<td>1028 ± 229</td>
<td>1442 ± 297</td>
<td>&lt;10^{-6}</td>
</tr>
<tr>
<td>q</td>
<td>.675 ± 104</td>
<td>.637 ± 172</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>ΔT₁ (msec)</td>
<td>183 ± 120</td>
<td>243 ± 131</td>
<td>n.s.</td>
</tr>
<tr>
<td>T∞ (msec)</td>
<td>690 ± 121</td>
<td>931 ± 198</td>
<td>&lt;10^{-3}</td>
</tr>
<tr>
<td>SACTc</td>
<td>108 ± 51</td>
<td>212 ± 164</td>
<td>&lt;.025</td>
</tr>
</tbody>
</table>

**LEGEND:** p* = statistical comparison between indices in patients with the sick sinus syndrome and patients with normal sinus node function using unpaired t-test. "n.s." = not significant.

Numbers in parentheses "( )" represent number of patients with successful fitting of sequences by computer. "SNRT", "SNRTmax" = sinus node recovery time and maximal sinus node recovery time respectively. "q", "ΔT₁", and "T∞" are computed indices of sinus node automaticity, "SACTc" of sinoatrial conduction (see text in Chapter IV, and Appendix B for further discussion). Results of indices are expressed as mean ± one standard deviation.
b) **Computed Indices – Pacing Rate 130 beats per minute**

After right atrial pacing at 130 bpm, q was greater in "normals", .675 +/- .104 compared to .637 +/- .172 in the "sick sinus syndrome" (p< .05).

ΔT1 was 183 +/- 120 msec in "normals" and 243 +/- 131 msec in the "sick sinus syndrome" (difference not significant).
Again, the asymptotic cycle length, \( T_\infty \), showed the most significant difference, being 690 \( \pm \) 121 msec in "normals", and 931 \( \pm \) 198 msec in the "sick sinus syndrome" \( (p < .001) \).

The computed sinoatrial conduction time, \( SACT_c \), was significantly greater in the "sick sinus syndrome", 212 \( \pm \) 164 msec compared to 108 \( \pm \) 51 msec in "normals", \( (p < .025) \).

For both pacing rates, and for both "normals" and the "sick sinus syndrome", \( T_\infty \), but neither \( q \), \( \Delta T_1 \), nor \( SACT_c \), was strongly correlated with pre-pacing cycle length. Figure IV-6 illustrates the highly significant correlation \( (r = .87, p < 10^{-7}) \) between \( T_\infty \) and the pre-pacing cycle length with right atrial pacing at 100 bpm (cycle length 600 msec) in the patients with the sick sinus syndrome.
Figure IV-6

Plot of asymptotic cycle length ("T_\infty") against prepacing cycle length. In the patients with the sick sinus syndrome after overdrive atrial pacing at 100 beats per minute (pacing cycle length of 600 milliseconds). A strong correlation exists between the two parameters.
c) **Computed Indices - Subgroups of Sick Sinus Syndrome**

Comparison of computed indices of sinus node automaticity (q, ΔT1, and T∞) showed no differences between patients with sinus bradycardia, with sinoatrial exit block, and with brady- and tachy-arrhythmias. Only a few sequences after pacing at 100 bpm in those seven with sinoatrial exit block were suitable for computation (prolonged secondary pauses occurred in all the others). However, the mean computed sinoatrial conduction time in these was high (400 +/- 59 msec), being significantly longer than in the others with the sick sinus syndrome (167 +/- 100 msec; p < .005). Even when the subgroup of patients with sinoatrial exit block was excluded, this mean computed sinoatrial conduction time (167 +/- 100 msec) in the remaining patients with the sick sinus syndrome was still significantly greater than in normals (92 +/- 53 msec; p < .005).
d) **Computed Indices - "Type 1 Secondary Pause Sequences"**.

In the patients with the sick sinus syndrome, sequences of the "Type 1 Secondary Pause" (Figure III-8, top panel), with a short first and maximal second post-pacing interval were fitted. The sinoatrial conduction time was always computed to be a negative value. Figure IV-7 is a typical example of the plot of a computer fit to such a sequence with maximum second post-pacing interval, illustrating in particular the negative computed sinoatrial conduction time "SACT". If one pacing cycle length was added to this value, the sum was usually of the order of 50 to 100 msec greater than the sinoatrial conduction time fitted from the other sequences in the same patient.
**Figure IV-7**

Computer plot of measured and fitted post-pacing sequence using the mathematical model. The layout is as in Figure IV-5. The measured first post-pacing interval is short (939 msec) and less than the extrapolated first post-pacing interval, giving a negative computed sinoatrial conduction time ("SACT") of -140 msec.
<table>
<thead>
<tr>
<th>MEASURED (J)</th>
<th>BEAT</th>
<th>938.51</th>
<th>963.51</th>
<th>988.51</th>
<th>1013.51</th>
<th>1038.51</th>
<th>1063.51</th>
<th>1088.51</th>
<th>1113.51</th>
<th>1138.51</th>
<th>1163.51</th>
<th>1188.51</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>988.51</td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>4</td>
<td>1042.23</td>
<td>4</td>
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<td>6</td>
<td>1027.24</td>
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</tbody>
</table>

\[\text{TINV} = 841.84\]
E. DISCUSSION

By fitting this model to post-pacing sequences, if the assumptions of the mathematical model are correct, for the first time, the relative contributions of sinoatrial conduction and sinoatrial automaticity to the first post-pacing interval and initial post-pacing sequence can be derived. Further, the component of automaticity can be divided into simple measures of the amount of suppression ($\Delta T_1$), the recovery from suppression ($q$), and a measure of the intrinsic pacemaker rate ($T_\infty$). An excellent fit to the model was observed in the majority of the sequences. However, the model has some theoretical limitations, and accordingly the assumptions on which the model is based will now be discussed.
a) Assumptions of the Model

Detailed information on the response of the action potential of the sinus node pacemaker in man to overdrive pacing is not available, and extrapolation from observations made in animal experimentation is necessary.

i) constant action potential duration:

During rapid atrial pacing in experimental animals the action potential duration of pacemaker cells in the sinus node has been shown to shorten (Steinbeck et al., 1980). However, following pacing, the action potential duration of the first and subsequent beats appears relatively constant.
ii) \( \Delta V_p \), the difference between the maximum diastolic and threshold potential of the pacemaker cell, is constant.

Accurate data on this value from experimental animals has not yet, to my knowledge, been published, the major problem being inability to define the threshold potential, due to smooth transition from phase 4 to phase 0 (Kodama et al., 1980). Despite the observations of both hypopolarisation and hyperpolarisation after atrial overdrive pacing (Lu et al., 1965; Steinbeck et al., 1980), visual inspection of the published recordings (Kodama et al., 1980) suggests that the change in \( \Delta V_p \) is much smaller than the associated changes in the maximum diastolic potential and the threshold potential.
iii) capture and rest of the sinus node by all pacing stimuli

As has been discussed in Chapter III, recent experimental studies (Steinbeck et al., 1980; Kerr and Strauss, 1981) have shown that while this assumption holds for lower pacing rates, with higher pacing rates atriosinus block is seen. In the previous chapter (Figure III-8, top panel, "Type 2 Secondary Pause"), sequences with a short first post-pacing interval, maximally prolonged second interval, and subsequent decay were described. At pacing rates of 100 and 130 bpm, these were only seen in patients with the sick sinus syndrome or with "intermediate" sinus node function. It was postulated that such sequences resulted from atriosinus conduction block of paced stimuli, including the last. There appears reasonable circumstantial evidence that the assumption of sinus node capture by all pacing stimuli is often incorrect. However, as the response in animals to high rates of pacing is characteristically either 2:1 or 3:1 atriosinus block (Steinbeck et al., 1980; Kodama et al., 1980; Kerr and Strauss, 1981), the sinus node is probably being driven constantly at an exact multiple of the basic pacing cycle length. Indeed, the excellent fitting to the model of the majority of sequences suggested that although the assumption of sinus node capture by all paced stimuli may often be incorrect, the information derived from fitting
the model did not critically depend on sinus node capture by all paced beats.

When sequences with a short first post-pacing interval, maximum second interval, and decrease thereafter (Figure III-8 top panel, "type 1 secondary pause") were fitted by the model, a negative sinoatrial conduction time was always computed (Figure IV-6). If one pacing cycle length was added to this value, the sum was usually greater, by the order of 50 to 100 msec, than the sinoatrial conduction time computed from the other sequences in the same patients. This suggested the presence of partial electrical activation of the sinus node by the last paced stimulus, rather than complete atriosinus block (Steinbeck et al., 1980) (see Figure III-12).

If atrial pacing is performed at rates close to the resting rate, it is possible that a situation of isorhythmic sinoatrial dissociation may occur, as illustrated in Figure IV-8. In ladder diagram form, this figure shows how although the atrium is captured by every pacing stimulus, the sinus node can beat independently. Following termination of pacing, the first post-pacing interval may be increased by components ("δ") of sinoatrial conduction, but the subsequent intervals reflect the unchanged sinus rate ("s"). Such events are probably responsible for "Type 3" sequences, (Figure III-6, bottom panel) where only the
Figure IV-8

Ladder diagram of electrical activity of sinus node ("SAN") and high right atrium ("ATRIUM") and schematic representation of high right atrial electrogram recordings ("HRA"). If "p" (atrial pacing interval) and "s" (sinus node automatic interval) are similar, the atrium can be captured by atrial pacing without sinus node capture, so called "isorhythmic sinoatrial dissociation". Following such pacing, the first measured interval in the high right atrium is prolonged by a component "c" of sinoatrial conduction, which may vary between zero and the sum of retrograde and anterograde sinoatrial conduction time depending upon the temporal relationship of the last paced stimulus to the almost simultaneous sinus node impulse. The subsequent intervals in the high right atrium (assuming constant anterograde sinoatrial conduction time) measure the unchanged sinus node automatic interval.
first post-pacing interval is prolonged, and subsequent intervals behave as for pre-pacing, as described in Chapter III. The only indirect way of assessing whether isorhythmic sinoatrial dissociation is possibly present during studies of sinus node function in man is the absence of the characteristic progressive cycle length decrease (in "Type 1" sequences, Figure III-6, top panel) or other cycle length changes (for example "Type 2" sequences, Figure III-6, middle panel) following overdrive pacing.

iv) absence of pacemaker shifts

Pacemaker shifts in the sinus node have been observed in experimental animals in response to many interventions, including vagal stimulation (Bouman et al., 1968), single atrial premature beats (Bonke et al., 1969) and atrial pacing (Grant et al., 1979b). Without having firm supporting evidence in this study, pacemaker shifts were considered one possible explanation for sequences which could not be successfully fitted to the mathematical model. Sequences which showed change in P wave and atrial electrogram morphology without change in atrial activation sequence have already been described (Chapter III), and were considered to probably be on the basis of pacemaker shifts (Steinbeck and Lüderitz, 1977). However such sequences were not fitted to the mathematical model because of
the assumed pacemaker shift. (Initial experience with such sequences had shown that they frequently could not be fitted to the mathematical model, with discontinuities in the sequence at the time of change of P wave and atrial electrogram morphology (see Figure III-11)). One other finding suggested that pacemaker shifts may have been responsible for the failure to fit of some of the computed sequences. In the intermediate group of patients, difficulty was experienced in fitting sequences to the model in the patients expected to have frequent pacemaker shifts, namely those with marked sinus arrhythmia associated with high resting vagal tone.

If pacemaker shifts occur, not only are cells with different membrane properties acting as the pacemaker, but the sinoatrial conduction time may differ.

v) constant anterograde sinoatrial conduction time

Animal experiments have shown constant, reduced, and increased anterograde sinoatrial conduction time in the first beat following overdrive pacing (Grant et al., 1979b; Steinbeck et al., 1980). In Figure IV-9, panels A and B show in ladder diagram form, the hypothetical effect of a short anterograde conduction time (which increases in the subsequent beats) of the first post-pacing sinus node impulse. This will result in overestimation of the second
Figure IV-9
Ladder diagram of initial post-pacing sequence showing sinus node ("SAN") and high right atrial ("RA") electrical activity. Panel A illustrates that if anterograde sinoatrial conduction time is constant, and if there are no pacemaker shifts, the second and subsequent post-pacing intervals as measured in the high right atrium are equal to the sinus node automatic intervals ("Tb", "Tc", etc.). However, if there is a shorter anterograde sinoatrial conduction time which progressively increases in subsequent beats, (Panel B), the high right atrial intervals will overestimate the true sinus node automatic intervals. If there is a pacemaker shift in the initial post-pacing beat, (Panel C), the second interval will overestimate the true sinus node interval.
and subsequent intervals, which when fitted to the model will underestimate the computed sinoatrial conduction time. Depressed sinoatrial conduction of the first post-pacing beat will have the reverse effect. In the absence of further information, it appears reasonable for the present to assume constant anterograde sinoatrial conduction time following termination of overdrive atrial pacing in man.

vi) **constant and minimal intra-atrial conduction time**

The conduction velocity in animals has been shown to be much slower in the sinus node than in the atrium (in the rabbit heart, 2-6 cm/sec and 70 cm/sec respectively (Sano and Yamagishi, 1965)), and hence the contribution of intra-atrial conduction is likely to be small in patients with normal sinus node function. It is possible that because of the frequently associated intra-atrial conduction disturbances in the sick sinus syndrome (in this study, mean P wave duration 126 +/- 17 msec compared to 106 +/- 22 msec in normals; p < .0005), the contribution of intra-atrial conduction delay may be greater in the sick sinus syndrome.

A comment is appropriate here with regard to placement of the stimulating and recording catheters. For simplicity, initially it will be assumed that the stimulation and rec-
ording occurs at the same site. The sinoatrial conduction time assessed using the mathematical model (assuming that all the assumptions of the model are correct), will be the conduction time from the atrial pacing site to the sinus node and back. Obviously, the further this catheter is sited from the sinus node, the greater will be the overestimation of the sinoatrial conduction time. The second theoretical situation considered will be a stimulating catheter remote from the sinus node, for example in the coronary sinus, and the recording catheter positioned adjacent to the sinus node. The measured sinoatrial conduction time will be the conduction time into and out of the sinus node, if the recording catheter is positioned such that it records the atrial activation as it enters, and then as it leaves the sinus node. The error in this situation is likely to be small. The third theoretical situation to be considered is a pacing catheter located adjacent to the sinus node and the recording catheter remote from the sinus node. Here, the measured sinoatrial conduction time will be the conduction time from the pacing catheter to the sinus node, and from the sinus node to the atrium, plus a large component of intraatrial conduction to the recording catheter, less the conduction time from the pacing catheter to the recording catheter. If the last two values are almost equal, then the error involved will be small. However, here there is more potential for error to occur. In summary, the ideal situation is for
both the recording and stimulating catheter(s) to be positioned adjacent to the sinus node, however only if both are remote from the sinus node is the error likely to be large.

b) **Failure to Fit the Mathematical Model**

In the sequences considered suitable for fitting, the most common reasons for failure to fit, as assessed by the criteria stated in the methods were:

i) **negative q value** (oscillating sequence, see Figure IV-4).

This occurred when moderate beat-to-beat fluctuation was present despite a decreasing trend of the sequence, particularly if the second post-pacing interval was marginally less than the third, and is potentially correctable by modification of the computer programme.

ii) **residual mean square value over 1000**

In 2% of sequences, predominantly in patients with the sick sinus syndrome, the sequence was satisfactorily fitted, but with a high residual mean square value. As for i) above, this usually occurred when moderate beat-to-beat variation of a random character was present, possibly due to shift in pacemaker site.
iii) negative computed sinoatrial conduction time

The computer programme used for fitting sequences in this study was biased toward the earlier points, particularly the second (the first interval was not used in the curve fitting procedure). The explanation for this was that the second interval was the major contributor to the residual mean square, by being the point most removed from the asymptotic cycle length (that is \( \Delta T_2 \) was the largest of the calculated \( \Delta T_j \)). Accordingly, if there was an overestimation of the second post-pacing interval, the value of \( q \) was underestimated and \( \Delta T_1 \) overestimated. This effect was most marked if only five intervals were fitted, and only the second interval showed any major difference from the asymptotic cycle length.

There were several explanations as to why the second interval might be overestimated:

a) **error in measurement:** due to variation in chart speed, imprecise definition due to variation in high right atrial signal morphology, or error in observation (however, as already discussed, intra- and inter-observer error was small).
b) variation in sinoatrial conduction time with or without a pacemaker shift: Figure IV-9 shows, in ladder diagram form, how either more rapid conduction from the sinus node to the high right atrium (panel B), or a pacemaker shift (panel C), can lead to underestimation of the first and overestimation of the second post-pacing interval.

Change in sinus node action potential duration during atrial pacing (Steinbeck et al., 1980) may also influence the first post-pacing interval, and lead to underestimation of the computed sinoatrial conduction time if shorter than the action potential duration of the first beat following pacing.
c) **Value of Derived Indices**

Intra-and inter-patient fluctuations of derived indices were observed, particularly of $\Delta T1$, which may have reflected continuing changes in resting autonomic tone, or cumulative effects of pacing.

Despite this, both the computed sinoatrial conduction time SACTc, and the asymptotic cycle length showed significant differences between the patients with normal sinus node function and those with the sick sinus syndrome. Furthermore, in two patients with the sick sinus syndrome who had sinoatrial exit block on pre-study ECG, when sequences could be fitted, the computed sinoatrial conduction times were not only above the range in normals, but also significantly ($p < .005$) above the mean in the other patients with the sick sinus syndrome. This does support the idea that sinoatrial exit block relates primarily to impaired sinoatrial conduction, with marked first degree sinoatrial block when 1:1 conduction is present.

The common ratio of the geometric progression $q$, did not appear to be of value in distinguishing normal and abnormal sinus node function. If any differences were to be present, a higher value, that is a $q$ approaching
1.0, would be expected to occur in the patients with the sick sinus syndrome, as was observed at the pacing rate of 100 bpm. However, the significant difference in the opposite direction at the pacing rate of 130 bpm was confusing. It was possible that this related to much less suppression in the patients with the sick sinus syndrome due to atriosinus entrance block at the higher pacing rate.

Having observed significant differences in some of the new indices between patients with normal sinus node function and those with the sick sinus syndrome, it was considered important to test, as described in the next chapters, the effects of pacing site, rate, duration, and autonomic influences on both post-pacing sequences and computed indices of sinus node function.
CHAPTER V

EFFECT OF PACING RATE AND SITE ON POST-PACING SINUS NODE

SEQUENCES

A) INTRODUCTION

Most previous studies in man which have looked at the effect of pacing rate on the initial post-pacing events, have observed only minor differences in the sinus node recovery time after different rates and duration of pacing (Mandel et al., 1971; Kulbertus et al., 1975; Jordan et al., 1977). Maximal first post-pacing interval has usually been observed with pacing at 100-130 bpm (Kulbertus et al., 1975; Jordan et al., 1977). With pacing rate 150 bpm or above, in patients with normal sinus node function, a shorter first post-pacing interval has been observed (Mandel et al., 1971; Kulbertus et al., 1975). A recent study (Kasanuki, 1980) found an increase in the sinus node recovery time with increasing pacing rate only in patients with the sick sinus syndrome.

Animal experiments have suggested marked differences in the extent of suppression of the sinus node with different atrial and ventricular pacing sites (Lange, 1965). Studies in man have demonstrated more severe depression with atrial compared to ventric-
ular pacing (Mandel et al., 1972). However, no difference has been demonstrated in man between left and right atrial pacing (Tonkin et al., 1980a). If so, electrophysiology pacing study of the sinus node using only an oesophageal pacing electrode (Stopczyk et al., 1972; Brunetto et al., 1979; Kraska et al., 1979; Santini et al., 1979) should give the same results as pacing using pervenously introduced right atrial catheters.
This part of the study was performed with the aim of assessing the effect of both atrial pacing rate and atrial pacing site on post-pacing sequences, and in particular on indices of sinus node function as tested by application of the mathematical model of overdrive suppression of the sinus node.
B) METHODS

The effect of atrial pacing rate on sinus node function was assessed in subgroups of the total patient population; in ten patients with normal sinus node function ("normals"), twelve patients with sick sinus syndrome ("sick sinus syndrome"), and seventeen patients with intermediate sinus node function ("intermediate"). In addition to the procedure already described (Chapter II), overdrive pacing for one minute was performed for multiple trials at each of multiple pacing rates, namely 80, 100, 130, 180, and 200 bpm. Those rates selected in individual patients depended on the resting cycle length, the atrioventricular nodal Wenckebach threshold, and the symptomatic and haemodynamic tolerance of the rapid pacing. Trials with pacing rates of 180 bpm or 200 bpm were only performed when associated with 2:1 or Wenckebach atrioventricular block. The results from these two rates were pooled in the data analysis. Post-pacing sequences were digitised, plotted, and if suitable fitted to the mathematical model by computer as already described (Chapter IV).

The effects of atrial pacing site were assessed by multiple trials of overdrive pacing at 100 and 130 bpm from both the high right atrium and the coronary sinus in patients in whom a coronary sinus catheter had been positioned for investigation of possible tachyarrhythmias. There were fifteen such patients, seven with normal sinus node function, and eight with intermediate sinus...
node function as defined in Chapter II. The intervals measured after trials of pacing from the coronary sinus were those recorded in the high right atrium.

The effects of right ventricular compared to high right atrial pacing on overdrive of the sinus node were not compared in this study.

The values of the sinus node recovery time and the computed indices of sinus node function will be expressed for each group as the mean +/- one standard deviation.
c) RESULTS

a) Pacing Rate

i) conventional indices

Right atrial pacing at 180 and 200 bpm was well tolerated. The incidence of induced atrial fibrillation was lower than expected, being seen in three of eight trials in a single patient with the sick sinus syndrome, and in one patient classified prestudy as having intermediate sinus node function (on the results of the study he was treated as having the sick sinus syndrome). Furthermore, in only one patient was atrial fibrillation sustained, in the other patient terminating spontaneously within thirty seconds.

Table V-1 summarises the mean sinus node recovery time observed in the three groups of patients.
<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>INTERMEDIATE</th>
<th>SICK SINUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>10</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>age (years)</td>
<td>46.5 +/- 16.5</td>
<td>57.2 +/- 16.5</td>
<td>73.9 +/- 6.0</td>
</tr>
<tr>
<td>cycle length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(msec)</td>
<td>786 +/- 147</td>
<td>870 +/- 148</td>
<td>1018 +/- 171</td>
</tr>
<tr>
<td>SNRT (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 bpm</td>
<td>1037 (one pt.)</td>
<td>1103 +/- 162</td>
<td>1496 +/- 405</td>
</tr>
<tr>
<td>100 bpm</td>
<td>1025 +/- 118</td>
<td>1115 +/- 159</td>
<td>1295 +/- 176++</td>
</tr>
<tr>
<td>130 bpm</td>
<td>968 +/- 132</td>
<td>1130 +/- 221</td>
<td>1517 +/- 384</td>
</tr>
<tr>
<td>180, 200 bpm</td>
<td>908 +/- 160*</td>
<td>942 +/- 200</td>
<td>1880 +/- 977+</td>
</tr>
</tbody>
</table>

LEGEND: SNRT = sinus node recovery time, expressed as mean +/- one standard deviation.

