Effects of Increased Transmural Pressures upon Atrial and Ventricular Rhythms in the Dog Heart-Lung Preparation

By Robert L. Vick, Ph.D.

A number of investigators have reported that isolated, perfused frog hearts beat faster when the perfusion pressure is raised, or that the beat can be initiated in quiescent atria or ventricles by increasing, within limits, the intraluminal pressure.\(^1\) Analogous results were obtained with isolated mammalian atrial-sac preparations perfused with Locke's solution.\(^2\) It is likely that the effects of such pressure increases are produced by stretch of the tissues. When the effect of stretch on cardiac tissue which had pacemaker activity was studied directly it was found that Purkinje strands which were firing infrequently increased to rapid regular activity with 10% elongation.\(^3\) The action potentials, measured with intra-cellular microelectrodes, showed typical pacemaker prepotentials. These results are consistent with the hypothesis that increased activity resulting from stretch might be a general property of cardiac pacemaker tissue. The work reported here was done as a first test of this hypothesis using in the dog heart-lung preparation increased intramural pressure as a means of producing stretch, and changes in rates of beating as evidence of altered pacemaker activity. Spontaneous activity originating from other parts of the heart was studied by destroying the dominant pacemaker, or by preventing conduction from areas of higher to those of lower activity.

Methods

The experiments were performed on dog heart-lung preparations which, because of economy of extracorporeal volume, did not require the addition of donor blood. The temperature of the blood was measured by a thermometer inserted through a side-arm of the brachiocephalic cannula. Congestion was prevented by the use of 20 mg/kg mepesulfate injected just before completion of the external circulation. The lungs were mechanically ventilated with a 95% \(\text{O}_2\)-5% \(\text{CO}_2\) mixture. Latent pacemakers were revealed in the atrium by crushing the area of the sino-atrial node; in the ventricle, by surgically interrupting the bundle of His. Heart rates were counted from semidirect electrograms taken from the tip of the right auricular appendage and from the septal area of the ventricular surface about midway between base and apex. In order to detect rapid changes, rates were measured with calipers in six-second intervals and expressed as beats per minute. A standard lead II ECG provided additional information about sites of origin and pathways of conduction of impulses. Aortic pressure was recorded by way of a tube passed through the left subclavian artery; and right atrial pressure (RAP) was recorded by way of a tube passed through the inferior vena cava. Statham transducers, carrier preamplifiers, and D.C. power amplifiers were used with a rectilinear penwriter system.

Right atrial and ventricular pressures were increased by tightening a ligature placed about the pulmonary artery while left-heart pressures were increased by adding to the outflow resistance. Maximum pressure values could be quickly achieved by simultaneously permitting an increase in the rate of inflow from the reservoir. Because in the heart-lung preparation changes in the rate of inflow of blood might alter the temperature of the heart and thereby affect the rate of pacemaker activity, the temperature of the heart was carefully observed throughout the experiments. The first large inflow of blood after a control period at lower inflow rates often increased blood temperature by as much as 0.5°C. However, during subsequent periods of elevated inflow no further rapid changes of blood temperature occurred as long as the maneuvers were repeated fairly frequently. The data reported were those taken in the absence of rapid temperature changes.

The effects of short periods (10-20 sec) of in-
creased pressures on atrial or ventricular rates were studied in a system which included a conventional Starling resistance and "venous" reservoir. The study of the effects of increased left-heart pressure was limited to such short periods because high left-heart pressure eventually results in elevated diastolic pressure and pulmonary edema. In the right heart the effects of longer periods of sustained pressure could be studied and for this a modified system was used in which a single pressurized, water-jacketed reservoir substituted for both Starling resistance and conventional "venous" reservoir. The reservoir was placed directly over the aorta and was connected by short tubes to the brachiocephalic artery and to the superior vena cava. The heart then pumped blood directly into the reservoir. The hydrostatic pressure of the column of blood in the reservoir was augmented by air pressure sufficient to yield an aortic mean pressure of about 100 mm Hg. The air space above the blood communicated with two 18-liter carboys connected in series which served to buffer the pressure changes which would occur as a result of changes in contained blood volume. The input of blood to the heart through the superior vena cava was controlled by means of an adjustable screw clamp placed on the other outlet from the bottom of the reservoir. With this system the pulmonary artery could be completely occluded while the coronaries were perfused with blood from the reservoir. When the desired level of pressure in the right heart was reached the inflow to the vena cava was clamped off and only coronary sinus blood entered the right heart. This was drained off into a bottle attached to the inferior vena cava in which the fluid level was kept at a height which produced a hydrostatic pressure equal to the desired right-atrial pressure. The volume of blood in the reservoir was usually sufficient to perfuse the coronaries for about five minutes.

