A GREAT deal of clinical information is available regarding the effect of numerous specific factors (for example, nervous stimulation and blood gas and electrolyte changes) on the rates of impulse formation in individual cardiac pacemakers. However, there are but few observations in the same person on the relative changes in the rates of two simultaneously-active pacemakers. The simultaneous rates of impulse formation in the sinoatrial node and in an ectopic ventricular focus in the same individual have occasionally been measured repeatedly.\(^1\)\(^\text{2}\)\(^\text{3}\) In any one patient, however, the data are not sufficient for a precise comparison of changes in the fundamental rates of the two pacemakers as a result of spontaneous variations.

In each of three patients with coronary artery disease and a sensitive carotid sinus cardiac reflex, during repeated electrocardiographic observations of the effects of carotid sinus pressure it was possible to measure the fundamental rates of impulse formation in two practically simultaneous cardiac pacemakers.

In each case, the two rates could be determined over fairly wide ranges of spontaneous variation. A direct, linear relationship was found to exist in each patient between varying rates of the two pacemakers: the sinoatrial node and a slower atrioventricular nodal pacemaker; the sinoatrial node and a faster atrioventricular nodal pacemaker; and the atrioventricular node and a slower ventricular pacemaker.

The presentation and analysis of our observations in these patients form the basis of the present report.

**Patients**

N. S. (BIH no. 17498), a 70 year old man, had had typical attacks of angina pectoris for at least 10 years. He was ambulatory throughout the three year period during which our observations were made. With the exception of occasional blood pressure elevations (to 190/90) there were no significant cardiovascular findings. Except for left axis deviation and the shifts in pacemaker described below, his electrocardiograms were always within normal limits. On 19 different days during a three-year period the cardiac effects of 101 applications of carotid sinus pressure were observed, 58 on the right and 43 on the left. Certain data in this patient have already been reported\(^4\) and other data are to be presented elsewhere.\(^5\)

M. S. (BIH no. M15069) was a 75 year old man with benign prostatic hypertrophy who was treated by two-stage suprapubic prostatectomy. In the past he had had frequent attacks of angina pectoris, but none had occurred within the previous year.
There was no evidence of congestive heart failure. His blood pressure was sometimes slightly elevated (to 170/100) and a chest plate showed very slight cardiac enlargement to the left. With the exception of the shifting pacemaker to be described below, his electrocardiograms showed only left axis deviation and left ventricular hypertrophy. On 31 days during a two-month period of hospitalization the electrocardiographic effects of 184 applications of carotid sinus pressure were observed, 178 on the left and 6 on the right. Numerous long control electrocardiograms were also recorded on most of these days. In addition to the studies reported below, other data on this patient will be presented elsewhere.3

J. O. (BIH no. M22920) was a 77 year old man with chronic bronchitis, chronic emphysema and cardiac enlargement. He had had increasing exertional dyspnea and a chronic productive cough for many years. There had been no chest pain. His electrocardiograms, as will be seen below, showed left bundle branch block in addition to changes in the site of impulse formation. On 15 days during an eight-week period the cardiac effects of 62 applications of carotid sinus pressure were observed, 61 on the left and 1 on the right. Numerous long control electrocardiographic observations were made on these and on several other days.

During the following two weeks the patient was hospitalized because of severe respiratory distress and the development of congestive heart failure. He developed a very rapid atrioventricular nodal tachycardia with 2:1 block which did not respond to digitalization and for which quinidine was then administered. As will be described elsewhere,4 the patient expired shortly after a sudden, quinidine-induced conversion of the tachycardia to a slower supraventricular rhythm. An autopsy revealed coronary artery sclerosis and myocardial fibrosis in addition to evidence of chronic pulmonary disease.

**Methods**

In each patient a continuous electrocardiogram was recorded on a direct-writing instrument immediately before, during and immediately after the application of manual pressure to either the right or the left carotid sinus. Patients N. S. and J. O. were in a sitting position during each pressure; patient M. S. was semirecumbent. Most of the pressures were of three to five seconds' duration; occasionally the effects of longer pressures (up to 60 seconds) were observed. At least three or four minutes were allowed to elapse between successive pressure tests in any one patient on the same day; this interval has been found to be well beyond the time generally required for the electrocardiographic changes produced by pressure to disappear. Excessive cardiac effects were avoided by watching the electrocardiogram during each pressure. Occasionally, patients N. S. and M. S. noted mild, very transient dizziness in association with carotid sinus pressure. No significant reactions occurred, however, during almost 350 applications of pressure in these three patients.

