Studies on the Effect of Exercise on Cardiovascular Function

I. Cardiac Output and Mean Circulation Time

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For technical reasons, the measurement of cardiac output during brisk walking is difficult. By using a slight modification of the Hamilton dye-dilution method, such measurements, and measurements of mean circulation time, were made at rest and at the end of a moderate work load in normal subjects. A motor-driven treadmill was used for the exercise. It was found that the cardiac output increases 1.7 to 1.9 times and the mean circulation time decreases about 34 per cent in normal young men and women after a 10 minute walk at 3 miles per hour and 5 per cent grade.

Restraining measurements of cardiovascular function in patients with asymptomatic heart disease are often perfectly normal and may not serve to differentiate such patients from normal individuals. For this reason, various forms of exercise tests have come into use in an attempt to uncover latent functional incapacity, but certain technical difficulties have been encountered in designing such tests. With regard to cardiac output, few available methods lend themselves readily to studies involving the usual forms of exercise such as walking or running. Grollman's acetylene method has been employed in this situation but some doubt exists, however justifiable, that the technic is valid at high output levels. There are obvious difficulties in connection with using the direct Fick procedure when subjects are walking or running, although it has been successfully applied in other, less physiologic forms of exercise.

The type of exercise employed is also of some consequence. Ideally, one should use a technic to which most subjects are already accustomed and in which the influence of training is reduced to a minimum. If the method is to be applied not merely to healthy individuals but to diseased subjects as well, the work load must be set at a fairly conservative level. On the other hand, it must be adjusted so that measurable circulatory change is induced, whether the subject be well or diseased. Finally, measurements must be made before and during, not after, the exercise, the latter having been maintained long enough to permit the attainment of a relatively steady physiologic state.

The following studies were carried out in the hope of developing a technic that meets most, if not all, these requirements, and of obtaining quantitative information concerning the hemodynamic response of the normal subject to exercise.

Method

The dye-curve technic for measuring cardiac output, as described by Hamilton, was chosen as the most suitable method for present purposes. The sequence followed in the experiments is shown in table 1. In-lying needles were eliminated by the use of polyethylene catheters. For injection of the dye, a PE-90 catheter (inside diameter 0.86 mm., outside 1.27 mm.) was introduced into the median basilic vein through a 15 gauge needle, the puncture site having previously been anesthetized. The catheter was then advanced about 30 cm. into the vein toward the heart and was taped in place. The external end was fitted with an adapter and a three-way stopcock. This accomplished, the guiding needle was withdrawn and allowed to remain on the catheter between the puncture site and the adapter. For collection of arterial blood samples, a PE-50 catheter (inside diameter 0.58 mm., outside 0.97 mm.) was introduced into the brachial artery of the other arm through a thin-walled 18 gauge needle, the puncture site and the tissues around the artery having previously been liberally infiltrated with procaine. It was found that the catheter can usually be intro-
duced without difficulty, although at times resistance is encountered in spite of the presence of vigorous, pulsatile blood flow from the open needle. The catheter was advanced about 5 cm. into the artery and the 18 gauge needle withdrawn entirely. The catheter was then carefully taped in place. A 22 gauge needle was inserted into the external end of the catheter and a three-way stopcock attached to the needle. Both venous and arterial catheters were kept filled with heparinized saline solution when not in use for injection of dye or collection of blood. The insertion of the catheters usually occasioned the subjects no discomfort whatever, but occasionally they complained of a slight aching sensation as the needle entered the artery.

Evans blue dye (T-1824) was injected through the venous catheter at zero time from a syringe calibrated to deliver a known amount of dye (2.0 cc. of a 0.5 per cent solution) at the end of the venous catheter. Less than one second was required for the injection.

Arterial blood samples were collected at two-second intervals from the arterial catheter. Flow from the catheter was not pulsatile, owing to its small internal diameter, but proceeded in a drop-by-drop manner. In order to insure the collection of adequate samples during the two-second intervals, a special collecting device, employing a vacuum to speed flow, was used. The device converts intermittent to steady flow and is described in full elsewhere.6

A motor-driven treadmill was used for the exercise. Subjects walked on it for 10 minutes at a speed of 3.0 miles per hour and at a 5 per cent grade. This level of exercise corresponds to an average oxygen uptake of 1214 cc. per minute and imposes no particular difficulty on normal subjects leading sedentary lives.

