Effect of Heart Rate, Exercise, and Nitroglycerin on the Cardiac Dynamics in Complete Heart Block

By Alberto Benchimol, M.D., Yeou-Bing Li, M.D., E. Grey D'Amore, M.D., Robert B. Voth, M.D., and Arnold S. Roland, M.D.

The presence of complete heart block offers a good opportunity to study cardiovascular functions, since one of the major variables of cardiac activity, i.e., heart rate, is maintained constant. In addition, if a cardiac pacemaker is implanted in a heart for treatment of complete heart block, total control of the cardiac rate is achieved, thereby providing an excellent opportunity for studying cardiovascular hemodynamics under a variety of fixed rates.

The present study was undertaken (1) to attempt to establish the most appropriate heart rate for permanent pacing; (2) to ascertain the hemodynamic consequences of complete heart block at a fixed slow heart rate, and the effect of increasing heart rate; (3) to determine the effects of exercise and nitroglycerin on the cardiac dynamics at various fixed heart rates. A patient with complete heart block resulting from coronary artery disease was studied.

Case Report

R. W. (no. 61-1624), a 45-year-old white man, a diabetic, had an uncomplicated myocardial infarction in 1956. He did well until June 1962, when he experienced a single, painless, syncopal episode, with transient loss of consciousness followed by apparent complete recovery. He was hospitalized 3 months later and found to be in congestive heart failure with complete atrioventricular block and an idioventricular rate of 30 beats per minute.

The blood pressure was 160/65 mm. Hg. The pulse rate varied from 22 to 36 and was irregular. The neck veins were distended and showed "cannon" waves. Auscultation of the heart revealed varying intensity of the first heart sound and a normal second heart sound. "Cannon" sounds were present. No heart murmur was heard. Pretilial and ankle edema was present. The remainder of the physical examination was noncontributory.

Venous pressure was 24 cm. saline. A phonocardiogram confirmed the auscultatory findings and also revealed the presence of third and fourth heart sounds. A previous electrocardiogram taken on June 28, 1962, revealed sinus rhythm, left axis deviation, and complete right bundle-branch block. On October 9, 1962, it showed atrioventricular dissociation, with an idioventricular rate of 30 per minute (fig. 1). A chest x-ray showed moderate cardiac enlargement (fig. 2). Local prominence of the left ventricular border with a paradoxical pulsation on fluoroscopy suggested a ventricular aneurysm.

The patient was placed on diuretics; isoproterenol, 20 mg. every 2 hours; ephedrine, 25 mg. every 6 hours; Lente insulin, 40 units daily; prednisone, 20 mg. twice a day; and was digitalized with digoxin (maintenance dose of 0.25 mg. a day). Despite this intensive program the ventricular rate failed to increase above 40. Signs and symptoms of congestive heart failure improved, but the venous pressure remained as high as 28 cm. saline. It was then decided that the implantation of an artificial cardiac pacemaker was indicated.

On October 23, 1962, right heart catheterization was performed. A no. 6 bipolar electrode catheter was inserted into the right medial antecubital vein and advanced to the apex of the right ventricle. The two external electrodes of this catheter were connected to the output of a portable transistorized pacemaker (Electrodyne Model TR-3) and the current of this electrical impulse was set to 1.8 milliamperes.

The cardiac output determinations were performed with use of the indicator-dilution technic. A no. 18 Courand needle was inserted into the right brachial artery for blood sampling and a second one in the left medial antecubital vein for injection of the indicator. Indocyanine dye (Car-
Figure 1

Date: 6/30/62—Note sinus rhythm and the pattern of a complete right bundle-branch block. Date: 10/15/62—Complete heart block with an idioventricular rate of 30 and an atrial rate of 60. Date: 12/19/62—After implantation of pacemaker. Complete heart block persists with an idioventricular rate of 72 per minute. Note that the pacemaker stimulus is always followed by a ventricular response.
diogreen) in a dose of 6.25 mg. was rapidly injected into the vein for each dye curve. The blood was withdrawn from the brachial artery, at a constant rate of 38.2 ml. per minute, by a withdrawal-perfusion pump (Model 600-900). A Gilford cuvette densitometer (Model 103 IR) was used to detect the injected dye. After each dye curve the blood was reinfused into the patient's venous system. The curves were recorded in the Electronics for Medicine (DR-8 Model) oscillographic recorder at a paper speed of 5 mm. per second.

