Studies of Cardiopulmonary Blood Volume
Measurement of Total Cardiopulmonary Blood Volume in Normal Human Subjects at Rest and during Exercise

By Gilbert E. Levinson, M.D., Albert D. Pacifico, M.D., and Martin J. Frank, M.D.

Several of the fundamental variables of hemodynamics, namely pressure, flow, resistance, and pulse rate, have received intensive and systematic study. Until recently, volume had not been accorded comparable study, in part because of inability to obtain valid and accurate measurements of anatomically meaningful circulatory compartments, and perhaps in part because of a tendency to regard volumes as static, passive, virtually structural aspects of the circulatory system. At present, an intensive and systematic study of the circulatory volumes is both possible and important, in view of the development of safer technics of catheterization of individual cardiac chambers, technical and conceptual advances in methods of measuring chamber volumes in vivo, and theoretical and experimental grounds for regarding volumes as dynamic factors, exerting active or permissive roles in circulatory adjustments.

For these reasons, we have undertaken an investigation of the cardiopulmonary blood volume and its components. Indicator dilution has been used to measure volumes because of its versatility and applicability to all compartments. Although this technic has been the basis for estimates of a variety of "central" blood volumes, measurements of the true cardiopulmonary blood volume in man have not previously been reported. This paper is a report of the technics employed and the results obtained in measuring total cardiopulmonary blood volume in a group of normal human subjects.

Methods

Eighty-one measurements of the volume of blood between right atrium and aortic root (hereafter referred to as cardiopulmonary blood volume) were obtained in 11 male and 4 female subjects, ranging in age from 14 to 54 years. In six subjects soft ejection systolic murmurs and possible pulmonary plethora on chest roentgenograms led to diagnostic cardiac catheterization, including oxygen sampling series, selective cinefluorography, and indicator dilution studies, with entirely normal results. The other nine subjects were volunteers.

All subjects were studied in the fasting state, under mild barbiturate sedation, in the supine position. In the volunteer subjects, polyethylene catheters (internal diameter, 1.13 mm; length, 70 cm) were introduced percutaneously, under local procaine analgesia, into the right brachial artery and median antecubital vein, and advanced into left ventricle and right atrium. Under pressure and fluoroscopic guidance, the left ventricular catheter was withdrawn into the aortic root immediately distal to the aortic valve, and the right atrial catheter was placed at the junction of the superior vena cava and the right atrium. In the subjects undergoing diagnostic catheterizations, the right heart catheter was an NIH or Goodale-Lubin catheter, introduced by brachial or saphenous venotomy and placed at the junction of superior vena cava and right atrium on completion of the diagnostic procedures. In some of the subjects undergoing diagnostic catheterization, the aortic catheter was...
an NIH type which, after being used for the recording of left ventricular pressures and for selective left ventricular injections of indocyanine-green dye, was withdrawn into the aortic root for the sampling of dilution curves.

At a pre-arranged signal, 6.6 mg of indocyanine-green dye in 1 ml of diluent, and a saline flush were injected rapidly into the right atrium from a calibrated pipette. The duration of injection of dye and flush were recorded, and the midpoint of injection of the dye was obtained from a knowledge of the volumes of catheter, dye injectate, and saline flush. This midpoint was taken as zero time. By means of Harvard infusion-withdrawal pumps, blood was withdrawn from the aorta through a Gilford densitometer at a constant rate of 0.8 to 2.0 ml per second into an air-free heparinized syringe. The output of the densitometer was recorded on a photographic recorder (Electronics for Medicine). The 90% response time of the sampling system, including catheter and densitometer cuvette, ranged from 0.56 to 0.7 sec. Calibration was by the integrated sample technic. Except for the small volumes required for calibration, all blood sampled was returned to the subject immediately after insertion of each dilution curve. This permitted the recording of two or more dilution curves for each subject, in each of several states, with negligible blood loss. Representative curves are shown in figure 1.

