Reproducibility of Cardiac Output Determination in Man by the Direct Fick Principle*

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The reproducibility of duplicate cardiac output determinations at rest in man by the direct Fick principle has been examined by a number of investigators.1-14 The results obtained in many of the earlier studies are suspect because the mixed venous blood sample was obtained from the right atrium or right ventricle. In the more recent studies, the mixed venous blood sample has been obtained from the pulmonary artery. The potential errors involved in the use of right atrial blood have been analyzed by Cournand.15 The necessity for maintenance of a steady state during direct Fick cardiac output determination in man has been stressed by Cournand et al.,4 Fishman and co-workers,9 Donald et al.,11 and Fritts and Cournand.12 The theory of steady state measurements has recently been analyzed by Zierler.13

The latent errors in cardiac output determination by the Fick principle even during the steady state have been explored by Fritts and Cournand,13 Visscher and Johnson,16 and Stow.17 The problems include potential phasic variations in blood flow and arteriovenous oxygen differences, time-average rather than volume-average blood samples from the pulmonary artery cardiac catheter and arterial needle, instantaneous rates of blood flow as opposed to mean rates of flow over finite periods of time, and variations in oxygen concentration in systemic and pulmonary arteries during the respiratory cycle. Experimental evaluation of some of these potential problems by Wood et al.19 demonstrated that the magnitude of these errors did not vitiate the use of the Fick principle for cardiac output determination in man.

The purpose of this paper is to present the results of analysis of 300 triplicate determinations of resting cardiac output by the Fick principle in patients with varied types of cardiopulmonary diseases. The data from 100 duplicate cardiac output analyses from other catheterizations will also be presented to permit comparison with the triplicate determinations.

Material and Methods

Four hundred cardiac catheterizations were performed in 308 patients with cor pulmonale, rheumatic, arteriosclerotic, hypertensive or congenital heart disease without left-to-right or right-to-left shunts. Constrictive pericarditis was diagnosed in two patients; acquired peripheral arteriovenous fistulae were present in five subjects. These studies represented 400 unselected consecutive catheterizations in whom technically satisfactory duplicate or triplicate Fick cardiac output determinations were made. These observations were secured in the course of right or combined right and left heart catheterization. In the latter event, the cardiac output data was obtained before left heart catheterization was initiated.

Cardiac catheterization was performed in the morning in the basal post-absorptive state. The catheter tip was placed in the right or left pulmonary artery; a Cournand needle was introduced into a femoral or brachial artery. Oxygen consumption was determined by the open circuit method;

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inspired gas was inhaled from a tank of compressed air. Expired gas was collected for two minutes in a 120 L Tissot spirometer. Blood collection was executed in the mid-period of expired gas collection. The second or third output determinations were made at five to ten minute intervals. Mixed venous and arterial blood samples were collected for each output determination. The arterial blood sample was not taken directly from the Cournand needle, but was obtained via a double three way stopcock connected to the needle by a 12 inch length of clear nylon tubing.

Oxygen consumption was derived from analysis of inspired and expired gas (on two separate expired gas samples) and the minute ventilation. Gas analyses were performed on a Scholander unit. Arteriovenous oxygen difference was calculated via blood gas analysis on the Van Slyke-Neill apparatus. Duplicate gas analysis was required to check within 0.02 volumes per cent for both oxygen and carbon dioxide. The respiratory quotient was utilized to correct for differences in the volume of inspired and expired gas. Duplicate blood gas analyses were required to check within 0.2 volumes per cent.

**RESULTS**

Four variables—the cardiac index, the arteriovenous oxygen difference, the oxygen consumption and the respiratory quotient—were scrutinized in four groups. Two hundred twenty triplicate studies were performed in patients with sinus rhythm; 80 such studies were carried out in subjects with atrial fibrillation. Seventy-eight duplicate investigations were consummated in patients with sinus rhythm and 22 in individuals with atrial fibrillation. These data are detailed in Tables 1 and 2,* and are summarized in Table 3. In the latter table the difference between any two values (for the four variables listed above) are expressed as a percentage of the mean of each.