At the end of the procedure the curves were calibrated with the same flow rate and densitometer attenuation as throughout the study. A zero point and three sample calibration points were obtained. The cardiac output, central blood volume, and mean circulation time were calculated by the Stewart-Hamilton formula.

The reproducibility of this technic has been previously tested in a series of 100 subjects, and it was found that repeated cardiac output determinations fluctuate within the range of ± ten per cent of the initial determination.

A Statham P23D strain gage was used for recording of pressures, which were registered immediately following the insertion of the dye curves. Mean pressure was obtained by electronic integration. Peripheral resistance and left ventricular work were calculated by the method of Gorlin et al.

The ejection time was calculated from the indirect carotid tracing with a Sanborn linear crystal microphone (Model 374) and measured from the beginning of the ascending limb to the dicrotic notch. The carotid tracing was used instead of the intra-arterial tracing because of better definition of the dicrotic notch. The carotid tracing and pressure pulses were recorded at a paper speed of 75 mm. per second.

The heart rate was varied (manually) with an external control knob on the pacemaker. The rate of pacing with this unit could be varied from 45 to 120 beats per minute.

Five cardiac outputs were obtained at the control rate and subsequently two determinations were made for each fixed heart rate. The time interval between the injections was approximately five minutes.

After completing the cardiac output studies the patient was taken to the operating room and a Chardack-Greatbatch adjustable rate-current implantable pacemaker was inserted. The operation was performed by Dr. Ivan D. Baronofsky. The wires were implanted in the free wall of the left ventricle and the control unit was inserted in the left lower quadrant of the abdominal wall (fig. 2). The patient tolerated the operation well and was discharged 10 days after surgery, at which time the heart rate was 72 beats per minute and he was free from symptoms and signs of heart failure. The patient remained asymptomatic and returned for repeat studies on December 19, 1962.

*Hynson, Westcott and Dunning, Inc.
†Harvard Instruments, Baltimore, Md.
‡Gilford Instruments Laboratory, Oberlin, Ohio.
§Electronics for Medicine, White Plains, N. Y.
HEMODYNAMICS IN COMPLETE HEART BLOCK

In interpretation and tabulation of results the following criteria have been established. The initial value of any measurement was considered to represent 100 per cent. The differences between the subsequent determinations at anytime during the study were expressed as percentage increase or decrease deviation from the control values.

Results
First Study, November 23, 1962. Cardiac outputs were measured while the heart was stimulated at various rates via an electrode catheter. At the time of this study the patient was still in heart failure and on maintenance doses of digoxin, 0.25 mg. daily.

Cardiac Index. The cardiac index at a control rate of 35 (patient's own pace) was below normal limits at 1.46 L./min./M.² With progressive increase in heart rate the cardiac index reached a maximum of 3.39 L./min./M.² (132-per cent increase) at a rate of 76 (117-per cent increase) beats per minute. A further increase in the heart rate to 100 resulted in a decrease in the cardiac index to 3.30 L./min./M.² (126-per cent increase) (figs. 3 and 4).

Stroke Index. There was a 7.2 per cent increase in the stroke index at the heart rate of

Figure 3
Cardiac hemodynamics with a variable heart rate. CO, cardiac output; CI, cardiac index; SV, stroke volume; SI, stroke index; CBV, central blood volume; CVBI, central blood volume index; Press, pressure; BA, brachial artery; Periph. resist., peripheral resistance; ET, ejection time.
Percentage changes in the cardiac index (CI), stroke index (SI), central blood volume index (CBVI), mean brachial artery pressure (Pressure), peripheral resistance (Resist.), and left ventricular work (Work). Note the fall in the stroke index as compared with the fall in the cardiac index as the heart rate was increased from 76 to 100 per minute. P = pacemaker.

76. However, increasing the heart rate from 76 to 100 beats per minute resulted in a 19.5 per cent decrease in the stroke index from the control value. Increasing the heart rate from 76 to 100 beats per minute resulted in a 26.7 per cent decrease in the stroke index as compared with a 6-per cent decrease in the cardiac index for the same change in rate (figs. 3 and 4).

Central Blood Volume Index. There was a 36.8 per cent increase in the central blood volume index from a control value of 0.57 L./M.² to a maximum of 0.78 L./M.² at a rate of 76 beats per minute.

Brachial Artery Pressure. The brachial artery pressure increased from 110/40 (systolic/diastolic) with a mean of 60 mm. Hg at the control rate of 35 to a maximum of 125/60 with a mean of 80 mm. Hg at a rate of 76 beats per minute, representing a 33-per cent increase in the mean pressure values.