Electrocardiographic intervals were measured to the nearest 0.01 second. The direct measurement of the time interval between successive beats has been taken to indicate the rate of impulse formation in the various pacemakers. This provides a much more accurate and more sensitive index of change in rate than does the more conventional measurement of the number of beats per minute.

**Observations**

In each of the three patients it has been possible, repeatedly, with carotid sinus pressure to produce a temporary shift in the control of the heart beat from the dominant site of impulse formation to a lower pacemaker, to identify both pacemakers electrocardiographically, and to measure the two different, practically simultaneous, fundamental rates of impulse formation. No attempt was made to vary the heart rate before pressure. However, spontaneous variations occurred from day to day, and observations were thus made over a fairly wide range of rates. In two of the patients (M. S. and J. O.), the same shift of pacemaker was occasionally observed to occur spontaneously for periods up to a few minutes; the rate of impulse formation in the lower pacemaker after this spontaneous shift could often be compared, within a few minutes, with its rate when the shift was brought about by carotid sinus pressure.

**Patient N. S.: Sinoatrial and Slower Atrioventricular Pacemakers**

In this patient, the dominant site of impulse formation before carotid sinus pressure, was always in the sinoatrial node: normal P waves followed by supraventricular type QRS complexes (fig. 1, N. S.). Fifteen of the 58 pressures on the right carotid sinus each resulted in a transient shift of the pacemaker to the atrioventricular node: disappearance of the P waves without alteration in the QRS complexes (fig. 1, N. S.). The number of atrioventricular nodal beats observed with any one pressure ranged from two to nine: in only 3 of the 15 pressures were there less than four
such beats, in 7 of the 15 pressures there were six or more. This effect of reflex vagal stimulation was not observed after left-sided pressure.

Typical cycle length changes of the two pacemakers during carotid sinus pressure are shown in figure 2. In the same figure, for comparison, are shown the changes in sinoatrial cycle length produced by a pressure in which no shift of pacemaker occurred. The shift to the atrioventricular node shown here was preceded, as in every case, by marked prolongation of the sinoatrial cycle length (that is, slowing of rate). The atrioventricular rhythm, once established, persisted after the end of pressure. The first three atrioventricular cycles show the disappearance of the vagal effect on the lower pacemaker, the cycle lengths becoming progressively shorter (that is, the rate increased). During the remainder of the period of atrioventricular rhythm the cycle length leveled off below the sinoatrial control value.

In the upper section of figure 7, the fundamental rates of impulse formation in the sinoatrial and atrioventricular pacemakers are shown for each of the 15 pressures which produced a shift of pacemaker. The average length of the six to eight sinoatrial cycles immediately before a pressure is plotted against the shortest atrioventricular cycle after that pressure. It is apparent that there is a direct relation between these values: as the length of the cycle of impulse formation in the sinoatrial node increases or decreases, there is a corresponding increase or decrease in the cycle of the atrioventricular pacemaker.

Patient M. S.: Sinoatrial and Faster Atrioventricular Pacemakers

The electrocardiographic features of the two pacemakers in this patient are shown in figure 3. The sinoatrial nodal pacemaker has normal P waves and supraventricular type QRS complexes. Sixty-one of the 178 pressures on the left carotid sinus were each followed by a run of beats from a pacemaker high in the
atrioventricular node: unchanged QRS complexes with inverted P waves in leads II and III, and upright P wave in lead I. The abrupt shift is shown in figure 1 (M. S.): in consecutive beats the normal upright P wave becomes inverted. Right carotid sinus pressure produced no electrocardiographic changes.

The detailed changes associated with two applications of left carotid sinus pressure, 20 minutes apart on the same day, are shown in figure 4. Both pressures show the same marked prolongation of sinoatrial cycle length (that is, slowing of rate). In one instance the dominant pacemaker, after pressure, remained in the sinoatrial node. In the other instance, however, 11 seconds after the end of pressure, when the sinoatrial cycle length had returned to its control value, there was a sudden shift to the atrioventricular nodal pacemaker at a very slightly faster rate (shorter cycle length). In 61 pressures, the average time from the end of pressure to the transition was 12 seconds (range 6 to 22.5 seconds). In every instance when this shift occurred the sinoatrial rate had returned to its control value and the first atrioventricular nodal cycle was very slightly shorter (that is, faster) than the last sinoatrial cycle. The activity of the atrioventricular pacemaker generally persisted for 5 to 40 seconds. As shown in the run of atrioventricular beats in figure 4, there was sometimes a transient, occasionally more marked, acceleration of rate during atrioventricular control. The cycle length at the end of a run, however, was usually slightly longer than at the beginning (average difference, 0.05 second), and the transition back to sinoatrial control was abrupt.