*To conserve space, Tables 1 and 2 have been omitted from publication, but will be available with reprint requests.
patient's values—the "per cent relative error." Since 220 triplicate determinations (for sinus rhythm) and 80 triplicate determinations (for atrial fibrillation) are available, 660 comparisons in the sinus rhythm group and 240 comparisons in the atrial fibrillation group were performed for cardiac index, arteriovenous difference, oxygen consumption and respiratory quotient.

**Triplicate comparisons in sinus rhythm:**

(a) Cardiac index: In 52 per cent the difference from the mean was 5 per cent or less; in 81 per cent the difference was 10 per cent or less; the difference was 15 per cent or less in 95 per cent. Standard deviation equaled 0.15 L./min./m² B.S.A.

(b) Oxygen consumption: The difference was 5 per cent or less in 63 per cent, 10 per cent or less in 92 per cent and 15 per cent or less in 98 per cent. Standard deviation totaled 8.6 ml./min./m².

(c) Arteriovenous difference: The difference was 5 per cent or less in 68 per cent, 10 per cent or less in 92 per cent and 15 per cent or less in 97 per cent. Standard deviation was 0.2 vol. per cent.

(d) Respiratory quotient: The difference was 5 per cent or less in 69 per cent, 10 per cent or less in 91 per cent, and 15 per cent or less in 98 per cent. Standard deviation was 0.03.

**Triplicate comparisons in atrial fibrillation:**

(a) Cardiac index: The variation was 5 per cent or less in 45 per cent, 10 per cent or less in 85 per cent and 15 per cent or less in 97 per cent. Standard deviation equaled 0.10 L.

(b) Oxygen consumption: The variation was 5 per cent or less in 62 per cent, 10 per cent or less in 92 per cent, and 15 per cent or less in 98 per cent. Standard deviation was 5.0 ml.

(c) Arteriovenous difference: The cumulative percentages at 5, 10, and 15 per cent variations were 67 per cent, 94 per cent and 99 per cent respectively; standard deviation was 0.2 vol. per cent.

(d) Respiratory quotient: The cumulative percentages at 5, 10, and 15 per cent deviations were 60 per cent, 87 per cent and 94 per cent respectively; standard deviation, 0.04.

**Duplicate Comparison in sinus rhythm:**

(78 comparisons)

(a) Cardiac index: The divergence was 5 per cent or less in 56 per cent, 10 per cent or less in 87 per cent, and 15 per cent or less in 99 per cent; standard deviation, 0.13 L.

(b) Oxygen consumption: The cumulative percentages at 5, 10, and 15 per cent differences were 60 per cent, 86 per cent

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![Figure 3: Distribution of differences between duplicate arteriovenous oxygen differences (first minus third determination).](image-url)
and 99 per cent respectively; standard deviation, 5.8 ml.

(c) Arteriovenous differences: The cumulative percentages at 5, 10, and 15 per cent variations were 60 per cent, 95 per cent and 99 per cent respectively; standard deviation 0.18 vol. per cent.

(d) Respiratory quotient: The cumulative percentages were 68 per cent, 91 per cent and 95 per cent at variations of 5, 10 and 15 per cent respectively; standard deviation, 0.04.

Duplicate comparisons in atrial fibrillation:

(22 comparisons)

(a) Cardiac index: The cumulative percentages at 5 and 10 per cent deviations were 64 per cent and 100 per cent respectively; standard deviation, 0.07 L.

(b) Oxygen consumption: The differences were 5 per cent or less in 82 per cent and 10 per cent or less in 100 per cent; standard deviation, 3.6 ml.

(c) Arteriovenous differences: The cumulative percentages at 5 and 10 per cent deviations were 77 per cent and 95 per cent respectively; standard deviation, 0.18 vol. per cent.

(d) Respiratory quotient: The cumulative percentages at 5, 10 and 15 per cent variations were 54 per cent, 86 per cent and 95 per cent respectively; standard deviation, 0.05.

