Effects of Ouabain and Vagal Stimulation on Sinus Nodal Function in Conscious Dogs

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SUMMARY. We studied the effects of intravenous ouabain administration (15 μg/kg) and vagal stimulation on instrumented conscious dogs. In these dogs, a special electrode was implanted on the epicardial surface over the sinus node and plaque electrodes were placed on the superior vena cava and left atrial appendage. Unipolar sinus electrograms were recorded through the terminals of the sinus electrode paired with the superior vena caval electrode. An electrode also was implanted around the desheathed cervical vagosympathetic trunk, and a coiled polyethylene tube with side holes was implanted cranial to it. Ouabain administration resulted in: (1) an increase in the sinus cycle lengths and sinoatrial intervals and increase in beat-to-beat variation of the sinus cycles and sinoatrial intervals, and (2) periods of sinus pacemaker shift, sinus arrest and sinoatrial block that occurred spontaneously or after atrial overdrive stimulation delivered through the electrode on the left atrial appendage. These effects of ouabain were abolished by intravenous administration of atropine (2 mg). Prior to vagal stimulation, intravenous propranolol (0.5 mg/kg) was administered to block sympathetic responses and 0.75% bupivacaine was injected through the polyethylene tube to block afferent transmission. Vagal stimulation in conscious dogs resulted in two types of responses: (1) slowing of sinus pacemaker rate accompanied by a decrease in diastolic slope and followed by sinus pacemaker shifts, and (2) gradual prolongation of the sinoatrial intervals followed by failure of sinoatrial conduction. An intravenous bolus of acetylcholine (0.1 mg) resulted in a response of type 2 in dogs in which vagal stimulation produced a response of type 1. The marked similarity between the effects of ouabain and vagal stimulation on sinus function and the abolition of the effects of ouabain by atropine suggest that the ouabain effects are vagally mediated. (Circ Res 51: 760-768, 1982)

THE regulation of impulse generation by the in situ mammalian sinus node until recently has been studied by noting changes in atrial activity during sinus rhythm or when atrial activity is perturbed by electrical stimulation. This approach is not satisfactory because changes in the interval between P waves can result either from changes in the rate of impulse generation by the sinus node pacemaker or from alterations in impulse conduction from the pacemaker to the atrium. A change in sinoatrial conduction time might result from a shift in the site of the pacemaker in the node, from a change in conduction velocity, or both. Recently, for example, Woods (Woods et al., 1981) recorded transmembrane potentials from the isolated canine right atrium and sinus node and showed that injection of acetylcholine into the sinus node artery causes transient arrest of impulse generation and more persistent block of sinoatrial conduction. We developed a method to record sinus node potentials through extracellular electrodes chronically implanted on the canine heart (Cramer et al., 1978; Hariman et al., 1980) and have shown that the unipolar electrogram recorded from the sinus node region can be used to identify the pacemaker activity in the node and to measure the interval between spontaneous impulse generation in the node and the onset of atrial activity. We now have used these methods to study the effects of changes in vagal activity on impulse generation and conduction. We administered ouabain to conscious dogs to enhance vagal tone and accentuate beat-to-beat changes in sinus node activity. Also, we developed a method which enabled us to stimulate the cervical vagus in the conscious dog and compare the effects of acetylcholine liberated from the nerve terminals to the effects of injected acetylcholine. We have obtained data indicating the changes in atrial rate consequent to vagal activity may result primarily from a change in the rate of impulse generation, usually accompanied by a shift in the location of the pacemaker, or can be due primarily to block of sinoatrial impulse transmission. Our findings for ouabain indicate that most of its effects on sinus node activity are mediated vagally.

