Sinus node sequences after atrial stimulation: similarities of effects of different methods

WILLIAM F HEDdle, MICHAEL E JONES, ANDREW M TONKIN

From the Department of Medicine, Flinders Medical Centre, Bedford Park 5042, South Australia, Australia

SUMMARY Sinoatrial conduction is commonly assessed from features of the initial cycle after a single atrial extrastimulus or eight beats atrial pacing. In contrast, sinus node automaticity is assessed by the duration of the first interval after prolonged atrial pacing. The return cycle and initial sequences after these different methods were compared in 10 subjects with normal sinus node function and 30 patients with sick sinus syndrome. Typically, sequences after all three methods showed a maximally prolonged first interval with a progressive decrease over five or more cycles. A model of recovery from overdrive suppression was used to compute the elements of conduction time and automaticity in the first interval. The sequences which followed a single extrastimulus and pacing were similar, the only index which increased significantly with prolonged pacing was associated with the degree of suppression of automaticity. The computed component of sinoatrial conduction in the return cycle was similar for all three methods. Thus all three conventional methods which consider only the initial post-stimulation interval measure both sinoatrial conduction and sinus node automaticity. The separate components of automaticity and conduction may be assessed by analysis of the total sequence.

Assessment of sinus node function is important in those patients presenting with symptoms suggestive of the sick sinus syndrome1 in whom diagnostic electrocardiographic features are either absent of equivocal. Investigations which may provide valuable additional information include prolonged ambulatory electrocardiographic monitoring,2,3 assessment of the heart rate response to autonomic interventions such as exercise and drugs,4,5 and intracardiac electrophysiology study.

Two basic procedures are used in the electrophysiological assessment of sinus node function. In the first the response to prolonged overdrive right atrial pacing for periods of between 30 s and 5 min is assessed.5–9 The interval between the last pacing stimulus and the first spontaneous atrial electrogram, “the sinus node recovery time”, has been widely used as a measure of sinus node automaticity. A variant of this index is the “corrected sinus node recovery time”, which is the recovery time minus the pre-pacing cycle length.9 A second group of tests is used to assess sinoatrial conduction time; these are usually based on the responses of the sinus node to a single atrial extrastimulus.10 The response of the sinus node to fixed rate pacing for eight beats at a cycle length just short enough to achieve atrial capture11 or more recently direct electrode recording of prepotentials from the sinus node region are alternative approaches.12–14 In recent years electrophysiological study has fallen out of favour, partly because of the considerable overlap of conventional indices between subjects with clinically normal sinus node function and those with abnormal sinus node function.

A mathematical model of recovery of the sinus node after overdrive suppression has been developed.15 When this is applied to the sequences that follow one minute of overdrive atrial pacing, separate indices of sinoatrial conduction and sinus node automaticity can be derived. Preliminary observations have suggested that the sequences that follow single atrial extrastimuli qualitatively resemble those that follow fixed rate pacing.

We have applied this mathematical model to different pacing modalities to compare their effects on sinus node function. We hoped that this might


Sequences after atrial stimulation

lead to the development of better methods for evaluation of sinus node function.

Patients and methods

Patient Selection
Thirty patients, aged 18–93 years (mean (SD) 71(14) years) were diagnosed as having the sick sinus syndrome on the basis of having symptoms of presyncope or syncope, and evidence of inappropriate sinus bradycardia, sinoatrial exit block, or sinus arrest. Many also had palpitation and evidence of atrial tachyarrhythmias, but these symptoms by themselves were regarded as not being sufficient for diagnosis of the syndrome.

Another 10 patients, aged 21–66 years (mean 37(15) years), had clinically normal sinus node function without a history of syncope of presyncope or bradyarrhythmias. These patients had electrophysiological study for investigation of regular, narrow QRS complex tachycardias.

Electrophysiological Study
Multiple 6 French electrode catheters were positioned under fluoroscopic control in fasting and non-sedated patients in whom cardioactive drugs has been discontinued for at least five elimination half-lives, and who had given their informed consent. A quadripolar electrode was positioned in the high right atrium for recording (proximal pair) and stimulating (distal pair), a tripolar electrode across the tricuspid valve to record the His bundle electrogram, and a bipolar electrode in the right ventricular apex for stimulation. Intravenous heparin 5000 units was given on completion of electrode placement. Programmed stimulation was performed with a Devices Neurolog isolated source simulator. Surface electrocardiographic leads and three or four concurrent intracavitary electrograms were recorded at 100 mm/s chart speed on a Minograph Model 62 recorder.

