Evaluation of Sino-atrial Node Function in Man by Overdrive Suppression

By William Mandel, M.D., H. Hayakawa, M.D., Ronald Danzig, M.D., and Harold S. Marcus, M.D.

SUMMARY
Sino-atrial node (SAN) function was evaluated in 46 patients, three of whom had the sick sinus syndrome. Patients were paced from the right atrium for 15 to 180 sec at rates of 90, 110, 130, and 150 beats/min. The rapid cessation of pacing was associated with suppression of the SAN at all paced rates and at all durations of pacing. The observed pause was terminated by a sinus beat in all instances. The duration of pacing had little influence on the duration of the observed pause. The pause increased as the pacing rate was increased until, at a rate of 150 beats/min, a marked decrease in the pause was noted. Atropine (1.5–3.0 mg iv) diminished but did not eliminate the SAN suppression. Subthreshold pacing did not suppress SAN function. Three patients with sick sinus syndrome had a greater degree of SAN suppression than normal patients (4732 ± 415 msec [SSS] M ± SEM; 1041 ± 56 msec for normal patients).

The determination of the duration of the pause following cessation of atrial pacing provides a technique for recognition of abnormalities of SAN function.

Additional Indexing Words:
Acetylcholine Atropine Sick sinus syndrome Reflex Atrial pacing

Changes in sino-atrial node (SAN) rate may occur because of alterations in autonomic tone,1–4 electrolyte concentration,5–6 or stretch.7–9 In addition, as early as 1884, Gaskell demonstrated pacemaker suppression by tetanic stimuli.10 This phenomenon of overdrive suppression has subsequently been investigated in detail in both isolated atrial tissue11 and intact animal preparations.12 Clinically, several authors have reported the successful use of overdrive in the suppression of rapid ectopic pacemaker activity.13–15 Little attention has, however, been paid to the response of the human sino-atrial node to atrial pacing. The aim of the present study was to define qualitatively and quantitatively the response of the human sino-atrial node to overdrive and the possible physiologic basis of overdrive suppression. In addition, the technique was applied to the evaluation of patients with disease of the sino-atrial node in an effort to ascertain the extent of sino-atrial pacemaker malfunction.

Methods
Right heart catheterization was performed in 46 patients in the postabsorptive state in the diagnostic cardiac catheterization laboratory. In all subjects sinus rhythm was present. The patient population included: 11 patients with no discernible heart disease, 14 with coronary artery disease, 11 with valvular heart disease, seven with undetermined heart disease, and three with the "sick sinus syndrome."16 There were equal numbers of males and females, and they ranged in age from 16 to 72 years. None of the patients received any medication before or during catheterization except those patients who were on maintenance doses of digitalis, diuretics, or nitroglycerin. Serum potassium was within the normal range in all patients.

From the Department of Cardiology, Cedars-Sinai Medical Center, and the Department of Medicine, University of California at Los Angeles, Los Angeles, California.

Supported in part by U. S. Public Health Service Grant RR05468.

Received January 11, 1971; revision accepted for publication March 17, 1971.
Under local anesthesia, a median branch of the basilic vein was isolated in the left antecubital fossa. A bipolar 6F pacing catheter was then positioned at the right atrial-superior vena caval junction so that reliable pacing could be obtained with pulses of minimum current and normal P-wave morphology. The intra-arterial blood pressure was monitored in every patient via either the brachial or femoral artery. In addition, in some patients a specially designed 6F quadripolar pacing catheter was employed so that atrial electrograms could simultaneously be recorded near the site of atrial pacing. A lead II electrocardiogram was also recorded. All records were displayed on a multichannel oscilloscopic recorder (DR-8 Electronics for Medicine) and photographed on paper at speeds of 50 mm/sec. We used a battery-operated pacemaker (Medtronic 5837), the rate of which was calibrated by means of a Monsanto interval timer, to pace the atrium. The characteristics of the pacemaker's stimulus were rectangular pulses of 2-msec duration with the current set to 1½–2 times diastolic threshold. Records were analyzed by measurement and averaging of the interval between six driven beats during stable atrial pacing and then of intervals between P waves from the moment pacing was stopped until a steady state was attained. A pause was observed after overdrive pacing; it was defined as the interval, in msec, from the last paced P wave to the first spontaneously occurring P wave. Similar measurements were made for the intra-arterial systolic and diastolic blood pressures. The initial pacing rate chosen was at least 10 beats/min above control values; it was then increased by increments of 20 beats/min. The rates used were usually 90, 110, 130, and 150 beats/min. In general, pacing was maintained at each rate for 180 sec. In one group of patients, pacing was carried out at each rate for periods of 15, 30, 60, and 180 sec. In eight patients, the pacing study was repeated after intravenous administration of 1.5 to 3.0 mg atropine. The SAN response to subthreshold pacing was evaluated in five patients after pacing at suprathreshold levels.