Methods

Animal Model

We studied 10 healthy dogs weighing 20-25 kg. Each dog was anesthetized with sodium pentobarbital, 30 mg/kg, iv. The heart was exposed through a right thoracotomy. A sinus nodal electrode 16.5 by 4.5 mm and containing 48 silver terminals was implanted on the epicardium over the sinus node and an indifferent electrode on the superior vena cava. A plaque electrode containing five contacts was implanted on the left atrial appendage. Electrocardiographic
electrodes (Beckman) were implanted in the subcutaneous tissue over the sternum and the spine at the level of the 3rd thoracic vertebra. The details of the sinus nodal, plaque, and electrocardiographic electrodes and the method of implantation have been described (Hariman et al., 1980). At intervals up to 7 days after implantation of the cardiac electrodes, each of five dogs was anesthetized as before, and a midline or lateral cervical incision was made. The right and/or the left vago-sympathetic trunk was separated from the common carotid artery and about 5 cm of the nerve was desheathed. A nerve electrode (Avery) used to stimulate the phrenic nerve in patients with phrenic nerve paralysis was implanted over the caudal part of the desheathed nerve (Fig. 1). Cranial to the nerve electrode, a coiled polyethylene tube with side holes was implanted around the desheathed nerve trunk. The wires from the sinus, plaque, electrocardiographic, and nerve electrodes and the polyethylene tube were externalized through Teflon skin buttons implanted on the scapulae. The animals were given intramuscular oxacillin (1 g/day) and gentamycin (40 mg/day) from the time of the implantation of the cardiac electrodes until about 7 days after the implantation of the nerve electrode.

Experimental Protocol

Data collection was started when "sinus arrhythmia" reappeared, usually about 3 days after implantation of either the cardiac electrodes or the nerve electrode. The dogs were allowed to become accustomed to the experimental conditions through repeated exposure to the laboratory. The dogs were studied while they were resting comfortably on a sling. Unipolar sinus electrograms, a bipolar high right atrial electrogram, and one lead of the electrocardiogram were monitored and recorded simultaneously as we have described earlier (Hariman et al., 1980). Atrial pacing through the left atrial plaque electrode was accomplished by means of a programmed digital stimulator capable of delivering rectangular pulses 2.0 msec in duration and at a minimum current strength which allowed reliable atrial capture. Ouabain (15 /ig/kg) was administered intravenously over a period of 30 minutes. Data were collected before, during, and for 30 minutes after ouabain administration during spontaneous rhythm or during and immediately after atrial pacing. In two dogs observed for more than 2 hours after ouabain injection, we found that maximum changes in sinus electrograms occurred within less than 30 minutes after ouabain administration. An intravenous bolus of atropine (2 mg) then was given and data collection was continued for another period of 30 minutes.

In dogs with implanted nerve electrodes, vagal stimulation was achieved with a Grass stimulator set at a frequency of about 50 Hz, with a pulsewidth of 1 msec; voltage was gradually increased from 0.1 to 20 V. In three dogs, 30- to 50-msec trains of submaximal stimuli consisting of 1-msec pulses at a frequency of 50 Hz were delivered during various parts of the sinus cycle at intervals of about every 20 beats. Prior to vagal stimulation, intravenous propranolol (0.5 mg/kg) was administered over 10 minutes to block sympathetic responses during the stimulation, and 0.75% bupivacaine HCl was injected through the coiled tube (0.5 to 2 ml) to block afferent transmission. Vagal stimulation could be accomplished for periods ranging from 3 to 28 days after the implantation of the nerve electrode without any indication that it caused the dog discomfort.

Statistical Analysis

We used analysis of variance for single-factor experiments having repeated measures (Winer, 1971) to analyze the average values of 100 consecutive sinus cycle lengths and sinoatrial intervals at various treatment points. When significant differences were detected among the treatment groups, Duncan's multiple range test was applied to compare individual means. The differences were considered significant when P values were <0.05. All data are reported as mean ± SD.

Results

Effects of Ouabain on the Sinus Cycles, Sinoatrial Intervals, and Sinus Pacemaker Sites

In all dogs, intravenous ouabain (15 /ig/kg) caused slowing of the sinus pacemaker rate, prolongation of sinoatrial intervals, and an increase in beat-to-beat changes in the sinus cycles and sinoatrial intervals. Figure 2 shows an example of this recorded from a conscious dog. During control conditions (Fig. 2A), the sinus cycles (Hariman et al., 1980) measured from sinus nodal electrograms recorded from sites 4, 7, and 8 all averaged 580 msec, and the sinoatrial intervals (Hariman et al., 1980) measured from sinus nodal electrograms from sites 4, 7, and 8 averaged 80, 110,
In each dog, ouabain increased the average sinus cycle length and the standard deviation. This increase in standard deviation indicates an increase in beat-to-beat variability of the sinus cycle. Intravenous atropine given after the ouabain administration caused a decrease in the average sinus cycle values and in the standard deviation, reflecting a decrease in beat-to-beat variability. We observed similar effects of ouabain and atropine on sinoatrial intervals in all dogs. The average values after ouabain show an increase accompanied by an increase in the standard deviation, indicating an increase in beat-to-beat variability. The effect of ouabain on the sinoatrial intervals was partly or completely abolished by atropine administration.