After a ten minute rest period, cycle length was recorded for one minute. Programmed stimulation was then undertaken to obtain the following data:

(a) Responses after fixed rate stimulation for one minute. Responses were assessed after three to five trials of one minute of overdrive high right atrial pacing at 100 beats per minute and at 130 beats per minute. A two minute rest period was allowed between each pacing trial.

(b) Responses after fixed rate stimulation for eight beats. Pacing trials were repeated 10 times in each patient, sinoatrial conduction time being calculated as the increment in the immediate post-stimulation interval above the mean of 20 pre-pacing cycle lengths.

(c) Responses to single atrial premature stimuli. Stimuli with coupling interval $A_1$ were introduced after every eighth beat during sinus rhythm. The first stimuli were placed at the end of diastole and the coupling interval was reduced by 10–20 ms until atrial refractoriness was detected. The sinus cycle lengths immediately preceding and following the premature stimulus were designated $A_1$ and $A_2$ respectively.

The sequences following atrial stimulation were digitised by means of a Hewlett Packard Model 9874A digitiser, 9872A plotter, and 9825A calculator with programs specifically written for this purpose. The first post-pacing interval was measured from the pacing spike to the initial rapid deflection of the first spontaneous high right atrial electrogram. For all the sequences that followed these different methods of stimulation we plotted cycle length against beat number. In addition, from the responses to single extrastimuli we plotted the normalised return cycle ($A_3/A_1$) against the normalised test cycle ($A_4/A_1$). Sinoatrial conduction time was estimated from this plot as described by Strauss as the mean value of $A_3$ in the last third of the zone of reset minus the mean value of $A_1$.

Mathematical Model
The mathematical model we used was developed by Dr Arieh Helfgott in this laboratory. In brief, if responses after overdrive suppression are the consequence of a single elimination or degradation process (such as clearance of extracellular potassium), and if constant action potential duration, constant difference between maximum diastolic and threshold potentials, capture and reset of the sinus node by all atrial extrastimuli, and absence of pacemaker shifts are assumed, recovery may be regarded as depending solely on the increase in the slope of phase 4 depolarisation. From this it can be shown that recovery and decrease in cycle length conforms to an exponential equation (Fig. 1):

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

In this relation, $j$ is an arbitrary notation for any beat in the sequence, $T_j$ its cycle length, $T_\infty$ the asymptotic cycle length to which recovery tends, and $q$ is simply a measure of the rate of recovery (the common ratio) during the sequence.

Computations
Sequences were regarded as being suitable for fitting to the model if the following criteria were satisfied:

(a) progressive decrease in post-pacing cycle length until at least the fifth interval, suggesting at least a degree of suppression of automaticity by atrial stimulation;

(b) there were no ectopic or escape beats in
the sequence; (c) no change in P wave morphology or atrial activation sequence to suggest pacemaker shift to a focus other than the sinus node.

Atrial electograms do not directly measure sinus node activity. In particular, after atrial stimulation which captures the sinus node, the first interval must contain two components; an automatic interval and an additional component of sinoatrial conduction into and out of the sinus node from the electrode (Fig. 2). If anterograde ( sinoatrial) conduction time is regarded as being constant, then electrograms after the first cycle accurately measure the recovery of automaticity. Accordingly, we used a computer program based on non-linear least squares techniques to obtain the curve of best fit to the second and subsequent cycles of all “acceptable” sequences, and from these we extrapolated a theoretical first automatic cycle. Computed sinoatrial conduction time was then derived as the difference between the measured first post-pacing cycle length and this extrapolated theoretical first cycle length (see Results). In the relation described, potential indices of sinus node automaticity are \( q, T_\infty \), and the increment in the first interval \( (T_1) \) due to suppression of automaticity \( (\Delta T_1 = T_1 - T_\infty) \).

For successful fitting of sequences to the model the following were regarded as necessary: (a) \( \Delta T_1 \), computed sinoatrial conduction time and \( T_\infty > 0 \); (b) \( 1 > q > 0 \); (c) residual mean square < 1000. The multiple correlation coefficient \( R^2 \) was used as a measure of goodness of fit and was usually > 0.98.