* p < .05 when compared to result in same patients at 100 bpm.
+ p < .005 and ++ p < .0005 when compared to patients with normal sinus node function.
In the patients with normal sinus node function, no increases were seen in the first post-pacing interval (or sinus node recovery time) with increase in pacing rate (Table V-1). Indeed the mean sinus node recovery time at 180 and 200 bpm, 908 +/- 160 msec, was significantly less compared to 1025 +/- 118 msec at 100 bpm (p < .05). No prolonged secondary pauses were seen at any pacing rate in this group.

Figure V-1 shows a typical example from a patient in the normal group. At all pacing rates, the first post-pacing interval is maximally prolonged and there is a decrease to an initial minimum by the fifth or sixth interval. Of the first intervals, the longest value (978 msec) is seen at 100 bpm, although the difference from 130 bpm (931 msec) and 200 bpm (939 msec) is minor.
Figure V-1

Electrocardiographic recordings, in a patient with normal sinus node function, of sequences following overdrive atrial pacing for one minute at 100, 130, and 200 beats per minute respectively. The arrow points to the last paced stimulus at each pacing rate. Maximal prolongation is seen in the first post-pacing interval at each rate, with progressive decrease to a minimum by about the sixth interval. (Intervals measured from 100 mm/sec recording).
The mean sinus node recovery time in the patients with "intermediate" sinus node function also showed no increase with increase of pacing rate above 130 bpm (see Table V-1) with the sinus node recovery time at 180 and 200 bpm (942 +/- 200 msec) significantly less than at 100 bpm (1115 +/- 159 msec) (p < .005).

However, in patients with the sick sinus syndrome, the converse usually applied (Table V-1), with the sinus node recovery time increasing with increase in pacing rate, as illustrated in Figures V-2 and V-3. Figure V-2 contrasts the progressive increase in mean sinus node recovery time with increasing pacing rate in the sick sinus syndrome with the progressive decrease in normals. For example, the sinus node recovery time in the sick sinus syndrome significantly increased from 1295 +/- 176 msec at 100 bpm to 1880 +/- 977 msec at 180/200 bpm (p < .05).
Figure V-2

Block diagram showing the differences in the response to increased atrial pacing rate (100, 130, and 180/200 beats per minute respectively) between patients with normal sinus node function ("N") and with the sick sinus syndrome ("S") as measured by the pooled mean sinus node recovery time ("SNRT"). Bars represent one standard deviation of the mean.

In the patients with normal sinus node function, ("N"), the mean sinus node recovery time significantly decreases with increasing pacing rate (for SNRT at 180/200 bpm compared to 100 bpm, p < .05). In the patients with the sick sinus syndrome ("S"), the mean sinus node recovery time significantly increases with increasing pacing rate (for SNRT at 180/200 bpm compared to 100 bpm, p < .05).
EFFECT OF PACING RATE

3000  2800  2600  2400  2200  2000  1800  1600  1400  1200  1000  800  600  400  200  0

100 bpm  130 bpm  180-200 bpm

N  S  N  S  N  S
Figure V-3

Electrocardiographic recordings in a patient with the sick sinus syndrome showing changes in post-pacing sequences with increase of atrial pacing rate from 80 to 180 beats per minute. First post-pacing interval (sinus node recovery time) increases with pacing rate, being 1400, 1490, 2440, 3535, and 4995 msec at pacing rates of 80, 100, 130, 160, and 180 beats per minute respectively. Secondary post-pacing pauses are seen at pacing rates of 130, 160, and 180 beats per minute.
Figure V-3 illustrates typical ("Type 1" sequence - see Chapter III for further discussion) post-pacing sequences at 80 and 100 bpm and progressively longer first post-pacing interval with higher pacing rate. In addition, prolonged secondary pauses are seen at 130, 160, and 180 bpm. In eight of twelve patients in this group the first post-pacing interval was more than 100 msec greater at 180 or 200 bpm compared to 100 bpm (p < .005 compared to incidence in normals; chi-squared test). Further, prolonged secondary pauses occurred more frequently at 180 and 200 bpm compared to 100 bpm (p < .0001; chi-squared test), and occurred in two patients in whom they had not been observed at lower pacing rates.
ii) Computed indices

In two patients with sinus node dysfunction, although sequences at all pacing rates showed no secondary pauses, the first post-pacing interval progressively increased with increase in pacing rate (Figure V-4). Furthermore, the sequence after right atrial pacing at 200 bpm most closely mimicked that occurring after atrial flutter.

Post-pacing sequences at high pacing rates were more frequently unsuitable for fitting to the mathematical model, with frequent occurrence of ectopic beats, escape rhythms, variable P wave morphology, and prolonged secondary pauses (the last were only observed in patients with the sick sinus syndrome).
Electrocardiographic recordings, in another patient with the sick sinus syndrome, of post-pacing sequences after one minute of right atrial pacing at rates of 100, 130, and 200 beats per minute respectively, and after a paroxysm of atrial flutter. The first post-pacing interval progressively increases with increasing pacing rate.
In patients with normal sinus node function, indices $q$, $\Delta T_1$, $T_\infty$, and $SACT_c$ derived by computer fitting of post-pacing sequences to the mathematical model, showed no significant differences between the different pacing rates (Table V-2). In only four of twelve patients with the sick sinus syndrome were sequences at 180 and 200 bpm suitable for fitting to the mathematical model. The computed indices in these patients did not significantly change, although there was a trend for $q$, $\Delta T_1$, and $SACT_c$ to increase, and for $T_\infty$ to decrease with the higher pacing rates.
### TABLE V-2  EFFECT OF PACING RATE ON COMPUTED INDICES

<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>INTERMEDIATE</th>
<th>SICK SINUS SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10)</td>
<td>(17)</td>
<td>(12)</td>
</tr>
<tr>
<td><strong>100 BEATS PER MINUTE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRT</td>
<td>1025 ± 118</td>
<td>1115 ± 159</td>
<td>1295 ± 176*</td>
</tr>
<tr>
<td>( T_1 &lt; T_2 )</td>
<td>3/40</td>
<td>10/81</td>
<td>19/63 *</td>
</tr>
<tr>
<td>SAEB</td>
<td>0/40</td>
<td>0/81</td>
<td>8/63 *</td>
</tr>
<tr>
<td>computed</td>
<td>8/10</td>
<td>13/17</td>
<td>10/12</td>
</tr>
<tr>
<td>( q )</td>
<td>0.635 ± 0.209</td>
<td>0.659 ± 0.121</td>
<td>0.694 ± 0.113</td>
</tr>
<tr>
<td>( \Delta T_1 )</td>
<td>313 ± 280</td>
<td>307 ± 272</td>
<td>264 ± 259</td>
</tr>
<tr>
<td>( T_\infty )</td>
<td>696 ± 51</td>
<td>798 ± 137</td>
<td>946 ± 159*</td>
</tr>
<tr>
<td>SACTc</td>
<td>115 ± 77</td>
<td>176 ± 89</td>
<td>209 ± 133</td>
</tr>
<tr>
<td><strong>180/200 BEATS PER MINUTE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRT</td>
<td>908 ± 160</td>
<td>942 ± 200</td>
<td>1880 ± 977*</td>
</tr>
<tr>
<td>( T_1 &lt; T_2 )</td>
<td>7/40</td>
<td>19/56</td>
<td>12/51</td>
</tr>
<tr>
<td>SAEB</td>
<td>0/40</td>
<td>0/56</td>
<td>22/51 *</td>
</tr>
<tr>
<td>computed</td>
<td>7/10</td>
<td>7/17</td>
<td>4/12</td>
</tr>
<tr>
<td>( q )</td>
<td>0.658 ± 0.113</td>
<td>0.732 ± 0.156</td>
<td>0.802 ± 0.101*</td>
</tr>
<tr>
<td>( \Delta T_1 )</td>
<td>209 ± 304</td>
<td>151 ± 73</td>
<td>335 ± 254</td>
</tr>
<tr>
<td>( T_\infty )</td>
<td>666 ± 97</td>
<td>755 ± 140</td>
<td>805 ± 249</td>
</tr>
<tr>
<td>SACTc</td>
<td>115 ± 78</td>
<td>97 ± 68</td>
<td>263 ± 243</td>
</tr>
</tbody>
</table>

**LEGEND:** Indices of sinus node function, "SNRT", "q", "\( \Delta T_1 \)", "\( T_\infty \)"; "SACTc", are abbreviated as in previous text. "\( T_1 < T_2 \)" = first post-pacing cycle length less than (maximal) second, expressed as number of such sequences/ total sequences; "SAEB" = prolonged initial post-pacing intervals consistent with sinoatrial exit block, expressed as number of such sequences/ total sequences; * = significantly different (p < .05) to result in normals.
b) **Pacing site**

Table V-3 summarises the results of coronary sinus pacing compared to right atrial pacing.

No significant differences were found between high right atrial and left atrial pacing from the coronary sinus at either 100 or 130 bpm, as assessed by the mean sinus node recovery time, the common ratio of the geometric progression q, the first post-pacing cycle length prolongation ΔTl, the asymptotic cycle length $T_\infty$, and the computed sinoatrial conduction time SACTc.
<table>
<thead>
<tr>
<th>TABLE V-3</th>
<th>EFFECT OF ATRIAL PACING SITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing Rate</td>
<td>100bpm</td>
</tr>
<tr>
<td></td>
<td>RAP</td>
</tr>
<tr>
<td>SNRT (msec)</td>
<td>1049 +/- 148</td>
</tr>
<tr>
<td>q</td>
<td>.671 +/- .102</td>
</tr>
<tr>
<td>ATI (msec)</td>
<td>214 +/- 113</td>
</tr>
<tr>
<td>T_∞ (msec)</td>
<td>722 +/- 91</td>
</tr>
<tr>
<td>SACTc (msec)</td>
<td>109 +/- 74</td>
</tr>
</tbody>
</table>

**Legend:** "RAP" = high right atrial pacing; "CSP" = coronary sinus pacing; computed indices abbreviated as in previous text.
D) DISCUSSION

The most important finding was a different effect of increased pacing rate in patients with the sick sinus syndrome compared to those with normal sinus node function. Although the suppression of the sinus node, as assessed by the duration of the first post-pacing interval, in patients with normal sinus node function was significantly reduced at faster rates of pacing, in the patients with the sick sinus syndrome the reverse applied. That is, as the pacing rate was further increased, the suppression of the sinus node as measured by the first post-pacing interval continued to increase. The reason for the decrease seen with higher rates in patients with normal sinus node function is possibly related to increasing atriosinus conduction block (Steinbeck et al., 1980; Kerr and Strauss, 1981). This leads to lower effective rate of pacing of the sinus node and to shortening of the first post-pacing interval if the last atrial paced beat is the one with atriosinus conduction block. This latter situation has already been discussed in Chapter III. In patients with the sick sinus syndrome, atriosinus conduction block would be expected to, and probably does (see Chapter III) occur at lower pacing rates than in patients with normal sinus node function. It is paradoxical, that despite an expected increase in atriosinus conduction block with higher pacing rates, the sinus node recovery time continues to increase in patients with the sick sinus syndrome. The long pauses observed were usually multiples of the basic cycle length, suggesting sinoatrial exit block. It is therefore possible that
the increase in the first post-pacing interval relates to either sinoatrial exit block caused by rapid stimulation of the perinodal tissue, or that despite atriosinus block, the electrotonic interaction is sufficient to markedly depress the function of the (abnormal) sinus node.
Another point to be stressed is that the maximum post-pacing intervals were seen over a wide range of pacing rates in different individuals. Further, in different trials at a given rate in a single patient variations in the first post-pacing interval were seen. Hence both pacing at multiple rates up to much faster rates than have previously been recommended, and for multiple trials at each rate is recommended, if the sinus node recovery time is to be used as an index of sinus node function.

Pacing at faster rates produces fewer sequences suitable for fitting to the mathematical model, however if it produces very long pauses, further analysis appears unnecessary. Whether computed indices of sinus node function after high (compared to low) rates of pacing are of more value than after lower rates of pacing requires assessment in larger numbers of patients.
With regard to pacing site, it appears from this study, that left atrial pacing from the coronary sinus produces suppression of the sinus node comparable to high right atrial pacing. In addition to supporting the results of studies which have used oesophageal pacing for assessment of sinus node function in man (Brunetto et al., 1979; Kraska et al., 1979; Santini et al., 1979), this helps clarify the mechanism of overdrive suppression in man. In particular, it suggests that it is the propagated action potential, rather than the electrical stimulus per se, reaching the sinus node that is responsible for the phenomenon. It does not however exclude the release of neurotransmitters from nerve terminals in the sinus node as being responsible, although experimental evidence (Steinbeck et al., 1980) suggests acetylcholine release from vagal fibres occurs only with direct stimulation of the sinus node and not with pacing at a distal site.
Having studied the effects of pacing rate and site, comparison of the effects of single paced beats, as in the measurement of the sinoatrial conduction time by a single premature atrial beat, with the effects of one minute of overdrive atrial pacing appeared a simple way of assessing the effect of pacing duration on sinus node function in man.
CHAPTER VI

SINOATRIAL CONDUCTION TIME

A) INTRODUCTION

One direct method and two indirect methods have been proposed to assess the anterograde sinoatrial conduction time, that is, the time for conduction of electrical activity from the sinus node to the atrium. The direct method, recently described by the Columbia University group (Reiffel et al., 1980), uses special catheter placement and signal filtering techniques to obtain a sinus node pre-potential from which the anterograde sinoatrial conduction time can be measured. This method has yet to obtain acceptance as a useful clinical procedure, although very promising.

The indirect methods, by responses to atrial pacing, indirectly measure the sum of both retrograde conduction from the atrium to the sinus node and anterograde conduction from the sinus node to the atrium.
Following observations of Cushny and Matthews (1897), Wenckebach (1903), Eccles and Hoff (1934), and Bonke and coworkers (1968; 1969, 1971), on the effect of atrial premature beats on the sinus node, the premature atrial stimulus method was developed by Bigger and Strauss working at Columbia University (Strauss et al., 1973). Wenckebach (1903), described how late induced atrial beats failed to capture the primary pacemaker region of the heart (the classic paper of Keith and Flack (1907) on the anatomy of the sinus node had not yet been published), but earlier induced atrial beats caused the post-pacing pause to be less than compensatory. Figure VI-1 shows two figures from Wenckebach's paper, illustrating how he considered the difference between the basal sinus node interval and the atrial interval (or return cycle) after early atrial premature beats (which reset the sinus node) represented conduction time to and from the sinus node. Furthermore, he postulated that the increase in the return cycle with increasing prematurity of the paced atrial beat related to an increase in retrograde conduction time into the sinus node (Figure VI-1).
Ladder diagram of response of the sinus node to progressively more premature induced atrial beats. "Ve" represents superior vena cava, "A" atrium, and "V" ventricle. In "Fig. 2" (top panel), arrows point to premature atrial beats, which even when 8 time units premature, fail to reset the primary pacemaker region, "Ve", with fully compensatory pauses following. In "Fig. 3", more premature atrial beats capture and reset the primary pacemaker region, with less than compensatory pauses following the premature beat. Note in addition, the postulated increases of conduction time from "A" to "Ve" and from "A" to "V" with increasingly premature atrial beats.

Reproduced with permission of the publisher from the paper on the length of the compensatory pause following stimulation of the mammalian heart by K.F. Wenckebach, 1903.
K.F. Wenckebach
"Über die Dauer der compensatorischen Pause nach Reizung der Vorkammer des Saugetierherzens."
Archiv für Physiologie: Physiol Abt des Archives für Anatomie & Physiologie. 1903, p. 57-64.
The premature atrial stimulus method described by Strauss et al. (1973) (to be referred to as "SACT SM") uses this difference between the first atrial cycle (the "return cycle" or "Ar") after an atrial premature beat which resets the sinus node, and the prestimulus cycle length ("Al") as a measure of the sum of the anterograde and retrograde sinoatrial conduction time. If the return cycle is measured between consecutive high right atrial electrogram signals, assuming both that anterograde conduction time is constant, and that there is no suppression of sinus node automaticity by the premature atrial beat, then the return cycle ("Ar") is longer than the prestimulus cycle length by a component of both retrograde (atriosinus) and anterograde (sinoatrial) conduction.
It is here that the importance becomes apparent of the assumption that there is no suppression of the sinus node automaticity by the atrial premature beat, if the return cycle less the prepacing cycle (or "Ar - Al") is to be equated with the sinoatrial conduction time. Figure IV-2 (in Chapter IV), illustrates the situation if the sinus node is suppressed by even a single paced atrial beat. In this situation, the value "Ar - Al" would be expected to overestimate the conduction time. The prolongation of the post-return cycle ("A_{r+1}"), in addition to the return cycle ("Ar"), after atrial extrastimuli has been frequently observed, both in experimental studies (Eccles and Hoff, 1934; Bonke et al., 1969; Klein et al., 1973; Ticzon et al., 1975), and in man (Strauss et al., 1973; Strauss et al., 1976; Engel et al., 1976; Breithardt and Seipel, 1978; Narula et al., 1978), suggesting probable suppression of sinus node automaticity by the premature stimulus. The prolongation of the post-return cycle ("A_{r+1}") in man has been of the order of 2% of the resting cycle length (Strauss et al., 1976; Engel et al., 1976).
The second indirect method, as described by Narula (1978), uses the first post-pacing cycle after right atrial pacing for 8 beats at a rate 5-10 beats per minute above the sinus rate, the conduction time (to be referred to as "SACT NM"), being the difference between the return cycle and the mean pre-pacing cycle length. This latter value is obtained from the mean of 10 cycles pre-pacing. The major assumptions of this method are:

1) That the sinus node is captured by at least the last paced beat.

2) That sinus node capture will not suppress the sinus node, or if it does, that the order of magnitude of suppression will be a very small fraction of the conduction time.

Initial reports showed good correlation between both methods of indirect assessment of sinoatrial conduction time (Narula et al., 1978). Furthermore, the mean prolongation of the second post-pacing interval was found to be small (Breithardt and Seipel, 1978), and of similar magnitude to the observed prolongation of the post-return cycle in the premature atrial stimulus method (2.2% and 2.1% of pre-pacing cycle length respectively) (Narula et al., 1978).

This part of the study was performed to answer three questions. First, do the sequences following premature atrial stimuli, and the atrial pacing as performed in the Narula method, behave in a similar way to sequences after one minute of overdrive atrial
pacing of the sinus node? Second, if they do, can fitting of the mathematical model of overdrive suppression of the sinus node assess the relative contributions of sinoatrial conduction and sinoatrial automaticity to the first post-pacing interval? And finally, if a computed sinoatrial conduction time can be derived, how does it compare with the other measures of sinoatrial conduction time?
B) METHODS

i) Sinoatrial Conduction Time - Strauss Method (SACT SM)

The Strauss sinoatrial conduction time was assessed by inducing progressively more premature atrial extra-stimuli during sinus rhythm (Strauss et al., 1973). The distal electrode pair of the high right atrial catheter was paced as previously described for overdrive right atrial pacing, using now a timed extrastimulus after every 8 to 10 beats of (sensed) sinus rhythm. The coupling interval of the extrastimulus was commenced at the pre-pacing cycle length, and diastole was scanned by making the extrastimulus progressively more premature by 10 msec. decrements until atrial refractoriness ensued.
A continuous recording at 100 mm/sec chart speed was made of surface electrocardiogram leads and intracavitary recordings (see Chapter II - "Methods") during this stimulation protocol. Then cycle lengths between consecutive high right atrial electrograms were digitised and the resulting sequence of cycle lengths plotted against beat number. The test cycle, "At" (the coupling interval of the premature beat as measured between high right atrial electrogram recordings), and the return cycle, "Ar", were "normalised" for cycle length variation by dividing by the immediate pre-pacing cycle "Al" (Seipel et al., 1974), then the normalised return cycle "Ar/Al" was plotted against the normalised test cycle "At/Al", as illustrated in Figure VI-2.
Figure VI-2

Plot for derivation of sinoatrial conduction time from the response of the sinus node to premature atrial stimuli during sinus rhythm (Strauss et al., 1976). The return cycle (Ar), "normalised" by dividing by the prepacing cycle (Al), is plotted on the ordinate against the "normalised" test cycle (At/Al) on the abscissa. As the ratio At/Al decreases below unity, initially, in "c" the zone of "non-reset", the return cycles are fully compensatory, with Ar/Al falling on the line "a". Then, in "b", the zone of "reset", the pauses are less than compensatory, with Ar/Al falling below the line "a". The line of best fit "d" is calculated for all points in the zone of reset "b", excluding those designated "f", which are data points related to very early induced atrial premature beats with incomplete or complete interpolation of the atrial premature beat. Line "e" is parallel to the abscissa passing through the intercept of the lines "d" and "a", giving the value "(I)" of Ar/Al at the junction between the zones of non-reset and reset (see text for further explanation).
More than four different measures have been proposed to derive the sinoatrial conduction time from this plot. Strauss and coworkers proposed the use of the mean "Ar/Al" value in the last third of the reset zone (Strauss et al., 1973). Initially they proposed dividing this value by two to obtain an approximation to the anterograde conduction time. This was based on the assumption that anterograde and retrograde sinoatrial conduction times are equal. However, they then proposed using the unchanged mean "Ar/Al" value in the last third of the reset zone as the measure of the sum of the anterograde and retrograde sinoatrial conduction time, and not attempting an approximation to the anterograde sinoatrial conduction time (Strauss et al., 1976). Experimental work (Miller and Strauss, 1974; Steinbeck et al., 1978) has supported this decision, by showing that anterograde conduction time is usually greater than retrograde conduction time. Currently there is no method of accurately dividing the indirectly measured sinoatrial conduction time into its two components of anterograde and retrograde conduction. In two patients with marked prolongation of the postreturn cycle ("Ar+1"), the difference between the return cycle and the post-return cycle was considered a better approximation to the sinoatrial conduction time (Strauss et al., 1976), than that derived from the mean "Ar/Al" in the last third of
the reset zone.

The second proposed measure (Seipel et al., 1974) was the mean of all values of "Ar/Al" in the reset zone. Strauss has pointed out that as the test stimulus becomes more premature, the return cycle may become more "contaminated" by suppression of automaticity of the sinus node (Strauss et al., 1976).

The third proposed measure (Steinbeck and Lüderitz, 1975) was the "Ar/Al" value ("I" in Figure VI-2) at the intercept between the zones of reset and non-reset.

The fourth proposed measure, particularly of value when the onset of the reset zone is not clearly defined, was the mean value of "Ar/Al" when "At/Al" is between 0.40 and 0.60 (that is, the coupling of the premature beat is between 40% and 60% of the sinus cycle length) (Jewell et al., 1980).

Other measures have been proposed (Masini et al., 1975), but are minor variations on those already presented, and were not studied here.

