Characteristics of Sinoatrial Conduction in Patients with Coronary Artery Disease

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SUMMARY Electrophysiologic studies were performed in 32 patients with angiographically documented coronary artery disease (CAD). Group I was composed of ten patients (31%) with severe stenosis (≥75%) proximal to the origin of the sinus node artery (SNA); group II was composed of five patients (16%) with moderate (50–75%) proximal stenosis; and group III was composed of 17 patients (53%) with insignificant (0–50%) proximal stenosis. The mean sinoatrial conduction time (SACT) for group I was 119 ± 18 msec; group II was 84 ± 16 msec; and group III was 72 ± 5 msec. The SACT was significantly longer in group I than in group III (P < 0.005).

In conclusion 1) in patients with CAD, SACT > 72 ± 5 msec is abnormal; 2) the results suggest a pathogenetic role of CAD in the development of sinus node dysfunction; 3) the SACT is a more sensitive indicator of subtle sinus node dysfunction in CAD patients than is heart rate, sinus node response to atrial extrastimuli, or sinus node recovery time; and 4) the ability to diagnose sinus node dysfunction in its early stages and recognition that coronary artery disease is an etiologic factor may allow for the elucidation of the natural history of the sick sinus syndrome.

THE RELATIONSHIP BETWEEN CORONARY ARTERY DISEASE and the clinical and electrocardiographic criteria establishing the diagnosis of the sick sinus syndrome is controversial. Most of the existing evidence supporting a cause-and-effect relationship is circumstantial. The prevalence of both the sick sinus syndrome and coronary artery disease in elderly individuals may be merely coincidental. Although many reports of the sick sinus syndrome include a large percentage of patients with coronary artery disease, a role for atherosclerotic heart disease in the pathogenesis of the sick sinus syndrome can only be inferred. While sinus bradycardia is a common clinical manifestation of acute inferior and lateral myocardial infarctions, factors other than sinus node ischemia could explain this phenomenon.

Experimental acute occlusion of the sinus node artery has resulted in variable provocation of sinus node dysfunction; it has been suggested that this inconsistent response is due to variable collateralization and occasional multiple origins of the sinus node artery in animals. Alternatively, the opposing effects of sinus node artery perfusion pressure and the stimulus of stretch may counterbalance one another in some, but not in all, animals studied.

To add further confusion to this controversy, anatomic examinations of the sinus node and its vascular supply in patients with sick sinus syndrome have frequently, but inconsistently, revealed coronary atherosclerosis. The problem is made more perplexing when one considers the accumulation of evidence to support the reasonable notion that many insults, of which ischemia is only one, probably play a role in the pathogenesis of the sick sinus syndrome.

Recently, Engel et al. failed to demonstrate a correlation between prolongation of the sinus node recovery time after atrial overdrive pacing and the pressure or the extent of atherosclerotic lesions proximal to the origin of the sinus node artery. It is the purpose of the present study to examine the possible relationship between coronary artery disease and other electrophysiologic parameters of sinus node dysfunction.

Patient Population

Thirty-two patients undergoing right and left heart catheterization for evaluation of suspected coronary artery disease were studied randomly with no prior knowledge of history regarding cardiac arrhythmias. The criteria for patient selection and inclusion into the study group were 1) normal sinus rhythm at the time of the catheterization and 2) the presence of at least one significant coronary lesion (>50% stenosis) as determined from a review of the video tape recordings immediately after coronary injections by an observer not directly involved in the electrophysiologic studies. The patients ranged in age from 36–70 years; there were 30 males and 2 females. None of the patients were taking cardiac drugs for at least 48 hours prior to the time of the study. Furthermore, no patient had prior treatment with digitalis preparation.

Methods

The patients were studied in the fasting state in the cardiac catheterization laboratory immediately prior to coronary angiography. Precatheterization sedation was achieved with Seconal, 100 mg, administered orally approximately one hour prior to the procedure.