STATISTICAL ANALYSIS

Data are presented as means (1 SD). Indices in each group after single extrastimuli were compared with indices after atrial pacing be means of Student’s paired \( t \) test. A given index in the two patient groups was compared by means of an unpaired Student’s \( t \) test. A \( p \) value < 0.05 was regarded as significant.

Results

CLINICAL INDICES

Tables 1 and 2 show basic electrophysiological data in the groups with normal and abnormal sinus node function respectively. Both mean age and resting cycle length were significantly greater in those with the sick sinus syndrome (\( p < 0.0001 \) for both).

SINOATRIAL CONDUCTION TIME CALCULATED FROM ATRIAL EXTRASTIMULI

In nine of 10 patients with normal sinus node function and in 23 of 30 patients with the sick sinus syn-
Sequences after atrial stimulation

Table 1  Basic electrophysiological data in 10 patients with normal sinus node function

<table>
<thead>
<tr>
<th>Case No</th>
<th>CL (ms)</th>
<th>Tᵢ Straus (reset) (ms)</th>
<th>Tᵢ Narula (ms)</th>
<th>SNRT 100 bpm (ms)</th>
<th>SNRT 130 bpm (ms)</th>
<th>SACT APB (ms)</th>
<th>SACT (ms)</th>
<th>SACT computed after FRP 100 bpm (ms)</th>
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CL, resting cycle length; Tᵢ, Strauss and Tᵢ, Narula, mean first interval after single atrial extrastimulus or eight beats atrial pacing during Strauss and Narula conduction time determinations; SNRT, sinoatrial recovery time; SACT APB, sinoatrial conduction time after single extrastimulus; FRP, fixed rate pacing; SACT 8 beats pacing, sinoatrial conduction time after eight paced beats; —, not done; nc, unable to derive or compute sinoatrial conduction time after single extrastimulus from post-stimulation sequence by application of the model.

Table 2  Basic electrophysiological data in 30 patients with sick sinus syndrome

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<th>Case No</th>
<th>CL (ms)</th>
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See footnote to Table 1 for abbreviations.
drome, sinoatrial conduction time after single extrastimuli could be derived from the plot of $A_r/A_1$ against $A_1/A_1$ (Tables 1 and 2). In those in whom it could not be calculated, either the points were widely scattered or, in the patients with sick sinus syndrome, there was no reset zone (3/7) or probable sinoatrial exit block (2/7). Sinoatrial conduction time in the patients with normal sinus node function (166 (55) ms) was not significantly different from that in the patients with sick sinus syndrome (195 (70) ms).

**Sinoatrial Conduction Time After Fixed Rate Atrial Pacing (Eight Beats)**

In eight patients with normal sinus node function and in 22 patients with the sick sinus syndrome, sinoatrial conduction time was assessed by the method described by Narula et al., and mean values were 204(81) ms and 229(103) ms, respectively (difference not significant).

**Sinus Node Recovery Time**

After atrial pacing at 100 beats per minute, mean sinus recovery time was significantly greater ($p < 0.0001$) in the patients with sick sinus syndrome (1415 (506) ms) than in those with normal sinus node function (1085 (126) ms). The sinus node recovery time at 100 beats per minute could not be obtained in two patients with normal sinus node function whose resting cycle length was less than 600 ms. Similar differences between those with normal and abnormal sinus node function were found after pacing at 130 beats per minute.

**Gross Analysis of Sequences After Atrial Stimulation**

Figure 3 shows an electrocardiographic recording of the typical events after an atrial extrastimulus in the zone of reset. Figure 4 illustrates this result as a plot of cycle length against beat number. After the return cycle there was a progressive decrease in cycle length, indicating suppression and then progressive recovery of automaticity.

![Electrocardiographic lead (L)II showing prolongation of not only the first but also subsequent cycle lengths (in ms) after a single atrial extrastimulus (S). (Measurements made from intracardiac recordings.](image)

Fig. 3

![Plot of cycle length against beat number during estimation of sinoatrial conduction time by single atrial extrastimulus ($A_r$). For purposes of illustration, responses to many extrastimuli are excluded; all followed the same pattern. The extrastimuli are shown in the lower half of the figure. After these extrastimuli, sequences had a maximally prolonged first interval in the return cycle ($A_r$) and then a progressive decrease in subsequent cycles ($A_{r+1}$, $A_{r+2}$, etc). Reproduced with permission from PACE, 1984;7:735-48.](image)

Fig. 4

Cycle length decreased until after the fourth post-stimulation interval in seven of the 10 patients with normal sinus node function and 19 of the 30 with abnormal sinus node function, when test extrastimuli were introduced during the zone of reset. This decrease often continued until the next extrastimulus was given eight cycles later.