Table VI-1 shows a summary of the results obtained by a selection of authors, and illustrates the variation in method of estimation of the sinoatrial conduction time.
<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>n</th>
<th>AGE*</th>
<th>DIAGNOSIS</th>
<th>METHOD**</th>
<th>SACT (A+R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauss et al., 1973</td>
<td>5</td>
<td>46-76</td>
<td>SSS</td>
<td>Last third of reset</td>
<td>68-156 (x2)</td>
</tr>
<tr>
<td>Seipel et al., 1974</td>
<td>5</td>
<td>32</td>
<td>N</td>
<td>All reset zone</td>
<td>77 ± 9</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>51</td>
<td>SSS</td>
<td>All reset zone</td>
<td>&gt;120 in 5</td>
</tr>
<tr>
<td>Dhingra et al., 1975</td>
<td>36</td>
<td>54 (28-83)</td>
<td>N</td>
<td>All reset zone</td>
<td>92 ± 30 (x2)</td>
</tr>
<tr>
<td>Masini et al., 1975</td>
<td>18</td>
<td>32-57</td>
<td>N</td>
<td>Last 5% of reset</td>
<td>140 ± 29</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>42-72</td>
<td>SSS</td>
<td>Last 5% of reset</td>
<td>254 ± 48</td>
</tr>
<tr>
<td>Steinbeck and Luderitz, 1975</td>
<td>5</td>
<td>45 ± 16</td>
<td>N</td>
<td>Intercept</td>
<td>56 ± 11 (x2)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>59 ± 28</td>
<td>SSS</td>
<td>Intercept</td>
<td>133 ± 25 (x2)</td>
</tr>
<tr>
<td>Strauss et al., 1976</td>
<td>19</td>
<td>66</td>
<td>SSS</td>
<td>Last third of reset</td>
<td>189 ± 88</td>
</tr>
<tr>
<td>Engel et al., 1976</td>
<td>20</td>
<td>--</td>
<td>N</td>
<td>All reset zone</td>
<td>169 ± 46</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>--</td>
<td>SSS</td>
<td>All reset zone</td>
<td>225 ± 105</td>
</tr>
<tr>
<td>Breithardt et al., 1977</td>
<td>20</td>
<td>32 ± 11</td>
<td>N</td>
<td>All reset zone</td>
<td>82 ± 19 (x2)</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>55 ± 15</td>
<td>SSS</td>
<td>All reset zone</td>
<td>126 ± 47 (x2)</td>
</tr>
<tr>
<td>Ueda et al., 1977</td>
<td>21</td>
<td>74 ± 7</td>
<td>N</td>
<td>Last third of reset</td>
<td>98 ± 22 (x2)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>76 ± 8</td>
<td>SSS</td>
<td>Last third of reset</td>
<td>137 ± 40 (x2)</td>
</tr>
<tr>
<td>Jewell et al., 1980</td>
<td>8</td>
<td>51</td>
<td>N</td>
<td>A_t/A_1 = 0.40 - 0.60</td>
<td>149 ± 45</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>60</td>
<td>SSS</td>
<td>A_t/A_1 = 0.40 - 0.60</td>
<td>295 ± 94</td>
</tr>
</tbody>
</table>

* Age in years is given as the mean with or without one standard deviation, or as the range. In the study of Engel et al., 1976, ages were not stated. ** For further explanation of the methods used by different authors see text. "n" = number of subjects studied; "N" = normal sinus node function; "SSS" = sick sinus syndrome; "SACT (A+R)" = anterograde plus retrograde sinoatrial conduction time, usually given as mean ± one standard deviation.
from the return cycle following a single premature atrial stimulus. Marked differences can be seen in the mean sinoatrial conduction time observed by different groups in patients with normal sinus node function. For example, the mean value of the sinoatrial conduction time varied between 77 msec (Seipel et al., 1974) and 184 msec (Dhingra et al., 1975). In Figure VI-2, the derivation of these measures is illustrated. The "At/Al" associated with the start of the zone of reset was visually selected from the plot, usually being between 0.65 and 0.85 (at "At/Al" of 0.79 in the plot shown in Figure VI-2). Then a line of best fit was calculated for the points below this value of "At/Al", with the exception of early points where a sudden decrease in the value of "Ar/Al" was seen (labelled "f" in Figure VI-2). This latter situation is probably due to failure of the pacing stimulus to fully reset the sinus node (Kerr et al., 1980). From this plot, the mean "Ar/Al" in the reset zone, and the value "I" of "Ar/Al" at the intercept of the line of best fit (labelled "d" in Figure VI-2) with the line of non-reset (labelled "a" in Figure VI-2), were calculated. The mean "Ar/Al" when "At/Al" was between 0.40 and 0.60 and in the last third of the reset zone were also calculated.
From these values were derived four different estimates of the sinoatrial conduction time, multiplying the mean of the prepacing cycles "Al" by the "Ar/Al" derived in the four different ways stated above:

1) from the last third of the reset zone,

\[ \text{SACT SM} = \text{mean } "Ar/Al" \text{ (last third of reset zone) } \times \text{ mean } "Al" \]

2) from the mean value of "Ar/Al" in the reset zone,

\[ \text{SACT SM (mean reset)} = \text{mean } "Ar/Al" \text{ (reset zone) } \times \text{ mean } "Al" \]

3) from the intercept of the line of best fit with the line of non-reset,

\[ \text{SACT SM (intercept)} = "I" \times \text{ mean } "Al" \]

4) from "At/Al" between 0.40 and 0.60,

\[ \text{SACT SM (0.40 - 0.60)} = \text{mean } "Ar/Al" \text{ (when } "At/Al" \text{ between 0.40 to 0.60) } \times \text{ mean } "Al" \]
The sequences following the premature atrial stimuli were also plotted (in the same format as described in Chapter III for post pacing sequences), with post extrastimulus cycle length on the ordinate and post extrastimulus beat number on the abscissa. These sequences were frequently found, as discussed in the results section of this chapter, to be suitable for fitting to the mathematical model of overdrive suppression of the sinus node. The method used, and criteria for fitting were as described in Chapter IV for sequences following overdrive atrial pacing.
Pre-pacing cycle length was recorded for up to one minute (a minimum of 10 consecutive cycles), and a mean "pre-pacing cycle length" was calculated from analysis of this recording. The right atrium was paced as described below. Pacing cycle length selected was, in the first twelve months of the study, started at the maximum cycle length below pre-pacing cycle length capable of obtaining atrial capture (Narula et al., 1978). Such pacing was continued for eight paced beats then ceased. After at least ten post-pacing cycles had been recorded, pacing was repeated for up to five trials at each of one or more pacing cycle lengths. The sinoatrial conduction time (SACT NM) was calculated by subtracting the mean pre-pacing cycle length from the first post-pacing cycle length. For each patient, a mean value of "SACT NM" was calculated from the SACT NM in the individual trials, and used in the data analysis. Atrial capture for the last three beats before cessation of pacing was considered necessary for the trial to be considered valid. Unusual results obtained from such pacing, such as negative or zero values for the sinoatrial conduction time (return cycle less pre-pacing cycle length) suggested the possibility that although the atrium was being captured, the sinus node was often not. The paper of Grant
and coworkers (1979b) gave strong experimental support to this concept, and accordingly, after the first year of this study, the pacing cycle length selected was 50 msec or more below the longest cycle length able to capture the atrium within eight beats.
The sequences following pacing were then digitised, and plotted (as previously described in Chapter III), and fitted, by computer (as previously described in Chapter IV) to the mathematical model of overdrive suppression.

In his paper describing his method of estimation of the sinoatrial conduction time, Narula (1978) used the mean of ten pre-pacing cycle lengths to measure the "resting" cycle length. Because of the marked cycle length variation frequently observed in both normal and sick sinus syndrome patients, it was decided to test the validity of using the mean of only ten cycles in the following way. In two normal patients long sequences of sinus rhythm were recorded in the resting state, and cumulative mean cycle length was calculated for 100 consecutive beats, and then plotted against the number of cycles.
The sinoatrial conduction time was assessed by the premature atrial stimulation method in ten patients with normal sinus node function ("normals") and in thirty patients with the sick sinus syndrome. The Narula method sinoatrial conduction time was assessed in nine patients with normal sinus node function and in twenty five patients with the sick sinus syndrome. In this chapter, as in Chapter IV, both conventional and computed indices will be expressed as the group mean +/- one standard deviation.
C) RESULTS

i) Sinoatrial Conduction Time – Strauss Method

a) conventional indices

In Table VI-2 are shown the results in the ten patients with normal sinus node function in whom the sinoatrial conduction time was estimated by the premature atrial stimulus method of Strauss. There were no significant differences (one way analysis of variance) between pooled mean values of any of the four indices tested, namely, the sinoatrial conduction times derived from the last third of the reset zone (161 +/- 55 msec), from the mean reset value (160 +/- 37 msec), from the intercept value (158 +/- 52 msec), and from "At/Al" between 0.40 and 0.60 (153 +/- 26 msec). In only four patients (#215, #238, #305, #429) were there major differences between these four indices (see Table VI-2). In patient #215, the sinoatrial conduction time varied from 114 to 202 msec, and in patient #305, from 73 to 130 msec according to the method used to estimate the sinoatrial conduction time. It should be stressed that for each patient these different estimates were derived from the same data.

The Strauss sinoatrial conduction time could be calculated from the plot of "Ar/Al" against "At/Al" (see Fig-
<table>
<thead>
<tr>
<th>Patient</th>
<th>SACT last</th>
<th>SACT mean reset</th>
<th>SACT intercept</th>
<th>SACT At/Al</th>
</tr>
</thead>
<tbody>
<tr>
<td># 215</td>
<td>173</td>
<td>158</td>
<td>202</td>
<td>114</td>
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<td># 230</td>
<td>168</td>
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<td>124</td>
<td>131</td>
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<td>206</td>
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<td>211</td>
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<td># 305</td>
<td>93</td>
<td>114</td>
<td>73</td>
<td>130</td>
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<td>not defined</td>
<td>not defined</td>
<td>172</td>
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<td>169</td>
<td>157</td>
<td>173</td>
</tr>
<tr>
<td># 429</td>
<td>281</td>
<td>224</td>
<td>233</td>
<td>177</td>
</tr>
</tbody>
</table>

mean +/-

one s.d. 161 +/- 55 160 +/- 37 158 +/- 52 153 +/- 26

Last third of reset, mean reset, intercept, and At/Al = 0.40 - 0.60, refer to the method of derivation of sinoatrial conduction time (from the same data plotted as in Figure VI-2; refer to text for further explanation).
ure VI-2) in 25 of 30 patients with the sick sinus syndrome (Table VI-3). Of the 5 of the 30 patients in whom the sinoatrial conduction time could not be calculated, sinoatrial exit block (two patients), scatter of values (two patients), and frequent atrial premature beats (one patient) prevented meaningful analysis of the data. In two other patients, (#351, #412), the reset zone was poorly defined, and an estimate of sinoatrial conduction time could only be derived using the fourth method above, namely from the mean "Ar/Al" when "At/Al" was between 0.40 and 0.60.
<table>
<thead>
<tr>
<th>Patient</th>
<th>SACT last third of reset</th>
<th>SACT mean reset</th>
<th>SACT intercept</th>
<th>SACT $A_t/A_1$ = 0.40 - 0.60</th>
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</thead>
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<td>#193</td>
<td>141</td>
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<td>251</td>
</tr>
<tr>
<td>#351</td>
<td>---reset zone poorly defined---</td>
<td></td>
<td></td>
<td>282</td>
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<td>#361</td>
<td>157</td>
<td>180</td>
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<td>#372</td>
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<td>335</td>
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</table>

mean ±

one s.d. 195 ± 70 213 ± 69 192 ± 52 230 ± 76

Sinoatrial conduction time "SACT" is expressed in milliseconds. "Last third of reset", "mean reset", "intercept", and "$A_t/A_1 = 0.40 - 0.60$" represent the four methods used for derivation of the sinoatrial conduction time from the plot of $A_t/A_1$ against $A_t/A_1$ (see text for further explanation).
The mean values of the sinoatrial conduction time calculated in this group were 195 +/- 70 msec from the last third of the reset zone, 213 +/- 69 msec from the mean reset value, 192 +/- 52 msec from the intercept value, and 230 +/- 76 msec from "At/Al" between 0.40 and 0.60.

In fourteen patients in this group, the regression line had a negative slope, (that is, "Ar/Al" increasing with decreasing value of "At/Al", as shown in Figure VI-2). Such a slope was associated with marked increase (up to 95%) in the value of the sinoatrial conduction time derived from "At/Al" between 0.40 and 0.60, compared to that derived from the intercept value (for example, the results in patient #193 in Table VI-3, with increase from 128 msec ("intercept") to 223 msec ("At/Al" between 0.40 and 0.60)).
In four patients the opposite was observed, with a positive slope of the regression line. In the remaining five patients, the regression line had minimal or zero slope, with all estimates of sinoatrial conduction time being almost identical in a given patient.

When the results were compared between normals and sick sinus syndrome, the mean values of the last three tests (mean reset, intercept, and "At/Al" between 0.40 and 0.60) were significantly greater in the sick sinus syndrome (p < .025, p < .05, and p < .005 respectively). The mean values calculated from the "Ar/Al" in the last third of the reset zone were not significantly different (0.2 > p > 0.1) between the two groups of patients.
b) sequences following single premature atrial stimuli

Figure VI-3 shows an electrocardiogram recorded during a Strauss conduction time determination, and is representative of those observed in this patient. It demonstrates maximal prolongation of the first interval following the atrial premature beat and progressive decay of the subsequent cycle length, as typically seen following one minute of overdrive pacing (see Chapter III). The unusual feature in this figure is that the sum (1442 msec) of the test cycle ("At" = 518 msec) and the return cycle ("Ar" = 924), is 132 msec greater than twice the prepacing cycle length (2 * "Al" = 1310 msec). In other words, the post-pacing interval ("Ar") was more than compensatory. The prolongation of subsequent post extrastimulus cycles is also emphasised. This sequence is suggestive of marked overdrive suppression of the sinus node by the single atrial premature beat. The typical electrocardiogram recorded in the majority of patients showed maximal prolongation of the first post-pacing cycle and progressive decrease toward the prepacing cycle length within five or more cycles. However, in the zone of reset, the sum "At + Ar" was usually less than 2 x "Al".

Figure VI-4 is a plot of cycle length against beat number from the Strauss conduction time determination in patient #372, selected to demonstrate the obvious pro-
Figure VI-3

Electrocardiographic recording of lead II showing prolongation of not only the first (924 msec) but also subsequent intervals (791, 755, 688, 684, and 675 msec respectively) following a single atrial extrastimulus. The sum (1442 msec) of the test cycle (At = 518 msec) and the return cycle (Ar = 924 msec) is greater than double (1310 msec) the pre-pacing cycle length (Al = 655 msec). When Ar/Al was plotted against At/Al as in Figure VI-2, this point fell above the compensatory line (labelled "a" in Figure VI-2). Intervals were measured, using the digitiser, between consecutive high right atrial electrogram signals on synchronous recording at 100 mm/sec chart speed.
Figure VI-4

Plot of cycle length against beat number during sinoatrial conduction time estimation using single premature atrial stimuli. For purposes of illustration, responses to many extrastimuli are excluded although all followed the same pattern. The extrastimuli can be seen in a progressively descending pattern in the lower half of the figure. The sequences following the extrastimuli with shorter coupling intervals, show maximally prolonged first interval and progressive decrease until the sixth to eleventh interval.
longation in the reset zone of the post-return cycles \( A_{r+1}, A_{r+2}, \ldots, A_{r+n} \) in addition to the expected prolongation of the return cycle \( A_r \) after each induced premature beat (seen as a descending sequence in the lower half of the figure). Late premature beats, in the zone of "non-reset" (as with the first premature beat in Figure VI-4) failed to influence the intervals after the return cycle \( A_r \), which was fully compensatory \( (A_t + A_r = 2 \times A_l) \).
Although usually less marked than in the illustrated examples, similar sequences were observed in the majority of patients. In fact, of the ten patients with normal sinus node function and of the thirty with sick sinus syndrome who had the Strauss sinoatrial conduction time performed, in seven normals and in nineteen with the sick sinus syndrome, some or all of the sequences in the reset zone satisfied the criteria for fitting by computer to the mathematical model of overdrive suppression of the sinus node.

c) computed indices - single premature atrial beats

From these sequences, indices of automaticity, $q$, $\Delta T_l$, and $T_\infty$, and the sinoatrial conduction time, $SACTC$, were computed by curve fitting analysis. Figure VI-5 shows an example of the curve fitted by computer to one such sequence. The similarity to the fitting by computer to sequences following overdrive atrial pacing (as in Figures IV-5 and IV-7) is stressed.

Both for patients with normal sinus node function, and for those with the sick sinus syndrome, the mean computed sinoatrial conduction time (103 +/- 17 msec and 160 +/- 67 msec respectively), was significantly less than conventional sinoatrial conduction time derived (using
Figure VI-5

Computer plot of fitted sequence (represented by stars) derived from measured sequence (represented by circles) following a single early atrial extrastimulus. Cycle length ("FPBCLT T(J)"") is plotted on the horizontal axis against beat number ("J") on the vertical axis. "TINF" represents the asymptotic cycle length. The difference between measured and extrapolated first post-pacing interval, the computed sinoatrial conduction time, is labelled "SACT".
"Ar/Al" in the last third of the reset zone) from the same post-pacing events, being 180 +/- 62 msec for normals (p < .005), and 202 +/- 60 msec for the sick sinus syndrome (p < .05).
Tables VI-4 and VI-5 show the computed indices in patients with normal sinus node function and the sick sinus syndrome respectively. Both the computed sinoatrial conduction time (103 +/- 17 msec) and the asymptotic cycle length, $T_\infty$ (736 +/- 175 msec), in patients with normal sinus node function were significantly less ($p < .025$ for both) than in patients with the sick sinus syndrome (computed sinoatrial conduction time 160 +/- 67 msec, and $T_\infty$ 919 +/- 175 msec). The other indices of automaticity, q, and $\Delta T_1$, failed to show significant differences between the two groups.

In three patients (two with the sick sinus syndrome and one with normal sinus node function) in whom scatter of data prevented definition of the zone of reset and hence calculation of the conventional sinoatrial conduction time, $SACT_c$ could be computed from one or more sequences.

The indices computed from fitting of sequences following premature atrial beats showed minor differences when compared to those derived from the sequences following one minute of overdrive pacing (Appendix D). For example, in the patients with normal sinus node function, at 100 beats per minute q was .632 +/- .123, $T_\infty$ 736 +/- 79 msec, and $SACT_c$ 92 +/- 53 msec. None of these were significantly different from q (.675 +/- .155), $T_\infty$ (736 +/-
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mean ± lsd. 180 ± 62  103 ± 17  .675 ± .155  136 ± 78  736 ± 175

**LEGEND:** "SACT SM" is conventionally derived sinoatrial conduction time (Strauss et al., 1976) from the last third of the reset zone; "SACTc" is computed sinoatrial conduction time; "q", "ΔT₁", and "T₀" are computed indices of automaticity abbreviated as in previous text.
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mean ± 1 s.d.  202 ± 60  160 ± 67  .643 ± .155  145 ± 143  919 ± 175

**LEGEND:** As for Figure VI-4; "SACT" is conventionally derived sinoatrial conduction time (using the last third of the reset zone), and is added for purposes of comparison; "SACTc" is computed sinoatrial conduction time; indices of automaticity "q", "AT₁", and "T₀" abbreviated as in previous text; * in patients #272 and #351 only one sequence could be successfully fitted by computer.
175) msec, and SACTc (103 +/- 17) msec from computing the Strauss sinoatrial conduction time sequences. Only 
\( \Delta T_1 \) (232 +/- 134 msec), was significantly greater after 
right atrial pacing at 100 beats per minute (compared to 
136 +/- 78 msec with Strauss sinoatrial conduction time; 
p < .05). In the sick sinus syndrome, when the computed 
indices after single atrial premature beats were comp-
ared to right atrial pacing at 100 beats per minute, \( \Delta T_1 \) 
and \( q \) were significantly greater with the latter. With 
the single premature beat, \( \Delta T_1 \) was 145 +/- 143 msec, and 
after pacing at 100 beats per minute 250 +/- 123 msec (p 
< .01). With the single premature beat, \( q \) was .643 +/- 
.155 and with pacing at 100 beats per minute, .720 +/- 
.092 (p < .025).

ii) Sinoatrial Conduction Time – Narula Method

a) mean cycle length

Figure VI-6 shows, from one of the two patients in whom 
this was studied, a plot of cumulative mean cycle length 
against number of sinus cycles. This was calculated from 
a long recording of sinus rhythm after the ten minute 
rest period that followed catheter insertion. The resul-
ts obtained in the other patient were similar, showing, 
as in Figure VI-6, large variation in the first ten cyc-
Figure VI-6

Plot of cumulative mean of cycle length against number of beats, taken from pre-pacing cycle length recording over two minutes after ten minute rest period. The mean taken from less than twenty beats is less representative than that taken from more than fifty beats.
les. After fifty cycles, there was minimal variation in the cumulative mean, suggesting that this cumulative mean was a better representation of the mean prepacing sinus node cycle length than the mean of ten or twenty cycles.

b) sinoatrial conduction time - Narula method

In Tables VI–6 and VI–7 the sinoatrial conduction time as conventionally measured by this method is presented. In nine patients with normal sinus node function the mean sinoatrial conduction time was $184 \pm 97$ msec. In twenty five patients with the sick sinus syndrome the mean sinoatrial conduction time was $242 \pm 119$ msec. These mean values were not significantly different, and only seven of the twenty-five patients with the sick sinus syndrome had a sinoatrial conduction time greater than $281$ msec ($=184 + 97$ msec; the mean value plus one standard deviation in the patients with normal sinus node function), indicating a low sensitivity of the test.

c) sequences

In the majority of sequences in both patients with normal sinus node function and in patients with the sick sinus syndrome, the first post-pacing interval was max-
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Mean ± 1 s.d.    184 ± 97  100 ± 51  .716 ± .144  178 ± 51  722 ± 114

LEGEND: "Pt. No." = patient number; "CL" = pre-pacing cycle length; "PaCL" = pacing cycle length; "T₁" = first post-pacing cycle length; "SACT NM" = sinoatrial conduction time derived by the Narula method; "SACTc" = computed sinoatrial conduction time; "q", "ΔT₁", and "T∞" are computed indices of automaticity abbreviated as in previous text. * Sequences in patient #206 were unsuitable for computation (note similarity between pacing cycle length and pre-pacing cycle length).
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<td>130</td>
<td>983</td>
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<tr>
<td>#428</td>
<td>1013</td>
<td>865/830</td>
<td>1172</td>
<td>159</td>
<td>127</td>
<td>.753</td>
<td>77</td>
<td>969</td>
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<tr>
<td>#431</td>
<td>945</td>
<td>840</td>
<td>1277</td>
<td>270</td>
<td>229</td>
<td>.629</td>
<td>234</td>
<td>898</td>
</tr>
</tbody>
</table>

Mean ± one standard deviation: 194 ± 72

Legend: "Pt." = patient number; "CL" = pre-pacing cycle length; "PaCL" = pacing cycle length(s); "T₁" = first post-pacing cycle length; "SACT NM" = Narula method sinoatrial conduction time; "SACTc" = computed sinoatrial conduction time; "q", "ΔT₁", and "T₀" computed indices of automaticity as described in text; in patients #193, #208, and #375, no post-pacing sequences were suitable for computation.
imally prolonged with progressive decrease of subsequent post-pacing intervals, as had been seen after overdrive atrial pacing for one minute (Chapter III), and after single atrial premature beats causing sinus node reset (presented earlier in this Chapter). This pattern was seen in 45/64 sequences in normals, and in 124/176 sequences in patients with the sick sinus syndrome. When the pacing cycle length was within 50 msec of the pre-pacing cycle length, the first post-pacing interval usually showed prolongation, but subsequent cycles did not show a progressive decrease.

d) computed indices

In the nine patients with normal sinus node function, 45/64 sequences satisfied the criteria for fitting to the mathematical model (see Chapter IV). Indices of sinoatrial conduction and automaticity were computed from the 35 (of 45) sequences successfully fitted (computed indices are presented in Table VI-6). In the twenty five patients with the sick sinus syndrome, 124/176 sequences similarly satisfied the criteria for fitting to the mathematical model, and indices of sinoatrial conduction and automaticity were computed in 92 (of 124) sequences successfully fitted (see Table VI-7). Of the mean values of the computed indices, only the asymptotic cycle length $T_\infty$, and the computed sinoatrial
conduction time SACTc, were significantly different between patients with normal sinus node function and the sick sinus syndrome (722 +/- 114 msec and 981 +/- 182 msec respectively for T\text{\textsubscript{N}} (p < .0005); 100 +/- 51 msec and 155 +/- 72 msec respectively for SACTc (p < .05)). This latter difference should be stressed, as the mean sinoatrial conduction time conventionally measured (Narula et al., 1978) was not significantly different in the patients with the sick sinus syndrome compared to the patients with normal sinus node function.

