Cardiac Arrhythmias After Chronic Embolization of the Sinus Node Artery: Alterations in Parasympathetic Pacemaker Control

JEROD M. LOEB, PH.D., DAVID E. EULER, PH.D., WALTER C. RANDALL, PH.D., JOHN F. MORAN, M.D., AND GISSUR BRYNJOLFSSON, M.D.

SUMMARY  Embolization of the sinus node artery was accomplished in dogs by injecting rapidly hardening vinyl latex into the sinus node artery. Embolization immediately shifted the pacemaker to a junctional focus; however, with time postoperatively, the pacemaker shifted to an atrial site. Variable episodes of pacemaker failure, sinoatrial block, junctional rhythm, wandering atrial pacemaker and idioventricular escape rhythms were commonly observed on Holter monitor in isolation but only rarely when the dog was in the laboratory. Severe bradycardia (38.9 ± 3.7 beats/min) was the predominant rhythm by 3–6 months postoperatively. In addition, these same dogs had a greater overall increase in heart rate after atropine than normal dogs (171.5 ± 13.5 vs 116.6 ± 15.9 beats/min above control; p < 0.02). Responses to vagal stimulation in this group were abnormal, as long periods of asystole and bradycardia were observed after stimulation was terminated.

These data suggest an alteration in parasympathetic pacemaker control after chronic embolization of the sinus node artery.

CHRONIC SINUS NODE dysfunction is an extremely variable clinical entity characterized by bradycardia, either alone or in combination with tachycardia, periodic pacemaker failure, sinoatrial exit block and sometimes atrial fibrillation.1 Although several studies have suggested neural involvement in the genesis of the rhythm disturbances underlying dysfunction of the sinus node, there is considerable debate as to the precise mechanism. Mandel et al. found abnormal parasympathetic responses manifested as a hyperresponsiveness to carotid sinus massage in eight of 31 patients with sinus node dysfunction.2 Dighton suggested reduced atrial cholinesterase to explain symptomatic sinus bradycardia and transitory vagal depressions of pacemaker activity ("vagal epilepsy") to explain sinoatrial block.3–4 Histopathologically, in chronic dysfunction of the sinus node, alterations have been observed at the atrial-nodal border area, in the node proper, as well as in neural structures surrounding the node.5–7

The purpose of the present investigation was to assess neural involvement in the dysrhythmias produced after chronic embolization of the sinus node artery. The mechanism of these dysrhythmias was related to an alteration in parasympathetic pacemaker control.

Preparation

Mongrel dogs of either sex that weighed 15–25 kg were anesthetized with sodium pentobarbital (30 mg/kg) and ventilated through a cuffed endotracheal tube by a Bird Mark 7 respirator. Lead II of the ECG was continuously monitored. Using sterile techniques, a thoracotomy was performed in the right fourth intercostal space and the heart suspended in a pericardial cradle. The sinus node artery was identified as a large atrial branch from the right coronary artery. The nodal artery was isolated for a distance of approximately 1 cm beginning at the atrioventricular sulcus and continuing toward the base of the heart. The vessel was tied proximally and catheterized distally using PE50 polyethylene tubing (Clay-Adams). Verification of arterial distribution was then made by injection of 0.5 ml of indocyanine green (CardioGreen, H. W. and D., Inc.). Visual inspection was used to document the area of perfusion to assure that dye was distributed to the junction of the superior vena cava and right atrium. In addition, injection into the sinus node artery has been shown to produce a transitory sinus bradycardia.8 Rapidly hardening red vinyl (Carolina Biological Supply) was then injected into the vessel in a volume sufficient to clear the green dye (about 0.5 ml) and thus fill the vessel and its distal branches. The area within the distribution of the vessel became ischemic in appearance within a few minutes. The ischemic area involved the entire sulcus terminalis extending from the superior vena cava-right atrial junction to the inferior vena cava-right atrial junction. Cavit and atrial tissue extending for at least 0.5 cm on each side of the sulcus terminalis was also involved.

The injection of latex into the sinus node artery was followed immediately by a slowing of the sinus rate and the appearance of a junctional rhythm. The catheter was then removed from the vessel. The chest
was closed in layers and the dogs were allowed to recover.

