BEHAVIOR OF STROKE VOLUME AT REST AND DURING EXERCISE IN HUMAN BEINGS *

By CARLETON B. CHAPMAN, JOSEPH N. FISHER AND BRIAN J. SPROULE

(From the Cardiopulmonary Laboratory of the Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Texas)

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The implications of Starling's law of the heart, as stated in the Linacre Lecture (1), make it clear that physical exercise brings about increased venous return and increased diastolic filling of the heart. This, in terms of the Starling concept, induces sufficient increase in the energy of contraction to drive increased volumes of blood into the aorta with each stroke. While Starling was aware that "the heart is subject to the control of the central nervous system by means of its inhibitor and augmentor nerves . . ." he undoubtedly placed the emphasis, insofar as cardiac adaptation to stress is concerned, on intrinsic response of the myocardium to change in end-diastolic fiber length. It follows, if Starling's Linacre Lecture is credited, that the heart must meet the demands imposed by physical exertion, in part at least, by increasing its stroke volume.

This was indeed found to be the case in older studies on the effect of exercise on human circulatory function (2–4); these studies served further to establish the view that increase in both stroke volume and pulse rate are utilized by the organism during exercise.

A different view has been gradually formulated by Rushmer who, using continuous measurements of internal left ventricular diameters (5) and circumference (6) in unanesthetized dogs exercising on a treadmill, was not convinced that response to such stress was entirely in accord with Starling's law. These results, and an examination of other workers' data on human subjects, ultimately led him to a radical revision of the older view concerning the interdependence of increase in stroke volume, pulse rate and arteriovenous oxygen difference in adaptation to exercise. In his words (7): "Evidence that the stroke volume need not change significantly during exercise which increases oxygen consumption by more than 10-fold has been accumulating in the literature during the last 20 years." In his most recent comment on the point, Rushmer modified his earlier views somewhat by invoking postural effects on stroke volume to explain the large amount of conflicting data in the literature, but he still holds that "the stroke volume increases but little during exertion and rarely exceeds recumbent control values" (8).

Because data on human subjects from our laboratory were in conflict with Rushmer's conclusions, it was decided to re-examine our results and to add new studies to fill in the gap between the resting state and very heavy exercise loads.

METHOD

Studies on 26 normal men, aged 19 to 63 (average 28) form the basis for this report. Data on 15 of the subjects were previously reported in studies on maximal oxygen intake (9, 10). Since the previous experiments were designed to yield information only under resting conditions (subject standing) and at exercise loads producing maximal oxygen intake, 11 additional subjects were tested under different conditions. In 5 subjects, initial measurements were made with the subject supine and at rest. Immediately following, the measurements were repeated with the subject standing at rest. Further measurements were then made at very low levels of exercise. In the other 6 subjects the procedure was the same except that no studies were done with the subject supine.

The experimental procedure was the same as that previously reported (9). Brachial venous and arterial catheters were inserted into the left arm. For measurement of cardiac output, 10 mg of Evans blue (T-1824) was delivered at the end of the catheter into the brachial vein with the subject at rest or, in the exercise studies, 1.5 minutes after beginning of exercise (during the collection of expired air). Arterial samples were collected at 1 second intervals in tubes containing powdered heparin, beginning at the time of injection and continuing for 40 seconds. Analysis of blood samples for dye content was carried out using a Beckman model DU spectrophotometer. The data were then plotted and extrapolated by the method of Hamilton, Moore, Kinsman, and Spurling (11). Such error as the sampling technique may in-

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troduce, especially at heavy work loads, is probably not a systematic one insofar as measurement of cardiac output is concerned.

Pulse rate and oxygen intake (expired air method) were measured over a period including that used for the determination of the cardiac output. After resting determinations were completed, the subject performed on a motor-driven treadmill for 2.5 minutes. Oxygen intake, cardiac output and pulse rate were measured during the last minute of the exercise period. Grades and speeds were set to provide increasing levels of exercise. In most subjects no more than 3 exercise periods, spaced at least 15 minutes apart, were used.