Each subject was studied at rest, a total of 38 measurements being obtained on the 15 subjects. In eight subjects, measurements were repeated during the last 6 minutes of a 13- to 26-minute period of leg elevation to the pedals of a bicycle ergometer, and again during a 13- to 26-minute period of leg exercise. A total of 17 measurements was obtained during passive leg elevation, and 26 measurements during exercise. Oxygen consumption was measured at rest and 3 minutes prior to the final dilution curve during exercise by an open-circuit respiratory system using the Beckman oxygen analyzer for the analysis of expired air.

Curves were plotted semilogarithmically and extrapolated to 1% of peak concentration. Cardiac output and mean transit time were calculated for each dilution curve by the usual Stewart-Hamilton formulas. The mean transit time was corrected for the delay introduced by the sampling system. The cardiopulmonary blood volume was calculated as the product of cardiac output and mean transit time. All calculations were performed on an IBM 1620 computer programmed for the digitized data after the semilogarithmic replotting of the primary data.

The results of the study were analyzed by conventional statistical technics for small samples. Correlations were evaluated by the product-moment correlation coefficient (r).

Results

The results of the study are listed in tables 1 and 2.

Cardiac Output, Heart Rate, and Stroke Volume at Rest

Cardiac output ranged from 2.19 to 5.29, with a mean value of 3.39 ± 0.84 L/min/m². The cardiac index was slightly (3.48 versus 3.37 L/min/m²) and insignificantly (P > 0.9) higher in the female subjects. Reproducibility of the measurements was excellent: the maximum and mean discrepancies between successive replications were 0.43 and 0.11 L/min/m², respectively, and the mean coefficient of variation for measurements of output was 3.4%.

Heart rate ranged from 45 to 131, with a mean value of 81 ± 21 beats per minute, and stroke volume from 34 to 55, with a mean of 42 ± 6 ml/beat/m². Exclusion from the series of the patients with extreme values for heart rate (mean rate of 45 per minute in an athletic male youth and mean rate of 131 per minute in an anxious adolescent girl) results in a change of 1 beat per minute in mean heart rate for the group and a change of less than 1% in mean values for cardiac output and cardiopulmonary blood volume. Heart rate was higher, by an average of 10 beats per minute, in the female subjects than in the male, and

\[ \text{Figure 1} \]

Dilution curves at rest (left) and during exercise (right) in patient E. S. Paper speed was 5 mm/sec with time lines at 1-sec intervals. The interruption of the horizontal line at top signaled the injection.
stroke volume index was less by 3 ml per beat, but these differences were not statistically significant \((P > 0.4)\). Rhythm was regular sinus in all instances.

**Cardiopulmonary Blood Volume at Rest**

The cardiopulmonary blood volume in individual subjects ranged from 301 to 546 ml/m\(^2\), with a mean for the group of \(422 \pm 76\) ml/m\(^2\). If 2.5 to 3.0 L/m\(^2\) is the average total blood volume in normal subjects,\(^6\)\(^,\)\(^7\) the cardiopulmonary blood volume represents 15.3% of total blood volume. Cardiopulmonary blood volume in the male subjects significantly exceeded that in the female subjects \((\text{means} = 447 \text{ and } 352 \text{ ml/m}^2, \text{respectively, } P < 0.05)\). Reproducibility of measurements was good. In the 13 patients with two or more measurements, the mean discrepancy between successive replications was 25 ml/m\(^2\) and the mean coefficient of variation was 3.7%.