While dogs remained undisturbed in their cages, lead II ECGs were recorded on tape using a Holter monitor (Cardiocassette II). The unit was programmed to record 30 seconds of ECG data every 30 minutes for up to 32 consecutive hours. All tapes were played back and recordings displayed on a Grass Model 7 polygraph at a paper speed of 25 mm/sec and mean heart rates were calculated for the entire recording period. Recordings were made daily for the first postoperative week and then 24–48 hours before a terminal experiment (see below) after 3–6 months. On at least one occasion, each dog was brought into the laboratory in the week before the terminal experiment for recording of an ECG. Atropine (0.2 mg/kg i.v.) was then administered to the dog and the rate and rhythm were recorded.

Another group of nine control dogs underwent ECG monitoring once after acclimatization to their cages. These dogs were brought into the laboratory and control recordings of lead II of the ECG were obtained in identical fashion. In addition, response to the administration of atropine 0.2 mg/i.v. was quantitated.

After the 3–6-month test period, six chronically occluded dogs were preanesthetized with phencyclidine hydrochloride (Sernylan) and anesthetized with α-chloralose (75 mg/kg). The trachea was cannulated and the dog ventilated with a Bird Mark 7 respirator. Both vagi were isolated in the neck and decentralized. Vagal stimulations were performed on the peripheral end of the nerve, as described below. The femoral artery was catheterized for the measurement of arterial pressure and the femoral vein for the administration of fluids. The chest was opened on the right side at the fourth intercostal space and the heart suspended in a pericardial cradle. Adhesions were carefully separated and the right atrium and sinus node area were exposed. Close bipolar plunge electrodes were placed into the regions of the anterior interatrial band, the limbus of the fossa ovalis and the eustachian ridge of the coronary sinus in order to map atrial activation. In addition, a bipolar suction electrode was used to sample the area for the point of earliest epicardial activation and, thus, the approximate pacemaker location. Lead II of the ECG was continuously recorded. All tracings were displayed on a Grass Model 7 polygraph at paper speeds of 25–100 mm/sec. Before the dog was sacrificed, the sinus node and sulcus terminalis were removed for histologic analysis.

Finally, an additional control group of four dogs was anesthetized with α-chloralose, the trachea cannulated and the dogs were ventilated. The femoral vein and artery were catheterized as described above. Both vagi were isolated in the neck and decentralized. A right thoracotomy was performed at the fourth intercostal space and the sinus node artery was identified, catheterized and embolized with vinyl latex, as previously described. Vagal stimulation was then performed on the efferent end of the nerve, as described in the results.

Data are presented as mean ± standard error of the mean. The significance levels were tested using the unpaired t test and values were considered statistically significant at the p < 0.05 level.

Results

As previously described, immediately after injection of vinyl into the sinus node artery, a junctional rhythm was produced. This pacemaker shift was transitory and the junctional rhythm usually disappeared within a few hours after surgery. The progression of cardiac rhythm was followed for 3–6 months in six dogs. A representative example is shown in figure 1. Panel A was recorded immediately before the injection of vinyl into the sinus node artery. The fast rate (167 beats/min) is consistent with the well-known vagolytic effect of pentobarbital anesthesia. Panel B was obtained from the Holter monitor approximately 12 hours after surgery and shows a new rhythm with an upright P wave at an average rate of 55 beats/min. Note the short PR interval (0.06 second). Panel C was obtained 2 days after surgery and reveals an increase in rate and a lengthening in the PR interval. The rhythm, however, is regular. Panel D was recorded 3 days postoperatively and shows a marked variation in cycle length. Panel E (4 days after surgery) shows a longer strip with similar rhythm disturbances evident. Panels F and G were recorded 6 months after surgery. Note the excessively slow rate in panel F (27 beats/min counted over a 5-minute period). Panel G was recorded on the same day as panel F and shows the occasional appearance of tachycardia (170 beats/min).

In the first few weeks immediately after emboliza-
tion of the sinus node artery, asystoles (mean 4.8 ± 0.9 second) were occasionally observed on Holter recordings. These asystoles were sometimes interrupted by junctional or idiioventricular escape beats. In addition, wandering atrial pacemakers, junctional rhythms and bradycardia were common. However, when studied in the laboratory, these same dogs did not usually exhibit dysrhythmias of comparable magnitude. When asystoles were present in the laboratory, atropine administration abolished them.