Mean stroke volume was calculated by dividing the cardiac output by pulse rate. Arteriovenous oxygen difference was derived from cardiac output and oxygen intake by use of the Fick equation.

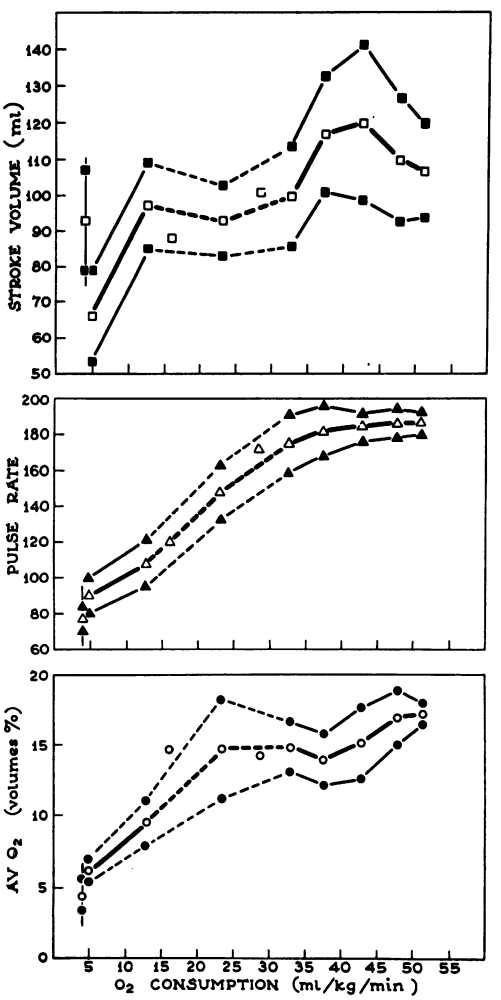

FIG. 1. STROKE VOLUME, PULSE RATE AND ARTERIOVENOUS OXYGEN DIFFERENCE WITH INCREASING LOADS OF EXERCISE. Data are tabulated in Table I. Supine resting values are at extreme left, connected by a vertical line. In each of the three plots, the central heavy line is the mean, the two outer lines representing one standard deviation above and below the mean. The dashed lines represent portions of the oxygen intake scale for which data are numerically inadequate (Table I). For example, at oxygen intake of 15 to 19.9 ml per kg per minute, only one value is available.

RESULTS

The data are set out in Table I and in Figures 1, 2 and 3.

For plotting, the data were grouped according to oxygen intake in milliliters per kilogram per minute, in 4.9 ml increments. In Figure 1 the mean oxygen intake for each group is plotted on the abscissa; the mean stroke volume in milliliters is plotted on the ordinate. Plotting stroke index in milliliters against oxygen intake expressed as liters per minute per square meter body surface yielded curves that were almost identical with those in Figure 1.

In Figure 2, data on four subjects are plotted in order to give some idea of individual variation in the response of stroke volume to increasing levels of exercise.

In Figure 3, a plot recently published by Rushmer (8) is the basis for the upper curve. His first plot of this type (7) was based on data obtained from seven groups of investigators who used the direct Fick or the dye dilution method for determining cardiac output during exercise. Subsequently he added data supplied by us, some of which were published in the paper by Mitchell, Sproule and Chapman (9), to obtain the plot used for construction of the upper curve in Figure 3. For present purposes, the plot was photographically enlarged and covered with a grid so that the values not otherwise available to us could be read off. Owing to the heavy grouping of the data at oxygen intakes below 500 ml per minute, the initial mean value used in our replot is an estimate. The other points on the replot are mean figures obtained by grouping individual stroke volume values for each 500 ml increment of oxygen intake (Table II). The second curve (labeled observed data) is the same as that plotted in Figure 1 except that the values on the abscissa are expressed in liters of oxygen per minute (instead of in milliliters of oxygen per kilogram per minute). It should be apparent, therefore, that the two upper curves are, in part, based on the same data. This is especially