The computed sinoatrial conduction time in both patients with normal sinus node function (100 +/- 51 msec) and with the sick sinus syndrome (155 +/- 72 msec), was significantly less than the sinoatrial conduction time conventionally derived in the respective group (184 +/- 97 msec in normals (p < .025); and 242 +/- 119 msec in the sick sinus syndrome (p < .005)).

The computed indices from the Narula conduction time were similar to the indices of sinus node function computed from the sequences following right atrial pacing for one minute, and following single atrial premature beats (Appendix D).

D) DISCUSSION

The theoretically ideal situation for both these indirect tests of sinoatrial conduction is capture of the sinus node by the
atrial pacing, but no suppression of automaticity, so that the first post-pacing interval represents the stable sinus node cycle length plus the anterograde and retrograde sinoatrial conduction time. This is illustrated in ladder diagram form for the Narula sinoatrial conduction time in Figure VI-7, Panel A. The same figure would apply to the Strauss sinoatrial conduction time if there was only a single atrial paced beat. In practice, theoretical and practical limitations apply to both tests and will now be discussed.
Figure VI-7
Ladder diagram of sinus node ("SAN") and high right atrial ("HRA") electrical activity. Panel A represents the ideal theoretical situation for the Narula conduction time. The last two of eight paced beats in the high right atrium capture the sinus node, reset it, but do not suppress its automaticity, with "Ta, Tb, ..., Tf" being equal. If anterograde sinoatrial conduction time of the post-pacing beats is also constant, the measured intervals "PPCL(2), ...., (6)"are equal to "Tb, ..., Tf". If in addition, "PPCL(2)" is equal to the pre-pacing cycle length, then PPCL(1) less the pre-pacing cycle length is equal to the sum of the retrograde and anterograde sinoatrial conduction time. Panel B represents the more probable situation with suppression of automaticity by the pacing such that "Ta > Tb > Tc >Td > Te".
i) Sinoatrial Conduction Time - Strauss Method

Despite the many publications on measurement of the sinoatrial conduction time by the premature atrial stimulus method, the best method of estimation of the conduction time from the data remains unresolved (Strauss et al., 1973, 1976; Seipel et al., 1974; Steinbeck et al., 1975; Masini et al., 1975; Engel et al., 1976; Jewell et al., 1980). To my knowledge, more than four measures have been proposed for this estimation, all using in different ways the points in the zone of "reset". As described in the Methods section of this chapter, these are, the mean value of the "normalised" return cycle ("Ar/Al") in, first, the last third of the reset zone (Strauss et al., 1976), second, the whole of the reset zone (Seipel et al., 1974), third, the part of the reset zone defined by "At/Al" between 0.40 and 0.60 (Jewell et al., 1980), and finally, the value at the intercept between the zones of reset and non-reset (Steinbeck and Lüderitz, 1975). Usually these values can all be determined, and it was found in this study that the mean values of these different measures did not differ significantly within each of the two groups studied. However, in some patients, including 19 with the sick sinus syndrome and 4 with normal sinus node function, marked differences were seen in the values of the sinoatrial conduction time derived from these four measures. In the 19 patients with the sick sinus syn-
drome in whom marked differences were observed, the value of
the normalised return cycle ("Ar/Al") either increased
(14/19) or decreased (5/19) as the value of the normalised
test cycle ("At/Al") decreased. The possible explanations
for these changes become apparent when the theoretical
problems associated with this method of assessment of the
sinoatrial conduction time are discussed.
a) theoretical problems

Strauss (1976, 1978b) has previously discussed the limitations of this method, but some points will be considered here that are of relevance to the application of the mathematical model to sequences following single premature atrial beats:

i) failure of sinoatrial node capture despite, apparent reset in the last third of the reset zone. Miller and Strauss (1974) in animal experiments showed shortening of the action potential duration by induced atrial extrastimuli via a probable electrotonic interaction, producing apparent reset of the sinus node in the absence of capture.
ii) **prolongation of retrograde atriosinus conduction** in response to early premature stimuli. Wenckebach (1903) first proposed that this was the explanation of the slight increase observed in the return cycle in the reset zone with increasing prematurity of the atrial extrastimulus. This has been shown to occur in animal experiments (Miller and Strauss, 1974; Steinbeck et al., 1978).

iii) **pacemaker shifts** have been shown in animal experiments to be a common response of the sinus node to atrial pacing. Both lateral and inferior shifts from the primary pacemaker region have been shown to occur in response to single atrial paced beats, although the magnitude of such shifts may be only of the order of one or two millimetres (Bonke, 1968; Bonke et al., 1969). There is currently no direct information available on the nature and magnitude of such shifts in the sinus node of man.

iv) **suppression of automaticity**

Eccles and Hoff (1934) proposed on the basis of their observations in the sinus node of the cat, that all the prolongations (relative to the pre-pacing cycle) of the return cycle in the reset zone were due to suppression of automaticity. Even though this assumpt-
ion is not fully correct, in that at least part of the prolongation relates to retrograde and anterograde sinoatrial conduction, there is good evidence that in man suppression by premature beats is common, with the mean post-pacing cycle ("A_{t+1}"") being of the order of 2% greater than the pre-pacing cycle ("A_{l}"") (Strauss et al., 1976; Narula et al., 1978).
When the plot of data is made for derivation of the sinoatrial conduction time, an interplay of the above points i) to iv) probably accounts for the relationship between the return cycle and the test cycle seen within individual patients. In this study, the observed sequences of intervals following single atrial premature beats suggested that suppression of automaticity was common in both patients with normal sinus node function and in patients with the sick sinus syndrome.
ii) Sinoatrial Conduction Time - Narula Method

Because a wide range of values for this index was observed, attention was directed toward the method of assessing the pre-pacing cycle length. Narula and coworkers (1978) proposed using the mean of ten prepacing cycles. As has been presented, the mean of more than fifty beats was found to be a much more representative cycle length. However, even estimation of the mean cycle length in this way still failed to take into account the transient fluctuations of cycle length due to changes in autonomic tone at the time of cessation of pacing. It therefore seemed a useful approach to look at the sequence following pacing, as had already been done with the sinus node recovery time and the Strauss method sinoatrial conduction time.
Two types of sequence were typically seen. First, when the pacing cycle length was within 50 msec of the pre-pacing cycle length, the intervals after pacing often behaved as though they were uninfluenced by the pacing (with the exception of the first interval which was usually longer—this can be explained without needing to postulate sinus node capture). Animal experimental evidence (Grant et al., 1979b) suggested strongly that this was due to isorhythmic sinoatrial dissociation, as has been discussed in Chapter IV. In this situation (see Figure IV-8), the pacing captures the atria but not the sinus node, with the latter still spontaneously discharging at a similar time and rate to the atrial pacing. That is, the artificial pacemaker and the sinus node are beating independently and not influencing each other. When the atrial pacing stops, the sinus node is again able to capture the atria. This may in part explain the strong dependence of the Narula sinoatrial conduction time on pacing cycle length (Breithardt and Seipel, 1978). The following circumstantial evidence supported the presence of isorhythmic sinoatrial dissociation. In some patients, single atrial premature beats caused significant depression of automaticity, as assessed by the post-pacing sequence. However, no evidence for suppression of automaticity was seen during the Narula method conduction time if it was done with atrial pacing cycle length close to pre-pacing cycle length.
Second, the majority of sequences resembled those following overdrive pacing for one minute, with maximally prolonged first post-pacing interval and progressive decrease in subsequent 5-15 cycles. These sequences were also similar to those that followed single atrial premature beats, and again were suitable for fitting to the mathematical model of overdrive suppression of the sinus node.

The application of the mathematical model to both types of sequence observed in these two tests used to estimate the sinoatrial conduction time will now be discussed.

iii) Application of Mathematical Model of Overdrive Suppression of the Sinus Node to Sequences Observed during estimation of the Sinoatrial Conduction Time

a) general comments

Sequences following a single atrial premature beat and following eight paced beats in the Strauss and Narula sinoatrial conduction time estimations respectively, were successfully fitted to the mathematical model of overdrive suppression. The indices so derived suggested that the first post-pacing interval contained a major component of suppression of automaticity, of the same order of magnitude as the computed sinoatrial conduction
time. The latter was significantly less than the conventional sinoatrial conduction time for both types of test. The indices computed from the sequences in both types of test were qualitatively similar to those computed from sequences following one minute of overdrive atrial pacing (see Appendix D). The computed indices did suggest a lesser magnitude of suppression of the sinus node, compared to overdrive atrial pacing for one minute. This particularly applied to the sequences following a single premature beat.

b) observations on application of mathematical model to sequences following single atrial premature beats
Wenckebach (1903) proposed that the sinoatrial conduction was responsible for the prolongation of the first interval after an atrial premature beat. A contrary view was proposed by Eccles and Hoff (1934), who proposed that the prolongation was a result of suppression of sinus node automaticity. The evidence of this study suggests that both sinoatrial conduction and suppression of automaticity contribute, by the same order of magnitude, to the prolongation of the first interval following atrial premature beats. In other words, this study suggests that suppression of automaticity by single atrial premature beats contributes a much greater component to the first post-pacing interval than has previously been recognised.
The analysis of computed data from Strauss sinoatrial conduction time sequences in this study does not provide a clear answer as to whether increase in retrograde sinoatrial conduction time, or suppression of automaticity, accounts for the frequently observed negative slope of the plateau phase (see Figure VI-2).

In several patients in whom all sequences following atrial extrastimuli could be fitted to the model, and in whom early atrial extrastimuli caused apparent sinus node reset, there was a further increase in the post return cycle ("A_{r+1}"), when "At/Al" was less than 0.50. When such sequences were computed, a negative value was derived for the sinoatrial conduction time. The probable explanations for this include pacemaker shifts (Bonke et al., 1969) and shortening of the action potential duration (Miller and Strauss, 1974).

It is appropriate to comment here on Strauss sinoatrial conduction time plots in which points fall to the right of the line of non-reset (Figure VI-2 "a" and Figure VI-3). It is likely that the explanation for these points is partial or complete sinus node capture combined with marked depression of automaticity. As a corollary to this, it is possible for points to fall on, or to the right of and above, the line of "non-reset" (label-
ed "a" in Figure VI-2), when sinus node capture and reset has occurred. For example, if the sum of the sinoatrial conduction time, and the prolongation of the return cycle due to depression of automaticity was equal to the prematurity of the test stimulus, then the point would fall on the line of "non-reset". If the sum was greater than the prematurity of the test stimulus (as in Figure VI-3), then the point would fall to the right of and above the line of "non-reset".

As the anterograde component of sinoatrial conduction is usually greater than the retrograde (Steinbeck et al., 1978), dividing the sum of both by 2, as was done in the early studies (Strauss et al., 1973), will underestimate the anterograde sinoatrial conduction time. If the action potential duration is shortened, or if there are pacemaker shifts inferiorly within the sinus node, the anterograde sinoatrial conduction time will be underestimated by the premature atrial stimulation method. However, this study suggests that suppression of automaticity in man by the single atrial extrastimulus appears to overcompensate for these sources of error, and leads to overestimation of the sum of anterograde and retrograde sinoatrial conduction time.
iv) Conclusions

The most striking finding in this part of the study was the close resemblance of sequences and indices computed from such sequences following both one (premature) and eight atrial paced beats, to those following one minute of overdrive atrial pacing. This leads to the conclusion, and the answer to the paradox mentioned in Chapter II, that the tests that have been proposed to measure sinoatrial automaticity, namely the sinus node recovery time after one minute of overdrive atrial pacing, and the tests that have been proposed to measure sinoatrial conduction, in fact both measure a combination of sinoatrial conduction and depression of automaticity. Differences between the results observed with the different tests probably reflect quantitative but not qualitative changes in response to different rate and duration of pacing.

It should be reemphasized that the indirect methods are not capable of separately assessing the anterograde and retrograde components of sinoatrial conduction, while direct recording techniques (Reiffel et al., 1980) measure only the anterograde conduction time. Which is of more value in assessing sinus node dysfunction is not known at the present time.

To further study the mechanism of post-pacing suppression of the sinus node, post-pacing sequences were studied in the presence of cardiac autonomic blockade, to be described in the following chapter.
CHAPTER VII

AUTONOMIC EFFECTS

A) INTRODUCTION

The presence of bradyarrhythmias, including marked sinus bradycardia, and sinoatrial exit block in asymptomatic individuals is well recognised (Brodsky et al., 1977; Sobotka et al., 1981). Sinus bradycardia in asymptomatic elderly individuals is probably benign in nature and may be a manifestation of higher vagal tone (Agruss et al., 1972). In this and other situations, difficulty arises if symptoms of presyncope or syncope are present in addition to sinus bradycardia, and no correlation is available between symptoms and electrocardiographic abnormalities. It becomes important to determine if the bradycardia is physiological and secondary to high resting vagal tone, or if it relates to pathology in the sinus node. By use of cardiac vagal blockade with atropine and "total" cardiac autonomic blockade with both atropine and propranolol, the "intrinsic" function of the sinus node and the extent of vagal influence can be assessed (Jose et al., 1966; Jose and Collison, 1970; Eckberg et al., 1971; Frick et al., 1976; Jordan et al., 1978; Desai et al., 1981).

In Chapters III, IV, and V, the typical response of the sinus node to overdrive atrial pacing was described. The majority of post-pacing sequences were suitable for fitting to the mathematical model of overdrive suppression of the sinus node. This present part of the study was performed to further assess the
usefulness of cardiac vagal and total cardiac autonomic blockade in assessment of sinus node function, but in particular to study the effects of such testing on the sequences following overdrive atrial pacing. It was hoped that this might help clarify the mechanisms of the post-pacing events seen in the basal state.
B) METHODS

i) Valsalva manoeuvre

Valsalva manoeuvre and carotid sinus massage were performed as described in Chapter II. Abnormal responses to carotid sinus massage were defined as:

i) **cardioinhibitory** - ventricular asystole for more than 3 seconds during carotid sinus stimulation,

ii) **vasodepressor** - decrease in systolic blood pressure of 50 mm Hg or greater with no associated cardiac slowing, or decrease in systolic blood pressure > 30 mmHg and symptoms reproduced,

iii) combined **cardioinhibitory** and **vasodepressor**, with both ventricular asystole for more than 3 seconds, and systolic blood pressure fall (Walter et al., 1978; Thormann et al., 1978).

ii) drugs

Cardiac vagal blockade was induced by the administration of atropine 0.03 mg/kg intravenously, except when specifically contraindicated by glaucoma, prostatism, angina pectoris, observation of ischaemic ST/T segment changes during atrial pacing, or previous adverse response to the drug. The first half of the dose was given as a bolus, and if no problems were observed, the second
half of the dose was administered one minute later. The cycle length post atropine was measured by the minimum value observed (mean of one minute recording), and, with the exception of one elderly patient, occurred between two and five minutes after completion of administration. In this patient, the minimum cycle length was not observed until ten minutes after completion of the drug.
Cardiac sympathetic blockade was achieved by administration of propranolol intravenously at the rate of 1 mg/min to a total dose of 0.15 mg/kg body weight. Blood pressure was recorded every minute during the administration. Contraindications to the use of propranolol were a history and/or physical signs of asthma, chronic obstructive airways disease, cardiac failure, or previous adverse response to beta-blockade. It should be re-emphasized that no patients were on cardio-active drugs, in particular verapamil, at the time of study. Measurements post propranolol were commenced with cycle length recording 10 minutes after completion of administration. If more than 30 minutes since completion of the dose had elapsed before measurements were completed, a supplementary dose of 0.03 mg/kg of propranolol was administered.
For induction of total cardiac autonomic blockade, if atropine had been given first, propranolol 0.15 mg/kg was given, and eight minutes after completion of the propranolol, a supplementary dose of 0.006 mg/kg of atropine was given. Conversely, if the propranolol had been given first, atropine 0.03 mg/kg was administered intravenously eight minutes after completion of the supplementary dose of propranolol discussed above. The drug, atropine or propranolol, given initially was not randomised. Usually atropine was administered first to avoid excessively slow heart rates in subjects with sinus bradycardia.

The intrinsic cycle length was defined as the mean cycle length of one minute of recording, 10 minutes after the propranolol and 2 minutes after the atropine.
The predicted intrinsic heart rate, and 95% confidence limits for the same, were calculated on the basis of age in the patients with the sick sinus syndrome, using the following formula (Jose and Collison 1970):

\[ \text{IHR (Intrinsic Heart Rate)} \ (\text{in beats per minute}) = 118.1 - (0.57 \times \text{age (in years)}) \].

iii) Pacing and data analysis

In 6 patients with normal sinus node function and in 25 patients with the sick sinus syndrome the response to overdrive atrial pacing (as has been described in Chapter III), was assessed at multiple rates of pacing, in the basal state and after administration of atropine, and atropine and propranolol. In many patients, after atropine, trials could not be performed at 100 bpm (pacing cycle length 600 msec) due to a decrease in the resting cycle length to 600 msec or below. For trials to be considered valid, pacing cycle length was required to be a minimum of 50 msec below the pre-pacing cycle length, due to the potential problem of isorhythmic sinoatrial dissociation already discussed (in Chapters III and VI).

Post-pacing sequences were recorded, digitised, plotted, and computed as already described (Chapters II, III and IV). As in
previous chapters, results will be expressed as the mean +/- one standard deviation of the respective index. Patients with normal sinus node function and with the sick sinus syndrome will be abbreviated as "normals" and "sick sinus syndrome".
C) RESULTS

i) Valsalva Manoeuvre

The graded Valsalva manoeuvre was performed by five patients with normal sinus node function ("normals") and by six patients with the sick sinus syndrome ("sick sinus syndrome"). The measures recorded were the mean minimum cycle length during or immediately after the strain phase, the subsequent maximum cycle length, the difference between these two measures, the number of beats following completion of the strain phase to the maximum cycle length, and the maximum cycle length less the pre-Valsalva cycle length.

Pooled mean values of each index for each group were derived at each pressure, after the mean value of each index at a given pressure had been measured for each patient. As expected the mean minimum cycle length in each group decreased, the maximum cycle length increased, and the difference between the maximum and the minimum cycle length increased with increasing strain pressure (see Table VII-1). The value of the minimum cycle length after strain at 10 cm of water was significantly greater in the patients with the sick sinus syndrome (p < .05). The absolute values of the minimum and maximum cycle lengths at the other strain pressures showed a trend to be greater in patients with the sick sinus syndrome (0.1 > p > .05). These differences were expected and were
<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>SICK SINUS SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 13</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>Cycle Length (CL) (msec)</td>
<td>851 ± 190</td>
<td>1041 ± 192</td>
</tr>
<tr>
<td>Strain Pressure (cm H₂O)</td>
<td>10  20  30</td>
<td>10  20  30</td>
</tr>
<tr>
<td></td>
<td>686 ± 140  662 ± 143  617 ± 168</td>
<td>856 ± 155*  798 ± 128  794 ± 174</td>
</tr>
<tr>
<td>Minimum Cycle Length (msec)</td>
<td>847 ± 216  881 ± 201  909 ± 177</td>
<td>952 ± 92  1002 ± 165  1050 ± 149</td>
</tr>
<tr>
<td>Maximum Cycle Length (msec)</td>
<td>22 ± 7   18 ± 8   20 ± 8</td>
<td>32 ± 12  28 ± 11  25 ± 5</td>
</tr>
<tr>
<td>Beats to Maximum CL</td>
<td>180 ± 129  220 ± 82  293 ± 56</td>
<td>169 ± 63  187 ± 187  .231 ± 208</td>
</tr>
<tr>
<td>Maximum CL - Minimum CL (msec)</td>
<td>-5 ± 46   30 ± 97  58 ± 97</td>
<td>20 ± 72  -30 ± 72  -68 ± 71*</td>
</tr>
</tbody>
</table>

**LEGEND:** "CL" = cycle length; "Pre CL" = pre Valsalva cycle length. All indices are expressed as the group mean ± one standard deviation. * p < .05 when compared to patients with normal sinus node function.
considered to only relate to the differences between the resting cycle lengths in the two groups (851 +/- 190 msec in patients with normal sinus node function, 1041 +/- 92 msec in patients with the sick sinus syndrome; 0.1 > p > .05). Of the other indices, only the difference between the maximum value after strain at 30 cm of water and the pre-Valsalva cycle length was significantly different in the sick sinus syndrome compared to normals (-68 +/- 71 msec in the patients with the sick sinus syndrome, versus 58 +/- 97 msec in normals; p < .05).
ii) Carotid Sinus Massage

Only two patients with the sick sinus syndrome were found to have coexistent carotid sinus hypersensitivity of cardio-inhibitory type, as defined above by sinus pauses of more than 3 seconds. Two patients in the "intermediate group" were found to have carotid sinus hypersensitivity, in one of the cardioinhibitory type and in the other of the combined type, with both marked hypotension and bradycardia in response to carotid sinus massage. In this last patient, hypotension was still present during carotid sinus massage despite ventricular pacing at 100 beats per minute, and also administration of atropine 0.03 mg/kg.
iii) **Atropine**

a) **cycle length**

The effect of cardiac vagal blockade on the cycle length in the two groups is presented in Table VII-2 and in Figure VII-1. In 6 patients with normal sinus node function and in 25 patients with the sick sinus syndrome, the pooled mean cycle length after atropine was 65% and 68% respectively of the pooled mean cycle length before atropine. The mean cycle length decreased significantly from 825 +/- 132 msec to 540 +/- 46 msec in patients with normal sinus node function, and from 1000 +/- 168 msec to 678 +/- 92 msec in patients with the sick sinus syndrome (p < .001 for each). Only 4 of 25 patients with the sick sinus syndrome showed a cycle length after atropine over 80% of the resting value, and in all four the resting cycle length was less than 900 msec. Looked at in terms of heart rate, 11 of these 25 patients had heart rates above 90 beats per minute, and 14 had heart rates below 90 beats per minute after atropine.