In all eight patients with normal sinus node function and in 20 of 22 with abnormal sinus node function, sequences after atrial pacing for eight beats had the same form—that is with maximally prolonged first post-pacing interval and a decrease in subsequent cycles. Sinoatrial exit block and widely scattered cycle lengths made sequences in the other two patients with sick sinus syndrome unsuitable for detailed analysis by the model. Sequences of post-pacing intervals were similar in most of the trials after one minute of atrial pacing. Cycle length tended to decline, irrespective of the pacing mode (after
Sequences after atrial stimulation

pacing at 100 beats per minute in 27/30 trials in the patients with normal sinus node function and in 56/95 trials in the patients with sick sinus syndrome. Thus, the mathematical model could be used to compare the effects of the different methods.

COMPUTED INDICES AND ANALYSIS OF SEQUENCES

After single extrastimuli

Thirty-nine of the 45 sequences suitable for computation in those with normal sinus node function and 170 of 208 in patients with sick sinus syndrome were successfully fitted. With the exception of one patient with normal sinus node function and one with sick sinus syndrome, all 25 patients in whom indices could be computed were from the 32 in whom sinoatrial conduction time could be derived as described by Strauss et al.10 In the other patients, scatter of cycle lengths, sinoatrial exit block, or frequent spontaneous extrasystoles prevented the derivation of either the conventional or the computed sinoatrial conduction time. When the Strauss conduction time could be derived but the sequences were unsuitable for computation, the post-pacing sequences did not show decay of cycle length for more than four intervals.

A comparison of results in the six patients with normal sinus node function and in the 17 with the sick sinus syndrome in whom sinoatrial conduction time after single extrastimuli could be derived conventionally and computed from the model showed that the computed sinoatrial conduction time was significantly less than the conventional sinoatrial conduction time in both patient groups (p<0.025 for both). This is of course to be expected because computed sinoatrial conduction time is simply conventional sinoatrial conduction time minus an element ΔT1 that we attribute to depression of sinus node automaticity. Of considerable importance, however, is the improved ability of computed sinoatrial conduction time to differentiate between patients with a sick sinus and those without. Mean computed sinoatrial conduction time in the controls was 103 ms with a standard deviation of 17 ms, giving a “range” (mean (2 SD)) of 69–137 ms. Nine of the 18 patients with sick sinus syndrome (50%) fell outside this range. Mean sinoatrial conduction time derived by the method of Strauss was 166 ms with a standard deviation of 55 ms, giving a “normal” range of 56–276 ms, which includes all but four of the sick sinus group.

Of the indices of automaticity after an atrial premature beat, T∞ was significantly greater in those with sick sinus syndrome (p<0.025), while q and ΔT1 were not significantly different from values in patients with normal sinus node function.

After eight beats fixed rate pacing

Computed indices in both groups of patients strongly resembled indices derived after single extrastimuli and atrial pacing for one minute. The mean values of ΔT1 were intermediate between those after single atrial extrastimuli and atrial pacing at 100 beats per minute and were not significantly different (178 (51) ms in controls and 172 (112) ms in those with sick sinus syndrome) in the two patient groups.

As was found after a single extrastimulus, computed sinoatrial conduction times (97 (52) ms in controls and 159 (71) ms in the sick sinus syndrome) were significantly different (p<0.025) in the two patient groups. T∞ was significantly longer in the group with sick sinus syndrome (1003 (187) ms) than in the controls (721 (111) ms, p<0.0005).

After one minute of fixed rate pacing

The longer sinus node recovery time in patients with the sick sinus syndrome was associated with a significantly greater asymptotic cycle length T∞ (p<0.005) and computed sinoatrial conduction time (p<0.05). ΔT1, an index of the extent of suppression of the sinus node, was no different in controls and those with abnormal sinus node function. The common ratio q was also similar between the two groups.

COMPARISON OF RESULTS AFTER SINGLE EXTRASTIMULI AND AFTER FIXED RATE PACING

Indices indicating effects of a single extrastimulus, eight beats, and one minute of atrial pacing are compared in Table 3. The mean value of the first post-stimulation cycle length was not significantly different in either group of patients after a single extrastimulus or atrial pacing for eight beats or one minute.