Previously, thermodilution cardiac outputs had been recorded utilizing a specially constructed #7 F thermodilution catheter positioned in the main pulmonary artery. A #6 bipolar catheter was passed through an antecubital vein in the left arm and positioned in the high right atrium. Single premature atrial stimuli, coupled to the preceding spontaneous atrial beat, were delivered by a specially constructed pulse generator at a milliamperage two times greater than the diastolic threshold of the right atrium for a 2.5 msec duration. A high right atrial electrogram as well as surface lead II was recorded on a multichannel oscilloscopic recorder (Electronics for Medicine, DR 8). The premature atrial stimuli were introduced in diastole during spontaneous sinus rhythm after every eighth sinus beat at progressively decreasing coupling intervals (in 10 msec increments). In this fashion, the sinus cycle length was scanned until atrial capture was lost. Scanning was begun at a prematurity equivalent to approximately 95% of the sinus cycle.

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Received July 28, 1976; revision accepted November 29, 1976.
Parameters Measured

Coronary Anatomy. After the electrophysiologic studies were completed and the data analyzed, the coronary angiograms were carefully reviewed, with special attention given to identification of the sinus node artery (SNA). Based on the anatomic descriptions of James,44 note was taken of the origin of the sinus node artery and location and extent of arteriosclerotic lesions within and proximal to it. These lesions were graded as insignificant (<50% narrowing), moderate (50–75% narrowing) or severe (75–100% narrowing). In addition, note was taken of the severity of stenosis of the three main coronary arteries and their larger branches. Coronary anatomy was then classified according to the number of major vessels diseased and severity of involvement. There was independent agreement of at least two observers regarding SNA location and disease in these angiograms.

Left Ventricular Function. Cardiac output and cardiac index were determined for each patient and correlated with the electrophysiologic status of sinus node function.

Heart Rate. The sensitivity of resting heart rate as an indicator of compromised vascular supply to the region of the sinus node was evaluated.

Zones of Response to Premature Atrial Stimulation. An attempt was made to identify the four zones of sinus node response to premature atrial stimuli identified by Strauss et al.45 These include: 1) zone of nonreset characterized by an A1–A2 interval equal to 2 × (A1–A2); 2) zone of reset characterized by an A2–A3 interval less than 2 × (A1–A2); 3) zone of interpolation characterized by an A1–A3 interval equal to the A1–A2 interval; 4) zone of sinus echo characterized by an A2–A3 interval shorter than A1–A2.

Sinoatrial conduction time (SACT). This interval was determined by the method of Strauss et al.45

Atrial Refractory Period. The atrial effective refractory period represents the longest A1–S2 interval that finds the atrial muscle refractory to an S2 depolarization.

Results

Coronary Artery Angiographic Data

The sinus node artery was identified in all patients and originated from the right coronary artery in 19 patients (60%) and from the left circumflex artery in 13 patients (40%). Lesions of the SNA itself were identified in three patients (9%). Lesions proximal to the origin of the SNA or within the SNA were found to be significant (50% or greater narrowing) in 15 patients (47%). Group I included ten patients (31%) found to have severe stenosis (≥75% narrowing); group II, five patients (16%) with moderate stenosis (>50–75% narrowing); and group III, 17 patients (53%) having no lesions or insignificant lesions (0–50% narrowing) proximal to the origin of the SNA. When significant proximal stenosis was present, it involved the right coronary artery in 60% of the cases and the left in 40%.

Ten patients had significant (>50%) stenosis of one major vessel (none in group I, 2 in group II, and 8 in group III). Two patients had significant double vessel disease (none in group I, none in group II, and 2 in group III). Twenty patients had significant triple vessel disease (10 in group I, 3 in group II, and 7 in group III).

Left Ventricular Function

Thirteen patients had significantly abnormal left ventricular function (cardiac index <2.5 L/min/m²); 4 in group I, 2 in group II, and 7 in group III.

Heart Rate

Sinus rate ranged from 47–100 beats/min (mean = 69 ± 2 beats/min) for the entire population. The mean sinus rate for group I = 68 ± 4.9 beats/min; group II = 75 ± 5 beats/min and group III = 69 ± 3.2 beats/min. There was no significant difference between the three groups of patients.