As time postoperatively increased (3–6 months), the duration of the asystoles decreased but the predominant rhythm on Holter monitoring was severe bradycardia. As shown in table 1, compared with normal unoperated control dogs, heart rate in the chronic embolism group was significantly less when Holter monitored in isolation (60.4 ± 4.6 vs 38.9 ± 3.7 beats/min; p < 0.05) than in the laboratory (99.1 ± 7.5 vs 77.8 ± 9.6 beats/min; p > 0.1). The administration of atropine (0.2 mg/kg) to nine normal control dogs in the laboratory increased basal heart rate by 116.6 ± 15.9 beats/min (from 99.1 ± 7.5 beats/min). However, 3–6 months after embolization of the sinus node artery, atropine administration to this group of dogs increased heart rate by 171.5 ± 13.5 beats/min (from 77.8 ± 9.6 beats/min). The maximum increase in rate after atropine in the operated group was significantly greater than in the control group (p < 0.02; table 1).

Each of the dogs with an embolized sinus node artery underwent ECG monitoring for a final 24-hour period. The dog was anesthetized and then prepared as described above. In each dog, pacemaker location was mapped first. Time relationships between the three stationary plunge electrodes and the roving suction electrode were used to approximate the point of earliest activation. In five of six animals, the earliest activation was localized to the rostral portion of the sulcus terminalis in the vicinity of the sinus node. The other dog had a point of initial activation at the caudal end of the sulcus terminalis.

The bradycardia on monitoring and the abolition of dysrhythmia by atropine suggested a parasympathetic mechanism. Therefore, vagal stimulations were performed next. In normal dogs, periods of vagal stimulation are followed by an immediate return to and acceleration above control heart rates — post-vagal tachycardia. Figure 2 shows an example of this phenomenon in a dog with an intact sinus node. The upper panel (control) shows an ECG and arterial pressure trace. The right cervical vagus was stimulated supramaximally (20 Hz, 5.0 msec, 8 V) for 30 seconds during the period indicated by the arrows. The central portion of the record during stimulation has been omitted. After termination of the stimulation, atrial activity returned in less than 1 second and the rate rapidly accelerated above control. To determine whether acute occlusion of the sinus node artery had any effect on the response to vagal stimulation, latex was injected into the sinus node artery and stimulation was repeated. The lower panels were recorded 3 hours after latex injection. The control rate is considerably slower and the rhythm appears unstable. However, the response to vagal stimulation was unchanged; the rate immediately returned to and then accelerated above the control level after the period of stimulation. Similar results were obtained in four dogs.

Figure 3 shows the results of short and longer periods of vagal stimulation in a dog anesthetized with chloralose with chronic sinus node artery embolization. Panel A shows the ECG (upper trace) and blood pressure recordings (lower trace) before, during and after a 1-second stimulus applied to the right cervical vagus. The stimulus was applied during the downward displacement of the time marker (middle trace). After removal of the stimulus, the heart rate did not immediately return to the control value. In fact, the duration of the bradycardia outlasted the duration of the stimulus, and the rate only gradually returned toward control. Panel B shows a similar response after stimulation of the left cervical vagus. Panels C and D

**Table 1. Effect of Chronic Sinus Node Artery Embolization on Heart Rate in the Conscious Dog**

<table>
<thead>
<tr>
<th></th>
<th>24-hour Holter (in isolation)</th>
<th>In Laboratory</th>
<th>Δ HR after Atropine (0.2 mg/kg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>60.4 ± 4.6 (45–66)</td>
<td>99.1 ± 7.5 (69–125)</td>
<td>116.6 ± 15.9 (51–168)</td>
</tr>
<tr>
<td>Sinus node artery embolized (3–6 months)</td>
<td>38.9 ± 3.7 (27–48)</td>
<td>77.8 ± 9.6 (52–110)</td>
<td>171.5 ± 13.5 (162–208)</td>
</tr>
</tbody>
</table>

*p < 0.05†  †Comparison between control dogs and dogs with embolized sinus node artery.

Values represent mean heart rate ± SEM (beats/min). Values in parentheses represent upper and lower ranges.
A Δ HR = absolute change in heart rate after atropine administration (± SEM).
were recorded from the same dog and show the response to 30 seconds of stimulation applied to the right and left cervical vagi. The central portion of the record during stimulation was omitted. The termination of stimulation was followed by prolonged asystole and bradycardia. In addition, junctional or idioventricular escape did not occur during the stimulation period. In panel C, after vagal stimulation, the arterial pressure catheter slipped into the left ventricle, explaining the low diastolic pressures for about 5 seconds. In all six dogs tested, both right and left vagal stimulation were followed by a prolonged period of asystole and bradycardia. The rate remained slow and did not return to the control level for 3-15 seconds after the termination of stimulation. Because it accentuated the dysrhythmias in conscious dogs, propranolol (1.0 mg/kg) was administered to some dogs in order to block β-adrenergic receptors. The adequacy of blockade was tested by stimulation of the right stellate ganglion before and after propranolol. Vagal stimuli were then repeated. Figure 4 shows an example of the results obtained in one dog. The upper panel shows the control record and the lower panel was recorded after the administration of propranolol. Control heart rate is markedly slower after propranolol administration. The presence of β blockade potentiated the duration of the vagal inhibition effect after termination of the stimulation period in all three dogs so tested.