TABLE I

Mean values at rest (supine and standing) and at increasing levels of oxygen intake of 26 normal men (average age 28)

Group (O_2 intake)		No.	Mean O_2 intake	Cardiac output	Pulse rate	Stroke vol.	AVO_2 diff.	Surface area
ml/kg/min Range	Mean		*L/min*	*L/min*		*ml*	*ml/100 ml*	*sq m*
Supine rest	3.9	5	0.304±0.034	7.2±1.5	77± 7	93±14	4.4±1.4	1.96±0.14
Standing rest	4.8	16	0.346±0.052	5.8±1.3	90±10	66±13	6.1±0.7	1.91±0.18
10–14.9	12.7	6	0.948±0.108	10.2±1.1	108±13	97±12	9.4±1.5	1.95±0.12
15–19.9	16.1	1	1.526	10.5	120	88	14.5	2.16
20–24.9	23.1	3	1.940±0.334	13.7±1.2	148±15	93±10	14.5±3.5	2.05±0.19
25–29.9	28.4	1	2.448	17.3	172	101	14.2	2.12
30–34.9	32.7	6	2.502±0.273	17.6±3.2	175±16	100±14	14.6±1.8	1.98±0.16
35–39.9	37.4	11	2.885±0.336	21.2±3.6	182±14	117±16	13.9±1.8	1.98±0.15
40–44.9	42.7	12	3.222±0.496	21.9±4.3	184± 8	120±21	15.1±2.4	1.95±0.21
45–49.9	47.8	7	3.401±0.602	20.5±4.0	186± 8	110±17	16.9±1.9	1.91±0.19
50+	51.1	3	3.380±0.463	19.9±3.3	186± 6	107±13	17.1±0.7	1.82±0.16

true of the portions depicting behavior of stroke volume at high oxygen intakes.

Results of tests of significance between points on the stroke volume curve in Figure 1 are given in Table III. They show that the resting supine value is significantly higher than the value obtained during standing rest. Both resting values (supine and standing) are significantly lower than the two highest values (117 and 120 ml). The standing resting value is significantly lower than all those obtained during exercise. In applying tests for significance to the replot of Rushmer's collected data, it was not possible to utilize the first value (resting) on the curve because the number of observations was not known. Comparison of the second value (96 ± 13 ml) with the other points on the curve shows it to be significantly lower than the last three points.

DISCUSSION

The present study demonstrates quite clearly that stroke volume increases with increasing levels of exercise although the relation is probably not

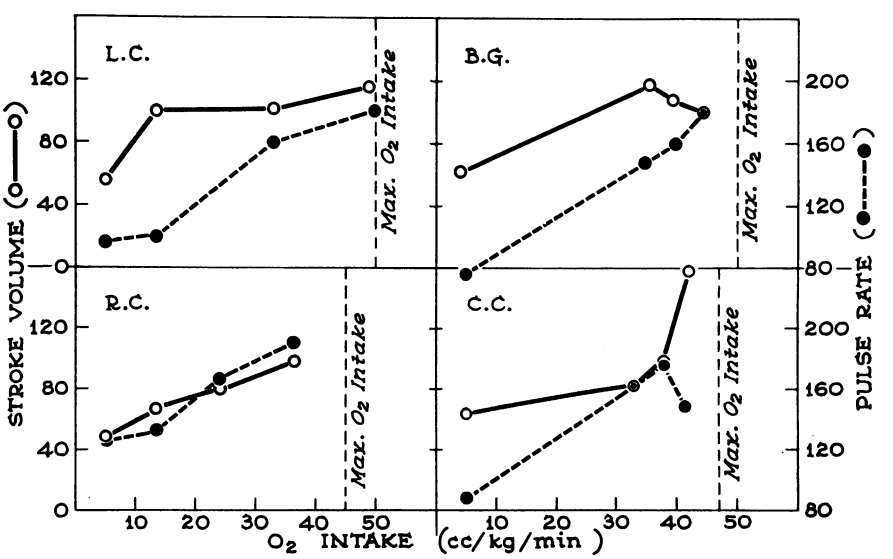

FIG. 2. RELATION OF STROKE VOLUME (SOLID LINE) AND PULSE RATE (BROKEN LINE) TO OXYGEN INTAKE IN FOUR INDIVIDUAL SUBJECTS. The first point (extreme left) is the standing resting value. Subsequent values were obtained at increasing exercise loads.