Zones of Response to Premature Atrial Stimulation

A zone of non-reset (ZNR) and a zone of reset (ZR) were identified in all 32 patients. The average range was determined by taking the means of the upper and lower limits of each patient’s zone of reset and non-reset. The interval width was determined by taking differences of the range of values for each individual and averaging these. The percent sinus cycle length was evaluated in a similar way. There was no significant difference in range, width or percent of sinus cycle length of ZNR or ZR between the three groups, nor between patients with significant and insignificant lesions (table 1). Zones of interpolation and re-entry were not identified in any of the 32 patients.

Sinoatrial Conduction Time

The SACT for the 32 patients ranged from 41–229 msec (mean, 88 ± 7 msec). The SACT for group I ranged from 51–229 msec (mean, 119 ± 18 msec); group II ranged from 45–129 msec (mean, 84 ± 16 msec) and group III ranged from 41–107 msec (mean, 72 ± 5 msec). In the 15 patients with significant lesion proximal to the origin of the sinus node artery (groups I, II), the mean SACT was 106 ± 13 msec. The SACT was significantly longer in patients with significant lesions than in patients in group III (P = 0.007) (figs. 1, 2). No correlation existed between SACT and cardiac index, heart rate (sinus cycle length), or atrial refractory period.

Atrial Refractory Period

The atrial refractory period for the 32 patients ranged from 200–450 msec (mean, 304 ± 12 msec). The atrial refractory period for group I ranged from 230–370 msec (mean, 309 ± 18 msec); group II ranged from 236–390 msec (mean, 280 ± 28 msec) and group III ranged from 200–450 msec (mean, 308 ± 18 msec). The mean atrial refractory period for all patients with significant lesions proximal to the sinus node artery was 299 ± 15 msec.

Discussion

The electrocardiographic criteria for sinus node dysfunction include sinus bradycardia, bradycardia-tachycardia, sinus arrest, and SA block. Possible electrophysiologic determinants of these ECG features are 1) a diminished rate of phase 4 depolarization; 2) an increased threshold potential; 3) an abnormal prolongation of action potential duration; 4) diastolic hyperpolarization; and 5) abnormal conduction through the perinodal fiber zone. To date, it has not
been possible to evaluate intracellular potentials in the intact human heart; however, these electrophysiologic properties can be assessed indirectly. The finding of a normal SACT by the extrastimulus technique in a patient with gross evidence of sinus node dysfunction somewhat narrows the field of possible sites of dysfunction. Either electrophysiologic properties intrinsic to the sinus node itself are abnormal, or alternatively, influences extrinsic to the conduction system, e.g., the autonomic nervous system, are deranged.

The mechanisms may be further narrowed by determination of SNRT. Recent studies suggest that SNRT prolongation is, in part, independent of autonomic influences. It appears that a component independent of autonomic influences can be distinguished from the component which is under the influence of the autonomic nervous system. Unfortunately, our present level of technology does not yet permit us to isolate the precise intrinsic sinus node electrophysiologic property which is abnormal.

The value of SACT determination is diminished by the unavailability of true normal values. Dhingra et al. studied a group of patients without apparent sinus node dysfunction, determined by absence of gross ECG characteristics. However, this was a very specific population of patients, i.e., patients with organic heart disease, mainly arteriosclerotic heart disease (ASHD). The mean SACT for this group was 92 ± 30 msec. The similarity of our total population of ASHD patients is reflected by the fact that there was no significant difference between the mean SACT of our patients and those of Dhingra et al.