Peripheral Resistance. The peripheral resistance decreased steadily from a control value of 1,920 dynes sec. cm.⁵ at a rate of 35, to 1,075, at a rate of 100, representing a 44-per cent decrease.

Left Ventricular Work.—The left ventricular work for the control rate of 35 beats per minute was low, 1.15 Kg. M./min./M.². There was a progressive increase up to a rate of 100, the work being equal to 3.64 Kg. M./min./M.² representing a 216-per cent increase. As the work increased there was an increase in the cardiac output, central blood volume, and brachial artery pressure with a decrease in peripheral resistance and no change in stroke volume (fig. 4).

Ejection Time.—The ejection time was 0.35 second at a rate of 35, decreasing to 0.24 second at a rate of 100 (31.4-per cent decrease) (figs. 3 and 4).

Time Intervals Measured in the Dye Curves. The mean circulation time, appearance time, build-up time, clearance time, and recirculation time decreased progressively as the heart rate increased.

Second Study, December 19, 1962. This study was performed 26 days after surgical implantation of a permanent pacemaker. At this time the patient was fully ambulatory and compensated. He was still taking digoxin in a dose of 0.25 mg. daily. All the cardiac output determinations were performed at a constant stimulated rate of 72 beats per minute.

Five control determinations were made at the rate of 72 and revealed a cardiac index of 2.65 L./min./M.², which was somewhat lower than the figures obtained in the first study for a rate of 76 (3.39 L./min./M.²).

Effect of Exercise in the Presence of a Fixed Heart Rate. The patient was exercised on a calibrated bicycle (Pedecisor, Model 103) * for a period of 4 minutes. The exercise load was 208 Kg. M./min. The patient tolerated the exercise without difficulty, and performed a total load of 832 Kg. M.

Heart Rate. The heart rate remained con-

*Electro-Medical Engineering Co., Burbank, California.
stant throughout the entire procedure at 72 beats per minute (fig. 5).

Cardiac Index. There was no significant increase in the cardiac index during exercise. At the end of 4 minutes of exercise the cardiac index was 2.64 L/min./M.² compared with 2.65 L/min./M.² obtained during the control period.

Stroke Index. No significant changes were observed during exercise. The control stroke index was 37 ml./beat/M.² compared with 36 ml./beat/M.² at the end of exercise.

Central Blood Volume Index. There was a slight decrease in the central blood volume index from a value of 0.80 L./M.² to 0.72 L./M.² (10-per cent decrease), recorded at the third minute of exercise.

Brachial Artery Pressure. There was a 25-per cent increase in the mean brachial artery pressure during the third minute of exercise, from a control value of 80 mm. Hg to 100 mm. Hg. These figures returned to the control level 10 minutes after exercise. The increase in the mean pressure was mostly due to an increase in the systolic pressure with very little or no increase in the diastolic pressure. The control values for the systolic and diastolic pressure were 120/60, the maximum increase occurred during 3 minutes of exercise and was 160/65 mm. Hg. These values were 130/60 (mean 85) mm. Hg 10 minutes after exercise.

Peripheral Resistance. A significant increase in the systemic resistance occurred with the highest value during the second minute of exercise—1,990 dynes sec. cm.⁵ (38-per cent increase) compared with a control value of 1,441 dynes sec. cm.⁵. This change paralleled the increase in brachial artery pressure, and returned to control levels 10 minutes after exercise.

Left Ventricular Work. There was a 20-per cent increase in the left ventricular work during the third minute of exercise and was 3.44 Kg. M./min./M.².

Time Intervals Measured in the Dye Curves. The mean circulation time, appearance time, build-up time, peak time, disappearance time, concentration time, and recirculation time did not change significantly throughout the study.

Effect of Nitroglycerin in the Presence of Fixed Heart Rate. One tablet of 1/150 gr. of nitroglycerin was given sublingually.

Cardiac Index, Stroke Index, Central Blood Volume Index, and Heart Rate. No significant changes occurred in these measurements after administration of nitroglycerin (fig. 6).
Brachial Artery Pressure. A decrease in the systolic, diastolic, and mean brachial artery pressure occurred after administration of nitroglycerin, with a maximum change recorded at 4 and 6 minutes. These values were 115/55 with a mean of 70 mm. Hg (19-per cent decrease) as compared with 130/60, mean 85, recorded at the control.