For the subgroups of the sick sinus syndrome, in 15 patients with sinus bradycardia, the cycle length after atropine was 68%, in 3 patients with sinoatrial exit block was 59%, and in 7 patients with brady- and tachy-arrhythmias was 73% respectively of the pre-atropine value. In the first two of these groups, the pooled mean cycle length...
<table>
<thead>
<tr>
<th>Condition</th>
<th>Pre Drug</th>
<th>Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL (6)</strong></td>
<td>825 +/- 132</td>
<td>540 +/- 46** (65%)</td>
</tr>
<tr>
<td><strong>SICK SINUS (25)</strong></td>
<td>1000 +/- 168</td>
<td>678 +/- 92** (68%)</td>
</tr>
<tr>
<td>sinus bradycardia (15)</td>
<td>1002 +/- 155</td>
<td>677 +/- 97** (68%)</td>
</tr>
<tr>
<td>sinoatrial exit block (3)</td>
<td>1079 +/- 306</td>
<td>688 +/- 54 (59%)</td>
</tr>
<tr>
<td>brady + tachyarrhythmias (7)</td>
<td>926 +/- 145</td>
<td>677 +/- 91* (73%)</td>
</tr>
</tbody>
</table>

* p < .01 ; ** p < .001; comparison of mean value before and after atropine by unpaired t-test. Numbers in parentheses represent number of patients in the given group; percentages in parentheses represent mean percentage change in cycle length after atropine.
Figure VII-1

Block diagram illustrating effect of cardiac vagal blockade ("atropine") and total cardiac autonomic blockade ("atr + prop") in 6 patients with normal sinus node function ("N") and in 15 patients with the sick sinus syndrome ("S"). Asterisks represent significant differences (p < .01) between the mean values in N and S. Blocks represent the mean value in the group, bars one standard deviation of the mean.
CYCLE LENGTH

Pre-drug  | Atropine  | ATR + PROP
0         | 200       | 400
N         | S         | N
1000      | 1200      | 1400
N         | S         | N
significantly decreased after atropine ($p < .01$ and $p < .001$ respectively).

When the cycle length both before and after atropine was compared between the patients with normal sinus node function and those with the sick sinus syndrome, there were significant differences in both states, with cycle length before atropine $825 +/- 132$ msec in patients with normal sinus node function and $1000 +/- 168$ msec in patients with the sick sinus syndrome ($p < .001$), and after atropine $540 +/- 46$ msec in patients with normal sinus node function, and $678 +/- 92$ msec in patients with the sick sinus syndrome ($p < .001$).

b) sinus node recovery time

Table VII-3 and Figure VII-2 show the effect of atropine on the sinus node recovery time and the corrected sinus node recovery time both in patients with normal sinus node function ("normals") and in those with the sick sinus syndrome ("sick sinus syndrome"). At the pacing rate of 100 bpm in normals (Figure VII-2) the mean sinus node recovery time significantly decreased from $1059 +/- 142$ msec before drugs to $702 +/- 63$ msec after atropine ($p < .001$) (34% decrease), and in the sick sinus syndrome from $1348 +/- 243$ msec to $952 +/- 127$ msec ($p < .001$) (29% decrease). Similar significant decreases were seen after atropine in both
<table>
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<th></th>
<th>PRE DRUG</th>
<th>ATROPINE</th>
<th>ATROPINE AND PROPRANOLOL</th>
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<tr>
<td><strong>100 bpm</strong></td>
<td></td>
<td></td>
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<tr>
<td>SNRT N</td>
<td>1059 ± 142</td>
<td>702 ± 63</td>
<td>949 ± 113</td>
</tr>
<tr>
<td>SNRT SSS</td>
<td>1348 ± 243</td>
<td>952 ± 127</td>
<td>1356 ± 346</td>
</tr>
<tr>
<td>CSRT N</td>
<td>250 ± 82</td>
<td>135 ± 72</td>
<td>192 ± 38</td>
</tr>
<tr>
<td>CSRT SSS</td>
<td>391 ± 171</td>
<td>242 ± 100</td>
<td>403 ± 172</td>
</tr>
<tr>
<td><strong>130 bpm</strong></td>
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<tr>
<td>SNRT N</td>
<td>939 ± 123</td>
<td>711 ± 26</td>
<td>944 ± 121</td>
</tr>
<tr>
<td>SNRT SSS</td>
<td>1358 ± 336</td>
<td>974 ± 221</td>
<td>1565 ± 594</td>
</tr>
<tr>
<td>CSRT N</td>
<td>144 ± 70</td>
<td>151 ± 35</td>
<td>196 ± 107</td>
</tr>
<tr>
<td>CSRT SSS</td>
<td>460 ± 477</td>
<td>306 ± 172</td>
<td>691 ± 626</td>
</tr>
</tbody>
</table>

**LEGEND:** "bpm" = beats per minute; "SNRT" = sinus node recovery time; "N" = patients with normal sinus node function; "SSS" = sick sinus syndrome; "CSRT" = corrected sinus node recovery time. Six patients with normal sinus node function were studied before drugs, and after atropine and atropine and propranolol. A total of 25 patients with the sick sinus syndrome were studied before and after atropine; in 15 of these 25 patients sequences were studied both at 100 and 130 bpm, in 7 only at 130 bpm, and in 4 only at 100 bpm. After atropine and propranolol 15 patients with the sick sinus syndrome were studied at 100 bpm, and 11 at 130 bpm. Values are given in milliseconds and expressed as the mean value for the group ± one standard deviation.
Figure VII-2

Block diagram illustrating effects of cardiac vagal blockade "atropine" and total cardiac autonomic blockade ("atr + prop") on the sinus node recovery time ("SNRT") at 100 beats per minute in patients with normal sinus node function ("N") and in patients with the sick sinus syndrome ("S"). Blocks represent the mean value in the group, bars one standard deviation of the mean.
groups of patients at the pacing rate of 130 bpm, from 939 +/- 123 msec to 711 +/- 26 msec in normals, and from 1358 +/- 337 msec to 974 +/- 221 msec in the sick sinus syndrome (p < .001 for both).

The corrected sinus node recovery time similarly showed significant decreases in both normals and the sick sinus syndrome after atropine. After pacing at 100 bpm, in normals the value decreased from 250 +/- 82 msec to 135 +/- 72 msec (p < .05) and in the sick sinus syndrome from 391 +/- 171 msec to 242 +/- 100 msec (p < .001).
When the sinus node recovery time after atropine was compared between normals and the sick sinus syndrome, it was significantly greater in the latter group at both 100 and 130 bpm (p < .001 and p < .01 respectively). The corrected sinus node recovery time showed less marked (when compared to the changes in the sinus node recovery time), but still significant differences between the normal and the sick sinus syndrome groups. For example, at 100 bpm, the corrected sinus node recovery time after atropine was 242 +/- 100 msec in the sick sinus syndrome compared to 135 +/- 72 msec (p < .05) in the normals.

c) post-pacing sequences

In the patients with normal sinus node function, after atropine, 15 of 15 sequences at 100 bpm, and 18 of 18 sequences at 130 bpm showed maximally prolonged first post-pacing interval and progressive decrease of subsequent cycles to usually reach a minimum value after the tenth post-pacing interval (Figure VII-3). No secondary pauses were seen after atropine in any patient with normal sinus node function. Two major differences were observed in comparison to the sequences observed before atropine (see Figures VII-3 and III-5). First, the initial minimum value was frequently not observed until well after the tenth post-pacing interval, with a loss of the marked fluctuation in cycle length seen in the basal (pre-drug) state. Second,
Figure VII-3

Plots before and after atropine of post-pacing cycle length ("PPCLj") against post-pacing beat number "j" following atrial pacing (130 beats per minute) for one minute in patient #244. Both sequences show a maximally prolonged first post-pacing cycle length, and progressive decrease in the subsequent cycles. The loss of cycle length fluctuations, the smaller differences between consecutive post-pacing cycles, and the larger number of beats necessary to achieve the minimum cycle length in comparison to the pre-atropine state are illustrated.
% =130 pre atropine
Ο =130 post atropine

BEAT NUMBER Ι
the magnitude of the differences between the second and subsequent cycle lengths was less than in the basal state. Following the achievement of the minimum cycle length, this then remained constant until the next pacing trial.
In the patients with the sick sinus syndrome, similar sequences to those described above were observed after atropine in the majority (111/137) of trials at 100 and 130 bpm. In these patients secondary pauses were very uncommon. In only one trial was a sequence suggestive of sinoatrial exit block seen. The only other type of secondary pause seen was that where the first interval was less than a maximally prolonged second post-pacing interval, and with progressive decrease in subsequent cycles (see Figures III-7 and III-8 "type 1"). This type of secondary pause was seen in one patient at 100 bpm, and in a single trial in each of three patients at 130 bpm. In patients with the sick sinus syndrome, 58/69 sequences after pacing at 100 bpm, and 53/68 sequences after pacing at 130 bpm, were suitable for computation.
Sequences starting with beats originating in the atrioventricular junction region (as assessed by initial activity of the His bundle, the same QRS morphology as sinus rhythm, and similar HV interval to sinus rhythm), were only observed in 2 patients with the sick sinus syndrome after atropine.

d) computed indices

In the six patients with normal sinus node function studied after atropine, 9 of 15 sequences at 100 bpm and 18 of 18 sequences at 130 bpm were successfully fitted by computer to the mathematical model (see Table VII-4). In the patients with sick sinus syndrome, 48 of 58 sequences at 100 bpm and 48 of 53 sequences at 130 bpm were successfully fitted ($R^2 > 0.98$).
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>q</th>
<th>ΔT₁</th>
<th>T₀₀</th>
<th>SACTc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N 100</td>
<td>6</td>
<td>.734 ± .101</td>
<td>210 ± 150</td>
<td>754 ± 34</td>
<td>123 ± 46</td>
</tr>
<tr>
<td>N 130</td>
<td>6</td>
<td>.594 ± .143</td>
<td>253 ± 198</td>
<td>705 ± 100</td>
<td>115 ± 15</td>
</tr>
<tr>
<td>SSS 100</td>
<td>19</td>
<td>.721 ± .104</td>
<td>272 ± 135</td>
<td>963 ± 167</td>
<td>169 ± 114</td>
</tr>
<tr>
<td>SSS 130</td>
<td>22</td>
<td>.599 ± .158</td>
<td>243 ± 132</td>
<td>924 ± 199</td>
<td>228 ± 173</td>
</tr>
<tr>
<td><strong>ATROPINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N 100</td>
<td>6</td>
<td>.590 ± .192</td>
<td>32 ± 21</td>
<td>585 ± 17</td>
<td>84 ± 29</td>
</tr>
<tr>
<td>N 130</td>
<td>6</td>
<td>.650 ± .185</td>
<td>38 ± 18</td>
<td>576 ± 29</td>
<td>92 ± 21</td>
</tr>
<tr>
<td>SSS 100</td>
<td>19</td>
<td>.697 ± .153</td>
<td>125 ± 91</td>
<td>711 ± 70</td>
<td>115 ± 57</td>
</tr>
<tr>
<td>SSS 130</td>
<td>22</td>
<td>.680 ± .120</td>
<td>119 ± 106</td>
<td>678 ± 84</td>
<td>193 ± 145*</td>
</tr>
<tr>
<td><strong>ATROPINE AND PROPRANOLOL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N 100</td>
<td>6</td>
<td>.753 ± .090</td>
<td>87 ± 29</td>
<td>762 ± 75</td>
<td>101 ± 36</td>
</tr>
<tr>
<td>N 130</td>
<td>6</td>
<td>.688 ± .298</td>
<td>87 ± 48</td>
<td>753 ± 57</td>
<td>157 ± 19</td>
</tr>
<tr>
<td>SSS 100</td>
<td>15</td>
<td>.739 ± .155</td>
<td>182 ± 116</td>
<td>942 ± 173</td>
<td>187 ± 79</td>
</tr>
<tr>
<td>SSS 130</td>
<td>11</td>
<td>.718 ± .087</td>
<td>206 ± 55</td>
<td>942 ± 100</td>
<td>145 ± 46</td>
</tr>
</tbody>
</table>

**LEGEND:** Computed indices of automaticity (q, ΔT₁, T₀₀) and of sinoatrial conduction (SACTc), are abbreviated as described in the text; all except q are in units of milliseconds, and all are expressed as the mean ± one standard deviation; "N 100" and "N 130" represent pacing at 100 and 130 beats per minute respectively in patients with normal sinus node function; "SSS 100" and "SSS 130" represent pacing at 100 and 130 beats per minute respectively in patients with the sick sinus syndrome; "n" represents the number of patients studied; * when patient # 298 with trial with probable sinoatrial exit block excluded, mean value becomes 161 ± 59 milliseconds.
The difference between the first and subsequent intervals was impressive after atropine, with the first interval falling well beyond the approximate 95% confidence limits extrapolated from the rest of the sequence.

When compared with the pre-drug values, in both patients with normal sinus node function and in those with the sick sinus syndrome, both $\Delta T_1$ (Figure VII-4) and $T_\infty$ were significantly decreased at both pacing rates. For example, at 100 bpm in normals, $\Delta T_1$ decreased from 210 +/- 150 to 32 +/- 21 msec ($p < .01$), and $T_\infty$ decreased from 754 +/- 34 msec to 585 +/- 17 msec ($p < .001$). The common ratio of the geometric progression, $q$, did not show any consistent change after atropine. Computed sinoatrial conduction time, SACTc, tended to decrease in both groups at both pacing rates after atropine, but only the differences in patients with normal sinus node function at 130 bpm (115 +/- 15 msec to 92 +/- 21 msec) and in patients with the sick sinus syndrome at 100 bpm (169 +/- 114 msec to 115 +/- 57 msec) were significant ($p < .05$ for both).

To follow on the observation of an apparent decrease after atropine in the beat to beat changes after overdrive pacing, a comparison was made of the relative magnitude of the mean computed indices and the mean sinus node recovery time, both before and after atropine. The clearest finding was a change in $\Delta T_1$ from being greater (in both groups and
Figure VII-4
Block diagram showing the effects of cardiac vagal ("atropine") and total cardiac autonomic blockade ("atr + prop") on the computed index of automaticity, ΔT1, at atrial pacing rate of 100 beats per minute. In patients with normal sinus node function ("N"), ΔT1 decreased significantly both after atropine (p < .01), and after atropine and propranolol (p < .05). In patients with the sick sinus syndrome, ΔT1 decreased significantly after both atropine (p < .001), and after atropine and propranolol (p < .025). Asterisks represent significant differences (p < .05), only present after cardiac vagal and after total cardiac autonomic blockade, between ΔT1 in the patients with the sick sinus syndrome compared to those with normal sinus node function.
$\Delta T1 \, [100 \, \text{bpm}]$

<table>
<thead>
<tr>
<th></th>
<th>pre-drug</th>
<th>atropine</th>
<th>atr + prop</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td></td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

$\Delta T1$ [msec]
at both pacing rates) than the computed sinoatrial conduction time (SACTC), to being less than SACTC. Before atropine, the latter was 11.6% and 12.2% of the mean sinus node recovery time at 100 bpm, and after atropine 12.0% and 13.0% respectively in patients with normal sinus node function and with the sick sinus syndrome. However ΔT1 changed from 20% and 27% at 100 and 130 bpm respectively in patients with normal sinus node function, to being 4.6% and 5.3% of the mean sinus node recovery time after atropine. In the patients with the sick sinus syndrome, ΔT1 changed from 20% and 18% of the mean sinus node recovery time at 100 and 130 bpm, to being 13% and 12% of the mean sinus node recovery time after atropine.

After cardiac vagal blockade, at 100 bpm pacing rate, both ΔT1 and T∞ were significantly greater in patients with the sick sinus syndrome compared to patients with normal sinus node function. ΔT1 was 32 +/- 21 msec in normals and 125 +/- 91 msec in the sick sinus syndrome (see Figure VII-4, which illustrates in block diagram form the marked differences in ΔT1 after cardiac vagal blockade). T∞ was 585 +/- 17 msec in normals and 711 +/- 70 msec in the sick sinus syndrome (p < .001). The other computed indices q and SACTC were not significantly greater in the sick sinus syndrome.

At the pacing rate of 130 bpm, similar significant differences in ΔT1 and T∞ were observed between normals and the
sick sinus syndrome ($\Delta T_1$ was $38 \pm 18$ msec in normals, $119 \pm 106$ msec in the sick sinus syndrome ($p < .05$); and $T_\infty$ 576 $\pm 29$ msec in normals and 678 $\pm 84$ msec in the sick sinus syndrome ($p < .005$)). Note that there were no differences between the indices $q, \Delta T_1$, and $T_\infty$ at the two rates of pacing within each group of patients. The mean value of the computed sinoatrial conduction time was not significantly different, but when patient #298 with probable sinoatrial exit block (and very large computed sinoatrial conduction time) was excluded, the mean value of the computed sinoatrial conduction time in the sick sinus syndrome was $161 \pm 59$ msec, significantly greater than both the value in normals, $92 \pm 21$ msec ($p < .025$), and in the same patients at 100 beats per minute, $115 \pm 57$ msec ($p < .05$).
iv) **Atropine and Propranolol (Cardiac Autonomic Blockade)**

a) **cycle length**

Table VII-5 and Figure VII-1 show the change in the mean cycle length in patients with both normal sinus node function and with the sick sinus syndrome following cardiac autonomic blockade with atropine and propranolol. It can be seen that in both groups, the mean change in the cycle length was of the order of a 10% decrease. The value in the sick sinus syndrome (961 +/- 191 msec) was significantly greater than in the normals (748 +/- 74 msec; p < .01), but with overlap between the two groups, which will now be further discussed.

In the 15 patients with the sick sinus syndrome given cardiac autonomic blockade, the predicted intrinsic heart rate calculated on the basis of age (see methods section in this Chapter), was compared with the observed intrinsic heart rate (see Table VII-6). Eight of the patients had an "abnormal" (beyond 95% confidence limits) and 7 a "normal" intrinsic heart rate. When the relationship between subgroup of sick sinus syndrome and intrinsic heart rate was considered, all three patients with sinoatrial exit block, 3 of 8 patients with sinus bradycardia, and 2 of 4 patients with brady- and tachy-arrhythmias had an abnormal intrinsic
### TABLE VII-5

**CARDIAC VAGAL AND AUTONOMIC BLOCKADE – CYCLE LENGTH**

<table>
<thead>
<tr>
<th></th>
<th>BASAL</th>
<th>ATROPINE</th>
<th>ATROPINE+ PROPRANOLOL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL (6)</strong></td>
<td>825 +/- 132</td>
<td>540 +/- 46 (65%)</td>
<td>748 +/- 74 (91%)</td>
</tr>
<tr>
<td><strong>SICK SINUS (15)</strong></td>
<td>1039 +/- 185</td>
<td>682 +/- 77 (65%)</td>
<td>961 +/- 191 (92.5%)</td>
</tr>
<tr>
<td>i) SB (8)</td>
<td>1060 +/- 165</td>
<td>673 +/- 88 (64%)</td>
<td>939 +/- 116 (89%)</td>
</tr>
<tr>
<td>ii) SAEB (3)</td>
<td>1079 +/- 306</td>
<td>688 +/- 54 (59%)</td>
<td>1108 +/- 378 (103%)</td>
</tr>
<tr>
<td>iii) BTS (4)</td>
<td>969 +/- 154</td>
<td>699 +/- 80 (72%)</td>
<td>894 +/- 124 (92%)</td>
</tr>
</tbody>
</table>

Cycle length expressed as mean +/- one standard deviation and in units of milliseconds; an additional ten patients with the sick sinus syndrome were given atropine only, and are not included in this table, which considers the results only in those patients given both cardiac vagal and full autonomic blockade; percentage changes from basal state are given in parentheses; SB represents patients with sinus bradycardia, SAEB with sinoatrial exit block, and BTS with brady- and tachyarrhythmias, respectively.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Subgroup*</th>
<th>Age (years)</th>
<th>PIHR (bpm)</th>
<th>95% confidence limits</th>
<th>IHR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#203</td>
<td>SB</td>
<td>66</td>
<td>80.5</td>
<td>± 12.1</td>
<td>51.2</td>
</tr>
<tr>
<td>#242</td>
<td>SAEB</td>
<td>18</td>
<td>107.8</td>
<td>± 16.2</td>
<td>78.3</td>
</tr>
<tr>
<td>#247</td>
<td>SB</td>
<td>55</td>
<td>86.8</td>
<td>± 13.0</td>
<td>63.5</td>
</tr>
<tr>
<td>#257</td>
<td>SB</td>
<td>79</td>
<td>73.1</td>
<td>± 11.0</td>
<td>59.9</td>
</tr>
<tr>
<td>#264</td>
<td>SAEB</td>
<td>78</td>
<td>73.6</td>
<td>± 11.0</td>
<td>39.6</td>
</tr>
<tr>
<td>#291</td>
<td>BTS</td>
<td>59</td>
<td>84.5</td>
<td>± 12.7</td>
<td>61.9</td>
</tr>
<tr>
<td>#335</td>
<td>SAEB</td>
<td>70</td>
<td>78.2</td>
<td>± 11.7</td>
<td>57.6</td>
</tr>
<tr>
<td>#388</td>
<td>BTS</td>
<td>74</td>
<td>75.9</td>
<td>± 11.4</td>
<td>58.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Subgroup*</th>
<th>Age (years)</th>
<th>PIHR (bpm)</th>
<th>95% confidence limits</th>
<th>IHR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#186</td>
<td>SB</td>
<td>67</td>
<td>79.9</td>
<td>± 12.0</td>
<td>73.2</td>
</tr>
<tr>
<td>#218</td>
<td>BTS</td>
<td>63</td>
<td>82.2</td>
<td>± 12.3</td>
<td>79.6</td>
</tr>
<tr>
<td>#220</td>
<td>SB</td>
<td>68</td>
<td>79.3</td>
<td>± 11.9</td>
<td>67.8</td>
</tr>
<tr>
<td>#233</td>
<td>SB</td>
<td>65</td>
<td>81.1</td>
<td>± 12.2</td>
<td>73.1</td>
</tr>
<tr>
<td>#272</td>
<td>SB</td>
<td>83</td>
<td>70.1</td>
<td>± 10.6</td>
<td>61.3</td>
</tr>
<tr>
<td>#312</td>
<td>SB</td>
<td>75</td>
<td>75.4</td>
<td>± 11.3</td>
<td>67.4</td>
</tr>
<tr>
<td>#428</td>
<td>BTS</td>
<td>66</td>
<td>80.5</td>
<td>± 12.1</td>
<td>72.4</td>
</tr>
</tbody>
</table>

Patients are grouped into those with abnormal and normal intrinsic heart rate ("IHR"). The predicted intrinsic heart rate ("PIHR") was calculated using the formula of Jose (Jose and Collison, 1970):

\[
\text{predicted intrinsic heart rate (bpm)} = 118.1 - (0.57 \times \text{age (in years)})
\]

and 95% limits were considered to be this value ± 15%.

