Reducing Heart Rate of the Dog by Electrical Stimulation

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The heart rate can be controlled by an electrical pacemaker when its frequency of stimulation is greater than that inherent in the heart. However, no method has been described, to our knowledge, by which a rapidly beating heart may be slowed by means of repetitive electrical impulses applied to the heart. The commercial pacemakers available for clinical application generate d-c electrical impulses with a duration of about 3 msec. Although the voltage and frequency of the impulses can be changed within certain limits, the duration of the impulses is kept constant. While studying the control of heart rate in dogs by means of an intracardiac electrical pacemaker, we found that the frequency of effective ventricular contractions, namely those that produced an arterial pulse or at least a clearly visible ventricular pulse, could be reduced by almost 50% by increasing appropriately the duration of the electrical impulse of the artificial pacemaker. It was soon determined that this effect was due to proper spacing between the make and break of the repetitive impulses. Electrotonus was not involved in the change of ventricular rate. This decrease of the frequency of effective ventricular contractions could be reproduced with pairs of impulses, each 3 msec in duration, when the two impulses of the pair were properly spaced. A decrease in ventricular frequency could also be induced when the interval between break and make of successive long impulses fell in an appropriate range; in which case it was the break that became the first and the make the second stimulus—just the reverse of the usual sequence when long impulses were used.

This finding was subjected to repeated tests in dogs with sinus rhythm and in several animals with experimentally produced arrhythmias. It was studied also in one patient with Stokes-Adams attacks due to intermittent A-V block, who had an intracardiac electrode catheter introduced to pace the heart. Our observations and a discussion of the mechanisms by which this reduction of heart rate is produced are the subjects of this communication.

I. Ventricular Stimulation

Methods

Thirteen dogs, weighing 18 to 23 kg and anesthetized with pentobarbital (20 to 25 mg/kg iv), were used for these experiments. Unipolar right atrial intracavitary electrocardiograms (RA ECG), right atrial (RA), and right (RV) and left ventricular (LV) pressures were recorded simultaneously by catheters. The catheters in the right atrium and ventricle were introduced via the jugular vein; the one in the left ventricle was introduced via a femoral artery. A thoracotomy was performed after the catheters were in place and intermittent positive pressure breathing was maintained throughout the entire procedure. A pericardiotomy was then done and a pair of platinum electrodes was hooked into the free wall of the right ventricle for stimulation by the artificial pacemaker. In some dogs the left atrium (LA) was cannulated after the chest had been opened and left atrial pressure was also recorded.

Electrocardiograms and pressures were recorded by a Sanborn multichannel direct-writer (14 channel model 350). The pacemaker was activated by a Grass, model S4C, impulse generator.
REDUCTION OF HEART RATE

In 11 dogs the ventricles were stimulated by long repetitive impulses (fig. 1, upper diagram). The voltage of the pacemaker was kept constant at two volts but the frequency and duration of the impulses were varied. The artificial electrical impulses were started at a frequency just below the inherent heart rate and then the durations of the repetitive impulses were varied between 3 and 500 msec in order to determine the range of impulse duration through which the pacemaker maintained complete control of effective ventricular contractions. This procedure was repeated as the frequency of the artificial pacemaker was reduced by decrements of 10 to 20 beats/min until a frequency was reached at which the control of effective ventricular contractions was incomplete at all impulse durations used.

In three dogs pairs of impulses each 3 msec in duration were used to stimulate the ventricles (fig. 1, lower diagram). In this case the frequency of the pairs of impulses was varied and also, at each frequency, the interval (from 3 to 500 msec) between the two impulses of the pair. In two of the dogs long impulses had been employed previously, in the third only pairs of short impulses were used.

With the long impulses, the artifacts produced consisted of a sharp deflection at the make and an oppositely directed one at the break. In the case of pairs of 3 msec impulses, the artifacts, one for each impulse, were diphasic. Figure 2 shows the manner of identifying the P and QRS complexes despite the distortion produced by the stimuli.