Peripheral Resistance. The fall in peripheral resistance paralleled the fall in brachial artery pressure, with a maximum decrease (16 per cent) occurring 4 minutes after administration of nitroglycerin.

Left Ventricular Work. Administration of nitroglycerin resulted in a 21-per cent decrease in the work of the left ventricle. This change appears to be the result of a 14-per cent decrease in the peripheral resistance and of a 17-per cent decrease in the mean brachial artery pressure, with flow remaining constant.

Time Intervals as Measured in the Dye Curves. The mean circulation time, appearance time, build-up time, disappearance time, clearance time, and recirculation time did not change significantly after administration of nitroglycerin.

Discussion

Variable Heart Rate. The cardiac output is basically dependent on the heart rate and stroke volume.26-29 Our results have shown that in the presence of complete heart block with an idioventricular rate of 35 per minute there is a marked decrease in the cardiac output, systolic, diastolic, and mean brachial pressures with an increase in the pulse pressure, peripheral resistance, and left ventricular ejection time.

A progressive increase in the heart rate with the artificial pacemaker from a control rate of 35 to a maximum of 100 beats per minute resulted in a 126-per cent increase in the cardiac index (fig. 5), and this increase was not accompanied by an increase in the stroke volume. This lack of increase in the stroke volume may indicate the presence of significant myocardial disease. The importance of the heart rate in regulating the cardiac output is further documented by our second study (postoperative) in which the heart rate was constant throughout the study while the patient was performing moderate exercise on a bicycle. Under these circumstances, there was no significant increase in the cardiac index nor in the stroke index. Therefore, our results indicate that increasing the heart rate alone was the major factor in increasing the cardiac output. In addition, with the increase in the systemic pressure and constant stroke index the left ventricular work increased significantly.

Optimum Rate of Pacing. The optimum rate of pacing may be defined as that rate which provides a maximal increase in the cardiac output, an increase or stable stroke volume without an excessive increase in the systemic pressure and left ventricular work. In our present case the cardiac index increased progressively from an initial rate of 35 up to the rate of 76, with the stroke index remaining constant. However, a further increase in the heart rate from 76 to 100 beats per minute resulted in a 6-per cent decrease in the cardiac index with a 26-per cent decrease in the stroke index (fig. 4). The “optimum” rate of pacing is usually achieved between 65 and 75 beats per minute where the maximal cardiac output is reached. Although further increments in the heart rate may result in further increase in the cardiac output, the greater decline in the stroke volume with an increase in the systemic pressure are perhaps undesirable consequences that should be avoided.

Effect of Exercise at a Fixed Rate. It was interesting to observe that moderate exercise at a fixed heart rate of 72 resulted in no increase in the cardiac output nor in the stroke volume. An observed 25-per cent increase in the brachial artery pressure and a 38-per cent increase in peripheral resistance with no change in the cardiac output or stroke volume appears to confirm the importance of peripheral vasoconstrictor activity as a mechanism in the regulation of flow.30 Perhaps visceral compensatory vasoconstriction during exercise, in this instance, is a major factor in this regulatory mechanism, with blood flow being increased to the exercising vasodilated skele-
nal muscle. Rushmer, Franklin, and Van Citters have shown that compensatory visceral vasoconstriction is not a predominant mechanism in exercise in normal dogs; perhaps it becomes a dominant mechanism when the cardiac output is not increased.

Effect of Nitroglycerin at Fixed Rate. The effects of nitroglycerin in a system such as this are interesting and worthy of comment. As is well known, tachycardia is one of the major effects of the nitrites on the circulatory system. The postulated vasodilating action of nitroglycerin in the coronary circulation is still uncertain. There has been strong indication that nitroglycerin does increase coronary blood flow in the presence of healthy coronary vessels, however, according to Gorlin et al. this increase in coronary flow does not take place in the presence of significant coronary artery disease. Nevertheless, nitroglycerin remains the best drug for relieving angina pectoris. Our data suggest that an unquestionable peripheral vasodilatation occurs, as revealed by a 17-per cent decrease in the brachial artery pressure and a 16-per cent decrease in the peripheral resistance at a constant flow rate and heart rate (fig. 6). The extent of fall in the mean pressure and peripheral resistance which occurred 3 to 4 minutes after administration of nitroglycerin was a striking phenomenon as was the complete lack of change in the cardiac output and stroke volume. These findings support the theory that one of the most important sites of action of nitroglycerin is the peripheral circulation, producing peripheral vasodilatation and thereby a decrease in the left ventricular work. In fact, the left ventricular work fell from 3.17 Kg. M./min./M.² to 2.48, representing a 21.7-per cent decrease. Therefore, one mechanism by which nitroglycerin could affect the requirements of the heart with coronary artery disease is by decreasing the left ventricular work for a given flow, which could account for the beneficial effect of this drug in relieving angina pectoris.