**Results**

**Duration of Pacing and Pause**

The response of the SAN to pacing for 15, 30, 60, and 180 sec at that rate that was associated with maximum overdrive suppression of the sino-atrial node was studied in 25 patients. No statistically significant change was seen in the length of the pause subsequent to pacing at these durations. The results of these experiments demonstrated a maximum pause, in percentage change (%Δ) (maximum pause/control P-P × 100), of 120 ± 4, 116 ± 4, 117 ± 4, and 118 ± 4% (mean ± SEM) for pacing at intervals of 15, 30, 60, and 180 sec, respectively. The results of a typical patient study are shown in figure 1.

**Rate of Pacing and Pause**

The response to different pacing rates for fixed periods (3 min) of pacing was studied in 40 patients. Overdrive suppression was seen at all rates in all patients studied. The maximum pause, expressed as a percentage change (maximum pause/control P-P × 100), for the group as a whole was 124 ± 2% (mean ± SEM) and was observed after pacing at a rate of 130 beats/min. The pause after pacing at 150 beats/min was only 109 ± 3% (P < 0.005).

Figure 2A summarizes the results obtained in all experiments, and the time course of a

---

**EFFECT OF PACING DURATION ON PAUSE**

![Graph](image)

**Figure 1**

The effect of right atrial pacing duration on the observed pause. The vertical axis shows the P-P interval in msec, and the horizontal axis shows successive beats after rapid cessation of pacing. The control P-P interval (770 msec) is indicated by the C to the left of the figure. Atrial pacing was then performed for various intervals (15, 30, 60, and 180 sec) at a rate of 130 beats/min and then rapidly stopped. The subsequent 15 P-P intervals are shown in the remainder of the graph. Maximum pause (920 msec) and minimum pause (850 msec) were observed after pacing for 30 and 60 sec, respectively. Note the significant suppression of SAN rate following the cessation of pacing with prompt return to control values.

*Circulation, Volume XLIV, July 1971*
A. EFFECT OF PACING RATE ON PAUSE

![Graph showing the effect of pacing rate on pause](image)

**Figure 2**

(A) The effect of the atrial pacing rate on the extent of observed maximum pause. The vertical axis shows the maximum pause in percentage change (%Δ), and the horizontal axis shows the pacing rate in beats/min. Values are expressed as the mean ± SEM. A progressive increase in maximum pause is noted as the pacing rate is increased from 90 to 130 beats/min. With an increase in rate to 150 beats/min there is a marked decrease in maximum pause.

(B) The effect of right atrial pacing rate on the observed pause. The vertical axis shows the P-P intervals in msec, and the horizontal axis shows successive beats after cessation of pacing. The control P-P interval (750 msec) is indicated by the C to the left of the figure. Atrial pacing was then performed for 3 min at various rates (90, 110, 130, and 150 beats/min) and then rapidly stopped. The subsequent 15 P-P intervals are shown in the remainder of the graph. Note the significant suppression of SAN rate following cessation of pacing with the maximum pause occurring after pacing at 130 beats/min. Prompt return to near control rates is seen after pacing at 90, 110, and 130 beats/min. After pacing at 150 beats/min there is a dramatic secondary depression of SAN rate.

typical experiment is shown in figure 2B. A prompt return to or almost to control SAN rate was noted after pacing at various rates and for various durations. However, a secondary substantial diminution in SAN rate was noted in 33% of patients studied and was seen only at pacing rates of 150 beats/min.

**Relationship of Control Rate to Maximum Pause**

The relationship between the control SAN rate and the maximum pause was evaluated in 31 patients. Figure 3 shows a plot of the data for all studies. Slower control rates were associated with a longer maximum pause (P < 0.001).

The mean control P-P interval for the three patients with sick sinus syndrome was 1240 ± 161 msec (48 ± 4 beats/min), and for the remainder of the patients studied it was 772 ± 36 msec (78 ± 2 beats/min). The maximum pause observed for patients with the sick sinus syndrome was 4732 ± 415 msec, while the maximum pause for the remainder of the patients studied was 1041 ± 56 msec.

**Effect of Atropine on Pause**

The effect of atropine on the duration of maximum sino-atrial node suppression was evaluated in eight patients, two of whom had sick sinus syndrome. After the rate associated with maximum SAN suppression had been determined, atropine (1.5 – 3.0 mg) was given intravenously, and the pacing study was repeated in 3 to 5 min. The results are illustrated in figure 4. Atropine in the doses used considerably diminished, but did not totally abolish, the pause after overdrive pacing. In addition, atropine abolished the secondary SAN suppression observed in some patients after pacing at 150 beats/min.
two patients with sick sinus syndrome demonstrated a dramatic diminution in SAN suppression after atropine administration.