A fourteenth dog was used to check the effectiveness of the artificial pacemaker over a 24-hour period. Two days before the experiment a pair of platinum electrodes was implanted, under aseptic precautions and during anesthesia, in the right ventricle of the dog through a thoracotomy. Wires were attached to these electrodes and the other ends of the wires were passed out of the chest paraspastically near the neck for connection to the Grass pacemaker. The chest was then closed, the pneumothorax relieved, normal respiration re instituted, and the animal permitted to recover. On the day of the experiment, the dog was placed in a Pavlov pouch and a catheter was inserted into the right ventricle via the jugular vein (under local anesthesia) for pressure recording. The Grass pacemaker was then adjusted to control the effective beating of the ventricles at a frequency below that of the inherent rate of the heart. Long impulses were used. The artificial pacemaker was temporarily disconnected until the dog was moved into a cage. The pacemaker was then reconnected to the wires in such a way, by means of a pulley and weight, that the animal could move around the cage. The effectiveness of the artificial pacemaker was checked at intervals by means of a limb-lead electrocardiogram and by palpation of the femoral pulse.

**FIGURE 1**

Upper portion is a diagram of long impulses used. The interval between impulses (make to make) is 600 msec, corresponding to a rate of 100/min. The duration of the impulse (make to break) is 150 msec. Lower portion is a diagram of pairs of short impulses used, each being 3 msec in duration. The paired impulses occur at a rate of 100/min (interval between pairs is 600 msec). The interval between the two impulses of each pair is 150 msec.

**FIGURE 2**

Record illustrates the method of distinguishing the ventricular response from stimulus artifact. The stimulating electrodes were on the right ventricle and the unipolar recording electrode in the right atrium. The make and break of each long electrical impulse are represented, respectively, by upward and downward deflection artifacts (unshaded and unlabelled). Each is followed by a downward deflection (two are shaded), the QRS complex. The P waves of sinus node origin (three are labelled), are equally spaced (rate 100/min) and independent of QRS. There is complete A-V dissociation. The rate of the electrical impulses is 120/min, with make and break 180 msec apart.
FIGURE 3
Record illustrates transition in control after electrical pacemaker was started. Simultaneous tracings are of the unipolar intracavitary right atrial electrocardiogram (RA ECG), right atrial (RA) and right (RV) and left ventricular (LV) cavity pressures, before and after stimulation of right ventricle with long impulses, 200 msec in duration, at a rate of 96/min. The pressure scales on left are in mm Hg. The frequency of the effective ventricular contractions is shown below tracing (beats/min). Discussed in text.

Results
Three types of responses to electrical stimuli were seen in these experiments (fig. 3): a) electrical stimuli not followed by any response of the ventricle, electrical or mechanical (first artificial stimulus of fig. 3); b) electrical stimuli followed only by an electrical response of the heart (QRST) without evidence of an effective ventricular contraction (second stimulus of each pair in fig. 3); and c) electrical stimuli followed by both an electrical response and an effective ventricu-
The sinus rates in these dogs ranged from 96 to 200/min. In 6 of the 13 dogs studied, the rate of effective ventricular contractions was reduced 45 to 50% of the control rates. This reduction of heart rate was maintained as long as the frequency and duration of the long impulses (or the frequency of the pairs of short ones and the interval between the two impulses of the pair) were unchanged. In the fourteenth dog, the reduced effective ventricular contraction frequency was maintained for 24 hours.

Such complete control was not obtained when the duration of the long impulse, or the time interval between the two impulses of a pair, was below 150 msec or above 360 msec. Most commonly, complete control was obtained when the interval was between 200
and 240 msec (fig. 4). The control became incomplete when the interval fell below the critical value (usually 150 msec). In such cases the slow ventricular rate was interrupted periodically by groups of more rapid beats.

Lengthening the interval between two stimuli of a pair without changing the rate of the artificial pacemaker led to loss of control of the frequency of effective ventricular contractions by the pacemaker. However, on lengthening still further the interval between the two stimuli of a pair, a certain critical duration range was reached during which the pacemaker once again regained complete control.

Figure 3 shows the events leading to control of the heart by the electrical pacemaker. The first three beats in the RA ECG were normally conducted sinus impulses. Large negative P waves were followed at a constant P-R interval by normal, mainly downward directed, QRS complexes (the typical appearance of a right atrial intracavitary electrocardiogram). Immediately after the third normally conducted sinus beat, the artificial electrical impulse started at the time of QRS (the stimulus artifacts are readily identified). The first was ineffective, the second initiated a QRS (see fig. 2) but the sinus impulse controlled the atria (interference). The third stimulus was again ineffective; the fourth behaved like the second. The effectiveness of the pacemaker in reducing the frequency of the ventricular contractions is clearly seen in the ventricular pressure pulse tracings. Only the first of each pair of artificial stimuli resulted in an effective ventricular contraction. The second, if it caused a mechanical response of the ventricles, produced no discernible pressure pulse in the left ventricle, but could be responsible for the small positive wave following the diastolic dip in the right ventricle.