We believe that our studies support the use of permanent artificial pacemaking in complete heart block, even when Stokes-Adams attacks are not of primary concern. The case report and the physiologic data presented in this paper indicate that refractory cardiac decompensation in the presence of complete heart block is a sufficient indication for the use of the implantable pacemaker.

Summary and Conclusions

The hemodynamic consequences of a complete heart block are described in a patient who developed complete atrioventricular block following an acute myocardial infarction.

Increasing the heart rate from 35 to 76 beats per minute with an artificial pacemaker resulted in a 132-per cent increase in the cardiac index, a 36.8-per cent increase in the central blood volume index, a 216-per cent increase in the left ventricular work, and a 33-per cent increase in the systemic pressure. There was a 44-per cent decrease in peripheral resistance and 31.4-per cent decrease in left ventricular ejection time. The stroke volume remained unchanged throughout the study.

Moderate exercise with a fixed cardiac rate of 72 beats per minute for 4 minutes resulted in no change in the cardiac output, stroke volume, and central blood volume and a 25-per cent increase in the systemic pressure, a 38-per cent increase in the peripheral resistance, and a 20-per cent increase in the left ventricular work.

Administration of nitroglycerin with fixed heart rate resulted in no change in the cardiac output, stroke volume, or central blood volume, but a 17-per cent decrease in the systemic pressure, a 16-per cent decrease in peripheral resistance, and a 21-per cent decrease in left ventricular work. This indicates that one of the major effects of this drug is on the peripheral circulation without necessarily increasing coronary blood flow.

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Meaning of the Scientific Revolution

It is not a simple question to answer why the scientific revolution occurred when it did. It started, as all serious historians would agree, in the late Middle Ages and early Renaissance, and was very slow at first. No great culture has been free of curiosity and reflection, of contemplation and thought. "To know the causes of things" is something that serious men have always wanted, a quest that serious societies have sustained. No great culture has been free of inventive genius. If we think of the culture of Greece, and the following Hellenistic and Roman period, it is particularly puzzling that the scientific revolution did not occur then. The Greeks discovered something without which our contemporary world would not be what it is: standards of rigour, the idea of proof, the idea of logical necessity, the idea that one thing implies another. Without that, science is very nearly impossible, for unless there is a quasi-rigid structure of implication and necessity, then if something turns out not to be what one expected, one will have no way of finding out where the wrong point is: one has no way of correcting himself, of finding the error. But this is something that the Greeks had very early in their history. They were curious and inventive; they did not experiment in the scale of modern days, but they did many experiments; they had as we have only recently learned to appreciate a very high degree of technical and technological sophistication. They could make very subtle and complicated instruments; and they did, though they did not write much about it. Possibly the Greeks did not make the scientific revolution because of some flaw in communication. They were a small society, and it may be that there were not quite enough people involved.

In a matter of history, we cannot assign a unique cause, precisely because the event itself is unique; you cannot test, to see if you have it right. I think that the best guess is that it took something that was not present in Chinese civilisation, that was wholly absent in Indian civilisation, and absent also from Greco-Roman civilisation. It needed an idea of progress, not limited to better understanding for this idea the Greeks had. It took an idea of progress which has more to do with the human condition, which is well expressed by the second half of the famous Christian dichotomy—faith and works; the notion that the betterment of man's condition, his civility, had meaning; that we all had a responsibility to it, a duty to it, and to man. I think that it was when this basic idea of man's condition, which supplements the other worldly aspects of religion, was fortified and fructified between the 13th and 15th centuries by the re-discovery of the ancient world's scientists, philosophers, and mathematicians, that there was the beginning of the scientific age. By the 17th century there were a handful of men involved in improving human knowledge, or "useful knowledge" as the phrases went, so that new societies like the Royal Society and the Academy were formed, where people could talk to each other and bring to the prosecution of science that indispensable element of working together, of communication, of correcting the other fellow's errors and admiring the other fellow's skills, thus creating the first truly scientific communities.—J. ROBERT OPPENHEIMER. “On Science and Culture.” Encounter, October, 1962, p. 5.
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