Effects of Changing Heart Rate in Man by Electrical Stimulation of the Right Atrium
Studies at Rest, during Exercise, and with Isoproterenol

By John Ross, Jr., M.D., Joseph W. Linhart, M.D., and Eugene Braunwald, M.D.

The role played by alterations in the heart rate in controlling the integrated responses of the circulation has been the subject of intensive investigation in recent years. It remains unclear, however, whether changes in heart rate that occur during a stress such as muscular exercise are essential to the adequacy of the cardiovascular response; moreover, the effects of altering heart rate alone in the absence of a circulatory stress have not been reported in human subjects without cardiac dysfunction. In the present report the effects of controlling and varying the heart rate at levels above those occurring spontaneously were examined in human subjects with normal atroventricular conduction and with little or no disturbance of cardiac function. To define the importance of changes in heart rate in the circulatory responses accompanying muscular exercise, the effects of exercise when the heart rate was not permitted to change were determined. In addition, the circulatory responses to the infusion of isoproterenol at a constant heart rate were studied.

Methods

Seventeen patients were studied in the postabsorptive state following the administration of sodium pentobarbital, 100 mg. intramuscularly. There were 15 male and two female subjects, ranging in age from 6 to 41 years, none of whom exhibited clinical evidence of impaired cardiac reserve. Following detailed clinical examination and cardiac catheterization, six of the subjects were considered to have functional heart murmurs, four had mild idiopathic left ventricular hypertrophy without obstruction to left ventricular outflow, and three had mild aortic stenosis with transvalvular pressure gradients between 6 and 19 mm. Hg. One patient each had an atrial septal defect, coarctation of the aorta, and minimal aortic valvular regurgitation; one patient was studied 6 months following the repair of a ventricular septal defect.

A bipolar electrode catheter* was advanced into the right atrium and its tip positioned in direct contact with the lateral wall of the atrium. The catheter was connected by two leads, one of which contained a 10,000-ohm resistor, through a stimulus isolation unit to a stimulator.† The high resistance in the leads ensured that minor resistance changes at the site of stimulation would not result in large current fluctuations, while the isolation unit prevented the accidental development of electrical potentials between the stimulator and other equipment attached to the patient.‡ Square wave impulses of between 50 and 90 volts and 6 msec. duration were provided by the stimulator, producing currents at the atrial wall that ranged from approximately 2.5 to 4.0 ma.

A second cardiac catheter was positioned with its tip in the right side of the heart, and systemic arterial pressure was recorded through a Courand needle inserted into the brachial artery. Cardiac output was determined by the indicator-dilution technic, with injection of indocyanine dye into the right side of the heart. The duration of the ejection period was determined from the carotid arterial pressure pulse tracing, which was obtained with a funnel pickup positioned over the vessel. Only tracings exhibiting a sharp upstroke and a clearly defined incisura were analyzed. The mean rate of left ventricular ejection was calculated by dividing the stroke volume index in ml./M.² by the duration of the ejection period in seconds. Exercise was performed in the supine position on a bicycle ergometer pedaled at 40 revolutions per minute for 6 minutes at

*NBH catheter, United States Catheter & Instrument Corp., Glens Falls, New York.
†American Electronics Laboratories, model 104A.

From the Cardiology Branch, National Heart Institute, Bethesda, Maryland.

Circulation, Volume XXXII, October 1965
an external work level of 500 foot pounds per minute.

The effects of progressively increasing the heart rate were determined in all 17 subjects in the resting state. Following the determination of cardiac output, systemic arterial pressure, and the ejection period at the spontaneously occurring heart rate, electrical stimulation of the right atrium was begun and the heart rate was elevated in increments of approximately 25 beats/min., the pressure and cardiac output determinations being repeated after the circulation had stabilized for 3 to 4 minutes at each new level of heart rate. The highest heart rate achieved in each patient varied and was limited either by a reduction in systemic arterial pressure, the systolic pressure not being permitted to fall below 90 mm. Hg, or by inability of the atriocentral node to transmit all of the impulses. In a few patients distressing palpitations limited the degree to which the rate could be elevated. However, most of the patients, while aware of the increase in heart rate, experienced no untoward symptoms during atrial stimulation.

The interrelationships between heart rate and the circulatory response to exercise were studied in seven subjects. First, exercise was performed without controlling heart rate, and during the sixth minute of exercise the alterations of cardiac output, systemic arterial pressure, heart rate, and ejection time that occurred were determined. The subjects rested for at least 15 minutes; the right atrium was then stimulated at a rate equal to or slightly exceeding that achieved spontaneously during the preceding period of exercise. In five of these subjects, while the heart rate was held constant at this level, a second bout of exercise identical to the first in duration and intensity was carried out, the cardiac output and arterial pressure being remeasured during the final minute of exercise.