Of all the computed indices, only ΔT1 was significantly greater (p<0.05) after fixed rate pacing (100 beats per minute) than after a single atrial extrastimulus. This held whether sinus node function was normal or abnormal. The common ratio q increased significantly (p<0.05) with fixed rate pacing in those with the sick sinus syndrome but not in controls. The indices T∞ and computed sinoatrial conduction time were not significantly different after the different methods of stimulation.

Discussion

We examined in detail sequences that followed all pacing modalities used in conventional assessment of sinus node function. The “normal” patients were not strictly a control group for patients with sick
Table 3  Comparison of computed indices after single extrastimuli and overdrive atrial pacing

<table>
<thead>
<tr>
<th></th>
<th>Single extrastimuli</th>
<th>8 beats pacing</th>
<th>Overdrive pacing (1 min, 100 bpm)</th>
<th>Overdrive pacing (1 min, 130 bpm)</th>
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<tr>
<td>Normal:</td>
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<tr>
<td>(T_1) (ms)</td>
<td>939 (171)</td>
<td>990 (178)</td>
<td>1085 (126)</td>
<td>986 (211)</td>
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<td>(q)</td>
<td>0.675 (0.155)</td>
<td>0.698 (0.136)</td>
<td>0.685 (0.090)</td>
<td>0.687 (0.100)</td>
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<td>(\Delta T_1) (ms)</td>
<td>136 (78)</td>
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<tr>
<td>(T_a) (ms)</td>
<td>736 (175)</td>
<td>721 (111)</td>
<td>733 (75)</td>
<td>677 (111)</td>
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<tr>
<td>Computed SACT (ms)</td>
<td>103 (17)</td>
<td>97 (52)</td>
<td>92 (67)</td>
<td>96 (61)</td>
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<td>Sick sinus syndrome</td>
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<td>(T_1) (ms)</td>
<td>1212 (182)*</td>
<td>1269 (200)*</td>
<td>1415 (506)</td>
<td>1541 (707)</td>
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<tr>
<td>(q)</td>
<td>0.643 (0.155)</td>
<td>0.706 (0.101)</td>
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<td>0.652 (0.174)</td>
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<td>(\Delta T_1) (ms)</td>
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<td>172 (112)</td>
<td>254 (130)</td>
<td>249 (131)</td>
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<tr>
<td>(T_a) (ms)</td>
<td>919 (175)*</td>
<td>1003 (187)*</td>
<td>887 (137)*</td>
<td>867 (146)*</td>
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<tr>
<td>Computed SACT (ms)</td>
<td>159 (67)*</td>
<td>159 (71)*</td>
<td>185 (114)*</td>
<td>178 (119)*</td>
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</table>

\(T_1\), first post-stimulation cycle length; \(q\), \(\Delta T_1\), and \(T_a\), computed indices of automaticity; SACT, sinoatrial conduction time (computed from \(T_1\), using model of sinus node recovery); *p < 0.05 by \(t\) test for comparison of grouped mean indices in those with normal sinus node function and those with sick sinus syndrome.

sinus syndrome, because they were significantly younger and aging itself affects sinus node function\(^{18}\); thus a case/control study with age matching is needed.

Although the methods proposed for indirect assessment of sinoatrial conduction time\(^{10,11}\) are based on only the lengthening of the first post-stimulus interval after atrial extrastimulus and fixed rate atrial pacing for eight beats, they usually also reduce the prolongation of second and subsequent intervals. The time course of this ongoing depression closely resembles that seen after prolonged atrial pacing and may be attributed to depressed automaticity of the sinus node. This suggests that sinoatrial conduction time as calculated by these methods is in fact a compound measurement composed partly of sinoatrial conduction time and partly of depressed sinus node automaticity. We used a mathematical model of overdrive suppression to identify the two separate components in the overall sequence of post-pacing intervals. The model allows us to compare the extent to which each of the pacing methods individually influences sinoatrial conduction and sinus node automaticity. The model is not applicable to all patients since a few post-pacing sequences cannot be fitted to the model because of strong autonomic effects on the sinus node, spontaneous atrial activity, and sinoatrial exit block.