**Relations Between Cardiopulmonary Blood Volume and Cardiac Output or Stroke Volume at Rest**

There was, as can be seen from figure 2, no correlation \((r = 0.07)\) between cardiac output

<table>
<thead>
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<td><strong>Effects of Leg Elevation and Exercise</strong></td>
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<th>Patient</th>
<th>Cardiac index, L/min/m(^2)</th>
<th>Heart rate, beats/min</th>
<th>Stroke volume, ml/beats/m(^2)</th>
<th>Cardiopulmonary blood volume, ml/m(^2)</th>
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\(R = \text{rest, } L = \text{leg elevation, } E = \text{exercise.}\)

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and cardiopulmonary blood volume. However, good correlation \( r = 0.79, P < 0.0001 \) is evident (fig. 3) between cardiopulmonary blood volume and stroke volume. That this correlation is not merely a reflection of the bimodal distributions related to sex difference, that is, of the lower stroke volume and cardiopulmonary blood volume prevailing in the female subjects, is evidenced by the high correlation \( r = 0.85, P < 0.001 \) between stroke volume and total cardiopulmonary blood volume for the 11 male subjects.

**Effects of Leg Elevation and Exercise**

With elevation of the legs, there were no significant changes in cardiac output, heart rate, or stroke volume. In all but one subject, however, the cardiopulmonary blood volume rose. The mean increase in the seven in whom increases occurred was \( 25 \pm 8 \text{ ml/m}^2 \), or 6.4% of the resting volume of 389 ml in these patients, and was statistically significant \( (P < 0.01) \). The mean change for the entire group of eight was an increase of \( 19 \pm 9 \text{ ml/m}^2 \); this change is not quite significant statistically \( (0.05 < P < 0.10) \) if a two-tailed t test is employed, but a one-tailed test, on the assumption that leg elevation is expected to produce a centripetal volume shift, leads to the conclusion that the change is not attributable to chance \( (P < 0.05) \).

With exercise, no further significant change in cardiopulmonary blood volume occurred despite significant increases in oxygen consumption, cardiac output, heart rate, and stroke volume of 138, 56, 43, and 9%, respectively, of the values during passive leg elevation \((P < 0.005)\). The response of cardiopulmonary blood volume ranged from 13% fall to 16% rise, a fall occurring in three subjects and a rise in five. The mean change was a statistically insignificant \((P > 0.4)\) increase of \( 13 \pm 15 \text{ ml/m}^2 \) or 3% of the value obtained during passive leg elevation.

That the subjects were in a steady state is indicated by the fact that the coefficients of variation for measurements of flow and volume were essentially the same during exercise and at rest: for the eight subjects, the coefficient of variation for output measurements was 3.2% at rest and 3.9% during exercise, and the coefficient of variation for volume measurements was 4.0% at rest and 4.8% during exercise. There were no differences in response based on duration of exercise and no significant differences between the values measured early in exercise and those measured later.

No significant correlations existed between changes in cardiopulmonary blood volume and changes in either cardiac output or stroke volume with exercise.

*Circulation, Volume XXXIII, March 1966*
Discussion

Cardiac Output, Stroke Volume, and Heart Rate

The mean cardiac output, stroke volume, and heart rate in this study are in agreement with values reported by other authors, using the oxygen Fick method, Evans blue or indocyanine-green dilution, or radiocardiography with precordial counting. Survey of the reports of cardiac output in normal subjects or "hospital normals" reveals the following ranges for the mean values: from 3.22 to 3.79 L/min/m² by the oxygen Fick method,8,9 from 3.2 to 3.76 L/min/m² by dye dilution with arterial sampling,10,11 and from 3.47 to 3.64 L/min/m² by radiocardiography.12,13 In the series of Bickelmann and associates,14 which is most comparable to our own in material (15 thoroughly normal subjects aged 20 to 46 years) and methods (indocyanine-green dye, arterial sampling, Gilford cuvette densitometers), the results were almost identical with those of the present study: cardiac index 3.39 ± 0.76 L/min/m², stroke volume index 44 ± 6 ml/beat/m², and heart rate 76 ± 12 beats per minute. The agreement between cardiac output values for normal men and women has also been reported by Huff and co-workers12 and Campione and co-workers.15

The range of individual values for heart rate in resting subjects extends from 50/min in the series of Braunwald and Kelly16 to 120/min in one of the subjects of Cournand and associates.17 With the exception of the groups reported by Lagerlöf and Werkö18 and by Donald and associates19 in whom the mean values exceeded 50 ml, the mean stroke volume index in the reported studies has ranged from 40 to 49 ml/beat/m². The means and ranges for output, stroke volume, and heart rate obtained in the present study constitute reassuring criteria as to the representative normality of our group of subjects.