Figure 4 shows the effect of varying impulse duration at a constant frequency of the electrical pacemaker. When impulse duration was 200 msec, the frequency of effective ventricular contractions was reduced to 96/min from the control rate of 176. As in figure 3, it was the make (upwardly directed stimulus artifact) which was effective. The break (downwardly directed stimulus artifact), on the other hand, although followed by QRS, did not produce an effective ventricular contraction. When the impulse duration was 260 msec, a definite premature ventricular contraction due to the break followed the effective ventricular response of the make. When the impulse duration was 320 msec both the make and the break (which were separated from each other by 320 and 300 msec respectively) produced equally effective ventricular contractions with a net rate of 192/min. When the impulse duration was lengthened to 360 msec, the frequency of completely effective ventricular contractions was again 96/min, with every effective ventricular contraction followed by a smaller premature ventricular contraction, as in the case when the impulse duration was 260 msec. However, in this instance it was the break and not the make which produced the effective ventricular contractions.

It is thus apparent that the reduction of the frequency of the effective ventricular contractions depends upon a proper timing of the two stimuli of the pair such that the second is premature. The second stimulus of each pair may or may not stimulate the ventricles. When it does, it must do so early enough after the first so as to activate the ventricles before they can fill adequately or even begin to fill. In this way, only one of the two stimuli gives rise to an effective ventricular contraction, thus reducing the frequency of such beats. In these experiments the sinus node control of the ventricles was prevented because the pair of stimuli: 1) kept the sinus node suppressed, or 2) caused complete S-A dissociation, or 3) caused complete A-V dissociation.

Figure 5 shows an experiment in which the sinus node was prevented from controlling the ventricles because of a complete A-V dissociation as illustrated in the diagram. Every artificial electrical impulse penetrated into the A-V junction (concealed retrograde conduction) and prevented the sinus heat.
Record illustrates one of the mechanisms involved in reducing the frequency of effective ventricular contractions. Pairs of impulses of short duration (3 msec), 200 msec apart, were used. The sinus node rate was 167/min, the artificial ventricular pacemaker, 120/min. Diagram between two tracings shows interrelation of electric events. A is atrial activation by sinus node (vertical lines); A-V, conduction in A-V junction (oblique lines); V, ventricular activation (vertical lines); shorter ones are sinus in origin; longer ones, artificial pacemaker. Failure of impulse to traverse A-V function is indicated by small horizontal bar at end of oblique line. Paper speed is twice as fast as in figures 3 and 4. Other conventions as in figure 3. Discussed in text.

from activating the ventricles by keeping the A-V junction continuously unresponsive. The artificial pacemaker in this case quickly took over control of the effective ventricular contractions at its reduced rate because the second ventricular stimulus of the pair occurred so early that the ventricles did not fill sufficiently to cause an effective contraction of the following beat.

The mechanism of the transition from sinus rhythm to artificial pacemaker control is clear in figure 5. The first two complexes of the RA ECG were sinus beats, with large inverted P waves followed by normal QRS complexes at a constant P-R interval. After the second beat a single electrical stimulus artifact occurred and was followed by a succession of pairs of stimulus artifacts. The P waves were equally spaced at a rate of 167/min but none of them led to QRS complexes after the artificial pacemaker started. Each artificial stimulus was followed by a QRS (the small polyphasic deflections). All the effective ventricular contractions (with one exception) after the artificial pacemaker started were due to the first of the pair of stimuli, the second being ineffective or possibly causing the tiny upward pressure wave after the diastolic dip. The exception was the first small premature left ventricular contraction caused by the single artificial stimulus. Further support for the mechanism of A-V dissociation is shown in figure 6 where the A-V dissociation was incomplete. The frequency of the major ventricular contractions was reduced from 158/min to 103/min after the artificial pacemaker was started. Each major ventricular contraction was followed by a small premature ineffective ventricular contraction and, in addition, the spacing between major ventricular contractions was not precisely regular. Thus, the sixth, eighth, and tenth major ventricular contractions were slightly premature and yet, despite this, were
FIGURE 6