To determine whether the magnitude of the differences between duplicate or triplicate determinations was related to the absolute level of the variable being studied, coefficients of correlation were determined. These revealed little or no relationship between the absolute level and the variability in repeated determinations of any of the four variables studied. The coefficients of correlation varied from -0.04 to +0.38.

Further analysis of the above data was performed to determine whether consistent differences were present between the initial and subsequent determinations, i.e. whether the initial values were consistently larger or smaller than the second or third determinations. As an example of the results obtained, some of the physiologic data obtained in the patients in Table 1A are shown in Figs. 1 to 4. The bell shaped curves of the differences between the first and third determinations clearly demonstrate the absence of unidirectional repetitive differences between repeat physiologic parameter determinations. Similar results were obtained in the patient data given in Tables 1B, 2A and 2B. A learning process was therefore not a factor in the results obtained in these studies.

Discussion

In considering the relative error of the Fick cardiac output determination, i.e. the difference between duplicate or triplicate values divided by the mean value, the analytic errors of the parameters making up the Fick equation must be considered. It is commonly stated that the error in blood oxygen analysis by the Van Slyke-Neillmanometric apparatus is 0.2 vol. per cent. Duplicate arterial or mixed venous blood oxygen contents in any one cardiac output determination were required to check within the same 0.2 vol. per cent. If the maximum errors in arterial and mixed venous blood oxygen contents are in

![Figure 4: Distribution of differences between duplicate analyses of respiratory quotient, first minus third determination.](image-url)
opposite directions, the total error in the arteriovenous oxygen difference may be as large as 0.4 vol. per cent. Since the total arteriovenous difference usually ranges from 4 to 6 vol. per cent, the blood gas analytic error may be as high as 7 to 10 per cent.

Inspired and expired gas analytic errors are of a much smaller order of magnitude. Inspired and expired gas oxygen analyses are required to check within 0.02 volume per cent. The maximum error in oxygen analysis is therefore 0.04 vol. per cent. Since the total oxygen difference between inspired and expired gas is 3 to 4 vol. per cent, the analytic error is only about 1 per cent. The carbon dioxide analytic error is of the same order of magnitude. The estimated maximum analytic error in the respiratory quotient is therefore about 2 per cent. Since minute ventilation could not be measured in duplicate in any one output determination, analytic errors in ventilation per se cannot be measured. This limitation may increase the actual overall error in oxygen consumption, carbon dioxide production (but not respiratory quotient) several fold.

The maximum assessable relative analytic error of the numerator of the Fick principle (including the errors in both oxygen analysis and measurement of minute ventilation) is probably of the order of 3 to 5 per cent and the corresponding maximum analytic error in the denominator is 7 to 10 per cent; the maximum relative analytic error of repeated cardiac output determinations is therefore in the range of 10 to 15 per cent.

In addition to analytic errors, deviations in multiple Fick output and associated parameters may be caused by inherent limitations in the Fick principle as discussed by Fritts and Courmand, 14 Visscher and Johnson, 15 and Stow. 16 It is virtually impossible to appraise the absolute magnitude of these latter errors quantitatively. The data of Wood et al. 17 suggest, however, that these errors are relatively small. Variations in the biologic state of the patient may also lead to relative errors in repetitive Fick cardiac output determinations. The role of these latter variations in the results obtained in the present study are also difficult or impossible to estimate. The mean oxygen consumption (for a total of 1100 individual oxygen consumption determinations in 400 patients) was 125 ml./Min./M. 7 , indicating that a basal state may readily be achieved during cardiac catheterization.

The median relative error for the four parameters analyzed in this study (i.e. cardiac index, oxygen consumption, arteriovenous difference and respiratory quotient) ranged from 3 to 6 per cent. Since the analytic error in the arteriovenous difference may possibly be as large as 7 to 10 per cent, these data suggest that much of the relative error in repeated Fick output determinations may be caused by analytic error rather than by merely representing biologic variations or inherent limitations in the validity of the Fick equation.