Statistical analysis of the data points in Figure 3 showed a significant increase of the mean sinus cycle and 50 msec, respectively. After ouabain administration (Fig. 2B), the sinus cycles prolong to an average of 790 msec and the sinoatrial intervals to an average of 100 and 160 msec. Ouabain also increased the magnitude of beat-to-beat changes in the sinus cycles and sinoatrial intervals. For example, the first sinus cycle in Figure 2B is 1100 msec, markedly longer than the second sinus cycle, which is 750 msec. Similarly, the two first sinoatrial intervals in Figure 2B measured from the sinus nodal electrogram from site 7 are 190 and 170 msec, markedly longer than the next two sinoatrial intervals, which are 110 and 130 msec. Intravenous atropine abolished these effects of ouabain. In Figure 2C, the sinus cycles after atropine administration average 520 msec, shorter than control values, and sinoatrial intervals measured from tracings recorded from sites 4, 7, and 8 average 80, 100, and 70 msec; all these intervals are close to control values.

Figure 3 shows a graphic representation of the mean ± so of 100 consecutive sinus cycle lengths and sinoatrial intervals for each of the six conscious dogs studied during control conditions, after intravenous ouabain, and after intravenous ouabain and atropine.
length after ouabain (958.5 ± 143.6 msec) compared to control (689.0 ± 154.9 msec) and a significant decrease after atropine (708.8 ± 96.1 msec) compared to the mean value after ouabain administration. No statistical difference was found between the mean values of the sinus cycle lengths and sinoatrial intervals during control conditions and after both ouabain and atropine administration.

We noted periods of sinus arrest, failure of sinoatrial conduction, and sinus pacemaker shifts during and after ouabain administration (Table 1). Figure 4 shows an example of this phenomenon. Prior to ouabain administration, diastolic and upstroke slopes are recorded from one recording site (Fig. 4A). The sinus cycles and sinoatrial intervals are relatively constant at about 420 and 55 msec, respectively. After ouabain administration (Fig. 4B), the dog shows episodes of atrioventricular arrest lasting up to 1300 msec (arrow), during which no sinus, atrial, or ventricular activity is recorded. During some of these episodes, a sinus potential not followed by atrial activity (arrow-Fig. 4C) was recorded through the sinus electrode. Frequently, sinus potentials recorded under these conditions were of low amplitude (arrow-Fig. 4C), suggesting that a decrease in the amplitude of the transmembrane action potential might be the cause of the failure of sinoatrial conduction. Following the diminutive sinus potential in Figure 4C (arrow), a larger sinus potential is followed by atrial activity, although with a sinoatrial interval of 125 msec, longer than the control interval. The sinus nodal electrogram for the last beat in Figure 4C shows only a diastolic slope, followed by a rapid positive-going deflection, suggesting that a sinus pacemaker shift has occurred for this beat (Hariman et al., 1980).

Ouabain-induced sinus arrest, sinoatrial block, and sinus pacemaker shifts also were abolished by atropine in dogs to which this drug was administered. Figure 5 shows another example of ouabain-induced failure of sino-atrial conduction. In Figure 5B, after ouabain administration, there is atrioventricular arrest lasting 1350 msec. During this time, a sinus potential is recorded (arrow). In contrast to the diminutive sinus potential in Figure 4C, the sinus potential (arrow Fig. 5B) that fails to conduct to the atria is of normal amplitude, compared to the other sinus potentials in the sinus nodal electrograms. In Figure 5C, after atropine, sinus rate is faster, the sinoatrial intervals are shorter, and no failure of sinoatrial conduction is seen.