Record illustrates incomplete A-V dissociation induced by artificial ventricular pacemaker. Pairs of impulses used were 180 msec apart (rate 103/min) compared with sinus rate of 158/min. Conventions as in figure 5. Broken vertical lines at V level of diagram indicate electrical impulses not followed by electrical response of the ventricles because of capture by sinus impulse. Discussed in text.

of greater amplitude than the others. The change in amplitude probably was due to a "treppe" phenomenon.7 The prematurity of these beats was due to the fact that the seventh, tenth, and thirteenth sinus impulses were conducted and "captured" the ventricles. Hence this was incomplete A-V dissociation. Furthermore, examination of the P-R interval of these conducted beats (see diagram) shows that the seventh sinus impulse has a normal P-R interval (0.10 sec) equal to that of the first and second sinus impulses, but the tenth and the thirteenth sinus impulses are conducted more slowly so that their P-R intervals are prolonged (to 0.12 and 0.14, respectively). Since all the P waves were equally spaced, the only explanation for this prolongation of the P-R interval must be the retrograde penetration of the preceding artificial ventricular stimulus into the A-V junction (concealed retrograde conduction8). In these two conducted beats, the artificial impulse which follows fell in the ventricular refractory period and so did not stimulate the ventricles. The seventh ventricular beat, which is considered to be a sinus capture, followed an artificial stimulus by the usual interval. Apparently the capture of the ventricles by the sinus impulse occurred before the artificial stimulus (with its normal latency) could become effective. It is, however, possible that this beat is a fusion beat.

Figure 7 shows an experiment in which the ventricular contraction rate was reduced from 176 to 96/min by the artificial pacemaker, but in which the make and break of the artificial impulses not only penetrated into the A-V junction but also reached the atria causing retrograde stimulation of the latter. This represents either sinus pacemaker suppression or complete S-A dissociation. The second stimulus of each pair led to no apparent mechanical contraction, as in the left ventricle, or a very ineffective premature one, as in the right ventricle.

Figure 7 shows also the transition in control. After two normally conducted sinus beats the artificial pacemaker started stimulating the ventricles. Both the make and break of the first artificial impulse gave rise to small premature ventricular contractions in both ventricles, the second smaller than
FIGURE 7

Record, obtained from animal shown in figure 3 under similar conditions except that paper speed was faster, illustrates some of hemodynamic changes found in transition of control of heart from sinus node to artificial ventricular pacemaker. The effective ventricular contractions were reduced from 176 to 96 beats/min. In RA, a and v represent the A and V waves respectively; A, a giant A wave. Rest of conventions as in figure 3. Discussed in text.

The first atrial contraction after the artificial pacemaker started was due to the sinus impulse; it occurred at the expected time and not early as it would have been were it due to the make of the first artificial impulse. Thus, there was a sinus P wave buried in the first make artifact and it, and not the make, controlled the atrium at this time. Thereafter, every make and break gave rise to A waves. The P wave that followed the first break occurred at a time that a sinus P wave was expected, but P had a different contour; it represents a fusion P wave and was responsible for the fourth A wave.
normal P wave, occurring on time, followed immediately after the second make; it, and not the make, was responsible for the next large atrial contraction. The second break was followed by an early P wave of abnormal contour; it represents a retrograde P wave and was responsible for the small atrial contraction at this time. From then on, every make and break was followed not only by QRS complexes but by retrograde P waves (see diagram at the right of fig. 7). Hence, in this case the sinus node was suppressed, or, more likely, a persistent complete S-A dissociation was present which prevented the sinus node from controlling the heart.

Several ancillary phenomena are illustrated in figure 7. During artificial stimulation giant A waves appeared. These giant A waves, alternating with smaller A waves, occurred in those beats in which the atrial contraction took place during ventricular contraction. They represent isovolumic atrial contractions occurring when the A-V valves were closed. Both right and left ventricular pressures increased in amplitude during artificial pacemaker control because of the reduction of the rate which permitted a longer filling time and higher end diastolic volume (and pressure). Figure 7 also shows, as expected with stimulation of the right ventricle, that the electromechanical time interval is shorter in the right ventricle than in the left. This difference, amounting to 0.04 sec, is considered to represent the transseptal conduction time (from right to left). The value obtained coincides with that reported by Lewis for transseptal conduction.