On many of the days when observations were made, long control electrocardiograms showed repeated spontaneous transitions back and forth between the sinoatrial node and the same atrioventricular nodal pacemaker. The average length of these spontaneous runs of atrioventricular beats varied from day to day; they sometimes lasted for several minutes. They were not preceded by slowing of the sinoatrial rate, nor were they associated with respiration or any apparent possible cause of reflex vagal stimulation, such as swallowing or
change of position. In every other respect this spontaneous activity of the atrioventricular pacemaker was identical with its activity following carotid sinus pressure within the same few hours’ period: the beginning and the end were abrupt; the first atrioventricular cycle was always shorter (that is, faster) than the last sinoatrial cycle; the last atrioventricular cycle was usually slightly longer (that is, slower) than the first atrioventricular cycle; and the rates of the spontaneous and the pressure-induced atrioventricular activity were the same. Very slight left carotid sinus pressure immediately stopped either spontaneous or pressure-induced activity of the atrioventricular pacemaker and restored sinoatrial nodal control. On those days when the spontaneous runs were long the pressure-induced runs also tended to be long. On days when there was no spontaneous atrioventricular nodal activity, such activity could usually be made to appear after left carotid sinus pressure, and the runs tended to be short.

In the middle section of figure 7 are shown the basic rates of impulse formation in the sinoatrial and the atrioventricular nodes of this patient. For each of the 61 pressure which was followed by a shift of pacemaker, the average length of the six to eight sinoatrial cycles immediately before the pressure is plotted against the cycle length of the first two atrioventricular beats. It is clear that there is a direct relation between the two rates: variations in the cycle of the sinoatrial node are accompanied by corresponding variations in the cycle of the atrioventricular nodal pacemaker.

Patient J. O.: Atrioventricular and Slower Ventricular Pacemakers

The electrocardiographic complexes during sinoatrial control of the heart beat in this patient are shown in figure 5: normal P waves and QRS complexes of left bundle branch block. However, during most of our observations, the dominant pacemaker was in the atrioventricular node (fig. 5): supraventricular type QRS complexes showing left bundle branch block with or without retrograde inverted P waves. Wandering of the pacemaker within the atrioventricular node was indicated by spontaneous changes in the position of the retrograde P waves: sometimes before and sometimes after the QRS complex. Minimal changes in the cycle length (0.03 second) accompanied these shifts, the shorter cycles (that is, faster rates) occurring when the P waves preceded the QRS complexes. Data concerning retrograde conduction and reciprocal beats from the atrioventricular node and from the ventricular focus described below will be presented elsewhere.

Digitoxin was administered in the absence of definite evidence of congestive failure but in an attempt to relieve severe respiratory distress. The patient received 0.6 mg. a day
for two days and then 0.2 mg. daily. An electrocardiogram on the day the drug was started showed sinoatrial rhythm; on the fifteenth day of drug therapy atrioventricular nodal control was first observed. Although digitoxin administration was immediately stopped, the activity of the atrioventricular pacemaker continued, and spontaneous sinoatrial control was not observed again until 40 days later. At this time, repeated spontaneous transitions were observed between sinoatrial rhythm and runs of faster atrioventricular nodal activity lasting for 20 to 60 seconds. The differences in rate were very slight, but in every instance the atrioventricular cycle lengths were shorter (that is, faster) than the closely associated sinoatrial cycles. Subsequently, sinoatrial control was observed with no evidence of atrioventricular nodal rhythm. After 17 days, no further digitalis glycoside having been administered, an atrioventricular nodal pacemaker again assumed control of the heart beat, this time at a very rapid rate (around 250 per minute) and with a 2:1 ventricular response.

In 32 of 61 instances, pressure on the left carotid sinus during atrioventricular nodal control produced an immediate shift to an ectopic pacemaker in the left ventricle: QRS complexes markedly different from the supraventricular ones and having the appearance of right bundle branch block (fig. 5). An example of this transition at the start of left carotid sinus pressure is shown in figure 1 (J. O.). The fifth complex, a fusion beat, marks the transition from atrioventricular nodal to ventricular control. Right carotid sinus pressure caused no electrocardiographic changes.