TABLE II

*Mean values obtained from the plot of collected data by Rushmer (8)**

Group (O_2 intake)	No.	Mean O_2 intake	Stroke volume
L/min		*L/min*	*ml*
0.5–1.0	54	0.730 ± 0.140	96 ± 13
1.0–1.5	29	1.202 ± 0.108	108 ± 25
1.5–2.0	23	1.728 ± 0.138	113 ± 34
2.0–2.5	17	2.230 ± 0.187	98 ± 21
2.5–3.0	19	2.776 ± 0.140	114 ± 32*
3.0–3.5	17	3.187 ± 0.138	132 ± 25*
3.5–4.0	8	3.722 ± 0.175	136 ± 31*

* Significant difference between values marked and initial value (96 ± 13); p values are <0.05, <0.001 and <0.01, respectively.

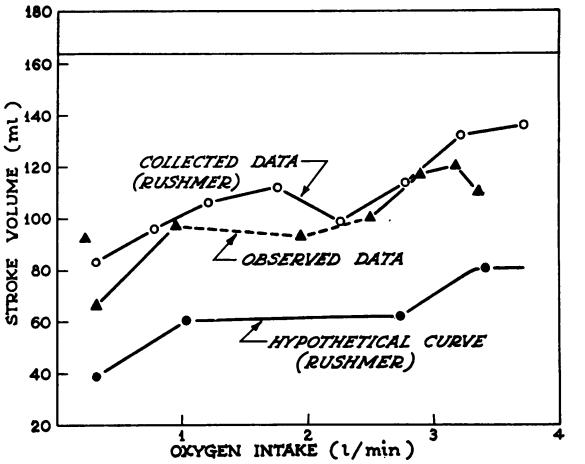

FIG. 3. COMPARISON OF STROKE VOLUME CURVES WITH INCREASING EXERCISE LOADS. Upper and lower curves were replotted from a publication by Rushmer (8). Data for upper curve given in Table II.

a linear one. The conclusion is true as stated whether one uses standing or supine resting conditions as a starting point. It would appear, in fact, that from one-third to about one-half of the increase in cardiac output near the maximal oxygen intake level (21.9 L per minute) over the resting (7.2 L per minute) is attributable to increase in stroke volume, depending on whether one uses the resting supine or resting standing value for comparison. If the value for stroke volume prevailing under resting supine conditions also obtained during heavy exercise, when the pulse rate was 184, cardiac output would have been 17.1 L per minute. The difference between the observed cardiac output near the maximal oxygen intake level and the theoretical value is 4.8 L per minute, which represents about one-third of the observed increase (14.7 L per minute). Using the resting standing value for stroke volume for comparison, the influence of increase in stroke volume upon cardiac output during heavy exercise is much more striking.

Careful inspection of the two plots published by Rushmer suggests that a definite upward trend is present in the second plot (8) (which includes our data); there may also be a slight upward trend in the lefthand portion of the first plot (7). It should be noted also that, when the data are regrouped as in Figure 3, stroke volume at high levels of exercise rises significantly above resting values, which may well include both supine and standing data. The intermediate portion of the stroke volume curve is still not convincingly determined; at such levels of exercise, stroke volume may possibly rise very slowly or may remain more or less constant.