II. Atrial Stimulation

Methods

In four dogs the stimulating electrodes were placed in the free wall of the right atrium instead of the right ventricle and stimulation carried out using an artificial pacemaker with long impulses.

Results

In only one dog were the ventricular contractions completely controlled by the artificial pacemaker and this occurred most commonly when the duration of the impulse was between 200 and 240 msec. The three instances of complete control by the artificial pacemaker developed in this dog at frequencies 67, 72 and 84% of the sinus rate when the impulse duration was 200 msec. A typical example is represented in the left panel of figure 8. Every make and break of the electrical impulse was followed by a P wave, and in turn by a QRS complex, both similar in contour to that seen before electrical stimulation was started. However, only the make produced an effective ventricular contraction; the break did not because it occurred before any significant filling of the ventricles could take place.

When the impulse duration was increased to 300 msec, as in the right panel of figure 8, both the make and the break were able to produce effective ventricular contractions and the frequency of ventricular contractions was increased above instead of reduced below the sinus rate. In the right hand panel the take over of the atria began with the break of the second artificial impulse. Thereafter, both make and break of the impulses stimulated the atria and gave rise to the enlarged A waves (because ventricular contractions due to the preceding stimulus occurred at these times). Both the make and break also produced effective ventricular contractions after the first four contractions which were of sinus origin. The first of these ectopic beats occurred early, and after that there was a transient alternans in both ventricles. Because the make and break of each impulse was effective in causing a ventricular contraction, the frequency of ventricular contraction increased.

The mechanism by which slowing is accomplished is shown in the left-hand panel of figure 8. The first three ventricular contractions, like the atrial contractions, were of sinus origin. The first artificial impulse started soon after the third sinus P wave. Its make and break gave rise to P waves, to atrial contractions, the fourth and fifth A waves, and to QRS complexes. The QRS of the make was not accompanied by any evidence of ventricular contraction but the QRS
Records show effect of changing duration of electrical impulse upon its ability to reduce rate of effective ventricular contractions. In left panel artificial atrial pacemaker was operating at a rate of 96/min with impulses 200 msec in duration. The sinus rate was 143/min. In diagram between top two tracings, shorter vertical line above top horizontal line represents a sinus impulse; long ones, artificial stimuli. Note progressive lengthening of S-A interval with each pair of stimuli. This applies also to P-R interval. In right panel impulse duration was increased to 300 msec while impulse frequency was left unchanged. Figures on top of two panels represent duration of artificial impulse in msec. Other conventions as in previous figures. Discussed in text.

of the break was. It caused the fourth ventricular contraction which was smaller than the others and was delayed. Thereafter, it was the make that caused effective ventricular contractions. The break, while leading to a QRS, did not lead to any evident ventricular contraction. Thus, each impulse gave rise to two atrial responses, two ventricular elec-
trical responses, but only one effective ventricular contraction (following the make).

During this study we had occasion to test the ability of an artificial pacemaker placed temporarily in the right atrium of a patient to reduce the ventricular frequency below that of the sinus rate. The result is shown in figure 9. The average sinus rate was 85/min. Every P wave was followed at a constant P-R interval by a QRS (with a left bundle branch block contour). After the third sinus beat, pairs of artificial impulses (3 msec in duration and 280 msec apart) were applied to the right atrium at a rate of 55/min. The artificial pacemaker took over control after the second pair of stimuli was applied. The first impulse of the pair thereafter produced a P wave followed by a QRS. The second impulse led to a P wave (superimposed on S-T) which was not followed by QRS because it came during the absolute refractory phase of the A-V junction. By this method the ventricular frequency was reduced. In this instance, therefore, not only was the frequency of effective contractions of the ventricles reduced but also the actual frequency of its electrical responses.

A similar reduction of the frequency of ventricular electrical responses did not accompany the reduction in frequency of effective ventricular contractions in the four dogs in which atrial stimulation was employed. In these dogs the break as well as the make led to a QRS even when it failed to produce an effective ventricular contraction. As a result the number of electrical responses of the ventricles rose while the frequency of effective ventricular contractions was reduced.