Periods of failure of sinoatrial conduction also could be elicited in three dogs following premature atrial stimulation or atrial overdrive. Figure 6 shows an example of this phenomenon in the dog from which the records in Figure 5 were obtained. During control conditions, atrial stimuli delivered at a cycle length of 200 msec for 30 seconds are followed by a rapidly returning sinus rhythm and no failure of sinoatrial conduction. After ouabain administration (Fig. 6B), similar atrial stimuli result in a long atrioventricular arrest of about 1300 msec. During this interval, a sinus potential (arrow) fails to conduct to the atria. Figure 6C shows that—after atropine administration—the long atrioventricular arrest, due to failure of sinoatrial conduction, no longer can be induced by atrial stimulation.

**Effects of Vagal Stimulation on the Sinus Cycles, Sinoatrial Intervals, and Sinus Pacemaker Sites**

Vagal stimulation in conscious dogs conducted on days on which ouabain was not administered, in general, produced changes similar to those produced by intravenous ouabain (Table 1). There were dog-to-dog differences in the effects of vagal stimulation on sinus function in the five conscious dogs studied. The

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**TABLE 1**

Sinoatrial Block, Sinus Arrest, and Sinus Pacemaker Shift Induced by Ouabain, Vagal Stimulation, or Acetylcholine
responses of the sinus node to vagal stimulation were of two types. Each dog exhibited only one of the two types of response in experiments on successive days. The first, seen in three dogs (Table 1), consists of slowing of sinus pacemaker firing rate accompanied by a decrease in diastolic slope and followed by a sinus pacemaker shift. Figure 7 shows an example of this response. During control (Fig. 7A), a diastolic slope and an upstroke slope are recorded only from sites 2 and 3 of the sinus electrode and precede primary negativity and the P waves. The sinus cycle is 420 msec and the sinoatrial interval 35 msec. During mild stimulation delivered to the right vagal trunk (Fig. 7B), the sinus cycle prolongs to 525 msec but the sinoatrial interval remains at 35 msec, similar to the control value. The slowing of the sinus rate is accomplished by a decrease in the diastolic slope. More intense vagal stimulation (Fig. 7C) results in further slowing of the sinus rate (sinus cycle prolongs to 630 msec), accompanied by a further decrease in the diastolic slope and only slight prolongation of the sinoatrial interval to 45 msec. Further increase in vagal stimulation (Fig. 7D) results in further slowing of the heart rate and disappearance of the previously recorded upstroke slope in traces from sites 2 and 3. This is suggestive of a sinus pacemaker shift, away from sites 2 and 3. Figure 7E shows that, during more intense vagal stimulation, resulting in further slowing of the heart, an upstroke slope now is recorded from site 9 of the sinus electrode. During control conditions, a trace recorded from site 9 did not show any upstroke slope. Thus, during intense vagal stimulation in this dog, the sinus pacemaker shifted from sites 2 and 3 to site 9; this represents a caudal shift of the sinus pacemaker. Similar caudal shift of the sinus pacemaker was observed in two other experiments.

The second type of sinus nodal response during vagal stimulation is characterized by prolongation of the sinoatrial intervals and failure of sinoatrial conduction. This response was seen in two dogs (Table 1). An example of this response can be seen in Figure 8. In Figure 8A, a short burst of stimuli delivered to the right vagus nerve is followed by an atrioventric-
ular arrest. During this episode, sinus potentials can be recorded; these sinus potentials are of slightly lower amplitude than those before vagal stimulation. The sinus potentials terminating the arrest are of normal amplitudes, but the sinoatrial intervals—measured in the traces from sites 8, 12, and 16 for these sinus potentials—are 90, 120, and 90 msec, longer than the sinoatrial intervals for the beats before vagal stimulation, which average 75, 80, and 70 msec. In Figure 8B, a longer train of vagal stimulation (VS) results in a longer period of atrioventricular arrest, during which two low amplitude sinus potentials fail to cause atrial depolarizations. The sinus potentials of normal amplitude which terminate the atrioventricular arrest are followed by atrial activity after sinoatrial intervals of 110, 180, and 100 msec (measured from records from sites 8, 12, and 16), longer than sinoatrial intervals for the beats prior to vagal stimulation. It also can be seen in Figure 8, A and B, that there is a slowing of the atrial rate due to a decrease in the diastolic slope and pacemaker shift indicated by the disappearance of the upstroke slope and appearance of a rapid, positive-going deflection in the
FIGURE 9. The effects of stimulation of right (panel B) and left (panel C) vagus on the sinus cycle, diastolic slope, and sinus pacemaker site. Panel A is the control. Thick lines indicate vagal stimulation. Abbreviations and calibration are as in Figure 2. See text for details.

