Normal Response Curve to Exercise of Relative Cardiac Output Measured with Radioiodinated Serum Albumin

By Sylvan L. Weinberg, M.D., G. Richard Grove, Ph.D., Robert E. Zipp, M.D., David C. Daniels, B.S., and James P. Murphy, B.S.

A simple, relatively precise, and clinically applicable indirect method of determining relative cardiac output is presented. The principle involved is a modification of the dye-dilution principle and is performed by external monitoring of intravenously injected radioiodinated serum albumin combined with a standard detecting and recording device. This procedure was performed serially before and after a standard Master test, and the results in 19 healthy individuals describe a relative cardiac output exercise response curve for normal individuals. The utilization of cardiac output in the manner presented may add another clinical measurement of cardiac function.

One of the most challenging problems in clinical medicine is the delineation of boundaries of normal and pathologic cardiac states. In a cardiac survey a multilateral approach is employed including a history and physical examination, studies of the pulse, venous and arterial pressures, and respiration under various standardized circumstances. A battery of laboratory tests may include a blood count, serum lipid, and other blood chemistry determinations. In addition, circulation time, electrocardiograms, and appropriate x-ray and fluoroscopic studies are obtained. This standard diagnostic appraisal all too frequently fails to distinguish boundaries of disease. In many instances, by existing standards, the conclusion may be reached that the patient's responses are "within normal limits." Among these individuals, normal by criteria previously described, there must exist differences in cardiac function and possibly in disease not demonstrated by these clinical tests. In an effort to add another parameter of cardiac function to the battery of diagnostic methods, the clinical applicability of a cardiac output test in response to exercise with external monitoring of intravenously injected radioiodinated serum albumin (RISA) has been explored.

The values obtained by this technic are an indirect measurement but certainly a function of cardiac output. The exact relationship between the measured and the true values of cardiac output is not definitely known; however, because of the preciseness of this technic, relative changes in cardiac output in a given individual can be determined with great confidence even though the relationship to the absolute values is not accurately known. Thus, this technic has the potential of providing additional information on the relative changes of cardiac output with exercise that may be of value in the clinical assessment of cardiac function.

Methods and Materials

The method of determining cardiac output used in this study is direct measurement of the mean residency time in the heart, which is probably related to cardiac output. A predetermined amount of RISA was injected into the antecubital vein, and the radioactivity level over the heart was detected by a scintillation probe and recorded on a rectilinear-strip chart recorder. The dosage of RISA was 5 mc, for the first measure of cardiac output. The amount was doubled for each succeeding output in the series, making a total of 75 mc. for the 4 determinations. The probe was placed at an arbitrarily chosen point 4 cm. above and 2 cm. to the left of the inferior end of the sternum. A characteristic curve shows the radioactivity level observed over the heart during initial mixing and
its exponential diminution, which theoretically decreases to the original level for a single cycle through the heart and may be marked by a second rise due to recirculation of the radioactive material. The area under the curve was analyzed in sections by planimetry and calculated from formulas derived for this type of exponential response. The details of these calculations have been described.$^{1,2}$

This method of performing cardiac output was used in 19 healthy adult individuals in conjunction with the standard 2-step exercise test as described by Master and co-workers.$^3$ The series included 6 women, 22 to 32 years of age, and 13 men, 20 to 36 years of age. Each subject was seated comfortably in a chair (fig. 1). Resting baseline data included pulse, blood pressure, respiratory rate, electrocardiogram, blood volume done by a radioactive iodine technic,$^4$ and cardiac output. Ample time was allowed for the patient to relax, so that the data from the first cardiac output might be as basal as possible. The procedure was explained to the patient in advance to allay any anxiety that might arise from seeing the unfamiliar equipment. The patient performed a standard 2-step exercise test, which consisted of the appropriate number of trips in accordance with the patient's sex, age, and weight in 1.5 minutes. Immediately following the end of exercise the entire battery of physiologic observations was repeated. An effort was made to perform the cardiac output immediately after exercise was completed. Speed was facilitated by leaving an indwelling needle with obturator in the antecubital vein during the period of exercise. Electrodes were left in place with the leads attached so that the electrocardiogram could be taken simultaneously with the cardiac output following exercise. Observations were repeated at 4.5 and 8 minutes after exercise.

**RESULTS**

There were no unusual changes in the pulse rate, blood pressure, or respiratory rate in the 19 cases. The series of 4 electrocardio-
grams for each patient in no instance revealed a positive exercise test. The data for cardiac output for each case and the averages are shown in table 1. While minor discrepancies occur in some instances a consistent pattern is apparent with the cardiac output rising sharply after exercise in the order of 1.5 to 2 times the resting level. At 4.5 minutes the cardiac output in most instances returned approximately to control levels and in nearly every instance the output recorded 8 minutes after exercise was below the resting level. The results plotted in figure 2 show data considered to be a normal cardiac output response curve following the exercise burden imposed by the Master test.