III. Effects of Ventricular Stimulation on Experimental Arrhythmias

Atrial flutter was produced in one dog by intravenous administration of 1 mg of atropine sulfate, followed by application of a brief rapid train of electrical stimuli to the right atrium. Flutter followed and the rate of atrial flutter so produced was 500/min while the ventricles responded at a rate of 250/min (fig. 10, left). The right ventricle was then stimulated artificially at various rates with impulses of 180 msec duration. It was found that the ventricular rate could be reduced to a range between 70 and 50% of its control value. Figure 10 presents a typical example. The rate of ventricular contractions was reduced from 250 to 175/min. The artificial pacemaker changed the mechanism from 2:1 A-V conduction to a complete A-V dissociation (see diagram). In this particular case it was the break that produced the effective ventricular contraction. The make did

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**FIGURE 9**

A continuous record (lead II) of the electrocardiogram of a patient. This patient had a pacemaker inserted intravenously to control Stokes-Adams attacks due to intermittent A-V block. The electrodes were temporarily moved into the right atrium when record was obtained. Arrows indicate beginning and end of artificial electrical stimulation of atrium. Rate of heart indicated above top tracing. Discussed in text.

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not because the contraction of the ventricles occurred before any significant filling could take place, although it was followed by an electrical response. The basic mechanism is identical to that described above for dogs with sinus rhythm. Both the make- and break-generated impulses penetrated into the A-V junction and kept it refractory so that a complete A-V dissociation was maintained.

In another dog ventricular tachycardia was produced by continuous rapid stimulation of the left ventricle with single impulses of 3 msec duration at a rate of 250/min (fig. 11, panel B) imitating a parasystolic focus. Then a second artificial pacemaker was introduced to stimulate the right ventricle with pairs of impulses of 3 msec duration, 180 msec apart, at a rate of 150/min. This right sided pacemaker led to the artifacts in RA ECG (panel C): The frequency of effective ventricular contractions was reduced from 250 to 150/min despite the presence of the more rapid left ventricular "parasystolic" pacemaker. At this time there was complete A-V dissociation.

FIGURE 10
Record of RA ECG and LA and LV pressure in animal with artificially produced atrial flutter, rate 500/min (with 3:1 A-V conduction), showing effect of ventricular electrical stimulation, at rate of 175/min with impulses 180 msec in duration, upon frequency of ventricular contractions. Both make and break caused QRS to appear but only the break led to an effective ventricular contraction. Diagram between top two tracings and its conventions as in figure 5. Discussed in text.
Four panels are portions of a continuous record of a dog, showing effect of paired stimuli from a second artificial ventricular pacemaker upon frequency of effective ventricular contractions previously controlled by an artificially induced (left) ventricular "parasystolic tachycardia." Two tracings show the RA ECG and LV pressure pulse respectively. A is the control; B, effect of induced artificial left ventricular tachycardia, which followed repetitive stimulation with single impulses, 3 msec in duration, at rate of 250/min. Solid vertical lines on top of ECG tracing represent time of occurrence of QRS in response to this pacemaker, which led to a similar frequency of response of ventricular contractions. Complete A-V dissociation was present. C shows results of stimulation of right ventricle at rate of 150/min by pairs of electrical impulses 180 msec apart, each 3 msec in duration, while artificial left ventricular pacemaker was maintained. Solid vertical lines above ECG, 240 msec apart, represent the parasystole going at rate of 250/min. Longer solid vertical lines below ECG represent stimuli from second pacemaker in right ventricles. When the right ventricular pacemaker was stopped, in D, the ventricular contraction frequency again increased to 250/min, the rate of the "parasystolic" pacemaker. When the "parasystolic" pacemaker also stopped, in E, the sinus node once again took over control of the ventricles at a rate of 167/min. Discussed in text.