Pathologic Analysis

Gross examination of the hearts from two dogs in the acute (2-4 days) stages after embolization revealed yellow discoloration along the sulcus terminalis extending into the atrium on one side and the superior vena cava on the other.

Histologic examination of the sinus nodes from these two dogs revealed infarct necrosis of the sinus node with extensive necrosis of the crista terminalis as well as necrosis of the adjacent walls of the right atrium and superior vena cava. In one dog, the attached segment of superior vena cava measured 6 mm in width and the infarction extended to the cut margin. On the atrial side of the node, a segment 7 mm wide was involved. There was a moderate amount of inflammatory reaction involving both the endocardium and epicardium, as well as focal proliferation of cellular connective tissue (healing). The area of the

---

**Figure 3.** Response of an anesthetized dog to varying periods of vagal stimulation 6 months after embolization of the sinus node artery. Lead II of the ECG and arterial pressure (AP) are shown. The middle trace in each panel is a time reference and indicates the stimulation period. Panel A shows 1 second of right cervical vagus (RCV) stimulation, panel B shows one second of left cervical vagus (LCV) stimulation, panel C shows 30 seconds of right vagal stimulation and panel D shows 30 seconds of left vagal stimulation. For clarity, the central portion of the stimulation record has been omitted in panels C and D.

**Figure 4.** Effect of β blockade on the response to vagal stimulation after chronic embolization of the sinus node artery. Lead II ECG and arterial pressure (AP) traces are shown. The upper panel (control) shows the effect of 10 seconds of right cervical vagal stimulation before and the lower panel (propranolol) after blockade of β receptors with propranolol. The central portion of the stimulation record has been omitted.
node contained two arteries with distended lumen that contained amorphous material. Hyalinization of the wall was also present. The distended arterial space and necrosis of the sinus node and adjacent muscle are shown in figure 5.

Serial examination of the sinus node region from a dog 6 months after embolization of the nodal artery revealed a healed infarct with fibrosis of the nodal area extending to the right atrium and the wall of the superior vena cava. Multiple dilated vessels were present, all containing amorphous material. In some sections, cartilagenous metaplasia of fibrous areas was noted with focal calcification. Some preservation of atrial muscle was present on the endocardial surface; however, no recognizable nodal tissue was found.

Discussion

Our results show that acute embolization of the sinus node artery immediately shifts the pacemaker to a junctional focus. Because the sinus node is somewhat resistant to anoxia as well as increases in extracellular potassium, it is unlikely that the immediate pacemaker shift is due to ischemia. Because the latex was injected under pressure, distention of the sinus node artery and the collagen matrix surrounding the sinoatrial node may have resulted in a depression of automaticity and a shift to the junctional region. Within a few hours of surgery, however, the pacemaker again shifted to an atrial focus. Similar results have been reported after acute removal of sinus nodal influences by various techniques, including cooling radon destruction, surgical excision, clamping and surgical exclusion. Recent evidence from our laboratory has shown that complete excision of the sinus node and crista terminalis is followed by return of an unstable atrial pacemaker. As reported in the present experiments, variable episodes of pacemaker failure, sinoatrial block, junctional rhythm, wandering atrial pacemaker and idioventricular escape were commonly found on ECG monitoring. In contrast to the dogs with embolized sinus node artery, ECG monitoring of normal control dogs revealed only sinus arrhythmia and occasional episodes of wandering atrial pacemakers. The arrhythmias in both groups of dogs were observed on ambulatory monitoring and more rarely when the dog was alert and brought into the laboratory. It is therefore clear that the level of autonomic tone may be an important determinant in the production of dysrhythmias after embolization of the sinus node artery, as it is in the production of sinus arrhythmia in the normal dog.