Our results demonstrate that even a group of ASHD patients does not represent a homogenous population with respect to sinoatrial conduction properties. Patients with significant arteriosclerotic lesions of the SAN artery or in vessels proximal to the origin of the SAN artery have longer SACTs than patients without such lesions. Thus, in our

### Table 1. Zones of Response to Premature Atrial Stimulation

<table>
<thead>
<tr>
<th>Zone of Nonreset</th>
<th>Mean upper and lower values (range ± SEM) msec</th>
<th>Interval Width (mean ± SEM) msec</th>
<th>Mean upper and lower values (range ± SEM) % of SCL</th>
<th>% of SCL (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Group</td>
<td>896 ± 29</td>
<td>168 ± 15</td>
<td>99 ± 0±2</td>
<td>18 ± 2</td>
</tr>
<tr>
<td>Group I</td>
<td>731 ± 32</td>
<td>174 ± 46</td>
<td>82 ± 4</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>Group II</td>
<td>631 ± 59</td>
<td>176 ± 39</td>
<td>99 ± 1±4</td>
<td>20 ± 3</td>
</tr>
<tr>
<td>Group III</td>
<td>906 ± 41</td>
<td>161 ± 22</td>
<td>99 ± 1±0</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>Zone of Reset</td>
<td>Mean upper and lower values (range ± SEM) msec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Group</td>
<td>714 ± 32</td>
<td>411 ± 27</td>
<td>80 ± 1±2</td>
<td>43 ± 2</td>
</tr>
<tr>
<td>Group I</td>
<td>302 ± 12</td>
<td>409 ± 49</td>
<td>78 ± 1±4</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>Group II</td>
<td>306 ± 19</td>
<td>330 ± 67</td>
<td>75 ± 1±6</td>
<td>38 ± 8</td>
</tr>
<tr>
<td>Group III</td>
<td>742 ± 46</td>
<td>436 ± 38</td>
<td>81 ± 1±2</td>
<td>46 ± 2</td>
</tr>
</tbody>
</table>

SCL = sinus cycle length.

Figure 1. Effect of extent of coronary artery lesions proximal to the origin of the sinus node artery on sinoatrial conduction time. Patients with severe proximal lesions (≥ 75% stenosis) group I have significantly longer SACT than patients with insignificant lesions.

Figure 2. Graphic display of sinoatrial conduction time for each of the 32 study patients. The majority of patients with severe coronary artery lesions proximal to the origin of the sinus node artery (group I) have SACT values greater than the mean SACT of group III patients (shaded bar = 72 ± 5 msec).
ASHD patients, a value of SACT > 72 ± 5 msec is abnormal and may represent covert sinus node dysfunction. These results confirm Dhingra's impression that their value of "normal" SACT was higher than anticipated.

It must not be concluded, however, that 72 ± 5 msec is the absolute normal for SACT in man. It is doubtful that reduced blood flow to the perinodal zone is the only factor involved in the pathogenesis of sinoatrial conduction defects. It is possible that patients in our group III could be further subclassified with respect to the presence or absence of other pathogenic factors such as amyloid deposition in the perinodal zone. Those patients who do not have amyloid deposition may have significantly shorter SACT than those that do, i.e., significantly shorter than 72 ± 5 msec.

The most consistent clinical observation with regard to sinus node dysfunction is that it is most commonly found in elderly individuals. The most frequent anatomic findings in these patients are coronary atherosclerosis, atrial amyloidosis, and diffuse fibrosis. Although arteriosclerotic coronary disease and amyloid infiltration are concomitants of the aging process, it has never been demonstrated that either of these two factors do in fact play an etiologic role in the sick sinus syndrome. Argus et al. demonstrated that sinus bradycardia in many elderly individuals is secondary to increased resting parasympathetic tone. Thus, it may be speculated that elderly patients as a rule do have either greater vagal tone or increased sinus node sensitivity to normal parasympathetic tone compared to younger individuals. Similarly, Dighton demonstrated that sinoatrial block may be mediated by increased vagal tone. On the other hand, Jose determined that the intrinsic heart rate varies inversely with age (IHR = 117.2 - [0.53 × age]). Thus it is most likely that the well-established phenomenon of slowing of the sinus rate with age is the result of a combination of factors both intrinsic and extrinsic to the sinoatrial region.