The effects of controlling the heart rate during a continuous infusion of isoproterenol were determined in five patients. Following the measurement of cardiac output, systemic arterial pressure and ejection time in the control state, isoproterenol was infused in doses ranging from 1 to 3 \( \mu \)g./min., and the measurements were repeated during administration of the drug. Isoproterenol was then discontinued and 15 minutes later electrical stimulation of the atrium was begun at a rate comparable to that occurring spontaneously during the drug infusion. Systemic arterial pressure and cardiac output were then redetermined with the heart rate maintained constant, before and during a second infusion of isoproterenol at a dose identical to that administered previously.

Results

The atrial rate could be readily controlled by stimulating the right atrium at a rate exceeding that of the sinus node. No persistent arrhythmias occurred. The electrocardiographic changes induced during sustained right atrial stimulation are shown in representative tracings (fig. 1). Each stimulus artifact initiated an atrial depolarization, the contour of which sometimes differed slightly from that of the normal P wave, while the configuration of the QRS complex was usually identical to that occurring spontaneously.

Effects of Increasing the Heart Rate Alone

The effects of stepwise increases in the heart rate on the cardiac index, stroke volume, ejection time, and ejection rate are summarized in figures 2 and 3. In general, as the heart rate was increased no striking alterations in the cardiac index occurred. When the heart rates were elevated from an average value of 80 ± 4 beats/min. (S.E.M.) to 121 ± 6 beats/min., the cardiac indices did not change significantly, the values at these two rates averaging 3.67 ± .32 L./min./M.² (S.E.M.) and 3.72 ± .34 L./min./M.², respectively (fig. 2). Further increases in heart rate resulted in small decreases in the cardiac output.
The effects on the cardiac indices of increasing the heart rate by atrial stimulation in 17 patients in the resting state. The change in cardiac index from the control level is plotted against the corresponding heart rate.

Since the cardiac index showed little change as heart rate was increased over a relatively wide range, there was a linear, inverse relationship between the heart rate and the stroke volume (fig. 3A). The left
ventricular ejection period also fell progressively as the heart rate was elevated (fig. 3B). Since the abbreviation of the ejection period was relatively less than the reduction in the stroke volume, the mean rate of left ventricular ejection also decreased progressively as the heart rate was increased (fig. 3C).

Effects of Controlling Heart Rate during Exercise

The effects of muscular exercise when the heart rate was not controlled are summarized in figure 4A. In each patient the increase in cardiac output that occurred during exercise was accompanied by an augmentation of heart rate, while the stroke volume remained essentially unchanged in four patients, increased in two, and decreased in one. The systolic ejection periods averaged 283 ± 7 msec. (S.E.M.) at rest and decreased to 229 ± 6 msec. during exercise, while the mean systolic ejection rates rose from an average level of 185 ± 19 ml./sec./M.² at rest to an average level of 253 ± 24 ml./sec./M.² during exercise.

The effects of exercise while the heart rate was held constant by electrical stimulation at a level comparable to that occurring spontaneously during exercise are shown in figure 4B. In each patient the increase in the cardiac index that occurred was similar to that noted during the previous exercise period (fig. 4A), but it was now accomplished entirely by an increase in the stroke volume. The systolic ejection periods decreased only slightly, from an average value of 228 ± 7 msec. during electrical stimulation at rest to 222 ± 7 msec. during exercise, while the mean ejection rates increased from an average value of 150 ± 19 ml./sec./M.² to 226 ± 24 ml./sec./M.². These interrelationships between heart rate, stroke volume, and ejection rate in one patient are shown graphically in figure 5.

Effects of Controlling Heart Rate during Isoproterenol Infusion

The changes resulting from the infusion of isoproterenol when heart rate was not controlled are summarized in figure 6A. In each patient an increase in the cardiac index

Figure 4

A. The effects of exercise on the stroke volume and heart rate when the heart rate was not controlled. The dotted lines indicate cardiac index isopleths, from 2 to 10 L./min./M.². B. The effects of exercise when the heart rate was controlled by electrical stimulation of the right atrium at a rate close to that achieved previously during exercise (panel A). The asterisks indicate the two patients in whom exercise and pacing were not performed simultaneously.
occurred and was accompanied by an increase in heart rate, whereas alterations in stroke volume were inconsistent. When the heart rate was held constant by electrical stimulation at the level previously attained during isoproterenol administration, reinfusion of this drug resulted in similar augmentation of the cardiac index; however, since the heart rate was unchanged, the increase was now mediated entirely through a large elevation of the stroke volume (fig. 6B).