It is apparent in this experiment that, despite the more rapid frequency of the left ventricular pacemaker, a lower stimulation frequency of the right ventricle with pairs of stimuli leads to a reduced frequency of effective ventricular contractions. The impulses from the left ventricular pacemaker are prevented from controlling the ventricles because they come during the refractory phase following stimulation of the ventricles by each of the pair of right ventricular impulses. This therefore imitates a case of complete intraventricular dissociation around the "parasystolic" pacemaker (similar to S-A dissociation), in which the more rapid pacemaker is not erased but is prevented from controlling the ventricles. These are the two together with complete intraventricular dissociation around the "parasystolic" pacemaker, both caused by the pairs of stimuli from the right ventricular pacemaker. The reduced frequency was maintained as long as the right ventricular stimulation was continued. When stimulation of the pacemaker in the right ventricle was discontinued, the left ventricular pacemaker again took over control of the ventricles (panel D). When the pacemaker in the left ventricle in turn was turned off, sinus rhythm was immediately restored to the ventricles (panel E).

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conditions which characterize parasystole.

The mechanism of slowing the frequency of effective ventricular contractions in this instance is similar to that described above for sinus rhythm. The first stimulus of the pair is followed by the effective ventricular contraction; the second produces a QRS but comes so early that no effective mechanical contraction is present. The two stimuli in each pair, however, produce a complete A-V dissociation preventing the sinus impulses from reaching the ventricles. There are, therefore, two regions of dissociation present, one in the A-V junction and the other around the left ventricular pacemaker.

Discussion

Two methods are described by which electrical stimulation can be used to reduce the frequency of effective ventricular contractions. They depend upon the use of an artificial pacemaker applied to the right ventricle (or atrium) by which properly spaced pairs of electrical stimuli of appropriate strength are produced. Such pairs of stimuli can be obtained from the make and break of long impulses or by means of pairs of impulses, each 3 msec in duration. The time interval between the pairs of electrical stimuli, i.e., the duration of the longer electrical impulse or the time intervening between the two impulses of the pair of shorter impulses, usually successful in reducing the rate of effective ventricular contractions, was found to vary between 150 and 360 msec in the dog. This time interval appears to be independent of the sinus rate, and of the rate obtained after stimulation. Results are also similar whether the stimulus is applied to the ventricle or atrium. It is possible to obtain this effect also when the break of the longer impulse is separated from the make of the next impulse by a similar interval of time.

The mechanism by which control of the ventricle is accomplished is based on one of two mechanisms. 1) The electrical impulses, in the case of atrial stimulation, discharge the sinus pacemaker or produce complete S-A dissociation so that sinus control of the heart is abolished: this occurs on occasion also with ventricular stimulation. 2) The electrical impulses, in most cases of ventricular stimulation, lead to complete A-V dissociation preventing the sinus impulses from reaching the ventricles.

The use of paired impulses of short duration seems the more advisable method for clinical application because it removes the possibility that the prolonged use of electrical impulses of long duration, with resulting electrotonic effects, may have a deleterious action upon the heart. However, this needs to be tested in animals. The impulses of short duration are similar to those produced by commercially available pacemakers which have been used in man for years without deleterious effects upon the heart.

In the present study it has been clearly demonstrated that the stimuli following the longer pauses are the ones that produce the effective ventricular contractions. The ones following the shorter pause are ineffective. This may come about in one of several ways:

1) The second stimulus of the pair, in the case of atrial stimulation, is not conducted to the ventricles and, therefore, no QRST follows. This was observed only in the one experiment on man. In the dog, so far, we have not been able to arrange the spacing of the pairs of atrial stimuli so that they prevent completely the control of the heart by the sinus node and at the same time have the second stimulus of the pair fall within the absolute refractory phase of the A-V junction produced by the first stimulus.

2) The second impulse of the pair stimulates the ventricles, but so early in the cycle that it leads to no discernible contraction in the ventricles or one so small as to be unable to open the semilunar valves. This occurs because the prematurity of the beat prevents a significant ventricular filling (starting as it does during the phase of isovolumic relaxation) or allowing only a small degree of ventricular filling (when it starts early during the rapid inflow phase). In such beats a QRS complex is present, showing stimulation of the ventricles. Since ineffective ventricular responses require the expenditure of energy by
the heart and the consumption of oxygen by it, it is possible that the energy cost in such cases, and the cardiac oxygen consumption of the pairs of beats, may be greater than that used before employing the artificial pacemaker even though the frequency of effective ventricular contractions declines.