Engel et al. failed to establish a relationship between both prolongation of the sinus node recovery time and heart rate with regard to the site of arteriosclerotic lesions in relation to the origin of the sinus node artery. Engel concluded that it was unlikely that sick sinus syndrome is related to atherosclerotic disease involving the SNA. In contrast, our study shows that another electrophysiologic parameter, the sinus-to-atrium conduction time, is correlated with the site of atherosclerotic involvement of the sinus node artery. Engel did not obtain SACT determinations in his patients, reasoning that prolonged SACT in the absence of prolonged SNRT is very unusual. However, this conclusion is grounded on the unverified assumption that SNRT is a more sensitive indicator of sinus node dysfunction than is SACT. Certainly, when gross electrocardiographic evidence for sick sinus syndrome exists, the two parameters frequently parallel one another in terms of deviation from accepted normal values, although exceptions to this relationship have recently been cited. Sinus node recovery time may be a relatively insensitive indicator of abnormalities of sinoatrial conduction. Previously there had been no comparison of the sensitivity of these electrophysiologic measures in patients without gross evidence for sick sinus syndrome. From the results of the present study, it is concluded that in patients with coronary artery disease, the SACT is a more sensitive indicator of subtle electrophysiologic abnormalities than is basal heart rate or SNRT in the preclinical stage of sinus node dysfunction.

The relative insensitivity of SNRT may be accounted for by anatomic considerations of the sinus node artery and the sinus node. The sinus node artery is of a larger caliber than anticipated from a knowledge of the extent of the area which it supplies. This disproportionately large size is considered by James to be of physiological importance. Based upon predictable responses of sinus rate to stretch and the special arrangement of the sinoatrial node cells around the sinus node artery, James suggests that distention and collapse of this vessel plays an important role in the regulation of sinus rate. Collapse of the artery results in an increase in tension on the pacemaker cell because of the relationship between the cells and the artery via the attachment of collagen to both the nodal cells and the arterial wall. Collapse of the artery thereby causes an increased sinus rate. Distention of the artery has the opposite effect, leading to relaxation of the nodal cells and slowing of the heart rate. A drop in pressure distal to a significant narrowing of a vessel proximal to the origin of the sinus node artery could possibly result in a stretch-dependent increase in sinus rate counteracting the depressant effects of ischemia. Similarly, a reduced intraarterial pressure could counteract the depressant effects of ischemia on SNRT. Hypothetically, the SNRT may fail to reflect the stimulant effect of increased tension on the pacemaker cell until advanced structural changes occur as may be the case of overt sinus node dysfunction.

Borman found that a considerable portion of the sinus node may be excised without affecting its pacemaker function. The extensive distribution of pacemaker type cells in the sinoatrial region provides an explanation for this finding. Furthermore, it has been demonstrated that the dominant pacemaker site shifts under certain circumstances. It is, therefore, not unreasonable to assume that these anatomic and electrophysiologic properties of the sinus node protect it from the insults of ischemia. Such protection would account for preservation of heart rate and SNRT in the presence of significant narrowing of vessels proximal to the origin of the sinus node artery.

Finally, it may be that the perinodal zone is less richly supplied by collaterals than is the sinus node itself and therefore manifests the effects of ischemia earlier.

Mention should be made of the limitations of the extrastimulus technique for determining the sinoatrial conduction time. Utilizing intracellular microelectrode recordings in the rabbit, Miller and Strauss determined that there was poor correlation between estimated and measured SACT (r = 0.64). The shorter than predicted measure of SACT was accounted for by a shortening of the sinoatrial action potential, a consequence of electrotonic interaction between sinus node and adjacent cells during repolarization. Thus, the SACT as estimated by the extrastimulus technique is probably a contaminated measure, reflecting both perinodal and intrinsic sinus node electrophysiologic properties. Nonetheless, the findings of Massini and the present study that estimated SACT is a more sensitive measure of sinus node dysfunction than is SNRT under certain circumstances suggests that SACT is a valuable addition to the indirect assessment of sinus node dysfunction.
Clinical Significance

Patients with coronary artery disease do not represent a homogenous population with regard to all parameters of sinus node function. Specifically, patients with significant atherosclerotic lesions proximal to the origin of the sinus node artery have significantly longer sinoatrial conduction times than patients without such lesions. This suggests that coronary artery disease is an etiologic determinant of sinus node dysfunction. Furthermore, prolongation of SACT appears to be a very sensitive indicator of early sinus node dysfunction in the setting of coronary artery disease. Other electrophysiologic parameters (heart rate, sinus node responses to extrastimuli and sinus node recovery time) appear to be less sensitive.