* Subgroups of the sick sinus syndrome abbreviated as follows:
  "SB" = sinus bradycardia; "SAEB" = sinoatrial exit block;
  "BTS" = brady-tachy syndrome.
heart rate. The numbers of patients studied were too small to assess whether the distribution of intrinsic heart rates was unimodal or bimodal.
b) **sinus node recovery time**

The mean values of the sinus node recovery time after atropine and propranolol, for both patients with normal sinus node function and the sick sinus syndrome, are shown in Table VII-3, and in Figure VII-2. The values in both groups of patients were not significantly different from before drugs, being 949 +/- 113 msec in normals and 1356 +/- 346 msec in the sick sinus syndrome after overdrive pacing at 100 bpm. At 130 bpm pacing rate, the values of the sinus node recovery time were 944 +/- 121 and 1565 +/- 594 msec in normals and sick sinus syndrome respectively. At both pacing rates, the mean sinus node recovery time was significantly greater in the sick sinus syndrome compared to normals (p < .01 at 100 bpm, and p < .05 at 130 bpm).
c) post-pacing sequences

In the patients with normal sinus node function, after atropine and propranolol, at 100 bpm, 20 of 23 sequences showed maximally prolonged first post-pacing interval with progressive decrease in subsequent cycles, such that they were suitable for fitting to the mathematical model of overdrive suppression. Likewise, at 130 bpm, 9 of 22 sequences were suitable for fitting to the model.

The sequences after atropine and propranolol (see Figure VII-5) were again different to those observed pre-drug and after atropine, although usually showing the same maximally prolonged first post-pacing interval and progressive decrease in subsequent cycles. The difference observed here in comparison to the basal state was a marked reduction or absence of the periodic fluctuation seen in the pre-drug state. However, unlike the sequences after atropine, the changes in cycle length of the initial post-pacing beats were of similar magnitude to those in the pre-drug state.

As after atropine, no secondary pauses of any type were seen in the post-pacing sequences in the patients with normal sinus node function. However, secondary pauses were seen in five patients with the sick sinus syndrome. First, sequences with the first post-pacing interval less than a
Figure VII-5

Plots of post-pacing cycle length ("PPCLj") against post-pacing beat number ("j") following overdrive right atrial pacing at 130 beats per minute for one minute. Both before ("pre A + P") and after ("post A + P") total cardiac autonomic blockade, sequences show a maximally prolonged first post-pacing cycle length and progressive decrease in subsequent cycle lengths. Compared to the sequence in the basal state, that after cardiac autonomic blockade shows similar cycle lengths and similar magnitude of cycle length changes, but absence of later cycle length fluctuations, and a larger number of cycles to reach a minimum cycle length.
maximally prolonged second interval were seen at 100 bpm pacing rate in two patients. Second, prolonged pauses which were multiples of the average post-pacing cycle length (suggesting sinoatrial exit block) were seen in four patients, in two of whom the same phenomenon had been observed in the pre-drug state. In the other two it had not previously been observed.
In the patients with the sick sinus syndrome, the majority of sequences followed the characteristic pattern of maximally prolonged first post-pacing interval and progressive decrease of subsequent cycles. As after atropine, often the sequences continued to show decreasing cycle length for many beats after cessation of pacing, with up to 100 cycles required for the attainment of a stable minimum cycle length. Of these sequences, 51 of 59 trials after pacing at 100 bpm, and 20 of 31 trials at 130 bpm, were suitable for computation. Those sequences unsuitable for fitting contained either secondary pauses, or atrial or ventricular ectopic beats.
d) **computed indices**

In the six patients with normal sinus node function, 19 of 20 sequences at 100 bpm, and all 9 sequences at 130 bpm were successfully fitted by computer to the mathematical model. In the patients with the sick sinus syndrome, 45 of 51 sequences at 100 bpm, and 14 of 20 sequences at 130 bpm were successfully fitted.

In the patients with normal sinus node function, cardiac autonomic blockade by atropine and propranolol decreased \( \Delta T_1 \) from 210 +/- 150 msec to 87 +/- 29 msec at 100 bpm (\( p < .05 \)), and from 253 +/- 198 msec to 87 +/- 48 msec at 130 bpm (\( p < .01 \); see Table VII-4 and Figure VII-4). The only other index to significantly change after cardiac autonomic blockade was SACTc at 130 bpm, which increased from 115 +/- 15 msec to 157 +/- 19 msec (\( p < .001 \)).

In the patients with the sick sinus syndrome, cardiac autonomic blockade caused a significant decrease in \( \Delta T_1 \) at 100 bpm, from 272 +/- 135 msec to 182 +/- 116 msec (\( p < .05 \)). No other significant changes in computed indices were observed.

At pacing rate 100 bpm after cardiac autonomic blockade, \( \Delta T_1 \), \( T_{\infty} \), and SACTc, were all significantly greater in
patients with the sick sinus syndrome compared to patients with normal sinus node function (see Table VII-4). $\Delta T_1$ was 87 +/- 29 msec in normals, and 182 +/- 116 msec in the sick sinus syndrome ($p < .001$), while $T_\infty$ was 762 +/- 75 msec in normals and 942 +/- 173 msec in the sick sinus syndrome ($p < .05$). The computed sinoatrial conduction time was 101 +/- 36 msec in normals and 187 +/- 79 msec in the sick sinus syndrome ($p < .05$). At 130 bpm, the indices $\Delta T_1$ and $T_\infty$ were significantly greater in the sick sinus syndrome compared to normals ($p < .01$ for both), but the computed sinoatrial conduction times were not significantly different between the two groups.

D) DISCUSSION

a) Valsalva Manoeuvre

Previous studies have reported a blunted heart rate response to Valsalva manoeuvre in patients with the sick sinus syndrome (Dighton, 1974, 1975). However, the results were expressed as a percentage change in atrial rate rather than change in cycle length, and simple calculations suggest that this difference was due solely to the different resting cycle length in the two groups, rather than a difference in response to the Valsalva manoeuvre. In fact, if mean resting cycle lengths are assumed (not stated in the papers) of 750 msec for controls and 1000 msec for sick sinus syndrome, then the percentage changes in response to Valsalva are identical.
This study found only minor differences in the response to Valsalva manoeuvre between patients with normal sinus node function and with the sick sinus syndrome, the different values observed relating to different resting sinus node cycle lengths. The numbers of patients studied were small, but sufficient to indicate that the manoeuvre does not appear to give any more information about sinus node function than can be obtained from the resting cycle length alone, or in other words, that it is unlikely to be a useful non-invasive screening test for sinus node function.
b) Cardiac Vagal Blockade

i) conventional indices

The effects of cardiac vagal blockade on prepacing cycle length, the sinus node recovery time, and the corrected sinus node recovery time were marked, with a 33% reduction in prepacing cycle length in both patients with normal sinus node function and in patients with the sick sinus syndrome, and with 25–35% reduction in the sinus node recovery time. The variance within each group decreased after atropine, and led to better distinction between normal and abnormal sinus node function.

The cycle length after cardiac vagal blockade appears to be a useful index of sinus node function. Although a cycle length over 635 msec after atropine (mean + 2 standard deviations in patients with normal sinus node function) is very suggestive for sinus node dysfunction, in this study only 15/25 patients with the sick sinus syndrome showed this abnormality. The presence of a heart rate below 90 beats per minute has been proposed as an index of sinus node dysfunction (Ferrer, 1973). However, in this study, only 14/25 patients with unequivocal sinus node dysfunction on clinical grounds had a heart rate less than 90 beats per minute (cycle length 667 msec) after atropine.
The changes in the post-pacing sequences after atropine were marked, with (usually), abolition of the cycle length fluctuation seen in the pre-drug state. Despite this, the sequences still showed the same pattern, with maximally prolonged first post-pacing interval and progressive (and decreasing) decay thereafter, the minimum cycle length not being reached for up to 100 beats. The two most likely explanations for this observation of prolongation of the first post-pacing interval and progressive decrease in subsequent intervals, are, first, incomplete vagal blockade, with the prolongation of the initial post-pacing interval relative to the subsequent cycle length relating to decay of vagal stimulation during or immediately following the pacing. Alternatively, it may represent the effects of overdrive suppression of the sinus node in the presence of complete vagal blockade. Experimental evidence does support the idea that overdrive suppression can occur independently of vagal innervation (Kodama et al., 1980). The reduction in the extent of overdrive suppression following atropine suggests however that the vagus nerve, or at least acetylcholine modifies the extent of suppression.

In further support of the argument that the observation of overdrive suppression after atropine was a true finding and not due to incomplete vagal blockade, the effect of overdrive in the transplanted (denervated) human heart should be considered. This was studied by Mason (1980), who in his
paper did not comment specifically on post-pacing intervals after the first in the denervated heart, but on close inspection of Figure 2 of his article, the second post-pacing cycle in the donor atrium (denervated) is longer than the third post-pacing cycle by about 10–20 msec, suggesting that the phenomenon of overdrive suppression of the sinus node can occur independently of autonomic innervation. This still does not exclude the possibility of a major role for neurotransmitters (particularly acetylcholine and noradrenaline) and of the "intrinsic" nervous system of the heart, in the phenomenon of overdrive suppression.
ii) fitting to mathematical model and computed indices.

With the absence of fluctuations due to changes in resting vagal tone, the number of beats that could be fitted was markedly increased. However, as the model considers only the initial post-pacing events, for the purposes of this study, only the results of fitting a maximum of ten post-pacing cycles were used.

Atropine administration increased the value of estimation of the computed sinoatrial conduction time. This value decreased significantly in both patients with normal sinus node function and the sick sinus syndrome, but the range in both normals and the sick sinus syndrome was narrowed, resulting in a significant difference between the mean values (not present before atropine).

Similarly with $\Delta T_1$ and $T_\infty$, there was a decrease in the absolute value, but the variance in each group decreased, leading to better discrimination between normal and abnormal responses.

The common ratio of the geometric progression, $q$, did not show any significant changes following atropine. It is possible that this relates either to the large interpatient variability of this index, or to identical recovery pro-
cesses (rate of change, not to be confused with magnitude of change) following overdrive in both normals and the sick sinus syndrome.

c) Total Cardiac Autonomic Blockade

i) completeness of autonomic block

The potential limitations of this method of producing cardiac autonomic blockade have previously been discussed elsewhere (Korner et al., 1973; Mason, 1980). The doses used in this study were 75% of the doses originally proposed (Jose and Collison, 1970) as being necessary for producing complete blockade. These doses were chosen because 95% of the autonomic blocking effects of the drugs is seen (Jose and Taylor, 1969) with much less risk of adverse side effects in a study group that contained many elderly patients. Indeed, in two elderly patients, an acute confusional state was present for 12 hours after an electrophysiology study during which atropine had been administered. On the basis of observations in these two patients, the presence of history and signs suggesting mild senile dementia should be considered a relative contra-indication to the administration of atropine. The loss in the majority of patients of cycle length fluctuations supported the presence of a high degree of autonomic blockade.
ii) conventional indices

Only minor differences were observed from pre-drug values of cycle length, sinus node recovery time, and corrected sinus node recovery time, after total cardiac autonomic blockade. The numbers in the brady- and tachy-arrhythmia and sinoatrial exit block subgroups of the sick sinus syndrome given cardiac autonomic blockade were too small (3 and 7 respectively) to draw any valid comparisons with the group in whom only sinus bradycardia had been observed.

The intrinsic cycle length (the resting cycle length after total cardiac autonomic blockade) has been proposed as a useful index of sinus node dysfunction (Jordan et al., 1978). The findings in this study supported this concept, although both the large overlap of intrinsic cycle length between normal and sick sinus syndrome patients (Figure VII-1) and "normal" intrinsic cycle length in 7/15 patients (using the "predicted normal intrinsic heart rate" on the basis of age) with sick sinus syndrome suggests a low sensitivity of this index.

Previous studies (Jordan et al., 1978; Desai et al., 1981) have suggested that frequently there are abnormalities of resting autonomic tone or abnormal responses to autonomic stimulation in patients with the sick sinus syndrome. They divided patients with the sick sinus syndrome (with approx-
imately equal distribution) into those with normal and with abnormal intrinsic heart rates. In this study, these findings were confirmed. The numbers of patients with sick sinus syndrome given total cardiac autonomic blockade were too small to assess whether the distribution of the ratio "intrinsic heart rate/predicted intrinsic heart rate" followed a bimodal or unimodal distribution. If the former were to be observed, it would indeed suggest that patients with the sick sinus syndrome do fall into groups with abnormal intrinsic sinus node function (abnormal intrinsic heart rates) and those with normal sinus node function, but abnormal autonomic influences. If the distribution was unimodal it would support abnormalities of intrinsic sinus node function of varying degrees, without needing to postulate abnormal autonomic effects. In support of this latter argument was the normal response (33% decrease) observed in this study, as assessed by percentage change in cycle length after atropine in the patients with the sick sinus syndrome.

The dividing line between the "sick sinus syndrome" and patients having normal intrinsic sinus node function but abnormal responses to vagal stimulation of sufficient severity to lead to syncope appears ill defined at the present time. Two patients from the "intermediate" group in this study had permanent pacemakers implanted for the latter situation despite normal responses to assessment of sinus
node function at electrophysiology study (including cardiac vagal and cardiac autonomic blockade).

In this study, atropine was usually administered first. It is theoretically possible that different responses to cardiac autonomic blockade using atropine and propranolol may be seen depending on the order of administration of the two drugs.

The problem which occurs when comparing intrinsic heart rates and intrinsic cycle length with reference values, is that most studies using total "cardiac autonomic blockade" have used different drug doses and timing (Jose and Collison 1970; Jordan et al., 1978; Desai et al., 1981). Use of previously determined reference values may be valid if it can be assumed that:
i) 75% of the dose of atropine and propranolol has identical effects to the proposed "full" doses of 0.02 mg/kg body weight of atropine and 0.20 mg/kg body weight of propranolol (Jose and Taylor, 1969).

ii) the time between propranolol administration and measurement is unimportant if the latter is done within the first 30 minutes after administration.

iii) effects are independent of the order or relative timing of the two drugs.

It is of interest that the denervated sinus node of donor heart transplants has been observed to have a mean resting heart rate of 85 beats per minute or greater (Mason, 1980), comparable to that observed after pharmacological autonomic blockade. In keeping with the limitations of the latter technique, Jose and Collison (1970) found a wide distribution of the intrinsic heart rate after atropine and propranolol, with two standard deviations for normals being 15% of the mean absolute value.

iii) sequences

In both patients with normal sinus node function and in patients with the sick sinus syndrome, sequences after total cardiac autonomic blockade continued to show maximally prolonged first post-pacing interval and progressive decay of subsequent cycles, suggesting strongly that, although the phenomenon of overdrive suppression is influenced by vagal and sympathetic innervation, it can occur
independently of these influences. This does not exclude the possibility that local release of acetylcholine or noradrenaline is involved in the mechanism. The possible role of effects of propranolol other than beta-blockade in the overdrive suppression that is observed after cardiac autonomic blockade must be remembered.
iv) computed indices

In further support of overdrive suppression of the sinus node being a phenomenon which can occur independently of cardiac autonomic influences, was the observation of lack of change after cardiac autonomic blockade in mean values of all indices of sinoatrial conduction and automaticity, with the exception of $\Delta T_1$. This index, which can be considered a measure of suppression of the sinus node by overdrive pacing, was significantly reduced after cardiac autonomic blockade, suggesting a modulating influence of autonomic innervation.

Many conventional and new indices of sinus node function have been studied. To put them into perspective and see which should be further evaluated, in the next chapter a comparison of the sensitivity and specificity of all these indices is made.
CHAPTER VIII

COMPARISON OF INDICES OF SINUS NODE FUNCTION

It would be hoped that invasive electrophysiological tests of sinus node function in man would be able to clarify the need or otherwise for permanent pacemaker implantation when non-invasive testing had failed to do so. Unfortunately the evidence to the present time is that usually the doubt that is present before the electrophysiology study is frequently present after. To quote Strauss (1976), in reference to current electrophysiological tests of sinus node function, "at present it is not clear that they do anything more than identify those patients with overt features of the sick sinus syndrome". This study, by looking in detail at post-pacing events at the time of electrophysiology study in two groups of patients, one with unequivocally normal, and the other with unequivocally abnormal sinus node function, aimed to look for better indices of sinus node function that potentially might help distinguish less overtly abnormal sinus node function.

a) Comparison of Currently Used or "Conventional" Tests

As has been presented, currently four different measures are conventionally used at electrophysiology study to assess sinus node function in man. These are, the sinus node recovery time (Chapters III and V), the corrected sinus node rec-
overy time (Chapter III), the sinoatrial conduction time by the method of Strauss (1973, 1976) (Chapter VI), and finally the sinoatrial conduction time by the method of Narula (1978) (Chapter VI).
i) **Specificity and Sensitivity**

To gain some insight into the relative values of the conventionally used tests of sinus node function, sensitivity, specificity, and predictive accuracy of a positive result, were assessed in the following way. First, the mean plus one standard deviation of the mean value of the respective index in the group of patients with normal sinus node function was chosen as the upper limit of the reference range. The sensitivity, specificity, and "predictive accuracy of a positive result", using the results in the patients with normal sinus node function and with the sick sinus syndrome, were calculated according to the formulae:
SENSITIVITY = true positive / (true positive + false negative)

SPECIFICITY = true negative / (true negative + false positive)

PREDICTIVE ACCURACY OF A POSITIVE RESULT = true positive /
                                             (true positive + false positive)

The calculated values are presented in Appendix C. In the basal state, the maximal sinus node recovery time (89%) and the sinus node recovery time (74%) at 100 bpm, and the maximal sinus node recovery time at 130 bpm (76%), were more sensitive than the resting cycle length (71%) in detecting sinus node dysfunction. The sinus node recovery time at 130 bpm had the same sensitivity (71%) as the resting cycle length. In the Narula conduction time assessment, the first post-pacing interval (72%) was much more sensitive than the sinoatrial conduction time derived from this interval by subtracting the prepacing cycle length (28%). Similarly in the Strauss sinoatrial conduction time estimation, the first post-pacing interval from the reset zone (80%) was more sensitive than the sinoatrial conduction time calculated by any of the proposed methods (see Chapter VI) from the same data.

Specificity varied between 76% for corrected sinus node recovery time at 130 bpm, to 100% for the first post-pacing
interval with the Narula conduction time.

The corrected sinus node recovery time, and the sinoatrial conduction time by both indirect methods showed a poor ability to detect abnormality in those patients with clearly abnormal sinus node function on clinical grounds.
The administration of atropine increased the sensitivity of and specificity of these tests. For example, the sinus node recovery time at 100 and 130 bpm had a sensitivity of 95% and a specificity of 100% (there were however only small numbers in the "normal" group). After cardiac autonomic blockade with atropine and propranolol, the sensitivity of the sinus node recovery time at both 100 and 130 bpm was 100%, with specificity of 80% and 83% respectively. It should be stated that these figures are based on only a small number of patients and should be used as a guide only.

It should be stressed here, that there were significant age differences between the patients with normal sinus node function and those with the sick sinus syndrome, which would be expected to favour the sinus cycle length and the sinus node recovery time as predictors of sinus node dysfunction as assessed above.

ii) sinus node recovery time

The sinus node recovery time and the maximal sinus node recovery time had the highest sensitivity and specificity of the conventional tests in the basal state. Even in those patients with clearly abnormal sinus node function, false negative results were seen. Reasons for this and for the relatively wide normal ranges quoted by different groups may
include:

a) large fluctuations in resting autonomic tone, which may have a marked influence on the sinus node automaticity;

b) the presence of sinoatrial entrance block in some patients with sinus node dysfunction, preventing equivalent net effect of atrial pacing on the sinus node compared with the effect of the same pacing rate in normal patients.

It should be stressed here, that the observations in this study suggested that sino-atrial entrance block is a physiological phenomenon at higher pacing rates, and it is only the lower rates at which it is seen in patients with the sick sinus syndrome that indicates abnormal sinus node function. Despite this, in this study the typical shortening of the sinus node recovery time after the administration of atropine in high doses to the patients with sinus node dysfunction suggested that this is an uncommon mechanism for the observation of a normal sinus node recovery time in patients with the sick sinus syndrome. Furthermore, if the sequence following overdrive pacing is observed to have the characteristic pattern observed in this study, it suggests full or partial penetration and capture of the sinus node by atrial pacing.
c) "intermittent" sinus node dysfunction.

Myocardial ischaemia has been observed to produce transient sinus node dysfunction (Hatle et al., 1976), in a similar way to the transient disturbances of atrioventricular conduction seen with acute inferior wall myocardial infarction. In the same way that in the presence of high vagal tone during sleep, sinoatrial Wenckebach and higher degrees of sinoatrial block can be observed in normals (Brodsky et al., 1977; Sobotka et al., 1981), abnormal sinus node function may only become overt when there is increased vagal tone. In addition, electrolyte disturbances or drug effects could be the responsible agent for the precipitation of the (previously covert) abnormality.
Some further points should be made on the sinus node recovery time and corrected sinus node recovery time as they are currently performed (see Table III-1). First, when stated, the intervals between pacing trials of the sinus node recovery time vary considerably between different studies. Observations made during this study, particularly in patients with the sick sinus syndrome, suggested prolonged duration of some effects of overdrive pacing, at least for more than one minute (Chapter VII). Therefore, intervals of even more than two minutes may be necessary to allow return to a "resting" state before pacing is resumed. If pacing is resumed before full return to a resting state, cumulative effects may influence the subsequent post-pacing intervals, giving rise to a potentially greater variability of first post-pacing intervals and the sinus node recovery time. Alternatively, the use of long duration of pacing in patients with the sick sinus syndrome may have greater potential, as does increased rate of pacing (Chapter V), to depress the sinus node maximally.

Second, the derivation of the "resting" cycle length for the corrected sinus node recovery time, by taking the mean of ten or twenty cycles before pacing, may give an unreliable estimate of the resting cycle length. When the cumulative mean of a long series of beats was assessed (Chapter VI), ten beats were found to give a much less reliable estimate.
than the mean of fifty or more cycles. Another estimate of the suppression of automaticity by the pacing can be obtained by comparing the first post-pacing interval with the mean or minimum cycle length post-pacing (Tonkin et al., 1980a). When the prepacing cycle length is used to "correct" the sinus node recovery time, the measurement is subject to the variation in autonomic tone, both related and unrelated to the pacing, that has occurred since the cycle length was measured. This may explain in part the large variability and lack of predictive value of this index. The same comments apply to the Narula method sinoatrial conduction time, which is measured in a similar manner.

Third, as has been presented, the sinus node recovery time, and the corrected sinus node recovery time measure a combination of sinoatrial conduction and suppression of automaticity of the sinus node. This leads to another possible explanation of how a "normal" sinus node recovery time may be found in patients with the sick sinus syndrome. Namely, either abnormal sinus node automaticity or sinoatrial conduction may be masked to some extent by a normal contribution of the other to the sinus node recovery time.
In this study, pacing trials were performed from both the right atrium and the coronary sinus, and no significant differences were found between the results from the two sites. This supports the use of oesophageal pacing (Stopczyk et al., 1972; Mitsui et al., 1973) for assessment of sinus node function (Brunetto et al., 1979; Kraska et al., 1979; Santini et al., 1979).