sinus nodal electrogram. Figure 9C shows a similar response when the left vagus is stimulated. Again, a decrease in the diastolic slope and disappearance of the upstroke slope in the sinus nodal electrogram can be seen during vagal stimulation (thick line). In Figure 9, B and C, the observed effects of vagal stimulation persist for up to 2 seconds after the end of stimulation.

Intravenous bolus injection of acetylcholine (0.1 mg) resulted in the second type of response in two dogs in which vagal stimulation produced the first type of response (Table 1). Figure 10 shows an example of the dog in which we observed the first type of response to vagal stimulation (Fig. 9). After injection of acetylcholine, a continuous trace of the sinus nodal electrograms (Fig. 10, B and C) reveals prolongation of the sinoatrial intervals and failure of sino-atrial and atrioventricular conduction. These changes are more prominent than the slowing in the sinus rate.

When submaximal trains of vagal stimuli were delivered during various parts of the sinus cycle, different degrees of prolongation of the sinus cycles and sinoatrial intervals were noted. Figure 11 shows an example of this phenomenon in the dog from which the records in Figure 8 were obtained. In panel A, a 30-msec train of vagal stimuli (arrow) delivered early enough in the sinus cycle (sinus potential to vagal stimuli interval is 250 msec) prolongs the cycle from 525 msec under control conditions to 570 msec, and the sinoatrial interval, from 110 to 130 msec (all these values are measured for the trace from site 12). These changes also can be seen for the following sinus cycle and sinoatrial interval for the following sinus beat (the sinus cycle remains prolonged at 560 msec and sinoatrial interval at 120 msec). In panel B, a train of vagal stimuli (arrow) delivered late in the sinus cycle (sinus potential to vagal stimulation interval is 480 msec) produces no change in the sinus cycle encompassing the stimuli or the sinoatrial interval immediately after the stimuli, but prolongation in the following sinus cycle and sinoatrial interval (the sinus cycle lengthens to 540 msec and sinoatrial interval to 120 msec).

Figure 12 shows the correlation between the intervals between sinus potentials and vagal stimuli and the sinoatrial intervals immediately following the stimuli. Data are from the same dog from which the records in Figure 11 were obtained. Trains of submaximal vagal stimuli delivered progressively later in

FIGURE 10. The effects of intravenous acetylcholine injection in the dog, from which the records in Figure 9 were obtained. Panel A is the control, panels B and C are continuous records following an intravenous bolus of acetylcholine (0.1 mg) given at the arrow. Abbreviations and calibration are as in Figure 2. See text for details.

FIGURE 11. The effect of submaximal trains of vagal stimuli delivered at various times during the sinus cycle on the sinus cycle lengths (S-S) and sinoatrial intervals (SAI) in the dog from which the records in Figure 8 were obtained. The numbers (in msec) indicate the sinus cycle lengths and sinoatrial intervals in msec, measured for the trace from site 12. Arrows indicate trains of vagal stimuli. Other abbreviations and calibration are as in Figure 2. See text for details.
the sinus cycles and sinoatrial intervals, induced by ouabain are primarily vagally mediated. The beat-to-beat variability suggests that the vagal impulses tend to occur in bursts (Jewett, 1964; Katona et al., 1970; Kunze, 1972). Ouabain also causes periods of sudden failure of sinoatrial conduction and sinus arrest, which are abolished by atropine and enhanced by atrial overdrive. Atrial overdrive may induce a baroreceptor reflex by increasing the ventricular rate; this reflex is known to be sensitized by ouabain.