Reproducibility of Measurements

The mean coefficient of variation for measurement of output in the present study (3.4%) is almost identical in magnitude with the error referred to as "measurement error" by Sleeper and co-workers.20 In their considerably more extensive series, measurement error was defined by comparison of simultaneous measurements obtained from the same needle; the standard deviation of the difference was 3% of the mean cardiac output. A larger variation (standard deviation = 10% of mean cardiac output) resulted when the simultaneous measurements were from the brachial and femoral arteries, and intermediate values when the simultaneous measurements were from the radial and brachial arteries of the same arm. That the discrepancies between paired measurements from different arteries were due to non-uniform distribution of dye was indicated by an increase in such discrepancies when peripheral flow alterations were induced. Sleeper and associates suggested that sampling from the root of the aorta would obviate these differences provided that the sampling technic could compensate for the necessarily increased length of the sampling tube. Their suggestion is confirmed by the present results in which the reproducibility of duplicate successive determinations was superior to that found in their series for brachial or femoral sampling. This finding indicates that aortic root sampling offers advantages in the accuracy of measurement of cardiac output.

The calculation of mean transit time is based on the same deflection readings used for calculating output. However, slurring of the curve will result in proportionally larger error in calculation of mean transit time than in measurement of area. The comparability of variation in measurement of flow and volume in the present study (coefficients of variation = 3.4 and 3.7%, respectively) demonstrates the adequacy of the technics used for sampling and for zero-time inscrption.

Cardiopulmonary Blood Volume

Numerous investigators have used the Stewart-Hamilton principle in estimating mean transit time-volumes, variously labeled "pulmonary," "cardiopulmonary," "central," and "intrathoracic" blood volumes. The values for such volumes, which were reviewed and discussed in a previous communication from this laboratory,21 range from 436 to more than 1,300 ml/m². Clearly, because of the temporal boundaries involved, none of the volumes...
obtained by various methods and investigators\textsuperscript{10, 22–29} represents true cardiopulmonary blood volume.

It is possible that the volumes measured in the present study are also inaccurate, with a systematic underestimate arising from incompleteness of mixing in the right atrium. If mixing in the right atrium is poor, and injection was into the flow stream selectively sampled by the right ventricle, then part or all of the right atrial volume will be excluded. The measured volume would then be anatomically imperfect but physiologically quite meaningful, since it consists of the volumes of the two circulatory pumps plus the segment of vasculature (pulmonary circulation and left atrium) interposed between them. The circulatory compartment between the two pumps, which may be referred to as interventricular volume, is probably what was measured by Milnor,\textsuperscript{30} and Dock and their associates,\textsuperscript{31} and ourselves\textsuperscript{21} and labeled by all three groups as pulmonary blood volume. It follows that the cardiopulmonary blood volume measured in the present study should exceed the pulmonary blood volume as measured by the above authors by a quantity approximating the sum of the volumes of the two ventricles. The normal subjects in the series of Dock and associates\textsuperscript{31} had a mean volume of 246 ml/m\textsuperscript{2}. In six normal subjects studied in this laboratory, the mean interventricular volume was 254 ml/m\textsuperscript{2}.\textsuperscript{2} If interventricular blood volume is, therefore, approximately 250 ml/m\textsuperscript{2}, and the volume measured in the present study (422 ml/m\textsuperscript{2}) represents the sum of ventricular and interventricular volumes, then the combined volume of the two ventricles should be about 170 ml/m\textsuperscript{2} in the normal subject. The latter figure is in excellent agreement with the sum of right ventricular end-diastolic volume (79 ml/m\textsuperscript{2}) measured by Evans blue dye dilution\textsuperscript{32} and left ventricular end-diastolic volume measured by radiocardiography (89 ml/m\textsuperscript{2}),\textsuperscript{33} thermodilution (97 ml/m\textsuperscript{2}),\textsuperscript{34} and indocyanine-green dye dilution (88 ml/m\textsuperscript{2}).\textsuperscript{35} If, moreover, the weight of the normal heart muscle (300 g or 170 ml/m\textsuperscript{2})\textsuperscript{36} is subtracted from the mean value for total cardiac volume (muscle plus blood content) measured by teleoentgenography (372 ml/m\textsuperscript{2}),\textsuperscript{37, 38} the resultant volume (approximately 200 ml/m\textsuperscript{2}) exceeds the intracardiac volume estimated in the present series (approximately 170 ml/m\textsuperscript{2}) by the reported anatomic capacity of the right atrium (approximately 30 ml/m\textsuperscript{2}).\textsuperscript{39}