If effect of pacing rate on the sinus node recovery time is considered, this study confirmed the findings of Kasanuki (1980), that in patients with the sick sinus syndrome, progressive increase in sinus node recovery time is seen with increasing pacing rate. This contrasts to normals, in whom either no change or a decrease in the sinus node recovery time is seen with increasing pacing rates. In patients with normal sinus node function the first post-pacing interval was greatest after right atrial pacing for one minute at 100 bpm (1106 +/- 173 msec, compared to 1034 +/- 226 msec at 130 bpm, 990 +/- 178 msec after eight paced beats (Narula conduction time assessment), and 970 +/- 146 msec after one paced beat which reset the sinus node (Strauss sinoatrial conduction time); see Appendix C). In patients with the sick sinus syndrome, the first post-pacing interval was greatest after right atrial pacing at 180 or 200 bpm (see Chapter V), with progressively smaller first post-pacing interval with right atrial pacing at 130 bpm (1792 +/- 821 msec), 100 bpm (1668
+/-.770 msec), pacing for eight beats (Narula sinoatrial conduction time; 1273 +/- 194 msec), and single atrial premature beats (1234 +/- 50 msec), respectively (Appendix C). Whether high pacing rates, such as 200 bpm are of any value in detecting patients with borderline sinus node function remains to be proven.
iii) sinoatrial conduction time

When estimated by the premature atrial stimulation technique (Strauss et al., 1973, 1976), this index has previously been found to be a less sensitive index of sinus node dysfunction than the sinus node recovery time (Evans et al., 1978). In this study, it was also found to be an insensitive test (see Appendix C). There has been a lack of standard methodology by different groups in derivation of the sinoatrial conduction time from the same data (see Table VI-I), such that in individual patients, the method chosen rather than the data itself can determine whether the results fall in or outside the normal range. The contribution of depression of automaticity has been considered to be only small in the indirectly measured sinoatrial conduction time (Strauss et al., 1976; Narula et al., 1978). Perhaps for the first time, the data in this study invalidates this assumption in humans.

The continuous atrial pacing method as described by Narula (1978) appears to have major limitations. The two most important theoretical assumptions of the method, namely sinus node capture, and absence of depression of sinus node automaticity may often fail to hold. This leads to a critical dependence on pacing cycle length, with marked variation in results, from negative to very high positive values, often seen in this study.
The first post-pacing interval with both these tests of sinoatrial conduction appeared in this study to be a better index of sinus node function than any estimate of the sinoatrial conduction time using the same interval. Prolonged sinoatrial conduction as defined by the range of values observed in the patients with normal sinus node function, only occurs in approximately 50% of patients with the sick sinus syndrome.

The direct recording of sinus node potentials by special catheter placement and filtering techniques appears to be very promising as a method that measures the anterograde sinoatrial conduction time independently of retrograde conduction and of components of automaticity (Reiffel et al., 1980). However, judgement as to which components of the "sinus node electrogram" signal should be used for measurement seem arbitrary and this test has not yet been proven to be of any greater value than the currently used indirect tests.

iv) cardiac vagal blockade and total cardiac autonomic blockade

As discussed above, in the relatively small groups of patients with normal sinus node function and with the sick sinus syndrome studied after atropine, and atropine and propranolol, in this study the sensitivity and specificity
of the cycle length, and the sinus node recovery time improved (Appendix C). Such testing has previously been shown to be of value in patients with symptomatic bradyarrhythmias in defining the respective roles of the autonomic nervous system and the sinus node in such bradyarrhythmias (Jordan et al., 1978; Desai et al., 1981). After atropine, and after atropine and propranolol, patients with the sick sinus syndrome could be divided into those with normal and abnormal cycle length for the given state. It has previously been suggested that this separates patients with abnormal intrinsic sinus node dysfunction from those with abnormal autonomic nervous influences on the sinus node (Jordan et al., 1978; Desai et al., 1981).
b) **post-pacing sequences**

i) **general observations**

The value of considering not only the first post-pacing interval, but also the subsequent post-pacing sequence has previously been stressed by Delius and Wirtzfeld (1976) and by Benditt and colleagues (1976). The latter group stressed the value of secondary pauses as a marker for sinus node dysfunction.

From the observations made in the present study, the following conclusions can be drawn. First, observation of the first post-pacing cycle length less than the second, when seen after low rates of pacing (80 to 100 beats per minute) is suggestive of atriosinus conduction block and sinus node dysfunction. Long secondary pauses suggestive of sinoatrial exit block appear specific but insensitive as a marker of abnormal sinus node function. Characteristic sequences were seen in the majority of trials of overdrive pacing both in patients with normal sinus node function and in patients with the sick sinus syndrome. This sequence consisted of a maximally prolonged first post-pacing interval with progressive but decreasing decay in subsequent intervals. Such sequences formed the basis for the development of the mathematical model (Chapter IV and Appendix B) by Dr. A Helfgott.
Such sequences were observed not only in the majority of sequences after one minute of overdrive high right atrial pacing, but also after pacing from the coronary sinus, and after single atrial premature beats and eight paced atrial beats. Sequences where this did not occur often included atrial and ventricular premature beats, junctional escape beats, or may have been due to incomplete capture or failure of capture of the sinus node by some or all of the paced atrial beats (Grant et al., 1979b; Steinbeck et al., 1980), overdrive acceleration of the sinus node (Lange et al., 1965; Jordan et al., 1977; Kodama et al., 1980), pacemaker shifts (Steinbeck and Lüderitz, 1977) and sinoatrial exit block following pacing.

When the effects of pacing rate and duration were studied, quantitative but not qualitative differences were seen. In the patients with the sick sinus syndrome, duration of the first post-pacing interval was directly related to the rate and duration of pacing.

The assumption of each of these tests is complete penetration and "reset" of the sinus node by the pacing beat(s). When it appears that this has occurred, the following conclusions can be drawn from the observations made in this study:
i) the morphology of the events that follow capture and re-
set of the sinus node are essentially the same, irrespective
of the atrial site, rate, and duration of pacing.
ii) these four tests of sinus node function all measure a
combination of sinoatrial conduction (retrograde and antero-
grade), and suppression of sinus node automaticity, the two
usually being of comparable magnitude.
iii) the quantitative effects depend on the rate and dur-
ation of pacing.

Many experimental observations in animal models suggest that
complex events occur at the level of the sinus node in re-
ponse to overdrive atrial pacing, with sinus node pacemaker
shifts (Bouman et al., 1968; Grant et al., 1979b), variation
in the maximum diastolic potential (Amory and West 1962; Lu
et al., 1965; Steinbeck et al., 1980; Kodama et al., 1980),
variation in the sinoatrial conduction time (Miller and
Strauss, 1974; Grant et al., 1979b; Steinbeck et al., 1980),
variation in the action potential duration (Lu et al., 1965;
Miller and Strauss 1974; Grant et al., 1979b), and change in
atriosinus conduction with higher pacing rate (Steinbeck et
al., 1980; Kerr and Strauss, 1981). The effect of pacing on
the threshold potential and the relationship between maximum
diastolic potential and the threshold potential is not
known, as the threshold potential in sinus node pacemaker
cells cannot be defined except arbitrarily. The biochemical
events at the membrane level associated with the phenomenon
of overdrive suppression are poorly understood at the pres-
ent time. Such events are likely to be complex rather than simple, in view of the many ionic channels present in the cell membrane of pacemaker cells in the myocardium (Noble 1979), although it is possible that changes in membrane transport and distribution of a single ionic species (for example K+, Na+, or Ca++) may be the final common pathway, with multiple modulating factors (such as drugs, acetylcholine, and sympathetic amines).

ii) P wave morphology variation

A not infrequent finding in this study, was marked change in P wave morphology of the initial post-pacing beats in the absence of change in gross activation sequence as studied by high right atrial and low medial right atrial recordings (Chapter III). Frequently, although the atrial activation sequence was unchanged (as assessed by intracavitary recordings), there appeared to be an associated change in the morphology of the high right atrial electrogram. Similar findings in a small group of patients have been observed by Steinbeck (1977), who suggested that they were on the basis of pacemaker shifts within the sinus node. The possible explanations for these P wave changes have been discussed in Chapter III. A limitation of these observations as made in this study was the presence of only three surface electrocardiographic leads with which to assess the P wave morphology.
This change in P wave morphology was seen before drugs in 25/331 sequences in the 35 patients with the sick sinus syndrome, and in only 2/149 sequences in the 22 patients with normal sinus node function. When the cycle lengths of such sequences were plotted against the beat number, there were clear discontinuities present at the time of change of P wave morphology. Typically, the initial P waves were different to those of stable sinus rhythm. It is possible that different P wave morphology in initial post-pacing beats may also be a marker for sinus node dysfunction, and warrants further study. Such changes were not observed in any patients after cardiac vagal blockade or total cardiac autonomic blockade with atropine and atropine and propranolol respectively, suggesting that they may have been on the basis of vagally induced pacemaker shifts.
iii) post-pacing sequences after one or eight paced beats

It should be stressed again, that typical post-pacing sequences were seen after one and after eight paced beats, in addition to their occurrence after one minute of overdrive atrial pacing. The typical decaying sequences seen in the reset zone during determination of the sinoatrial conduction time by the Strauss method strongly suggested that such sequences were markers for capture and reset of the sinus node. The problem of isorhythmic sinoatrial dissociation, demonstrated in the experiments of Grant and coworkers (1979b), appears to have its clinical electrophysiological correlate when the atria are paced at cycle lengths close to that of the sinus node, when either satisfactory penetration and capture, or partial or complete failure to capture the sinus node may occur.

iv) post-pacing sequences after total cardiac autonomic blockade

In the basal state, there are marked fluctuations in cycle length related to fluctuations in autonomic tone. Such changes may markedly influence the initial post-pacing sequence, and have been considered one reason for the lack of specificity and sensitivity of conventional electrophysiological tests of sinus node function. In the studies of sinus node function by atrial overdrive pacing after
cardiac vagal +/- sympathetic blockade, such cycle length fluctuations were usually absent; the characteristic sequences observed suggested that the cardiac autonomic nerves were not necessary for overdrive suppression to occur, but that they may have had a modulating influence.
c) Mathematical Model

The development of the mathematical model of overdrive suppression of the sinus node by Dr. A Helfgott and the subsequent testing of the model by myself requires further comment.

i) theoretical considerations

There are some important assumptions that were made in the absence of knowledge at the present time with respect to the following events, some of which may be clarified by animal experimental models.

First, it was assumed that pacemaker shifts are unimportant in the sinus node in man. The answer to this is not known, but certainly shifts of pacemaker site within the sinus node in response to atrial pacing and to vagal stimulation is of major importance in experimental animal models (Bouman et al., 1968; Bonke, 1968; Bonke et al., 1969; Grant et al., 1979b). This may explain to some extent the variability between the results of curve fitting to different sequences in the same patient in the basal state. A decrease in pacemaker shifts would be expected after cardiac autonomic blockade. More important than the presence or absence of pacemaker shifts is how much they influence the time for atrial activation and the relationship between the action potential configuration, including the phase 4 slope, in the
different pacemaker cells.

It was assumed that the difference between the threshold potential and the maximum distolic potential remains constant in the sinus node pacemaker cells. The major problem is defining the onset of the action potential (and hence the threshold potential and the action potential duration) in a primary pacemaker cell, with a smooth transition occurring between phase 4 and phase 0 of the action potential. So, even in experimental animal models, where cellular membrane action potentials have been accurately recorded, this question at the present time remains unanswered.

One further assumption was that the anterograde sinoatrial conduction time was constant with each post-pacing sinus node beat. Observations in animal experiments have shown increased, unchanged, and decreased anterograde sinoatrial conduction time of the first post-pacing interval (Grant et al., 1979b; Steinbeck et al., 1980). In which direction this change occurs in man, if at all, is not known at the present time.

ii) application of mathematical model

When the model is fitted to post-pacing sequences, what is the meaning and value of each of the derived indices? The sinoatrial conduction time is the simplest to understand,
being an added component present only in the first post-pacing interval, due to the fact that the recordings are from a site (the high right atrium) removed from the sinus node itself. The value of the sinoatrial conduction time computed from the model, as with the other indices to be discussed, requires prospective testing in a group of patients with possible abnormal sinus node function, to assess the predictive value of a prolonged sinoatrial conduction time.

The other indices are more difficult to understand. The common ratio of the geometric progression, q, is a non-dimensional number which relates to the rate of recovery processes following overdrive suppression. No clear relation between this index and sinus node dysfunction was present in this study, suggesting that either, in its current state of development, the mathematical model is not sufficiently sophisticated to detect such differences, or that the recovery process occurs at the same rate in both normals and the sick sinus syndrome, and both before and after cardiac vagal blockade and total cardiac autonomic blockade. ΔTI, is a measure of the extent of suppression of automaticity of the sinus node by pacing, and is greater in patients with sinus node dysfunction. Similarly, T∞, which is an index of the resting state to which the sinus node tends with recovery, is clearly greater in patients with sinus node dysfunction.
Post-pacing sequences following cardiac vagal and cardiac autonomic blockade were successfully fitted to the mathematical model of overdrive suppression of the sinus node. The indices derived thereby more clearly distinguished normal and abnormal responses of sinoatrial conduction and automaticity than did indices derived in the pre-drug state. In particular, ΔT1 was significantly different between patients with normal and abnormal sinus node function after atropine.

Appendix D summarises, in both patients with normal sinus node function and in those with the sick sinus syndrome, the mean computed indices from the Strauss and Narula method sinoatrial conduction time assessments (Chapter VI), and from overdrive atrial pacing at 100 and 130 beats per minute. For most indices, within a group in a given state, there were only minor differences between the different forms of atrial pacing. The values of ΔT1 showed the most change, and were greater with overdrive atrial pacing compared to the sinoatrial conduction time tests, both in patients with normal sinus node function and in patients with the sick sinus syndrome.

These results emphasize the qualitative similarity of all pacing tests of sinus node function.
iii) Conclusions

If the assumptions of the model are correct, then by its application to post-pacing sequences, the relative contributions of sinoatrial conduction and suppression of automaticity of the sinus node can be indirectly estimated in man.

d) Clinical and Research Implications

The problem of low sensitivity and specificity of current tests of sinus node function remains in those patients in whom the decision as to whether or not to implant a permanent pacemaker is clinically equivocal. It seems strongly indicated to undertake a prospective study of tests of sinus node function in a large group of such patients, examining:

i) conventional indices

ii) high pacing rates

iii) cardiac vagal and autonomic blockade

iv) indices of sinoatrial conduction and automaticity derived from fitting post-pacing sequences to the mathematical model of overdrive suppression

v) form of postpacing sequences, for example changes in P wave morphology, and sequences suggesting atriosinus block of the last paced beat,
in order to determine the value of the above tests in the group of patients with clinically equivocal sinus node function. In such a study criteria of normality based on results in this and further studies should be derived, and the sensitivity, specificity, and predictive value of each index assessed.
Further testing of the assumptions involved in the mathematical model using experimental animal models would be of importance, with the ability in such models to accurately control the ionic state and to measure sinus node activity both directly and indirectly. Such studies may provide answers to the unresolved questions of the duration of the action potential, the relationship of the threshold potential and the maximum diastolic potential, pacemaker shifts, and variation in sinoatrial conduction time anterogradely after the first post-pacing beat. On the basis of such observations, modifications could be made to the mathematical model to increase its accuracy.
APPENDIX A

STUDY PROTOCOL

i) Catheter Placement

ii) Heparin 5000 units intravenously

iii) Rest period of ten minutes

iv) Recording of pre-pacing cycle length

v) Overdrive atrial pacing for 1 minute with five trials at each pacing rate, and two minutes intervening between each trial:

100 bpm x 5

130 bpm x 5

Additional trials when possible at pacing rates of 80, 150, 180, and 200 bpm (beats per minute).

vi) Strauss method sinoatrial conduction time

vii) Narula method sinoatrial conduction time

viii) Assessment of AV node function and study for arrhythmias using programmed atrial and ventricular stimulation with single and paired premature beats, and atrial and ventricular pacing at incremental rates

ix) Graded Valsalva manoeuvres

x) Carotid sinus massage

xi) Atropine (0.03 mg/kg body weight) or propranolol (0.15 mg/kg body weight) intravenously
xii) iv) - x) repeated

xiii) propranolol or atropine intravenously with supplementary doses of the first administered drug

xiv) iv) - x) repeated
APPENDIX B

MATHEMATICAL MODEL OF OVERDRIVE SUPPRESSION

OF THE SINUS NODE (DR. A. HELFGOIT)

Theoretical Mathematical Considerations

Overdrive atrial pacing results in a considerable perturbation of sinus node function, probably related to changes in transmembrane concentrations and/or fluxes of one or more ionic species. Although return to steady-state sinus node function might theoretically occur over an infinitely variable time, this mathematical model aimed to analyse the initial post-pacing cycle lengths (PPCL), during which there is progressive decrease in post-pacing cycle length prolongation, and when the effects of pacing might be expected to be maximal.

For each post-pacing interval $T_j$, the prolongation $\Delta T_j$ of PPCL with respect to the asymptotic cycle length ($T_\infty$) toward which consecutive PPCL tend, may be defined by the relation

$$\Delta T_j = T_j - T_\infty \quad j = 1, 2, \ldots, n. \ (1)$$

The mean slope $s_j$ of the pacemaker potential $V(t)$ of post-overdrive beat $j$ may be expressed as

$$s_j = \tan \alpha_j = \frac{\Delta V}{T_j - t_a} \quad j = 1, 2, \ldots, n. \ (2)$$
where $\alpha_j$ is the mean slope angle, $\Delta V_p$ is the increment in pacemaker potential to threshold $V_{th}$, $T_j$ is the post-pacing cycle length interval number $j$, and $t_a$ is the action potential duration.

Assuming that variations in $t_a$ and $\Delta V_p$ are minor, for very late PPCL as $j$ approaches infinity and $T_j$ approaches $T_\infty$, $\bar{s}_j$ approaches its maximal value

$$\bar{s}_\infty = \tan \alpha = \frac{\Delta V_p}{T_\infty - t_a} \quad j = 1, 2, \ldots, n. \quad (3)$$

For PPCL$_j$, we define the normalised mean slope depression, $D_j$, as

$$D_j = \frac{\bar{s}_\infty - \bar{s}_j}{\bar{s}_j} \quad j = 1, 2, \ldots, n. \quad (4)$$

Substituting (2) and (3) into (4) gives the simple linear relation

$$\Delta T_j = c D_j \quad j = 1, 2, \ldots, n. \quad (5)$$

where $c = T_\infty - t_a = \frac{\Delta V_p}{\bar{s}_\infty} = \text{constant}$

From (5) we obtain the important decay law, $q_j$, which holds for both sequences of $D_j$ and $\Delta T_j$

$$q_j = \frac{D_{j+1}}{D_j} = \frac{\Delta T_{j+1}}{\Delta T_j} \quad (0 < q_j < 1) \quad j = 1, 2, \ldots, n. \quad (6)$$

Assuming further, that sinus node recovery from overdrive suppression is due to exponential decay of a single phenomenon,
such as clearance of extracellular potassium, effecting a progressive increase in slope of phase 4 depolarisation, we put \( q_j = q \) constant for all \( j \) in (6), and established that the sequences \( \Delta T_j \) and \( D_j \) \( (j = 1,2,\ldots,n) \) are geometric progressions and that the final expression for the PPCL sequence, substituting (6) into (1), is

\[
T_j = T_\infty + \Delta T_1 q^{j-1} \quad j_1 = 1,2,\ldots,n
\]  

Computing

Two least squares computer programmes to minimise the sum of squares of the function \( T_j \) were written in FORTRAN IV language. The first programme estimated linear parameters \( q, \Delta T_1, \) and \( T_\infty \). The second programme estimated \( q, \Delta T_1, \) and \( T_\infty \) as non-linear parameters, using the standard Harwell subroutine package V801AD (double precision version), which employs the modified Marquardt routine.
### APPENDIX C

**SENSITIVITY, SPECIFICITY**

**BASAL STATE "CONVENTIONAL" INDICES**

<table>
<thead>
<tr>
<th>INDEX</th>
<th>SSS</th>
<th>N</th>
<th>M+1SD</th>
<th>Sens&lt;sup&gt;V&lt;/sup&gt;</th>
<th>Spec&lt;sup&gt;V&lt;/sup&gt;</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>1030 +/- 180</td>
<td>787 +/- 144</td>
<td>931</td>
<td>71%</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>SNRTmax 100</td>
<td>1668 +/- 770</td>
<td>1106 +/- 173</td>
<td>1279</td>
<td>89%</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>SNRT 100</td>
<td>1412 +/- 469</td>
<td>1064 +/- 180</td>
<td>1244</td>
<td>74%</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>CSRTmax 100</td>
<td>649 +/- 736</td>
<td>291 +/- 108</td>
<td>399</td>
<td>57%</td>
<td>79%</td>
<td>73%</td>
</tr>
<tr>
<td>CSRT 100</td>
<td>504 +/- 477</td>
<td>243 +/- 108</td>
<td>351</td>
<td>60%</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>SNRTmax 130</td>
<td>1792 +/- 821</td>
<td>1034 +/- 226</td>
<td>1260</td>
<td>76%</td>
<td>88%</td>
<td>87%</td>
</tr>
<tr>
<td>SNRT 130</td>
<td>1520 +/- 656</td>
<td>972 +/- 209</td>
<td>1181</td>
<td>71%</td>
<td>82%</td>
<td>80%</td>
</tr>
<tr>
<td>CSRTmax 130</td>
<td>772 +/- 825</td>
<td>289 +/- 125</td>
<td>414</td>
<td>59%</td>
<td>82%</td>
<td>77%</td>
</tr>
<tr>
<td>CSRT 130</td>
<td>586 +/- 696</td>
<td>231 +/- 109</td>
<td>340</td>
<td>59%</td>
<td>76%</td>
<td>71%</td>
</tr>
<tr>
<td>SACT NM T1</td>
<td>1273 +/- 194</td>
<td>944 +/- 216</td>
<td>1160</td>
<td>72%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SACT NM</td>
<td>242 +/- 119</td>
<td>184 +/- 97</td>
<td>281</td>
<td>28%</td>
<td>88%</td>
<td>69%</td>
</tr>
<tr>
<td>SACT NMc</td>
<td>155 +/- 72</td>
<td>100 +/- 51</td>
<td>151</td>
<td>45%</td>
<td>86%</td>
<td>76%</td>
</tr>
<tr>
<td>SACT SM T1(r)</td>
<td>1234 +/- 50</td>
<td>970 +/- 146</td>
<td>1116</td>
<td>80%</td>
<td>88%</td>
<td>86%</td>
</tr>
<tr>
<td>SACT (Ar-Al)</td>
<td>241 +/- 83</td>
<td>164 +/- 38</td>
<td>202</td>
<td>70%</td>
<td>86%</td>
<td>83%</td>
</tr>
<tr>
<td>SACT SM r/3</td>
<td>195 +/- 70</td>
<td>161 +/- 55</td>
<td>216</td>
<td>26%</td>
<td>89%</td>
<td>70%</td>
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<tr>
<td>SACT SM reset</td>
<td>213 +/- 69</td>
<td>160 +/- 37</td>
<td>197</td>
<td>61%</td>
<td>78%</td>
<td>73%</td>
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<tr>
<td>SACT SM I</td>
<td>192 +/- 52</td>
<td>158 +/- 52</td>
<td>210</td>
<td>39%</td>
<td>78%</td>
<td>64%</td>
</tr>
<tr>
<td>SACT SM .4-.6</td>
<td>230 +/- 76</td>
<td>153 +/- 26</td>
<td>179</td>
<td>79%</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>SACT SMc</td>
<td>160 +/- 67</td>
<td>103 +/- 17</td>
<td>120</td>
<td>63%</td>
<td>86%</td>
<td>82%</td>
</tr>
</tbody>
</table>