The usual colorimetric method of estimation of dye concentration was modified in the following way: 0.1 cc. of heparinized whole blood was diluted to 1.0 cc. total volume with a normal saline solution and was centrifuged in a Hellige tube. The supernatant diluted plasma was then analyzed for dye content in an Evelyn colorimeter at 620 millimicrons, using a special microadapter.7

Use of whole blood for the analyses, instead of serum or plasma, necessitated a change in the usual method of calculating the factor for conversion of density readings to milligrams of dye (K factor). Since the dye is distributed solely in the plasma fraction of whole blood, it is necessary to take the hematocrit reading into account in making the calculation. Known solutions of dye in heparinized whole blood were made up in the usual way, and 0.9 cc. normal saline solution was added to 0.1 cc. aliquots. The diluted blood was then centrifuged for 10 minutes at 2,000 revolutions per minute. The Evelyn colorimetric reading was obtained as for an ordinary sample. The K factor was calculated as density reading/amount of dye in supernatant volume. Thus, for a known solution containing 0.299 mg. dye per 5 cc., the calculation is as follows:

\[
\text{Hematocrit} = 50.08 \text{ per cent}
\]
\[
\text{Amount plasma in 5 cc.} = 2.5 \text{ cc.}
\]
\[
\text{blood}
\]
\[
\text{Volume dye solution added} = 0.06 \text{ cc.}
\]
\[
\text{Total liquid} = 2.56 \text{ cc.}
\]
\[
\text{Concentration dye per cc.} = 0.117 \text{ mg.}
\]
\[
\text{Amount plasma per 0.1 cc.} = 0.05 \text{ cc.}
\]
\[
\text{blood}
\]
\[
\text{Total dye in 0.1 cc. blood} = 0.0058 \text{ mg.}
\]
\[
\text{Density reading} = 0.434
\]

Once the K factor is determined for a given lot of dye, it is not necessary to recalculate it for each individual subject unless the hematocrit reading is well outside the normal range. K factors, calculated in the above manner, for hematocrit readings ranging from 40 to 51 per cent were within less than 1 per cent of each other, owing to the large plasma dilution factor (about 16:1). Nor is the normal increase in hematocrit as a result of exercise (from 45.3 ± 2.3 per cent at rest to 47.4 ± 2.4 per cent during exercise) large enough to introduce significant error.

Dye curves were constructed by plotting density readings against time in seconds (fig. 1). The terminal portion of the curve, and the point at which it crosssed the baseline, were determined by plotting values between the peak of the curve and the beginning of recirculation on semilog paper. A straight line was fitted to these points and the requisite terminal values were read from it. The area of the curve was determined by planimetry and was used for the calculation of mean dye concentration and mean circulation time. More specifically, the latter was defined as the time taken by one-half of the dye to pass the sampling point; it was obtained by determining the point in time at which a line dividing the area under the curve in half intersected the baseline.
Fig. 1.—Sample dye curves, at rest and during exercise, showing the extrapolated values after the beginning of recirculation.

To calculate cardiac output, the mean density reading obtained by planimetry (total area divided by duration of curve) from the dye curves, was divided by the K factor and the result multiplied by 10,000 to obtain mean concentration of dye per liter of blood. The value was then inserted into the formula:

\[
\text{Cardiac output in liters/minute} = \frac{60 \times \text{total amount of dye injected}}{\text{mean concentration dye per liter} \times \text{duration of curve in seconds}}
\]

The subjects used for the study were in good health and had no evidence of cardiovascular disease. They were fasting at the time of testing. There were 11 women, aged 22 to 30 (average 24.2), and 23 men, aged 18 to 39 (average 25.2).

RESULTS

The complete data are set out in tables 2 and 3. The resting figures are comparable with those obtained by other workers using the dye-curve method. For example, the resting figure for cardiac output obtained by Asmussen and Nielsen was \(6.86 \pm 2.1\) liters per minute, the corresponding figure in the present study being \(6.91 \pm 1.03\) liters per minute. The value reported by Ring and co-workers, using a method very similar to our own, was somewhat lower (6.44 \(\pm\) 4.3 liters per minute). Figures given by other workers for the cardiac index vary from \(3.2 \pm 0.2\) to \(3.8 \pm 0.3\) liters per minute per square meter. Our value for the cardiac index (in young men) is \(3.63 \pm 0.59\) liters per minute per square meter of body surface area.