The present study also redefines normal values for SACT. In patients with coronary artery disease, an SACT greater than 72 ± 5 msec represents an abnormal prolongation.

Having the means of diagnosing sinus node dysfunction in its early stages and provided with evidence that coronary artery disease is an etiologic factor, elucidation of the natural history of the sick sinus syndrome can be attempted. Once necessary, longitudinal studies have been carried out, the value of medical and surgical interventions favorably altering the progression of the disease can be evaluated.

The immediate clinical significance of early detection of sinus node dysfunction cannot be overemphasized. Certain antiarrhythmic drugs may suppress sinus node automaticity and sinoatrial conduction such as digitalis, propranolol, and quinidine. The results of the present study suggest that patients with an increased probability of developing sinus node rhythm disturbances secondary to these antiarrhythmic agents can be identified.

Acknowledgment

The authors would like to acknowledge the technical assistance of Mr. Avile McCullen, and the assistance of Lance Laforteza in preparation of the art work. Miss Amy Chin provided biostatistical assistance and Mrs. Betty Garrigues, editorial assistance.

References

Alternans of the ST Segment in Prinzmetal’s Angina

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SUMMARY Alternans of the elevated ST segment (STEA) was found in 8 of 21 patients (38%) with Prinzmetal’s variant angina. In addition to STEA, all eight patients had varying cardiac arrhythmias: multiple premature ventricular depolarizations in eight, ventricular tachycardia in five, and ventricular fibrillation in three. There was no consistent temporal relationship between the occurrence of STEA and the cardiac arrhythmias. Alternans occurred during periods when no arrhythmias were present. All eight patients underwent coronary angiography. Spontaneous coronary artery spasm was documented angiographically in three patients including two who had minimal or no coronary atherosclerotic disease. Six patients had severe, fixed, occlusive coronary artery disease. Possible mechanisms for STEA include: 1) failure of regions of myocardium to depolarize on alternate beats due to variation in conduction and refractoriness between ischemic and nonischemic zones of myocardium, and 2) electrical alternans of the transmembrane action potential during phases 2 and 3 (repolarization) caused by changes in the rate and extent of electrolyte transfer across cell membranes during ischemia.

It is postulated that STEA is an electrocardiographic sign in the surface ECG of a dysequilibrium of refractory periods during ischemia and reflects an unstable electrical state of the myocardium.

Patient Selection and Methods

The criteria used for the selection of patients with Prinzmetal’s angina were 1) the presence of multiple episodes of reversible ST-segment elevation greater than 2 mm in more than one lead of a standard 12 lead electrocardiogram; 2) the absence of evolutionary changes of myocardial infarction on serial electrocardiograms; and 3) the absence of elevation of serum creatine phosphokinase (CPK), lactic dehydrogenase (LDH), or glutamic oxaloacetic transaminase (SGOT). The diagnosis of alternans of the ST segment or ST-T complex was based on the occurrence of consecutive alternation in the configuration of the ST segment or ST-T complex in the presence of a regular cardiac rate. This did not include the common alternation of the ventricular complex encountered with coupled sinus beats and extrasystoles. In addition, a stable baseline was an essential requirement. Conditions known to be associated with electrical alternans, such as pericardial effusion,4-7 cardiac tamponade,8 certain drug intoxications,9 serum electrolyte abnormalities,10,11 and the long QT syndromes12,13 were ruled out. All patients were monitored continuously in a coronary care unit and episodes of ST segment elevation were recorded. All eight patients with STEA underwent coronary arteriography and two underwent exercise stress testing. Provocative induction of coronary artery spasm by parasympathomimetic agents or ergot derivatives was not done.

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Received August 19, 1976; revision accepted November 15, 1976.
Characteristics of sinoatrial conduction in patients with coronary artery disease.
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Circulation. 1977;55:569-574
doi: 10.1161/01.CIR.55.4.569
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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