Subthreshold Pacing and Pause

Five patients were subjected to the standard pacing study and, subsequently, to pacing at subthreshold currents. None of the five patients thus studied demonstrated any depression of SAN function immediately following cessation of subthreshold stimulation, nor did any patient develop a secondary depression or overshoot of SAN rate.

Blood Pressure and Pause

In an effort to assess the role of reflex autonomic discharge on SAN suppression, the relationship between maximum pause following cessation of pacing and the change from control in both systolic and diastolic blood pressures during pacing was noted for 20 patients. Systolic arterial pressure decreased during pacing in half of the patients and increased in the other half. There was no correlation between change in systolic pressure during pacing and the extent of the maximum SAN pause. Although 17 of 20 patients increased their diastolic pressure during pacing, there was no relationship between the extent of change of diastolic pressure and maximum SAN pause. In figure 5 the time course of the intra-arterial systolic and diastolic blood pressures is shown for a typical patient.

Discussion

Overdrive suppression of the sinus node has been demonstrated in vitro and in vivo in the anesthetized animal. The findings in these preparations cannot be extrapolated to human beings for several reasons: (1) the animals were anesthetized; (2) they were usually

The control P-P interval versus maximum pause. The vertical axis shows the maximum pause in msec, and the horizontal axis shows the P-P interval, in msec, before pacing. The interrupted line is a line of identity. The solid line is the regression line obtained from the observed points, with the shaded area indicating one standard deviation. N is 31, with an r value of 0.84 and a P value of <0.001.

The effect of atropine on the maximum observed pause. The vertical axis represents maximum pause in %A. The horizontal axis demonstrates, to the left, results obtained before administration of atropine and, to the right, results obtained after administration of atropine. The open circles signify patients without disease of the SAN, and the X symbols signify patients who have the sick sinus syndrome (SSS). Note the marked increase in observed pause in patients with SSS and the marked decrease in pause following atropine administration.
SINO-ATRIAL NODE FUNCTION

BLOOD PRESSURE VRS PAUSE

Observed blood pressure prior to, during, and immediately after 3 min of right atrial pacing. The horizontal axis represents successive beats after cessation of pacing. In the upper panel, the vertical axis represents the range of systolic blood pressure, and in the lower panel the vertical axis represents the range of the diastolic blood pressure. The upper panel shows the time course for changes in systolic pressure, and the lower panel shows the time course for the diastolic pressure. Control systolic and diastolic pressures are to the left of the graph and are noted by C. There is an increase in systolic pressure seen immediately after cessation of pacing, with a maximum pressure increase following pacing at 150 beats/min.

subjected to extensive surgery (thoracotomy); and (3) usually they were free of gross heart disease. Anesthesia and surgery are likely to alter both the tonic and reflex autonomic discharge, and the presence of cardiac disease may alter the response of the sinus node to overdrive. The present report demonstrates the phenomenon of overdrive suppression in normal man and in patients with cardiac disease of various types and severity.

Control of Sino-atrial Node Function

Multiple factors have been demonstrated to be of importance in the control of the spontaneous firing rate of SAN pacemaker tissue, including: (1) the slope of phase 4 of the SAN action potential, (2) the threshold potential, (3) the maximum diastolic potential of the SAN cell, (4) temperature, (5) acetylcholine, (6) catecholamines, (7) atropine, (8) potassium, or (9) stretch.1, 3, 5–9, 14, 17–23 Cardioacceleration has been associated with enhanced slope of phase 4, decrease in threshold, diminished maximum diastolic potential, catecholamines, atropine, increase in potassium, increased temperature, and stretch. In contrast, slowing of the firing rate of the sinus node has been associated with diminished slope of phase 4, increase in threshold, increased maximum diastolic potential, acetylcholine, decreasing temperature, and beta-blockade.

Evaluation of Findings in Humans

The results obtained in this investigation support previous laboratory studies which demonstrated suppression of spontaneous impulse formation immediately upon cessation of a superimposed drive. The laboratory studies demonstrated, in addition, a nearly linear response between the drive frequency and the degree of suppression and subsequent post-suppression overshoot of cardiac rate. The initial negative chronotropic effect thus demonstrated was felt to be due to a local release of acetylcholine, and the subsequent cardioacceleration, to catecholamine release.4, 11, 12 Other authors have suggested that changes in potassium flux during overdrive are, in part, responsible for pacemaker suppression9, 22 although the experimental data regarding the effects of changes in extracellular potassium on the rate of the SAN pacemaker are still unclear.19–21

In contrast to previous in vivo and in vitro studies, the duration of pacing, within the range used in this present study, had no significant effect on the maximum observed pause. This may reflect substantial differences in the response of the autonomic nervous system of the awake, unanesthetized human. It was important to note that as short a period as 15 sec of overdrive can result in a substantial suppression of SAN function, a finding which may have substantial clinical significance in the patient with disease of the SAN.