Discussion

The cardiovascular effects of varying the ventricular rate have been examined by electrical stimulation of the right ventricle in patients with complete heart block.\textsuperscript{2-13} Interpretation of these studies has been limited, however, by the serious impairment of cardiac function that generally accompanies heart block, and by loss of the atrial contribution to ventricular filling.\textsuperscript{14-16} The method employed in the present investigation, a technic similar to one previously suggested,\textsuperscript{17} was designed to permit study of the effects of altering the heart rate in patients without heart block and its attendant abnormalities. Sustained right atrial stimulation did not induce cardiac arrhythmias in the present group of patients. During studies in 43 other patients, six episodes of arrhythmia have occurred. These included five transient periods of atrial fibrillation and a single brief episode of ventricular tachycardia, which reverted spontaneously to sinus rhythm. It is noteworthy, however, that significant cardiac disease was

Figure 5

A. The effects of exercise without control of the heart rate in a single patient are shown in the left panel. The broken diagonal lines indicate mean systolic ejection rates from 100 to 300 ml/sec./M². Note that mean systolic ejection rate increased. B. The effects of electrical stimulation of the right atrium at a rate close to that achieved previously during exercise (open circle) and of then exercising the patient with the heart rate held constant at a rate of 146/min. The connecting dashed arrow between the rest and exercise points represents the resultant effect of these two changes. Increasing heart rate with the subject at rest reduced the mean systolic ejection rate and the duration of the ejection; when exercise was carried out at a constant heart rate, the mean systolic ejection rate increased strikingly with little additional prolongation of the ejection period.

Circulation, Volume XXXII, October 1965
present in all these patients, and that the arrhythmias were usually preceded by frequent premature atrial contractions when the catheter was merely positioned in the right atrium.

In patients with complete heart block, when the ventricular rate is increased above that of the idioventricular pacemaker a definite elevation of the cardiac output has been noted; however, when the rate is increased above approximately 80 per minute, the cardiac output has usually declined, although rarely no change, or even an increase in cardiac output has occurred.\textsuperscript{2-13} The results in the present investigation on patients without atrioventricular block differ from these findings. There was no consistent increase in the cardiac output as heart rate was elevated, even in the four patients in whom the basal rate was below 60/min. Furthermore, no consistent reductions in the cardiac output occurred as the rate was elevated to approximately 150/min. These observations make it clear that the response to elevations of heart rate in patients with complete heart block must be greatly modified by underlying cardiac dysfunction. Furthermore, the findings in the present group of subjects are in accord with experiments in intact dogs, in which little change in the cardiac output was noted during wide variations in heart rate to levels in excess of 200/min.\textsuperscript{18}

The reductions in the systolic ejection periods that accompanied progressive increases of the heart rate in each patient (fig. 3B) agree closely with values predicted from the regression equations of Weissler and his co-workers, which were derived from single observations of heart rate and ejection period in many subjects.\textsuperscript{10, 20} This finding thus supports the contention that such equations may be useful by revealing deviations from this normal relationship. It is remarkable that the relation between heart rate and ejection period

\textbf{Figure 6}

\textit{A. The responses to isoproterenol infusion when heart rate was not controlled. The dotted lines represent cardiac index isopleths, from 2 to 6 L./min./M.\textsuperscript{2}. B. The responses to isoproterenol when heart rate was controlled by electrical stimulation of the atrium at a rate similar to that occurring previously during isoproterenol administration.}
remains constant when it is determined in three widely divergent circumstances: (1) in a large group of subjects whose resting heart rates varied considerably, presumably as a result of variations in the background sympathetic tone to the heart; (2) in the subjects in the present investigation in whom heart rate was progressively altered by electrical stimulation (fig. 3B); (3) in the same subjects during muscular exercise (fig. 5B). It is known that the systolic ejection period is abbreviated by sympathetic stimulation of the heart and that it tends to be prolonged by increasing the stroke volume. Hence, it is possible that the operation of these two opposing factors was responsible for the stability of the above relationship when exercise was carried out at a constant heart rate (fig. 5B). Likewise, the decreases in stroke volume that are associated with increases in heart rate in the resting state (fig. 3A) are undoubtedly partially responsible for the shortening of the ejection period. However, studies in the isolated papillary muscle, the isolated heart, and in the intact dog heart after ganglionic blockade indicate that, even when the degree of shortening or the stroke volume are held constant, an increase in heart rate results in an abbreviation of the duration of contraction.