### Table 2.—Cardiac Output, Cardiac Index, and Mean Circulation Time at Rest and during Exercise in 23 Normal Young Men

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Resting</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CO</td>
<td>CI</td>
</tr>
<tr>
<td>K. W.</td>
<td>25</td>
<td>5.18</td>
<td>2.88</td>
</tr>
<tr>
<td>G. M.</td>
<td>23</td>
<td>7.57</td>
<td>4.05</td>
</tr>
<tr>
<td>R. K.</td>
<td>19</td>
<td>6.58</td>
<td>4.09</td>
</tr>
<tr>
<td>W. K.</td>
<td>20</td>
<td>5.43</td>
<td>2.70</td>
</tr>
<tr>
<td>J. G.</td>
<td>18</td>
<td>8.03</td>
<td>4.67</td>
</tr>
<tr>
<td>F. G.</td>
<td>27</td>
<td>6.45</td>
<td>3.26</td>
</tr>
<tr>
<td>J. D.</td>
<td>19</td>
<td>9.19</td>
<td>5.11</td>
</tr>
<tr>
<td>J. D.</td>
<td>19</td>
<td>6.39</td>
<td>3.29</td>
</tr>
<tr>
<td>S. K.</td>
<td>20</td>
<td>6.32</td>
<td>3.40</td>
</tr>
<tr>
<td>T. M.</td>
<td>21</td>
<td>8.31</td>
<td>4.18</td>
</tr>
<tr>
<td>J. E.</td>
<td>22</td>
<td>6.69</td>
<td>3.56</td>
</tr>
<tr>
<td>J. T.</td>
<td>21</td>
<td>8.89</td>
<td>4.42</td>
</tr>
<tr>
<td>D. S.</td>
<td>21</td>
<td>6.61</td>
<td>3.63</td>
</tr>
<tr>
<td>E. S.</td>
<td>30</td>
<td>7.32</td>
<td>3.50</td>
</tr>
<tr>
<td>E. G.</td>
<td>22</td>
<td>7.27</td>
<td>3.62</td>
</tr>
<tr>
<td>F. D.</td>
<td>29</td>
<td>7.09</td>
<td>3.65</td>
</tr>
<tr>
<td>P. A.</td>
<td>22</td>
<td>7.03</td>
<td>3.70</td>
</tr>
<tr>
<td>W. G.</td>
<td>19</td>
<td>6.45</td>
<td>3.39</td>
</tr>
<tr>
<td>J. L.</td>
<td>24</td>
<td>5.28</td>
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<td>W. S.</td>
<td>32</td>
<td>6.15</td>
<td>3.20</td>
</tr>
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<tr>
<td>D. H.</td>
<td>38</td>
<td>6.72</td>
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</tr>
<tr>
<td>R. G.</td>
<td>38</td>
<td>7.84</td>
<td>3.77</td>
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</tbody>
</table>

Mean... 25.2 6.91 3.63 18.2 12.17 6.32 12.1
S.D....... 1.03±0.59±3.0±3.07±1.37±2.2

In relative terms, the cardiac output in the men increased 1.76 times the resting value during exercise, the corresponding figure for women being 1.89. There was wide variation in response to exercise, however, from individual to individual. In one man, the cardiac output increased only 1.13 times the resting value, and in one woman, at the other extreme, the increase was over fourfold.

Mean circulation time decreased consistently during exercise. In terms of per cent of the resting value, the average decrease for the men was 33.4 and for the women it was 35.7.