The details of the changes associated with left carotid sinus pressure are shown in figure 6. The shift here from the atrioventricular to the ventricular pacemaker was immediate, with little time for slowing of the atrioventricular rate (that is, prolongation of the cycle). In other instances, definite atrioventricular slowing was observed before the shift occurred. Pressure was continued, on this occasion, for 10 seconds. During the pressure and for 14 seconds after pressure was stopped, the ventricular focus maintained control at a fairly constant rate. There was then an immediate shift back to the atrioventricular pacemaker whose rate progressively rose back to and then above the control level.

On many of the days when observations were made, long control electrocardiograms showed varying degrees of spontaneous activity of the ventricular focus. This ranged from single premature ventricular beats to complete ventricular rhythm such as occurred during carotid sinus pressure. The spontaneous runs of ventricular rhythm sometimes lasted for as long as one minute and were not associated with any apparent extrinsic cause of reflex vagal stimulation. Left carotid sinus pressure had no effect on the rate when applied during the spontaneous runs. On a number of days it was possible to compare the cycle lengths of a pair of spontaneous ventricular beats not separated by an atrioventricular beat, of a spontaneous run of ventricular beats, and of a ventricular run during left carotid sinus pressure: all were the same. The ventricular activity could usually be seen during carotid sinus pressure even on days when it did not appear spontaneously.

The fundamental rates of impulse formation in the atrioventricular node and in the ventricular focus could thus be determined. In the lower part of figure 7, the average of six to eight atrioventricular cycles preceding each of the 32 applications of left carotid sinus pressure is plotted against the average of 6 to 10 ventricular cycles during the respective pressures. There is a direct relation between the
two values: changes in the cycle length of impulse formation in the atrioventricular node are associated with corresponding changes in the cycle of the ectopic ventricular focus.

**Discussion**

These observations establish a fact of fundamental importance in the normal and pathologic physiology of the cardiac impulse-forming system in man: the physiologic variables which determine the rate of impulse formation in the sinoatrial node also combine to determine the rate of certain active and passive ectopic pacemakers. Several other observers have commented on parallel changes in the rate of the sinoatrial node and of simultaneously active ventricular pacemakers: the idioventricular center in complete heart block; spontaneous ventricular parasystolic foci; and experimental ventricular parasystolic foci. In none of the clinical reports, however, have sufficient data been presented on any one patient to permit a precise comparison of spontaneous changes in the fundamental rates of the two pacemakers.

The fundamental rates of impulse formation of the two pacemakers in each of our three patients could be measured only a few seconds apart. Shifts in control of the heart beat were produced by carotid sinus pressure. The basic rate of the dominant pacemaker could readily be determined before each pressure, and spontaneous variations from day to day provided a fairly wide range of rhythmicity in each case. In order to determine the fundamental rate of impulse formation of the lower pacemaker in each patient, it was essential to distinguish clearly any possible alterations of this rate caused by neurogenic stimuli associated with the carotid sinus pressure.

In patient N. S., reflex vagal stimuli slowed the rate of the sinoatrial node and permitted escape of a slower pacemaker in the atrioventricular node. These stimuli also had a depressing effect on the rate at which the atrioventricular rhythm first appeared. Immediately after the end of pressure, as the vagal effect disappeared, the atrioventricular rate increased, and within a few beats became fairly constant. The occurrence of constant cycle lengths at the end of the majority of the atrioventricular runs suggested that this represented the fundamental rate of the lower pacemaker uninfluenced by vagal or by rebound sympathetic stimulation. In each instance, the shortest (that is, the fastest) atrioventricular nodal cycle was taken as the measure of its basic rate.

In patient M. S., after the end of reflex vagal stimulation there was a shift of the pacemaker from the sinoauricular node to a faster pacemaker high in the atrioventricular node. Several observations indicate that the shift was not a direct effect of vagal stimuli: the change of pacemaker occurred, on the average, 12 seconds after the end of carotid sinus pressure, at a time when the typical vagal slowing of the sinoatrial rate had disappeared; carotid
sinus pressure reapplied during an atrioventricular run always restored sinoatrial control immediately. Such marked lability has been described as a characteristic feature of this type of high atrioventricular nodal rhythm. The reflex vagal stimulation is accompanied by reciprocal sympathetic inhibition and may be followed by rebound of the previously-inhibited sympathetic stimuli. The shift of pacemaker in this patient, like other changes in impulse formation observed after the end of carotid sinus pressure, can be explained by this mechanism. The pressure-induced atrioventricular nodal control clearly represented activation of an already potentially active, faster pacemaker: atrioventricular nodal activity following carotid sinus pressure was identical with the spontaneous atrioventricular nodal activity that often occurred during the same observation period; atrioventricular nodal activity occurred after carotid sinus pressure even on days when it did not occur spontaneously. The first cycle of the pressure-induced activity has been considered to give the best measure of the basic rate of this faster pacemaker. Subsequent, transient acceleration of the atrioventricular rate often occurred, probably as a result of sympathetic stimulation, but by the end of a run the rate was usually slightly below its starting level. It is of interest that the starting rates of pressure-induced and spontaneous runs of atrioventricular nodal activity observed close together on the same day were identical.