In normal human subjects, the response to submaximal levels of supine exercise consists of a large increase in heart rate, the contribution of changes in stroke volume to the elevation in cardiac output often being relatively small. In the present study, when heart rate was held constant, the increases in cardiac output that occurred during exercise were similar to those observed when rate was permitted to change. However, the increases in output were, of necessity, mediated entirely through large augmentations in the stroke volumes. This effect of exercise on the stroke volume at a fixed, rapid heart rate is qualitatively similar to that observed in those patients with complete heart block and a fixed but slow heart rate who are capable of increasing cardiac output during exercise, and in whom increases in the stroke volume also occur. It is thus apparent that when peripheral metabolic demands are increased by muscular exercise, the cardiac output can rise through a mechanism not ordinarily called upon. Moreover, since the cardiac output was not altered by changes in the heart rate alone in the resting state, it is clear that in the absence of augmented metabolic requirements, homeostatic mechanisms can maintain cardiac output constant despite wide variations in the heart rate. The concept that cardiac output is regulated primarily through mechanisms other than changes in heart rate receives additional support from other studies, both in man and experimental animals, in which wide variations in the ventricular rate had little influence on the cardiac output responses to exercise. Recently, Levine et al. have focused attention on the use of the mean systolic ejection rate in describing left ventricular function, and the relative effects of heart rate, sympathetic stimulation, and stroke volume on this variable are therefore of interest. It is apparent that increasing the heart rate alone decreased the stroke volume and the ejection period, as well as the mean ejection rate (figs. 2C and 5B). Although the latter finding might suggest that the velocity of muscle shortening decreased with increasing heart rate, recent studies utilizing metal markers sutured to the ventricular epicardium have shown that both systolic and diastolic ventricular dimensions decrease as rate is increased, and that the velocity of shortening actually increases slightly. Thus, since a greater degree of fiber shortening is required to eject a given stroke volume when the ventricle is small than when it is large, the mean ejection rate does not provide an accurate estimate of fiber shortening rate when heart rate is increased by electrical stimulation. When exercise was carried out at a constant heart rate, although little change in the ejection period occurred, a large increase in the mean rate of ejection was observed (fig. 5B). This finding suggests that a marked positive inotropic effect occurred during exercise, although again, the concomitant

_Circulation, Volume XXXII, October 1965_
alterations in ventricular size must be considered in this interpretation. In other studies in man in which the velocity of shortening was measured during exercise with the heart rate held constant, marked increases in this velocity occurred, thus substantiating the suggestion that a positive inotropic influence is exerted on the heart during exercise.  

The cardiovascular responses to isoproterenol infusion were similar to those that occurred during exercise, being characterized by increases in the cardiac index, large elevations of heart rate, and usually by minimal changes in stroke volume. These findings resemble those reported in previous studies concerned with the circulatory effects of isoproterenol.  

Again, as with exercise, when heart rate was held constant by electrical stimulation of the atrium, cardiac output increased, but this increase was now accomplished through an alternative mechanism, an augmentation of the stroke volume.

Summary

A technic is described for controlling the heart rate in patients with normal atrioventricular conduction by means of an electrical pacemaker catheter that stimulated the right atrium. When the heart rates of 17 patients in the resting state were elevated from an average of 80 to 121 beats/min., the cardiac indices remained virtually unchanged and averaged 3.67 and 3.72 L/min./M², respectively. Further increases in the heart rates resulted in small reductions in the cardiac indices to an average value of 3.21 L/min./M² at 148 beats/min. The stroke volumes, ejection periods, and mean rates of ejection decreased as heart rate was increased.

The role of heart rate in the circulatory response to exercise was examined in seven patients. When the heart rates were controlled by electrical stimulation at rates comparable to those previously achieved spontaneously during exercise, it was observed that cardiac output rose normally with exercise and that this rise was accomplished entirely through an increase in the stroke volume. In five patients the effects of isoproterenol infusion were also studied before and during control of the heart rate at the level reached spontaneously during isoproterenol administration. Again, when the heart rate was not permitted to rise, the increases in cardiac output with isoproterenol were mediated through increases in the stroke volume. These studies indicate that in the absence of augmented metabolic requirements, homeostatic mechanisms maintain cardiac output relatively constant despite large induced changes in the heart rate. However, when metabolic demands are increased by muscular exercise, or the circulation is stimulated by catecholamines, cardiac output can rise through an increase in stroke volume, even when alterations in the heart rate are prevented.

References


Circulation, Volume XXXII, October 1965
CHANGING HEART RATE


NEW MANUSCRIPTS

Authors are requested to send all new manuscripts for CIRCULATION to:

Howard B. Burchell, M.D.
CIRCULATION
Plummer Building
200 First Street SW
Rochester, Minnesota 55902

Please note that correspondence concerning manuscripts sent to CIRCULATION before July 1, 1965 should be addressed to Herrman L. Blumgart, M.D., 330 Brookline Avenue, Boston, Massachusetts 02215.
Effects of Changing Heart Rate in Man by Electrical Stimulation of the Right Atrium: Studies at Rest, during Exercise, and with Isoproterenol
JOHN ROSS, JR., JOSEPH W. LINHART and EUGENE BRAUNWALD

Circulation. 1965;32:549-558
doi: 10.1161/01.CIR.32.4.549

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1965 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/32/4/549

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/