The failure of sinoatrial conduction can be explained by two mechanisms (Woods et al., 1981). First, failure of sinoatrial conduction can occur if impulse generation in the sinus nodal pacemaker is impaired, i.e., the amplitude of the sinus pacemaker potential is reduced (Fig. 4C) so that it is unable to cause excitation of the surrounding tissue (Scherf, 1969). A more marked effect of vagal activity on sinus pacemaker impulse formation results in abolition of the sinus pacemaker potential (sinus arrest-Fig. 4B). Second, failure of sinoatrial conduction is expected to occur if impulse formation in the sinus pacemaker is maintained but the sinus nodal fibers around the pacemaker undergo changes in excitability and passive electrical properties that cause decremental conduction out of the sinus nodal pacemaker and block of impulse propagation. This, in turn, is responsible for the failure of sinoatrial conduction. This type of failure of sinoatrial conduction is exemplified in Figure 5B, which shows that there is no demonstrable reduction in the amplitude of the sinus potential (arrow) which fails to propagate to the atria.

Thus, it seems that the first cause of failure of sinoatrial conduction and sinus arrest noted above is associated with a relatively more intense vagal effect on fibers of the sinus pacemaker, whereas the second cause of failure of sinoatrial conduction is due to a relatively more intense vagal effect on fibers around the sinus pacemaker site. The different causes for failure of sinoatrial conduction may be explained by differences in sensitivities of various sinus nodal fibers to acetylcholine (Hoffman, 1977) and/or by local differences in density of vagal innervation in various dogs. We believe that the latter is the more likely explanation, since day-to-day experiments for each of the conscious dogs with ouabain-induced failure of sinoatrial conduction exhibited only one of the two mechanisms that can cause failure of sinoatrial conduction. Further support for this belief is provided by the results of vagal stimulation and acetylcholine injection, which are discussed below.

The effect of vagal stimulation on the transmembrane action potentials in the sinus node has been studied in isolated right atrium of rabbit hearts (Bowman et al., 1968). Our study performed in conscious dogs allowed us not only to verify the findings reported by Bowman et al., but also to observe the day-to-day variability in responses to vagal stimulation and to compare these responses to the responses to ouabain and acetylcholine administration. Vagal stimulation in some conscious dogs resulted in prolonga-
tion of the sinus cycles which was associated with a decrease in diastolic slope and followed by a shift in the sinus pacemaker site (first type of response); in other dogs, vagal stimulation resulted in prolongation of the sinoatrial intervals and failure of sinoatrial conduction (second type of response). The marked similarity between sinus nodal responses to vagal stimulation and the observed effects of ouabain administration supports the concept that the effects of ouabain are vagally mediated.

The two types of responses observed in different dogs during vagal stimulation are also somewhat similar to the two types of effects of ouabain in different dogs. Those responses again can be explained by different sensitivities of sinus nodal cells to acetylcholine released during vagal stimulation or by different densities in various areas of the sinus node at both pacemaker and nonpacemaker sites. Since responses observed after acetylcholine injection differed from those during vagal stimulation (Figs. 9 and 10), the latter is probably the more likely explanation.

Consistent with the results of Levy et al. (1969, 1970, 1972, 1978), the vagal effects on the sinus node persist for up to 2.0 seconds after the end of vagal stimulation. This can be explained by the time necessary for the chemical breakdown of acetylcholine by acetylcholine esterase. We observed also a "latent" period at the end of the sinus cycle, during which a train of vagal stimuli did not alter the sinus cycle encompassing the vagal stimuli or the sinoatrial interval of the oncoming sinus beat (Levy et al., 1969, 1970, 1972; Stuesse et al., 1978; Jalife and Moe, 1979). This latent period just before the oncoming sinus potential probably represents the already activated inward current responsible for the sinus potential, which is much stronger than the enhancement of the outward current activated by vagal stimulation (Jalife and Moe, 1979). The latent period also in part may represent the time needed for the release of acetylcholine from vagal terminals and for its action on the sinus nodal cells (Stuesse et al., 1978). The latent period may also represent the delay of muscarinic response that has been observed when acetylcholine is applied ionophoretically to a sinus node preparation (Hill-Smith and Purves, 1978; Osterrieder et al., 1981). This delay has been estimated to be more than 30 msec and could be as long as about 100 msec.

The use of direct records of sinus node electrograms to study sinus node activity in the in situ heart should help to clarify the mechanisms responsible for alterations in human sinus node activity after the administration of drugs and as a result of disease.

References


INDEX TERMS: Sinus node • Vagus • Acetylcholine • Sinus electrogram

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