How valid is the model? It assumes that all sinus node cells follow the same process of recovery, that the anterograde sinoatrial conduction time of all cycles in the sequence is constant, and that there are no pacemaker shifts, or if these are present, that they contribute negligibly to the sinoatrial conduction time. There is evidence from animal experimentation that the cycle length changes seen after atrial extrastimuli relate to changes in the primary pacemaker location.\(^{17}\) Further, the atrial electrical events do not correlate well with events within the sinus node.\(^{18}\) Even if the above assumptions are shown to be incorrect in man, certain conclusions can be drawn from this study which are most important in highlighting the limitations of widely used techniques of assessment.

CONVENTIONAL METHODS OF DETERMINATION OF SINOATRIAL CONDUCTION TIME ARE IMPURE

The derivation of sinoatrial conduction time from cycles that follow a single atrial extrastimulus or eight beats of fixed rate pacing assumes that the contribution of depression of automaticity is an insignificant part of the return cycle. The post-pacing sequences observed in this study strongly suggest that this does not hold. The results indicate that depression of automaticity either because of depression of the primary pacemaker, pacemaker shift,\(^{17}\) or both together, may contribute up to 50% of the prolongation of the return cycle over the pre-pacing cycle length. Although suppression of automaticity by atrial extrastimuli has been shown in both experimental animal preparations and in man\(^{11}\) it has been considered to be of only minor importance.

Other factors affecting automaticity may also operate when sinoatrial conduction time is estimated by atrial pacing. At times, pacing at a cycle length within 30–50 ms of that of the sinus node may result in acceleration due to electronic interaction and shortening of action potential duration\(^{19}\) and isorhythmic sinoatrial dissociation.\(^{20}\) Furthermore, computed sinoatrial conduction time more reliably differentiates between controls and those with sick sinus syndrome than do conventional indirect methods of estimation of sinoatrial conduction time. The
Sequences after atrial stimulation

mean computed values for sinoatrial conduction time showed a 56 ms difference between sick sinus patients and controls. The difference derived conventionally from the same data was 29 ms. This difference is compounded by the much reduced standard deviation of the computed sinoatrial conduction time of the normal group (17 ms) as compared with the conventional sinoatrial conduction time (55 ms). Thus only four sick sinus patients could be identified by conventional methods, whereas nine were identified by the computational method.

SEQUENCES AFTER SINGLE ATRIAL EXTRASTIMULI AND FIXED RATE PACING ARE QUALITATIVELY SIMILAR AND DIFFER ONLY IN THE EXTENT OF SINUS NODE SUPPRESSION

Observations on the sequences that follow both single atrial extrastimuli and atrial pacing showed that most had a maximally extended first interval with a decline in the prolongation in subsequent cycles. The most obvious effect of prolonged pacing was greater suppression of automaticity (reflected by $\Delta T_1$), and this effect occurred whether sinus node function was normal or abnormal. Other indices computed by fit to the model showed pronounced similarity. In particular, the different methods of stimulation gave the same mean computed sinoatrial conduction time. The asymptotic cycle length that followed recovery was no different with the various methods and probably reflects only resting sinus node automaticity.

SUPPRESSION OF THE SINUS NODE BY OVERDRIVE IS THE SAME IN PATIENTS WITH NORMAL AND ABNORMAL SINUS NODE FUNCTION

The only indices of automaticity which differed significantly between the two patients groups were resting cycle length and $T_{\alpha}$ (which as discussed may be primarily dependent on resting cycle length). As not only resting cycle lengths but also mean age were significantly different in those with normal and abnormal sinus node function, indices relating to this cycle length may have been less discriminatory if patients of similar ages had been compared.

In conclusion, this study suggests that previously used stimulation methods for electrophysiological testing of sinus node function (sinus node recovery time and sinoatrial conduction time derived from the first interval after atrial single extrastimuli or atrial pacing) are qualitatively similar and differ only in the extent of pacemaker suppression that they produce. The fact that they measure both sinoatrial conduction and sinus node automaticity may explain their frequent failure to distinguish between normal and abnormal function, given the heterogeneous nature of bradarrhythms with which patients present. It might be expected that sinus node function will be better assessed by pure indices of automaticity or conduction, the latter obtained either directly by electrode recording11–14 or from application of simplified versions of the mathematical model.

We acknowledge the contribution of Dr Arieh Helfgott who developed the mathematical model and we thank Sister Lyn Bartlett, Mr R Blood, and Mrs Sue Love for their help with this study.

This work was supported by grants of the Life Insurance Medical Research Fund of Australia and New Zealand, the National Heart Foundation of Australia, and the Lions South Australian Heart Research Foundation.

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