These considerations support the conclusion that the volume measured in this investigation approximates the sum of the ventricular and interventricular blood volumes. Blumgart and Weiss,\textsuperscript{40} in their classic studies of circulation time measured with radium C, predicted, on the basis of experiment plus physiologic reasoning, that the transit time through right ventricle, pulmonary circulation, and left heart, which they could not measure directly, would be 7.5 sec. The cardiopulmonary blood volume estimate corresponding to that transit time (14.6% of total blood volume) is insignificantly different from the value (15.3% of total blood volume) calculated in the present study.

**Relations Between Cardiopulmonary Blood Volume and Cardiac Output or Stroke Volume**

In previous studies, stroke volume has been shown by Milnor and co-workers\textsuperscript{30} and by ourselves\textsuperscript{21} to be related to pulmonary or interventricular volume and, by Doyle and co-workers,\textsuperscript{10} to a central blood volume measured from pulmonary artery to a peripheral artery. In Milnor’s report, a weaker relationship also existed between the volume measured and cardiac output, but such a relationship was not described by Doyle and associates and, in the previous report from this laboratory, the relationship between volume and output per minute was, at best, equivocal. The results of the present study seem to confirm our previous conclusion that the cardiopulmonary volume plays a role in the regulation of stroke volume.

**Effects of Exercise**

Previous workers have concluded that, with exercise, the central blood volume is increased,\textsuperscript{16, 41–43} decreased\textsuperscript{28, 44} or unchanged,\textsuperscript{29, 45–46} These disparate conclusions resulted from use of volume estimates based on different concepts and technics. In one of the studies\textsuperscript{44} volumes were estimated by the slope-volume
principle of Newman and associates.47 The increased volumes were obtained from mean transit times involving, by reason of peripheral venous injection, peripheral arterial sampling or both, indefinite temporal boundaries.16, 41-43 Wang and associates,48 from studies performed in animals, and Marshall and Shepherd,49 from studies performed in human subjects, have offered evidence that, with peripheral injection or peripheral collection, the slope volume does not, either quantitatively or qualitatively, reflect changes in pulmonary blood volume, because it is affected by linear dispersal of indicator in peripheral vessels. Moreover, with venous injection or arterial sampling, the peripheral vascular redistribution of flow with exercise may give spuriously elevated mean transit times for calculation of central blood volume.50, 51 When volumes of narrower boundaries and better anatomical definition are studied, as with the precordial counting of isotopic indicators28, 29 and with pulmonary artery-to-aortic root dilution curves46 the central volumes have been decreased28 or unchanged29, 46 with exercise. The small increase reported by Giuntini and associates52 in pulmonary blood volume measured by radiocardiography may reflect the effect of leg elevation, since the resting measurements were not made with the legs elevated.