Results

1. EFFECTS OF ELEVATED PRESSURES UPON SINUS RATE

The right-heart pressure was elevated for repeated periods of 10 to 15 seconds in 17 heart-lung preparations. The increases, recorded as mean right atrial pressure, ranged from 2 to 34 cm of water and were always accompanied by clearly discernable increases in heart rate. The pacemaker which responded was judged by the pattern of the ECG to be located in the sino-atrial node. Representative results are illustrated in figure 1. This record was taken from an experiment in which right heart pressure was rapidly elevated by simultaneously increasing the input of blood while limiting or blocking the output by constricting the pulmonary artery. Typically the
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changes in rate followed closely upon the changes in pressure. The combined results of all experiments are shown in figure 2. Maximum net increases in heart rate are plotted against simultaneous mean right atrial pressures. In most experiments the maximum response was obtained at about 15 to 20 cm of water pressure with little further response at higher pressures, while in a few preparations the magnitude of the rate increase progressed up to the maximum pressure reached of 25 to 30 cm of water.

Three experiments done with the combination reservoir-resistance showed that the effect did not accommodate within five minutes (fig. 3). By studying several levels of right atrial pressure it was demonstrated that under these conditions the rate increase was proportional to the right atrial pressure increase up to a limit of about 20 cm of water.

Increased outflow resistance in preparations dominated by normal sinus pacemakers produced no consistent alterations in heart rate which could be ascribed directly to increased left-heart pressure. However, the rate was affected indirectly when the increased left ventricular end diastolic pressure imposed a back pressure upon the right ventricle which increased the resistance to outflow from that chamber. In such a preparation the heart rate rose when the right atrial pressure rose and the pacemaker remained in the sinus node. An occasional premature ventricular contraction or coupled beat was the only disturbance of sinus domination.

2. EFFECTS OF ELEVATED PRESSURES UPON A-V NODAL RATE

Following removal of dominance by the faster sino-atrial pacemaker the control of the rate of beating of the atrium shifts to the general area of the A-V node. In the heart-lung preparation in which the S-A region has been crushed by a clamp, this shift can be confirmed by emergence of a slower heart rate, by the absence of a P wave in the ECG, and by the occurrence of electrical activity in the atrial and ventricular electrograms at nearly the same time (no "A-V delay"). In such a preparation short periods (10-20 seconds) of elevated right-heart pressure were followed by corresponding changes in the atrial rate (10 experiments). In six of the preparations this maneuver coincided with an apparent shift in the location of the pacemaker. It was characterized in the ECG by the reappearance of a P wave and in the electrograms by the occurrence of a potential difference in the atrium which preceded that of the ventricle by a period about equal to the normal "A-V delay." This was taken as evidence that pacemaker activity had been initiated in areas adjacent to but not included in the SA crush. When the right atrial pressure was restored to normal low levels, the pacemaker reverted to the A-V nodal area.

In four experiments, in which no shift of the A-V nodal pacemaker occurred, atrial rate increases still accompanied right atrial pressure elevations. Data from these experiments are plotted in figure 4. The results are similar to those from the experiments in which the SA node was intact, in that greater rate increases followed higher right atrial pressures up to about 15 cm of water with little change or a decreased response at higher pressures.
Combined results of acute right-heart pressure elevation in four heart-lung preparations. SA node crushed, A-V nodal rhythm throughout. Otherwise same as figure 2. The three points of greatest rate increase were all obtained in the same experiment.

Typical effects of two levels of elevated right-heart pressure maintained for several minutes. Heart-lung preparation, SA node crushed, A-V nodal rhythm throughout. Otherwise same as figure 3.

In every one of ten experiments in which levels except in one preparation in which rate increased proportionally up to a right atrial pressure of 30 cm of water. In three experiments done with the combination resistance-reservoir preparation and in which no shift occurred it was found that an undiminished faster atrial rate accompanied right heart pressures sustained for up to six minutes. The results from an experiment representative of this group are illustrated in figure 5.

In every one of ten experiments in which...
the SA area had been crushed and in which the tests were performed, there was evidence of the emergence of separate ventricular pacemakers under the influence of increased right or left heart pressure. Upon release of the pressure, the dominance of both chambers returned to the A-V nodal pacemaker. In two experiments the atrial pacemaker was initially speeded, then slowed as the ventricular emerged (fig. 6A). In others the ventricular pacemaker was detected without slowing of the atrial pacemaker (fig. 6B). Close scrutiny of all electrograms and electrocardiograms confirmed that during the period of rate changes the atria and the ventricles were responding to two separate pacemakers, i.e., there was no evidence of conduction in either direction. The ECG indicated that the ventricular pacemaker was sometimes high in the ventricles (QRS virtually unchanged: fig. 6A) and sometimes nearer the apex (fig. 6B). In two of the experiments the independent ventricular pacemakers emerged only after administration of epinephrine (4 μg/min) or metaraminol (300 μg). In one experiment 100 mg of calcium ion had been administered previously.