**BASAL STATE COMPUTED INDICES**

<table>
<thead>
<tr>
<th>SNRT 100</th>
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<tbody>
<tr>
<td>&quot;q&quot;</td>
</tr>
<tr>
<td>&quot;AT1&quot;</td>
</tr>
<tr>
<td>&quot;T∞&quot;</td>
</tr>
<tr>
<td>&quot;SACTc&quot;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNRT 130</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;q&quot;</td>
</tr>
<tr>
<td>&quot;AT1&quot;</td>
</tr>
<tr>
<td>&quot;T∞&quot;</td>
</tr>
<tr>
<td>&quot;SACTc&quot;</td>
</tr>
</tbody>
</table>
**ATROPINE "CONVENTIONAL" INDICES**

<table>
<thead>
<tr>
<th></th>
<th>M ± 1SD</th>
<th>Sensy</th>
<th>Specy</th>
<th>PA</th>
<th>CL</th>
<th>SNRT 100</th>
<th>CSRT 100</th>
<th>SNRT 130</th>
<th>CSRT 130</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>678 ± 92</td>
<td>540 ± 46</td>
<td>586</td>
<td>84%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SNRT 100</td>
<td>952 ± 127</td>
<td>702 ± 63</td>
<td>765</td>
<td>95%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>CSRT 100</td>
<td>242 ± 100</td>
<td>135 ± 72</td>
<td>207</td>
<td>53%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SNRT 130</td>
<td>974 ± 221</td>
<td>711 ± 26</td>
<td>737</td>
<td>95%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>CSRT 130</td>
<td>306 ± 172</td>
<td>151 ± 35</td>
<td>186</td>
<td>82%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**ATROPINE + PROPRANOLOL "CONVENTIONAL" INDICES**

<table>
<thead>
<tr>
<th></th>
<th>M ± 1SD</th>
<th>Sensy</th>
<th>Specy</th>
<th>PA</th>
<th>CL</th>
<th>SNRT 100</th>
<th>CSRT 100</th>
<th>SNRT 130</th>
<th>CSRT 130</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>961 ± 191</td>
<td>748 ± 74</td>
<td>822</td>
<td>67%</td>
<td>83%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>SNRT 100</td>
<td>1356 ± 346</td>
<td>949 ± 113</td>
<td>1062</td>
<td>100%</td>
<td>80%</td>
<td>86%</td>
<td>86%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>CSRT 100</td>
<td>403 ± 172</td>
<td>192 ± 38</td>
<td>230</td>
<td>87%</td>
<td>80%</td>
<td>84%</td>
<td>84%</td>
<td>84%</td>
<td>84%</td>
</tr>
<tr>
<td>SNRT 130</td>
<td>1565 ± 594</td>
<td>944 ± 121</td>
<td>1065</td>
<td>100%</td>
<td>83%</td>
<td>86%</td>
<td>86%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>CSRT 130</td>
<td>691 ± 626</td>
<td>196 ± 107</td>
<td>303</td>
<td>82%</td>
<td>83%</td>
<td>83%</td>
<td>83%</td>
<td>83%</td>
<td>83%</td>
</tr>
</tbody>
</table>

**LEGEND:** SSS = patients with the sick sinus syndrome; N = patients with normal sinus node function; M ± 1SD = mean ± one standard deviation from patients with normal sinus node function; Sensy, Specy, and PA represent sensitivity, specificity, and predictive accuracy of a positive result, for the given index; CL = pre-pacing cycle length; SNRTmax = maximal sinus node recovery time; SNRT = sinus node recovery time; CSRTmax = maximal corrected sinus node recovery time; SACT NM T1 = first
post-pacing cycle length from Narula conduction time assessment;
SACT NM = sinoatrial conduction time calculated by the method of
Narula; SACT NMC = sinoatrial conduction time computed from
post-pacing sequence of Narula method; SACT SM T1 (r) = first
post-pacing cycle length (return cycle) from premature atrial
stimulation (Strauss) method of assessment of sinoatrial
conduction time (reset zone only); SACT (Ar-Al) = return cycle
less pre-pacing cycle from Strauss sinoatrial conduction time
assessment (reset zone only); SACT SM r/3, SM reset, SM I, SM
.4-.6, represent sinoatrial conduction time calculated from plot
of return cycle against test cycle from Strauss sinoatrial
conduction time as described in Chapter VI; SACT SMc = computed
sinoatrial conduction time calculated from Strauss sinoatrial
conduction time post-pacing sequences; computed indices of sinus
node function, q, ΔT1, and T∞, and SACTc are as described in
Chapters IV, V, and VI. Note that the numbers of patients with
normal sinus node function studied after these drugs was small,
and hence the specificity, and the predictive accuracy of a
positive result, are approximate estimates only.
APPENDIX D

COMPARISON OF COMPUTED INDICES OF SINUS NODE FUNCTION

I. NORMALS

<table>
<thead>
<tr>
<th>BASAL</th>
<th>n</th>
<th>q</th>
<th>ΔT1 (msec)</th>
<th>T∞ (msec)</th>
<th>SACTc (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SACT SM</td>
<td>8</td>
<td>.675 +/- .155</td>
<td>136 +/- 78</td>
<td>736 +/- 175</td>
<td>103 +/- 17</td>
</tr>
<tr>
<td>SACT NM</td>
<td>7</td>
<td>.716 +/- .144</td>
<td>178 +/- 51</td>
<td>722 +/- 114</td>
<td>100 +/- 51</td>
</tr>
<tr>
<td>SNRT 100</td>
<td>17</td>
<td>.632 +/- .123</td>
<td>232 +/- 134</td>
<td>736 +/- 79</td>
<td>92 +/- 53</td>
</tr>
<tr>
<td>SNRT 130</td>
<td>14</td>
<td>.675 +/- .104</td>
<td>183 +/- 120</td>
<td>690 +/- 121</td>
<td>108 +/- 51</td>
</tr>
<tr>
<td>SNRT 180/200</td>
<td>7</td>
<td>.658 +/- .113</td>
<td>209 +/- 304</td>
<td>666 +/- 97</td>
<td>115 +/- 78</td>
</tr>
</tbody>
</table>

ATROPINE

| SNRT 100    | 6  | .590 +/- .192 | 32 +/- 21 | 585 +/- 17 | 84 +/- 29   |
| SNRT 130    | 6  | .650 +/- .185 | 38 +/- 18 | 576 +/- 29 | 92 +/- 21   |

ATROPINE AND PROPRANOLOL

| SNRT 100    | 6  | .753 +/- .090 | 87 +/- 29 | 762 +/- 75 | 101 +/- 36  |
| SNRT 130    | 6  | .688 +/- .298 | 87 +/- 48 | 753 +/- 57 | 157 +/- 19  |
## II. INTERMEDIATE

<table>
<thead>
<tr>
<th>BASAL</th>
<th>n</th>
<th>q</th>
<th>ΔT1 (msec)</th>
<th>Tₚ₀ (msec)</th>
<th>SACTc (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRT 100</td>
<td>17</td>
<td>.659 +/-.121</td>
<td>307 +/- 272</td>
<td>798 +/- 137</td>
<td>176 +/- 89</td>
</tr>
<tr>
<td>SNRT 180/200</td>
<td>7</td>
<td>.732 +/-.156</td>
<td>151 +/- 73</td>
<td>755 +/- 140</td>
<td>97 +/- 68</td>
</tr>
</tbody>
</table>
### III. SICK SINUS SYNDROME

<table>
<thead>
<tr>
<th>BASAL</th>
<th>n</th>
<th>q</th>
<th>ΔT1 (msec)</th>
<th>T&lt;sub&gt;∞&lt;/sub&gt; (msec)</th>
<th>SACT&lt;sub&gt;c&lt;/sub&gt; (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SACT SM</td>
<td>19</td>
<td>.643 +/- .155</td>
<td>145 +/- 143</td>
<td>919 +/- 175</td>
<td>160 +/- 67</td>
</tr>
<tr>
<td>SACT NM</td>
<td>22</td>
<td>.700 +/- .130</td>
<td>171 +/- 111</td>
<td>981 +/- 182</td>
<td>155 +/- 72</td>
</tr>
<tr>
<td>SNRT 100</td>
<td>28</td>
<td>.720 +/- .092</td>
<td>250 +/- 123</td>
<td>931 +/- 162</td>
<td>185 +/- 116</td>
</tr>
<tr>
<td>SNRT 130</td>
<td>21</td>
<td>.637 +/- .172</td>
<td>243 +/- 131</td>
<td>931 +/- 198</td>
<td>212 +/- 164</td>
</tr>
<tr>
<td>SNRT 180/200</td>
<td>4</td>
<td>.802 +/- .101</td>
<td>335 +/- 254</td>
<td>805 +/- 249</td>
<td>263 +/- 243</td>
</tr>
</tbody>
</table>

### ATROPINE

<table>
<thead>
<tr>
<th>BASAL</th>
<th>n</th>
<th>q</th>
<th>ΔT1 (msec)</th>
<th>T&lt;sub&gt;∞&lt;/sub&gt; (msec)</th>
<th>SACT&lt;sub&gt;c&lt;/sub&gt; (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SACT SM</td>
<td>14</td>
<td>.573 +/- .105</td>
<td>96 +/- 86</td>
<td>699 +/- 72</td>
<td>198 +/- 135</td>
</tr>
<tr>
<td>SACT NM</td>
<td>8</td>
<td>.676 +/- .170</td>
<td>75 +/- 68</td>
<td>723 +/- 74</td>
<td>95 +/- 45</td>
</tr>
<tr>
<td>SNRT 100</td>
<td>19</td>
<td>.697 +/- .153</td>
<td>125 +/- 91</td>
<td>711 +/- 70</td>
<td>115 +/- 57</td>
</tr>
<tr>
<td>SNRT 130</td>
<td>22</td>
<td>.680 +/- .120</td>
<td>119 +/- 106</td>
<td>678 +/- 84</td>
<td>193 +/- 145</td>
</tr>
</tbody>
</table>

### ATROPINE AND PROPRANOLOL

<table>
<thead>
<tr>
<th>BASAL</th>
<th>n</th>
<th>q</th>
<th>ΔT1 (msec)</th>
<th>T&lt;sub&gt;∞&lt;/sub&gt; (msec)</th>
<th>SACT&lt;sub&gt;c&lt;/sub&gt; (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SACT SM</td>
<td>7</td>
<td>.655 +/- .171</td>
<td>55 +/- 31</td>
<td>884 +/- 88</td>
<td>199 +/- 41</td>
</tr>
<tr>
<td>SACT NM</td>
<td>9</td>
<td>.562 +/- .166</td>
<td>112 +/- 145</td>
<td>932 +/- 122</td>
<td>137 +/- 54</td>
</tr>
<tr>
<td>SNRT 100</td>
<td>15</td>
<td>.739 +/- .155</td>
<td>182 +/- 116</td>
<td>942 +/- 173</td>
<td>187 +/- 79</td>
</tr>
<tr>
<td>SNRT 130</td>
<td>11</td>
<td>.718 +/- .087</td>
<td>206 +/- 55</td>
<td>942 +/- 100</td>
<td>145 +/- 46</td>
</tr>
</tbody>
</table>

The data presented here is from analysis of the post-pacing sequences by
non-linear curve fitting analysis to the mathematical model (of Dr. A. Helfgott) of overdrive suppression of the sinus node presented in Appendix B and in Chapter IV. SACT SM, SACT NM represent Strauss method and Narula method sinoatrial conduction time assessments respectively. SNRT 100, SNRT 130, and SNRT 180/200 the sinus node recovery time at 100, 130 beats per minute, and the pooled results from 180 and 200 beats per minute respectively. With the exception of the SACT SM and SACT NM computed indices in the patients with the sick sinus syndrome after atropine, and atropine and propranolol, the data presented here have already been presented in Chapters IV, V, VI, and VII (in Tables IV-2, V-2, VI-4,5,6,7, and VII-4). "n" represents the number of patients in whom sequences were successfully fitted in each test/state.
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1. Patient Selection

A major problem was to determine prospectively a suitable control group for the subjects with the sick sinus syndrome.

Those available could be separated into three groups:

1) Young subjects being studied for paroxysmal supraventricular tachycardia with no history of syncope and normal ECG monitoring.

2) Patients being investigated for ventricular arrhythmias often with a history of syncope but without any ECG evidence of sinus node dysfunction. Sick sinus syndrome is known to be frequently associated with coronary artery disease which many of these patients had.

3) Patients undergoing investigation for syncope of unknown cause with or without evidence of distal conduction disease. Sick sinus syndrome is known to be associated with distal conduction disease.

Because of the preliminary nature of this study, it was considered most appropriate to test the model in a group of unequivocally normal subjects in addition to those with sick sinus syndrome.
It was hoped that once the processing was streamlined, comparisons with the other groups above could be made. The selection chosen left a significant age difference between the "normals" and "sick sinus syndrome" groups, of which cognisance had to be taken in interpretation of all results.

2. Morbidity from Studies

In simple terms, there was minimal morbidity from the electrophysiology studies performed. The two minor problems encountered were as follows: prolonged femoral vein bleeding was encountered in two elderly females with sick sinus syndrome which required prolonged (20-30 minutes) femoral vein compression with satisfactory results. In two elderly males an acute confusional state occurred for 6-12 hours after the study during which Atropine 0.03 mg/Kg had been administered. These required observation only and were normal the following day.

3. Variation

The major components of variation were within individual subjects, and between subjects. The magnitude of these errors was of the order of $10^2$ greater than those due to random and systematic errors.
4. **Validation of Model**

Dr. Helfgott directed considerable efforts to validation of the model. To test the exponential nature he performed sequential analysis with sequences of 10 intervals, progressively predicting the preceding beat (using $T_6-T_{10}$ to predict $T_5$, $T_5-T_{10}$ to predict $T_4$ etc.).

The real validation of the model depends on direct recording of sinus node action potentials so that the component of sinoatrial conduction is eliminated. This is now feasible in both man (using extracellular sinus node recordings) and in animal models. The former is to be done in the near future in this laboratory.

5. **Meaning of Indices**

The following Tables give the mean values of the first post-pacing interval and computed indices in those subjects in whom the Strauss and Narula conduction times, and overdrive pacing at 100 and 130 bpm were done. These provide a gradation in duration and frequency of pacing from one single premature beat, to eight paced beats at cycle length ~100 ms less than sinus rhythm, to one minute of pacing at 100 bpm, up to one minute of pacing at 130 bpm. The index $q$ is a measure of the rate of recovery of the sinus node from overdrive.
The index shows a trend to increase with increasing rate (up to 100 bpm) and duration of pacing in the sick sinus syndrome, suggesting a disturbance of the recovery process. This index does not follow a clear pattern in patients with normal sinus node function, and there are not significant differences between the values of \( q \) in the two groups.

The value of \( q \) in assessing sinus node function was disappointing. A higher value of \( q \) (slower rate of recovery from overdrive suppression) was expected in patients with sinus node disease, and a lower value (more rapid recovery from overdrive suppression) in patients with normal sinus node function. This lack of difference suggests rate of recovery is not an important determinant of sinus node dysfunction. Alternatively, inter and intra-patient variation in this index (and the small patient members in the normal group) may be decreasing its sensitivity. Additionally, the small patient numbers in the "normal" group limits interpretation of this result.

The index \( \Delta T_1 \), which does not correlate with resting cycle length, \( q \), or \( T_\infty \), and which is a measure of extent of suppression of the sinus node by pacing also shows a progressive increase with increase in pacing rate (up to 100 bpm) and duration, suggesting greater depression of sinus node automaticity by the pacing. This index is not significantly different between patients with normal and abnormal sinus node function. This lack of difference is critical in understanding why current electrophysiologic tests of sinus node function have often failed to differentiate between normal and abnormal sinus node function.
The indices above are clearly influenced by the mode of pacing but independent of sinus node disease. In contrast are the indices computed SACT and $T_\infty$ (asymptotic cycle length) which are independent of pacing mode, but significantly increased in the presence of sinus node disease.

6. Considerations on Mechanism of Sick Sinus Syndrome

On the basis of the above observations, my opinion is that in the sick sinus syndrome two major abnormalities are present. First, depressed "intrinsic" automaticity of the sinus node. As discussed on page 204, it is my feeling that this is a problem within the sinus node itself and not related to autonomic tone, although there is some evidence to the contrary view. The second abnormality is impaired sinoatrial conduction from the sinus node to the atrium, manifest either as prolonged sinoatrial conduction time or sinoatrial exit block.

That the sinus node is equally depressed by the same pacing modality in patients with normal and in patients with abnormal sinus node function is strongly suggested by the data above. The differences between the sinus node recovery time in subjects with normal and abnormal sinus node function relates to the resting cycle length and the sinoatrial conduction time. The major advantage of overdrive suppression is to bring out manifestations of abnormal sinoatrial conduction (sinoatrial entry and exit block).
Tests directed toward measuring the sinoatrial conduction time (directly recorded SACT) and retrograde refractoriness of the sinus node as recently described by Kerr are the most promising current simple approaches to assessment of sinus node function.

7. Calculation of Indices of Non-Linear Regression Lines and the Confidence Limits of the First Post-Pacing Interval

Dr. A. Helfgott has written a complex and sophisticated computer programme to fit the mathematical model:

\[ T_j = T_\infty + \Delta T_1 \cdot q^{(j-1)} \]

to the observed post-pacing intervals and thus to derive indices \( q \), \( \Delta T_1 \), \( T_\infty \), and SACT. (Dr. A. Helfgott, Personal Communication, unpublished).

Initial calculations are done using the second and subsequent post-pacing intervals. The strategy adopted is first to estimate \( q \) by a multiplicity of methods (Dr. A. Helfgott, Personal Communication).

Once \( x_j \), an estimate of \( q^{j-1} \) is made, initial estimates of the parameters \( T_\infty \) and \( \Delta T_1 \) can be derived using the linear relationship:

\[ T_j = T_\infty + \Delta T_1 \cdot x_j. \]
Using these initial estimates, a complex non-linear least squares curve fitting programme is used to derive final values for $q$, $\Delta T_1$, and $T_\infty$.

Finally, a theoretical value $T_1$ for the first post-pacing interval is calculated, the difference between this value and the measured first-interval $T_1$ being the sinoatrial conduction time.

Appendix F contains a sample computer output from the programme.

Dr. Helfgott has developed a complex method specifically for the model to construct 95% confidence limits for the first post-pacing interval. Details of this lengthy and complex method are available on request from Dr. Helfgott.

8. Specificity and Sensitivity

The calculations of sensitivity and specificity were performed to gain some indication of the relative values of the many indices as predictors of sinus node disease in this patient population. The specificity and sensitivity derived thereby should not be construed to apply to any other populations than that investigated.

The relative values of these tests in a population under investigation for possible sick sinus syndrome and their false positive rate in a population without sick sinus syndrome requires further evaluation. The problem is how to clinically have a "gold standard" for definition of the sick sinus syndrome.
Additional References


APPENDIX F - SAMPLE COMPUTER OUTPUT

NEXT PATIENT - PLEASE ENTER FOLLOWING IDENTIFICATION DATA AND/OR PRESS "RETURN" KEY AFTER EACH ITEM

NAME ?:
SEX ?: 
MEDICAL RECORD NUMBER (M.R.N.) ?: 
STUDY NUMBER ?: 223
GENERAL REMARKS ?: LGL

NEXT ELECTROPHYSIOLOGY TRIAL - PLEASE ENTER DATA AS FOLLOWS AND/OR (FOR DATA UNCHANGED) PRESS "RETURN"

DRUGS ?: PRE
COMMENTS ?: SNRT
PACING SITE & RATE (B.P.M.) ?: RAP 100
PACING DURATION ?: 1 MINUTE
TRIAL NUMBER ?: 5

*** NOTE: FOLLOWING DATA MUST BE ENTERED!!! ***

N - NUMBER OF PPB ?: 10
T1,T2,T3,...,TN POST PACING BEATS CYCLE LENGTH TIME (PPBCLT)
996.99,801.80,768.81,755.81,744.81,743.07,742.32,741.06,739.31,732.56

INPUT

NAME: 
SEX: F  M.R.N.: 
STUDY: 223
GENERAL REMARKS: LGL

DRUGS: PRE
COMMENTS: SNRT

PACING: SITE & RATE = RAP 100 BPM DURATION=1 MINUTE
TRIAL NUMBER: 5

MEASURED PPBCLT SEQUENCE:
997.0 801.8 768.8 755.8 744.8 743.1 742.3 741.1 739.3 732.6

.../2
OUTPUT

RESULTS OF COMPUTATION (CURVE FITTING)

USING ONLY MEASURED PPBCLT T2,T3,...,TN

MODEL A (GEOMETRIC PROGRESSION Q=CONST.)

FIRST APPROXIMATION (USING SNRT3 STRATEGY)

PARAMETERS:
Q = 0.43796771
DT(2) = 63.60612 M.SEC.
TINF = 739.60505 M.SEC.

THEORETICAL PPBCLT SEQUENCE, WITH ((T1)) AN EXTRAPOLATED VALUE

((884.84)) 803.2 767.5 751.8 744.9 741.9 740.6 740.1 739.8 739.7

DIFFERENCE = MEASURED T(J) - COMPUTED T(J):

112.2 -1.4 1.3 4.0 -0.1 1.1 1.7 1.0 -0.5 -7.1

EXTRAPOLATED S.A.N. CONDUCTION TIME = T1-((T1)) = 112.15479

***** IMPROVEMENTS & FINAL APPROXIMATION *****
(METHOD: MODIFIED MARQUARDT ROUTINE)

<table>
<thead>
<tr>
<th>I</th>
<th>V(I)</th>
<th>S.D. OF V(I)</th>
<th>T∞</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.73757577E+03</td>
<td>0.16537133E+01</td>
<td></td>
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<tr>
<td>2</td>
<td>0.63670211E+02</td>
<td>0.30142865E+01</td>
<td>ΔT₂</td>
</tr>
<tr>
<td>3</td>
<td>0.51660024E+00</td>
<td>0.39553804E-01</td>
<td>q</td>
</tr>
</tbody>
</table>

RESIDUAL SUM OF SQUARES= 0.48573226E+02

DEGREES OF FREEDOM= 6

VARIANCE - COVARIANCE MATRIX

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>-0.20692456E+01</td>
<td>-0.46089096E-01</td>
</tr>
<tr>
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<td>0.90859234E+01</td>
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</tr>
<tr>
<td>3</td>
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<td>-0.46440504E-03</td>
<td>0.15645034E-02</td>
</tr>
</tbody>
</table>

.../3
PARAMETERS:  \( Q = 0.51660024 \)
\[ DT(2) = 63.67021 \text{ M.SEC.} \]
\[ TINF = 737.57577 \text{ M.SEC.} \]

THEORETICAL PPBCLT SEQUENCE, WITH \((T1)\) AN EXTRAPOLATED VALUE

\((860.82)) 801.2 770.5 754.6 746.4 742.1 739.9 738.8 738.2 737.9

DIFFERENCE = MEASURED \(T(J)\) - COMPUTED \(T(J)\):

136.2 0.6 -1.7 1.2 -1.5 1.0 2.4 2.3 1.1 -5.3

EXTRAPOLATED S.A.N. CONDUCTION TIME = \(T1 - (T1)\) = 136.16572

****  ****  ****  ****