The relative errors in repeated Fick output determinations observed in the large number of studies reported in this paper demonstrate that the Fick principle is at least a reliable method of obtaining reproducible cardiac output values. The fact that reproducible data are obtained does not, however, establish the validity of the technique beyond all doubt. The problem of potential pulmonary tissue oxygen consumption, recently raised by Fritts et al., 14 remains to be fully evaluated. Pulmonary tissue oxygen consumption would, if of significant magnitude, result in overestimation of cardiac output by Fick principle.

Since approximately 80 to 85 per cent of repeat cardiac output observations at rest check within 10 per cent, experimental variations that are greater than 10 per cent, may, with fair certainty, be considered significant. Variations of more than 15 per cent have more than a 95 per cent chance of representing meaningful alterations in the output.

**Summary**

The results of cardiac index, oxygen consumption, arteriovenous oxygen difference and respiratory quotient determina-
tions in triplicate in 300 studies and in duplicate in 100 studies are presented. The median relative error between duplicate or triplicate determinations ranged between 3 to 6 per cent for the above four parameters, demonstrating the high degree of reproducibility of Fick cardiac output data in this laboratory. These parameters are reproducible within 10 per cent in 80 to 85 per cent and within 15 per cent in more than 95 per cent of the observations made.

RESUMEN
Se presentan los resultados del índice cardiaco, consumo de oxígeno, diferencia arteriovenosa de oxígeno y determinaciones del cociente respiratorio por triplicado en 300 estudios y por duplicado en 100 estudios. El error medio relativo entre determinaciones duplicadas y triplicadas varió entre 3 y 6 por ciento para los parámetros anteriores, demostrando el elevado grado de reproducibilidad de los datos del rendimiento cardíaco de Fick en este laboratorio.

Estos parámetros se pueden reproducir dentro de 10 por ciento en 80 a 85 por ciento y dentro de 15 por ciento en más del 95 por ciento de las observaciones hechas.

ZUSAMMENFASSUNG
Berichte über die Ergebnisse der Herzindexes, Sauerstoffverbrauches, der arterio-venösen Sauerstoffdifferenz und des respiratorischen Quotienten bei dreifachen Untersuchungen in 300 Fällen und doppelten Untersuchungen in 100 Fällen. Der mittlere relative Irrtum zwischen der dopelten und der dreifacher Bestimmung lag zwischen 3-6% für die erwähnten 4 Bereiche und demonstrierte so einen hohen Grad von Zuverlässigkeits der Werte des Herzmintervolumens nach Fick in unserem Laboratorium. Diese Bereiche sind reproduzierbar in 10% bis 80 und 85% und in 15% bei mehr als 95% der gewonnenen Beobachtungsergebnisse.

REFERENCES
18 Fritts, H. W., Jr. and Courand, A.: "The Application of the Fick Principle to the Meas-
AORTIC VALVULAR SURGERY WITH ARTIFICIAL VALVES

Patients with aortic valvular disease who presented themselves for operative correction relative to the effectiveness of prosthetic replacement in the surgical treatment are reported. Experience to date in 115 patients so treated demonstrates the effectiveness of this technique. The operative mortality due to technical factors has been low, and the clinical results have been excellent. Since the operative mortality now occurs primarily in those patients with myocardial failure, its prevention, if possible, is advisable by earlier detection and surgical correction.


LEFT ATRIAL MYXOMA

A case of left atrial myxoma associated with an atrial septal defect and removed by the trans-atrial septum approach is presented. A pathologic study of the junction of the tumor and the atrial septum in four necropsied cases revealed no evidence of myxoma invasion beyond the elastic fibers of the second endocardial layer; excision of the atrial septum is not necessary for complete removal.


PRELIMINARY EXPERIMENTS ON USE OF AIR TIGHT CULTIVATION METHOD

A new method, originally devised by Tao and improved by using a silicone-coated slide glass, for determining the blood level of antituberculous chemotherapy is described. By this method the tubercle bacillus is cultivated in a medium consisting of the serum only without any artificial supplement and the cultivation is done in an almost air tight state by using a cover of a layer of liquid paraffin oil. Preliminary experiments in rabbits show that this method may be available for routine clinical use.