**DISCUSSION**

The heart’s function as a pump is to maintain an adequate blood flow to the tissues of the body. To provide appropriate increases in blood flow in response to specific demands is an equally important function of the pump. The importance of cardiac output in physiologic and disease states has been recognized for many years. Since the introduction of dilution technics for determining cardiac output by Stewart5-7 and their modifications by Hamilton and co-workers,8-10 the need for simplification of methods to permit wider clinical application has been apparent. Rushmer11 has emphasized the potential clinical importance of a practical means of measuring cardiac output in response to a work load in the diagnosis and prognosis of heart disease. At the present time, however, measurement of cardiac output and its response to exercise has not achieved full clinical usefulness. In order for a measure of cardiac output to be applicable clinically, certain criteria must be met. These might include accuracy, reproducibility, safety, convenience, capability of serial repetition, and noninterference with therapeutic or diagnostic activities. The experiments reported here suggest that externally monitored RISA as used in this series of patients fulfills the criteria of clinical applicability. Data for reproducibility and internal precision have been previously documented,1,2 indicating a 50 per cent probable error of 17.5 per cent in 98 cases and an average probable error of 6.1 per cent in 3 serial determinations in the same patient for a series of 20 individuals.

**Table 1.—Pulse Rate and Cardiac Output before and after Exercise**

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Fig. 2. Average cardiac output data from 19 normal patients showing the output response following the standard Master test in relation to time. The average cardiac output in liters per minute is 7.35 resting, 11.65 immediately postexercise, and 8.33 and 6.79 at 4.5 and 8 minutes postexercise, respectively. There is a 50 per cent probable error of 17.5 per cent.

The internal precision is particularly pertinent in situations where repeated observations are made in the same patient for a comparison of varying physiologic states. The cardiac output with externally monitored RISA inflicts no trauma to the patient other than that of a venipuncture. It can be done at the bedside with the patient in a recumbent or sitting attitude. It may be repeated at any interval of time from several minutes to greatly extended periods of time depending on the nature of the physiologic problem being observed. With regard to safety, the amount of radioactive exposure must be considered. A series of 4 cardiac output determinations done in approximately 12 minutes utilizes a total of 75 μc. While no absolute data for radiation tolerance can be defined at this time, the radioactivity involved is minimal by present standards. It is considerably less than that used in other methods recorded for estimating cardiac output by isotope technics.12-14 Although the amounts of radioactive materials used in this technic are considerably less than other technics described, the cardiac output is relative and its precise relation to outputs measured by other methods has not been determined.

In the series of patients presented, serial cardiac output determinations are correlated with the Master 2-step test. The Master test has been evaluated recently by Ford and Hellerstein,15 who found it to be sound physiologically in that it imposes a similar energy demand on individuals of different age and weight. They emphasized the failure of patients with heart disease to increase oxygen utilization normally during exercise. They speculated that this might be due either to a failure to increase cardiac output in response to exercise or to a reduced arteriovenous oxygen difference, probably the former. The data presented here indicate that a predictable change in cardiac output does, in fact, occur in response to the exercise load of the Master test in normal patients. The changes in car-
cardiac output follow a pattern that might be termed the normal cardiac output response curve. It would appear that measurement of the cardiac output in response to the Master test may be a valuable supplement to the other data obtained in conjunction with the Master test, such as pulse, blood pressure, electrocardiogram, and oxygen consumption. The cardiac output response curve may form a standard by which abnormal functions of the heart may be detected where other parameters are within normal range. Preliminary data show variations from the normal cardiac output response curve in various disease states such as arteriosclerotic, valvular, and congenital heart disease.

SUMMARY

The clinical applicability of this method of performing cardiac output by means of externally monitored radioiodinated serum albumin has been demonstrated. Serial cardiac output determinations have defined a normal cardiac output curve in response to the load imposed by the Master test in normal patients. The potential usefulness of the cardiac output response curve is suggested as a valuable supplement to the physiologic data obtained in conjunction with the Master test in defining boundaries of normal and disordered cardiac function.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Es demonstrate le applicabilitate clinic del metodo de determinar le rendimento cardiac per sequer al extero le radioactivitate de iodo$^{131}$ in albumina serial. Determinaciones serial del rendimento cardiac ha resultate in le definition de normal curvas de responsa del rendimento cardiac sub le effetto del carga imponite per le test de Master in subjectos normal. Es suggeste que le curva del responsa del rendimento cardiac es de valor como supplemento al datos physiologie obtenite in conjunction con le test de Master pro definir le limites inter normalitate functional e dysfunction del corde.

REFERENCES

6. ---: Researches on the circulation time in organs and on the influences which affect it. IV. The output of the heart. J. Physiol. 22: 159, 1897.
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