3. EFFECTS OF ELEVATED PRESSURES UPON INTRAVENTRICULAR RATE

Following acute surgical A-V dissociation there was usually a steady ventricular beat which in 20 preparations ranged from 24 to 72 per minute. The configuration of the ECG indicated that the dominant ventricular pacemaker was usually in the base of the ventricle. Administration of epinephrine (2 or 4 μg/min) or metaraminol (100 to 300 μg) increased the ventricular rate to a range of 43 to 111 beats per minute.

Of seven experiments in which right heart pressure was acutely elevated, four showed negligible increases or decreases in ventricular rates, one showed a modest increase in rate (12%) while in two the rate was more than doubled. Generally larger responses were seen after administration of one of the adrenergic agents. In a total of eleven experiments in which the tests were made during the effects of metaraminol or epinephrine all but one showed ventricular rate increases ranging from modest (12%) to more than four-fold.

Acute elevation of outflow resistance or in-
flow volume in the A-V dissociated heart-lung preparation resulted in small increases in aortic pressure (up to 145 mm Hg or less). Beating slowly and without the aid of "atrial priming" the heart was dilated and essentially in "failure." Because of the rapid development of pulmonary edema in such conditions the number of these tests were limited. In twelve experiments in which they were performed, maximum heart-rate increases ranged from 0 (3 experiments) to a high of 18 beats per minute. There was an overall average increase of 3.5 beats per minute.

**a. Effects of Adrenergic Amines**

Administration of metaraminol or epinephrine (infusion) improved the dynamics of the hearts by causing increases in rate and contractility. Because the artificial resistance, and the inflow volume were not changed, the mean systolic pressure was only slightly increased. In these conditions acute elevation of the inflow volume and the systemic resistance resulted in maximal increases in mean systemic pressure ranging up to 250 mm Hg. In every one of 20 experiments ventricular rates were increased during the periods of elevated pressure, the largest response in each experiment ranging from 6 to 156 beats per minute increase over control. Three levels of response are shown in figure 7. With reduction of the resistance and inflow and return of the pressure to control levels the ventricular rate also returned to approximately control levels. The rate increases occurred sometimes without pacemaker shift great enough to be detected in the ECG, (fig. 7B) sometimes with shifts to entirely new foci (fig. 7C), and sometimes with coupled or mixed foci (fig. 7A and C). There appears to be a direct relationship between the level of aortic pressure achieved and the magnitude of the ventricular rate increase (fig. 8). In general, the larger rate increases occurred at the higher pressure levels.

**Discussion**

These experiments were designed to show if elevated transmural pressure can affect pacemakers in the heart-lung preparation as evidenced by changes in rate or rhythm either under the influence of the sino-atrial node or when the heart is dominated by normally latent pacemakers. They have shown that the normally dominant SA nodal pacemaker is stimulated during increased transmural pressure and that the normally latent pacemakers in the A-V node and ventricle are also stimulated. This occurred both when the latter were freed from dominance and permitted to discharge spontaneously following SA crush or A-V dissociation and when they emerged from faster pacemakers as coupled beats or as ectopic or parasystolic foci. There is no evidence to indicate that this is anything other than a direct effect upon the cardiac tissue. Since the phenomenon has been demonstrated in isolated hearts, there is no question of stimulating any central reflex afferents. Experiments with local anesthetics and ganglion blocking agents make it unlikely that local "reflexes" are involved. While adrenergic blockers have not been used, the local release...
of epinephrine or norepinephrine may be excluded from consideration because of the rapidity with which heart rates declined to control after the elevated pressure was released. These results directly provide no evidence about the mechanism of such responses. However, they do increase the importance of the observation that stretch of slowly discharging Purkinje tissue resulted in action potentials of greater frequency and exhibiting the unstable rising baseline (prepotential) characteristic of pacemaker activity. Taken together, these results provide strong support for the hypothesis that cardiac pacemaker tissues in general respond to stretch with enhanced activity.

The results with pacemakers of atrial origin are more clearly consistent with this hypothesis than are those obtained with independently beating ventricles. This is in large part related to the way in which meaningful pressure alterations in each of the chambers can be accomplished and in part to the question of whether the conditions under which enhanced ventricular pacemaker activity appeared are best interpreted as being that of stretch.