This study shows a stepwise increase in the maximum pause as the pacing rate was increased. There was, however, a sharp cutoff
in maximum pause observed when the pacing rate was increased above 130 beats/min. This diminution in maximum pause may be the result of enhanced sympathetic discharge during very rapid pacing rates, which would decrease the sino-atrial node recovery time. This observation may be correlated with the fact that, regardless of the rate of overdrive pacing, higher intrinsic sinus rates were associated with a shorter maximum pause. In addition, the above concept is supported by the observations of Vincenzi and West,4 Furchgott et al.,24 and Amory and West,11 who demonstrated release of catecholamines during suprathreshold stimulation.

These results stress the concept that the phenomenon of overdrive suppression must be modified by conditioning factors in vivo. In other words, whatever the mechanism of overdrive suppression there are compensatory factors that may either lengthen or shorten it. An attempt was made to assess the role of possible reflex changes secondary to changes in blood pressure associated with atrial pacing. No correlation was demonstrated between the duration of SAN suppression and the change in systolic or diastolic blood pressure secondary to pacing. However, the experiments with atropine do serve to demonstrate the effects of conditioning factors.

Atropine

Atropine, in a dose of 1.5 to 3.0 mg, markedly decreased the duration of overdrive suppression. This finding suggests that most but not all overdrive suppression of the SAN may be caused by release of acetylcholine during pacing, as was found in the animal.12 Our data confirm previous animal studies demonstrating partial but not complete elimination of the pause after overdrive, suggesting that other factors are important in SAN suppression.9,12 Jose, in studies on intrinsic cardiac function in man, found that atropine, in doses of 0.04 mg/kg intravenously, totally blocked any chronotropic response of the heart to vagal stimuli for 20 min.25,26 In our studies some patients received less than this ideal dose, but the response of our study group, as a whole, was quite similar. It is possible that atrial pacing at rates above control SAN rates results in reflex increase in parasympathetic tone, which accounts for the postpacing SAN suppression. The elimination of the SAN suppression in the atropinized patient would tend to support this conclusion. However, Lu et al.9 have demonstrated that postpacing SAN suppression is reversible by atropine in the isolated tissue preparation, thus ruling out a reflex mechanism. This phenomenon, therefore, appears to be related to acetylcholine release unrelated to neural control but dependent upon the rate of atrial contraction.

Subthreshold Pacing

Suprathreshold pacing has been demonstrated to cause a release of both acetylcholine and norepinephrine.4 Lu has recently pointed out that subthreshold stimulation may have similar effects.27 In the five patients studied by subthreshold pacing, no change in SAN rate was observed after cessation of pacing. However, prior studies have pointed out a differential sensitivity between the less sensitive upper node and the more sensitive lower node.9 Because of the relative insensitivity of locating the precise site of pacing via the catheter technique, it is possible that the lack of change in SAN rate after overdrive subthres-

Figure 6

Electrocardiogram recorded during the termination of an episode of supraventricular tachycardia. The cessation of the tachycardia (140 beats/min) is followed by a marked suppression of SAN function. The observed pause of 2500 msec is ended by a sinus beat.
hold pacing in this study was related to stimulation site.

Clinical Correlations

A corollary to iatrogenic overdrive pacemaker suppression is seen in clinical circumstances. Patients with intermittent episodes of rapid tachycardia will frequently demonstrate significant SAN depression immediately following the termination of the tachycardia. It is, however, the patient with the sick sinus syndrome who may demonstrate profound depression of SAN function following the cessation of an episode of tachycardia. In one of the study patients, spontaneous termination of an episode of supraventricular tachycardia (rate 140 beats/min) was followed by profound suppression of SAN function (pause, 2500 msec; fig. 6). In the three patients with the sick sinus syndrome, pauses of 2500–6000 msec have been demonstrated after either overdrive pacing or spontaneous termination of tachycardia. This suppression of SAN function far exceeds the mean maximum pause of 1041 msec seen in the present group of patients. Although too few patients have been studied for definitive conclusions, the determination of the duration of SAN suppression following atrial pacing appears to be a useful technique in the evaluation of the extent of human SAN disease.

Acknowledgment

The authors would like to thank Dr. Mario Vassalle for his critical review of the manuscript.

References


Circulation, Volume XLIV, July 1971


Evaluation of Sino-atrial Node Function in Man by Overdrive Suppression
WILLIAM MANDEL, H. HAYAKAWA, RONALD DANZIG and HAROLD S. MARCUS

Circulation. 1971;44:59-66
doi: 10.1161/01.CIR.44.1.59
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1971 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/44/1/59

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/