In patient J. O., reflex vagal stimulation slowed the rate of the atrioventricular pacemaker and permitted the escape of a slower focus of impulse formation in the left ventricle. The atrioventricular nodal rhythm persisted for 40 days at a normal range of rates and its nature could be determined only toward the end of the period. At this time, before complete sinoatrial control returned, short runs of sinoatrial rhythm interrupted the atrioventricular activity. In these spontaneous transitions, the atrioventricular cycle was always slightly faster than the sinoatrial cycle, indicating an active pacemaker in the atrioventricular node.

Although this rhythm developed during digitalin administration, its persistence for 40 days after the drug was stopped makes it appear unlikely that the disturbance was due to the drug. As further evidence of the spontaneous instability of the impulse-forming system in this patient, it is of interest that, during sinoatrial control following the observations reported here, without further digitalis having been given, an active rhythm again developed in the atrioventricular node, this time at a very rapid rate. The identical features of the spontaneous and pressure-induced ventricular activity indicate that, by depressing the atrioventricular node, the reflex vagal stimulation simply permitted the parasystolic focus to become manifest without the interference of another, faster pacemaker. The fundamental rate of the ventricular focus could readily be determined since it was not affected by the reflex vagal stimuli; during any one pressure the rate of the ventricular focus changed very little; the rate continued unchanged even after the end of a pressure; the transition back to atrioventricular nodal control was always abrupt, and carotid sinus pressure had no effect on the rate when applied during spontaneous ventricular activity.

A comparison of the varying rates of impulse formation in each of the pairs of pacemakers shows similar features in the three individuals. As can be seen in figure 7, the cycle lengths in each instance vary together in a direct and linear fashion. The three lines describing the relationships would have approximately equal slopes of 0.9 to 1.0. This means that, in each case, a given increase or decrease in the cycle length of one pacemaker is accompanied by an approximately equal increase or decrease, respectively, in the cycle length of the other. However, inasmuch as each faster pacemaker has the shorter cycle length, the percentage change in its rate is greater than the corresponding percentage change in the rate of the slower pacemaker (with a longer cycle). In terms of the number of beats per minute, the change is also greater in the faster pacemaker. The difficulty of distinguishing different sites of impulse formation or active and passive
ectopic rhythms, even in the same individual, by the rate alone, is apparent. In each instance, the slowest rate of the faster pacemaker overlaps with the fastest rate of the slower pacemaker. In patient N. S. this overlap is slight, but in patients M. S. and J. O. it includes a rather wide range of rates.

Further observations are necessary to determine whether the same quantitative relationship between the two cycle lengths that was seen in our three patients will pertain to other individuals. It should be noted that once a relationship between the varying rates of two pacemakers in the same individual is established, an excellent opportunity is presented for studying the effects of cardio-active drugs on these pacemakers.

In contrast to these findings, it is known that certain paroxysms of rapid ectopic rhythm may continue for long periods of time at the same rate. They may also recur at varying rates which bear no definite relation to the preceding or succeeding sinoatrial rates. Further observations are necessary to differentiate the ectopic rhythms whose rates are and are not susceptible to change.

**Summary**

Quantitative observations in three individuals establish the fact that the physiologic variables which determine the rate of impulse formation in the sinoatrial node also determine the rates of certain active and passive ectopic pacemakers.

**Sumario Español**

En cada uno de tres individuos, la presión al seno carotídeo produjo un cambio en el pacificador control dominante de las contracciones cardiacas a uno ectópico, mas lento o mas rápido. En cada caso, fue posible medir la frecuencia fundamental de los dos prácticamente simultáneos pacificadores sobre marcadas diferencias en frecuencia: se encontró, una relación directa y lineal.

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Quantitative Studies in Man of the Cardiovascular Effects of Reflex Vagal Stimulation Produced by Carotid Sinus Pressure: II. Rates of Impulse Formation of Two Cardiac Pacemakers in Each of Three Individuals

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