An adequate range of pressures can be produced in the right atrium by adjusting the height of the fluid level of the reservoir above the atrium. On the other hand, the pressure within the ventricles is essentially determined by the force of the ventricular contraction which, if other factors are constant, is related within limits to the volume and resistance load and through them can be altered. This invokes the well-known Frank-Starling principle. However, the slowly beating isolated ventricles responded to the added resistance load with but little increased force of contraction, as evidenced by the small maximum pressure increment. Under these conditions only a limited pressure range could be explored and to determine the effects of producing higher pressures it was necessary to employ some means of increasing ventricular contractility. For this purpose adrenergic amines were chosen because their actions would most closely parallel a physiological response. Under the influence of these agents and in response to the same work load the ventricles generated considerably greater aortic pressures and new or increased pacemaker activity appeared during the elevated pressure.

Now it is well known that in the "hierarchy" of pacemakers the activity of the ventricles is considerably less than that of the right atrium. Hence, it may be that the effects upon ventricular rate at low pressures were insignificant because of a low order of ventricular spontaneity and that the increases in rate which accompanied the higher pressures occurred because the adrenergic agents enhanced the automaticity of the ventricles. However, this does not tell us why the ventricles should beat faster under increased pressure at all and it follows that some stimulus must have been provided to account for the new or increased pacemaker activity which occurred only during the periods of elevated pressure. One possible source of this stimulation may be found in a consideration of the structure of the ventricular walls. Rushmer has pointed out that during contraction the various muscle layers of the ventricle do not shorten to the same extent and that tension develops in the connections between layers. There is reason to suppose that such tension stretches some fibers and that the more forceful the contraction, the more likely is such stretching to occur. If this be the case, among those fibers which are stretched should be some with pacemaker potentialities. However, that such a series of events does occur is speculative and remains subject to doubt. There may be other means, not known or considered, whereby forceful ventricular contractions or elevated intraventricular pressure may aid in the initiation of spontaneous beats.

In summarizing the effects of epinephrine or metaraminol upon the independently beating ventricles it is safe to conclude that at least two factors may have been involved: 1. the chronotropic action which initially was
seen as an increase in the control rate, and 2. the inotropic action which made possible the increased force of contraction which was necessary to generate the higher pressures during which new or more rapid pacemaker activity occurred. It would be fortunate if there were available a means of increasing contractility which did not itself alter automaticity so that there might be a clear test of any direct effect of contractile force upon ventricular pacemaker activity. However, the necessity for using adrenergic amines in these experiments in order to provoke from the ventricles new or increased pacemaker activity in response to high or suddenly increased pressures, should not preclude consideration of this possible mechanism of some ectopic beats or rhythms in the functional situation. In the physiological environment the heart is provided with adrenergic support and extra work loads, as in exercise, are accompanied by adrenergic outflow. Hence it is the heart-lung preparation with the epinephrine infusion, for example, which more closely parallels the physiological situation.

In an assessment of the relative importance of the various means by which heart rates may be influenced one might conclude that the results reported here probably have little application to normal control of the heart rate. Not only are the autonomic mediators, which are released in the course of nervous control of the heart rate, more effective in altering pacemaker activity but such stretch of the SA node might not normally occur. However, it must be anticipated that under appropriate circumstances atrial dilatation or high arterial pressure might influence cardiac rhythm either through normally dominant or latent pacemakers. One might then look for a role of these conditions in the genesis of certain arrhythmias. For example, it is known that the level of arterial pressure is important in the genesis of hydrocarbon-epinephrine arrhythmias and that atrial stretch enhances the production of fibrillation under methacholine or aconitine, and may be involved in the initiation of the frequent fibrillation with mitral stenosis, or the tachycardia or atrial fibrillation sometimes occurring after heavy exercise.

Summary
The effects of increased transmural pressures upon atrial and ventricular rhythms have been studied in the heart-lung preparation of the dog. Increases in right-heart pressure resulted in increased sinus rates when the SA node was intact. When the SA node was crushed and an A-V nodal rhythm revealed, increased right-heart pressure resulted in more rapid A-V nodal rhythms in some preparations while shifts to more rapid pacemakers, adjacent to the SA node, were detected in others. Independent ventricular pacemakers emerged during periods of elevated pressure in every preparation in which the sinus node had been crushed.

Left-heart pressure was increased by augmenting the systemic resistance, the minute volume, or both. In A-V dissociated hearts, epinephrine or metaraminol were administered to enable the generation of higher aortic pressures (above 150 mm Hg). During the periods of elevated pressure, new or increased pacemaker activity was seen in the independently beating ventricle.

These results and others cited show that atrial dilatation or elevated arterial pressure may participate in the genesis of some cardiac arrhythmias.

References
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