Previous studies have shown alterations in parasympathetic control of pacemaker function after removal
of either only the sinus node or the sinus node and crista terminalis. In the present experiments, after 3–6 months of chronic embolization, intravenous atropine administration produced a greater increase in heart rate in dogs with an embolized sinus node artery (171.5 ± 13.5 beats/min) than in normal dogs (116.6 ± 15.9 beats/min). In the operated dogs severe bradycardia developed by 3–6 months, which may reflect an increase in local levels of acetylcholine or an increase in sensitivity to acetylcholine. The higher rate after atropine in the dogs with an embolized sinus node artery may be explained by a change in intrinsic automaticity of the dominant pacemaker, possibly through a chronically higher level of parasympathetic tone. An alternative explanation may be a greater sensitivity to normal levels of sympathetic tone or circulating catecholamines. In contrast to the marked tachycardias after atropine administration in the present study, in dogs in which the sinus node and crista terminalis were excised, heart rates never exceeded 150 beats/min after atropine.

In the present experiments, mapping studies indicated that the pacemaker location was in the rostral position of the sulcus terminalis. These results may be compared with pacemaker location after excision of the sinus node and crista terminalis, in which subsidiary pacemaker location was considerably more distal (inferior vena cava-right atrial junction). These results support the concept of a hierarchy of pacemakers, in which more rostral pacemakers are capable of achieving higher rates. Certain similarities exist between the infarction and excision models — in both, subsidiary pacemakers are quite unstable, basal heart rates are lower and atropine eliminates arrhythmias.

In the period immediately after vinyl injection into the sinus node artery, the time required for recovery from vagal stimulation was not different from that in the control state (fig. 2). The abrupt return to and acceleration above control rate in the normal dog after vagal stimulation is well recognized. In fact, cycle length returns to and begins to exceed the control value almost immediately after the termination of the stimulation.

The rapid termination of acetylcholine action (within 2 seconds) is primarily a function of enzymatic hydrolysis. Acetylcholinesterase concentrations have been shown to be considerably higher in the region of the sinus node than in other portions of the heart. This fact probably accounts for the rapid termination (within one or two beats) of vagal activity in the normal dog. However, in the experiments reported here, after chronic embolization of the sinus node artery, even stimulation periods as short as 1 second were always associated with bradycardic effects prolonged well beyond the termination of the stimulation. Similar results followed both right and left vagal stimulations. In the presence of β blockade, the vagal depression of automaticity after 10 seconds of stimulation was even more potentiated (fig. 4). It is likely that an increase in sympathetic tone would occur as a consequence of vagally induced bradycardia and hypotension. This higher level of sympathetic tone probably assists in recovery from vagal stimulation, and propranolol would eliminate this effect, thereby potentiating the bradycardia. The dysrhythmias present in these dogs when monitored in isolation could easily result from an abnormal parasympathetic control system. The reduction of dysrhythmias in the laboratory may simply reflect vagal withdrawal coincident with excitement of the dog in the laboratory environment.

Much presumptive evidence exists for either an increased sensitivity to acetylcholine or a local increase in acetylcholine concentration in the sinus node area in some cases of sinus node dysfunction. Recent experiments from our laboratory have shown that either atropine or treadmill exercise can abolish the periodic asystoles after chronic surgical removal of the sinus node and crista terminalis. Branch and Beckett reported an excessive slowing in rate in response to low doses of acetylcholine in a line of pug dogs susceptible to syncope and sudden death, and postulate a decrease in local cholinesterase as the mechanism. The present experiments provide direct insight into a specific abnormality of the parasympathetic nervous system after chronic embolization of the sinus node artery. Obviously, a key question concerns the mechanism of the enhanced response to vagal stimulation. The sinus node artery provides the major (but not the sole) source of blood to the region of the sinus node. Because the sinus node artery distributes to a fairly large area, embolization of the vessel, while producing necrosis of the sinus node, may also result in ischemic damage of ectopic pacemakers in the perinodal area, thereby altering their intrinsic automaticity or sensitivity to neuromediators. Alternatively, there may have been a change in local cholinesterase in the vicinity of the dominant pacemaker or a change in acetylcholine released from neural elements. Certainly the final proof for any of these hypotheses must await further experimentation.

Acknowledgments

The authors express their thanks to Mira Milosavljevic for her expert assistance in preparing the histologic sections and to Loretta Dalaskey and Judy O’Neill for secretarial assistance.

References

9. Jones SB, Euler DE, Hardie E, Randall WC, Brynjolfsson G:
14. Flack M: Investigation of the sino-auricular node of the mammalian heart. J Physiol (Lond) 41: 64, 1910
Cardiac arrhythmias after chronic embolization of the sinus node artery: alterations in parasympathetic pacemaker control.
J M Loeb, D E Euler, W C Randall, J F Moran and G Brynjolfsson

Circulation. 1980;61:192-198
doi: 10.1161/01.CIR.61.1.192

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 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/61/1/192

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/