TABLE III

*Test of significance applied to data in Table I and Figure 1 (top)**

Comparison	Mean values	p
Resting supine vs. resting standing	93 vs. 66	Less than 0.01
Resting supine vs. value at 35–40 ml/kg/min	93 vs. 117	Less than 0.05
Resting supine vs. value at 40–45 ml/kg/min	93 vs. 120	Less than 0.02
Resting supine vs. value at 45–50 ml/kg/min	93 vs. 110	Not significant
Resting standing vs. value at 10–15 ml/kg/min	66 vs. 97	Less than 0.01
Resting standing vs. value at 20–25 ml/kg/min	66 vs. 93	Less than 0.01
Resting standing vs. value at 30–35 ml/kg/min	66 vs. 100	Less than 0.001
Resting standing vs. value at 35–40 ml/kg/min	66 vs. 117	Less than 0.001
Resting standing vs. value at 40–45 ml/kg/min	66 vs. 120	Less than 0.001
Resting standing vs. value at 45–50 ml/kg/min	66 vs. 110	Less than 0.001
Resting standing vs. value at 50+ ml/kg/min	66 vs. 107	Less than 0.01

* $t = m_1 - m_2/\sqrt{(SEm_1)^2 + (SEm_2)^2}$.

The actual situation in normal subjects who are neither highly trained nor habitually inactive seems, therefore, to be similar to that suggested in Rushmer's hypothetical curve (Figure 3) except that the values for stroke volume it represents are too low. None of the curves is consonant with the view that stroke volume increases very little during exertion and rarely exceeds recumbent control values even at heavy exercise loads in which oxygen intake is about ten times the resting intake. As it stands, the statement is applicable only to the situation prevailing in mild exercise. One might question its general validity even in this case since, in human subjects, exertion often follows periods of quiet standing when stroke volume is unquestionably at its lowest. As for heavy exercise, such as that producing maximal oxygen intake, it seems to be impossible for normal human subjects to make the necessary adaptation *without* increasing stroke volume. Thus, although Rushmer's original rejection of "generally accepted dogma" (7) appears to have been too sweeping, a resolution of the difficulty is reached by allowing for the influence of position on resting stroke volume, *vis-a-vis* those prevailing at low levels of exercise, and by noting the impressive extent to which stroke volume is utilized at high levels.

The matter is, in fact, of some theoretical importance. If it could be shown that adaptation to exercise over the full physiologic range can be accomplished solely, or even primarily, by increase in pulse rate, the significance of changes in intrinsic myocardial reactivity would be doubtful. That intrinsic myocardial response changes during exercise has been demonstrated (12), although it has not been possible to study the phenomenon quantitatively at high exercise loads. The role of the Starling mechanism in adaptation to exercise thus again comes into focus. It is a question, in a sense, of what Starling actually meant by the law bearing his name. If one insists that he considered venous return to be the vital initiating factor in cardiac response to exercise, and the keystone in his whole theoretical arch, then to an extent Startling's law may be invalid. If, on the other hand, one considers that the fundamental feature of the law, as set out by Frank (13), Straub (14) and Patterson and Starling (15), is a relationship between "force of contraction," or stroke work, and end-diastolic volume, evidence now available indicates that the principle plays a definite role in cardiac response to exercise. The increase in stroke volume seen with increasing loads of exercise is a manifestation of this role and would be difficult to explain if some such principle were not operative.

A complete understanding of the cardiovascular response to exercise is by no means at hand. Obviously, individual differences in response are considerable, as suggested by Figure 2. Factors determining what mechanism will be dominant, especially at low to moderate levels of exercise, are not known. Very probably, physical training, age and body composition are involved. There can be little doubt, however, that in higher organisms, including man, adaptation to exercise requires an intricate interdigitation of neural, myocardial and chemical factors and that ability to increase stroke volume is one of the mechanisms involved.

CONCLUSIONS

1. Increase in stroke volume is one of the mechanisms normally utilized in cardiovascular adaptation to exercise in man.

2. The relative importance of the mechanism appears to be greatest at the transition from rest (subject standing) to mild exercise and at levels of exercise approaching those producing maximal oxygen intake.

3. The highest levels of stroke volume reached during heavy exercise are significantly greater than those prevailing at rest, whether the subject is supine or standing.

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