The conclusion that exercise does not appreciably alter the total cardiopulmonary blood volume should not be construed to mean that important redistributions within this volume do not take place. Indeed, available evidence makes it seem most likely that such redistributions do occur. Rushmer and associates53 have reported that left ventricular diameters usually decrease in dogs during treadmill exercise. In human subjects, studies employing orthodiagraphy,54, 55 cinefluorography,56 indicator dilution,57 and radioopaque clips sutured to myocardial surfaces58 also indicate that a decrease in ventricular dimensions is usually associated with muscular effort. If the right and left ventricular components of total cardiopulmonary blood volume diminish with muscular exercise, then constancy of the total cardiopulmonary blood volume, as demonstrated in the present study, conceals an increase in the interventricular (or pulmonary) component. The radiographic measurements reported by Cournand and associates55 indicate such an increase in pulmonary blood volume both in active subjects and in subjects leading sedentary lives. In the former, the increase in pulmonary blood volume was accompanied by a decrease in the volumes of the ventricles, so that the total cardiopulmonary blood volume remained unchanged. Moreover, increase in the volume of blood within the capillary bed of the lungs during exertion is indicated by the data of Lewis and co-workers59 and of Johnson and co-workers.60 Nevertheless, it is clear from the present study that the magnitude of the total cardiopulmonary blood volume in normal man is not significantly affected by muscular exercise.

Summary

The volume of blood in the heart and lungs can be measured, by the Stewart-Hamilton principle, as the product of cardiac output and the mean transit time from right atrium to the aortic root. Although previous investigators have estimated a variety of central blood volumes, measurements of the true cardiopulmonary blood volume in man have not previously been reported.

Eighty-one measurements of the total cardiopulmonary blood volume were obtained in 15 normal human subjects. At rest, total cardiopulmonary blood volume ranged from 301 to 546 ml/m², with a mean of 423 ml/m², and it represented 15% of estimated total blood volume. Cardiopulmonary blood volume was significantly larger in the male subjects than in the female. Reproducibility of measurements was good: the mean discrepancy between successive replications was 25 ml/m² and the mean coefficient of variation 3.7%. There was no correlation between cardiac output and cardiopulmonary blood volume but a significant correlation (r = 0.79, P < 0.0001) was evident between cardiopulmonary blood volume and stroke volume.

With elevation of the legs to the pedals of a bicycle ergometer, a small but statistically
significant increase occurred in cardiopulmonary blood volume, but no significant changes occurred in cardiac output, heart rate, or stroke volume. With exercise, no further significant change in cardiopulmonary blood volume occurred, despite significant increases in output, rate, and stroke volume.

Analysis of cardiac output measurements, both at rest and during exercise, indicates that aortic root sampling is characterized by an appreciably higher reproducibility than that reported for peripheral arterial sampling.

Acknowledgment

We are pleased to acknowledge the assistance in the catheterization laboratory of Miss Sandra Welten, R. N., Miss Gloria Salge, R. N., and Miss Georgina Abich, and the technical assistance of Mr. Henry Oldewurtel and Miss Sharon Malone, and to thank Miss Christine Berlane for the preparation of the manuscript.

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The Danger of Technical Language

Technical expressions are a danger for every system of philosophy, whether Indian or European. For they may become formulae which hinder the natural development of thought in the same way as ruts in a road hinder traffic. So to find out what are its real contents it is reasonable to test a system of thought by setting aside the expressions which it has coined for its own use and compelling it to speak in ordinary comprehensible language.—ALBERT SCHWEITZER: Indian Thought and Its Development. New York, Henry Holt and Company, 1936, p. IX.
Studies of Cardiopulmonary Blood Volume: Measurement of Total Cardiopulmonary Blood Volume in Normal Human Subjects at Rest and during Exercise
GILBERT E. LEVINSON, ALBERT D. PACIFICO and MARTIN J. FRANK

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