The ideal way of slowing the ventricles would be to stimulate the atria in such a way as to lead to interference with the passage of the second atrial stimulus to the ventricles. This last has not yet been accomplished in the dog because of the relatively short refractory period of the A-V junction, particularly when the ventricular rate is rapid. It has been accomplished in the patient as described in this report. Since even an ineffective heart beat uses energy and consumes oxygen, the effect of reducing the total number of electrical responses of the ventricles ensures a reduction of the energy used by the heart per minute as well as of its oxygen consumption. In cases such as that shown in the patient, an adequate cardiac output per minute can be maintained with the slowing of heart rate at a lower energy and oxygen cost to the heart. This might, therefore, be of value in cases of tachycardia of the ventricles, otherwise uncontrollable, in which it is apparent that the rapid rate is detrimental to the patient.

Another way in which slowing of the effective ventricular contraction rate may be beneficial is in cases in which the fast heart rate per se decreases effective filling and thereby decreases cardiac output per minute. With slowing of the ventricular rate in such cases an augmented cardiac output would result and thus relieve the circulatory insufficiency. In the one awake and closed-chest dog in which cardiac output was determined by the indicator dilution technique, the cardiac output was unchanged. After inducing the slowing, with an artificial pacemaker (from 130 to 90/min), of the effective beats, cardiac output per minute was found essentially unchanged (3000 ml/min and 3200 ml/min, respectively). In this case the stroke output increased from 23.1 ml to 35.5 ml as the effective ventricular contractions declined in frequency.

This type of approach may be useful in slowing the rate of effective ventricular contractions in cases of rapid ventricular response due to otherwise uncontrollable atrial flutter, atrial fibrillation, supraventricular paroxysmal tachycardia and ventricular paroxysmal tachycardia. It may be valuable also in marked sinus tachycardia. It was shown in the present experiments that this reduction of ventricular rate can be produced in atrial flutter and paroxysmal ventricular tachycardia.

### Summary

1) The frequency of effective ventricular contractions could be reduced by almost 50% in dogs by stimulating the ventricles (or atria) with electrical impulses of long duration (2 volts, 200 to 350 msec).

2) A similar result was obtained when pairs of impulses (2 volts), each 3 msec in duration, were used, with the time interval between the two impulses of the pair similar to that between the make and break of the long impulses (noted above).

3) The dogs were under general anesthesia and positive pressure breathing was maintained. After thoracotomy, platinum electrodes were implanted in the epicardial surface of the right ventricle or atrium. Pressures were measured in all heart chambers and the unipolar electrocardiogram was recorded from the right atrium with a catheter electrode. Several frequencies of stimulation, below the inherent sinus rate, were tested and at each frequency the time interval between pairs of stimuli was progressively increased from 100 to 350 msec.

4) In all dogs reduction of the frequency of the effective ventricular contractions could be obtained with pairs of stimuli 200 and 350 msec apart. Only the make of the long impulse or the first of the pair of short impulses produced an effective ventricular contraction, while the break of the long impulse or the second short impulse stimulated the ventricles so early in the cycle that no effec-
tive mechanical contraction followed. However, the refractory period produced by the break prevented the sinus impulse from reaching the ventricles. The several mechanisms involved are discussed.

5) In one dog the reduction of the frequency of the effective ventricular contractions could be maintained during the 24 hours of survival.

6) The method was applied to a patient being treated for Stokes-Adams attacks. Right atrial stimulation produced a noticeable reduction in ventricular frequency. This involved a reduction in the frequency of electrical responses of the ventricles as well, ensuring a reduction of the per minute energy cost and oxygen consumption of the heart. Such a reduction of the frequency of electrical responses of the ventricles could not be accomplished, so far, in the dog by atrial stimulation.

7) Reduction of the frequency of effective ventricular responses was obtained in one dog with induced atrial flutter and in another with a pacemaker induced "parasystolic" ventricular tachycardia by employing an artificial ventricular pacemaker similar to that used with sinus rhythm.

8) The significance of the findings is discussed. This experimental approach suggests a possible method of slowing the heart rate in clinical cases of ventricular or atrial tachycardia refractory to other methods of treatment.

9) Finally, this approach offers a means of studying certain properties of the heart in the dog which may give insight into the mechanisms involved in some of the more complex arrhythmias encountered in man.

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Reducing Heart Rate of the Dog by Electrical Stimulation
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