DISCUSSION

From the practical point of view, the dye curve technic is more suitable for measurement of cardiac output during exercise than any of the available methods. It does not require special cooperation on the part of the subject, as does the acetylene method, and
does not require measurement of oxygen consumption as do both the acetylene and direct Fick procedures. It also avoids the necessity for catheterization of the heart, a technic that might involve considerable risk to the subject in experiments of this type. Since the validity of the dye curve method, both at rest and during exercise, now seems to be well established,\textsuperscript{2,11,12,18} it is difficult to sustain an objection to its use in appropriate situations. Its application in the present study was not particularly troublesome technically, but required a special collection device, similar to that described by Ring, and associates,\textsuperscript{8} and a slight modification of the usual method of colorimetric analysis, the latter permitting use of small samples of heparinized whole blood. The other alternative to the method used is the oximetric technic developed by Wood and colleagues.\textsuperscript{14,15} Theoretically, this technic is the best available for recording dye curves, since it follows changes in dye concentration more precisely than does serial sampling of arterial blood. In addition, the necessary analytic work is somewhat less. There remains some doubt, however, about the possibility of quantitating curves obtained with the ear oximeter for calculation of cardiac output, although calibration of those obtained with the cuvette oximeter appears to be more satisfactory.\textsuperscript{9} The technic still requires arterial puncture and the preparation of blood samples containing known amounts of dye. Moreover, the per cent saturation of arterial blood with oxygen must not be allowed to change appreciably during the determination. For the present study, the serial sampling technic proved to be quite satisfactory, but it must be admitted that a two-second sampling interval may well be too long for use in experiments involving very rapid dye curves. A shorter sampling interval, such as was used by Ring and co-workers, is clearly more desirable. Inspection of the curves obtained at the work loads used in the present study, however, seems to indicate that at this level of work, a two-second sampling interval introduces no great error. Some portion of the curve near the peak may not be registered when the two-second interval is used; this may result in a slightly lower mean concentration of dye and a correspondingly high cardiac output. In fact, however, the mean cardiac output during exercise in our normal subjects is somewhat lower than that reported by other workers using the same method at comparable work loads.\textsuperscript{2} Heavier work loads, and faster dye curves, would, of course, necessitate the use of a shorter sampling interval.

The study shows that, at the work load used, the cardiac output during exercise may be almost double the resting output in normal young individuals. The decrease in mean circulation time as a result of exercise was around 34 per cent for both groups and was quantitatively somewhat more predictable than the increase in cardiac output. That there is a definite, though rough, inverse correlation between increase in cardiac output, on the one hand, and decrease in mean circulation time, on the other, seems certain. The present data, however, are not suitable for proving the existence of such a relationship. Successive experiments, in the same subjects and using increasing work loads, are needed for the purpose.

Because of the wide variation in response of the cardiac output to exercise in normal individuals, normal standards are difficult to construct. It would, therefore, be hazardous to compare results of the test in a single individual with those obtained by the same test.
in the group of normals. Comparison of groups of individuals who have cardiovascular disease with normal groups, on the other hand, is possible and the results of such a comparison will be presented in a future paper.

Conclusions

1. The dye-curve technic is readily applicable to the study of changes in cardiac output and mean circulation time produced by exercise in the human being.

2. By applying the technic to normal subjects before and at the end of a 10-minute walk on a motor driven treadmill running at 3 miles per hour and set at a 5 per cent grade, it was found that the exercise causes the cardiac output to increase about 1.7 times in men and 1.9 times in women.

3. The mean circulation time, under the same conditions, decreases about 34 per cent in both groups of normal subjects.

Addendum

The circulation times as given are median, not true mean, values. As pointed out by Hamilton and associates, the true mean circulation time corresponds to the point representing the center of gravity of the curve, and not to the point that divides it into two halves. Recalculation of the data, using Hamilton's equation, shows that in the present work the mean and median circulation times are almost, but not quite, identical. Correct mean circulation times for the subjects tested will be presented in part III of the present series of studies.

Acknowledgment

We wish to express our sincere thanks to Miss Phyllis Waldsmith, Laboratory Technologist, without whose technical skill and unfailing good nature the work could not have been done.

Sumario Español

Por razones técnicas, la medida del trabajo cardíaco durante un andar acelerado es difícil. Por medio de una ligera modificación del método de dilución de tinte de Hamilton, estas medidas al igual que tiempos promedio de circulación fueron determinados durante el descanso y al final de ejercicio moderado en sujetos normales. El ejercicio se hizo en un molino de rueda de andar movido a motor. Se encontró que el trabajo cardíaco aumenta de 1.7 a 1.9 veces y el tiempo de circulación promedio disminuye como 34 por ciento en hombres jóvenes normales y mujeres luego de una caminata de 10 minutos a 3 millas por hora y una pendiente de 5 por ciento.

References


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