Reliability of the Determination of Cardiac Output in Man by Means of the Fick Principle

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Two determinations of cardiac output using the Fick principle were performed within a 15 min. time period in a series of 167 patients representing a wide spectrum of cardiac and pulmonary disorders. The reproducibility of the 2 readings was found to be satisfactory, attesting to the reliability of the practical application of the Fick principle as employed in clinical medicine.

The practical application of the Fick principle was made possible when a safe method for obtaining samples of mixed venous blood became available with the advent of cardiac catheterization. This classical indirect method of determination of the volume of blood flowing through the lungs has become within the last decade, the standard method against which other procedures aimed at determination of cardiac output are checked. Early workers, particularly Cournand et al., appreciated the importance of basal condition of the patient, a "steady state," for obtaining reliable determination of the resting cardiac output. The reproducibility of such estimations was tested on small groups of patients by Cournand, and subsequently by Donald et al., and was found to be satisfactory. However, in 1953, the practical application of Fick's principle in humans, particularly under certain abnormal conditions, was subjected to criticism by Visscher and Johnson, who suggested that very large errors could occur by reason of a phasic variation in blood oxygen content. Oximetric studies by Wood et al., and theoretical considerations by Stow, presented evidence that such errors, though they may exist, affect the accuracy of determinations much less than was suggested by Visscher and Johnson. In the light of this controversy, it was thought that the reliability of the determination of cardiac output by the

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performed after an interval of between 10 and 15 min. during which time the patient was resting. Samples of mixed venous blood were collected with each determination of cardiac output. Samples of arterial blood were withdrawn through a needle or indwelling arterial cannula from the brachial or femoral artery. In the earlier stages of the study, arterial samples were obtained during 1 of the 2 determinations of cardiac output. Later, an effort was made to obtain arterial samples simultaneously with mixed venous blood samples in both determinations. Consequently, duplicate arterial samples were available only in approximately one-third of the cases. Collection of expired air was done with great care, to avoid leaks in the system. The flutter valves were tested before and after each use, and the mouthpiece was carefully fitted in the patient's mouth. Displacements of the Tissot spirometer bell were compared with each other and with the readings from the previous day. Determinations in which major discrepancies in the volume of ventilation occurred were discarded, and the procedure was repeated. The total volume of minute ventilation was calculated, with the usual correction factors, from the quantity of expired air in the spirometer. Two separate samples of expired air were withdrawn each time and analyzed in the Scholander apparatus, in which the contents of oxygen, carbon dioxide and nitrogen were determined. The duplicate samples were required to check within 1 per cent. Blood samples were analyzed for oxygen and carbon dioxide content by the manometric technic of Van Slyke and Neill and duplicate determinations were also required to check within 1 per cent. Packed cell volume determinations were performed on each blood sample and were required to show identical readings in the resting samples.

RESULTS

The distribution of the 167 cases was as follows: 13 patients had no significant cardiovascular disorder; 30 had cardiac failure caused by coronary heart disease ("arteriosclerotic"); 21 were in cardiac insufficiency from hypertensive heart disease; 48 had chronic valvular disease of rheumatic etiology; 38 had chronic pulmonary disease with or without evidence of cor pulmonale; 8 patients suffered from a variety of other cardiovascular disorders.

All cases were pooled regardless of the clinical diagnosis and divided into 2 classes: those with normal or near-normal arterial oxygen saturation, the dividing line being placed arbitrarily at 90 per cent saturation, and those with arterial oxygen saturation lower than this. Patients with arterial oxygen saturation at or above 90 per cent (group A) were further subdivided into 3 classes: (a) those with normal cardiac output (arteriovenous oxygen difference of less than 4.5 vol. per cent) (27 cases); (b) those with moderately reduced cardiac output (arteriovenous oxygen difference between 4.6 and 6.5 vol. per cent) (58 cases), and (c) those with severely reduced cardiac output (arteriovenous oxygen difference of more than 6.5 vol. per cent) (23 cases). The anoxemic group B, consisted of 59 cases.

The reproducibility of the 2 independent determinations of the cardiac output was tested separately for the 3 component measurements of the Fick formula, for the arteriovenous oxygen difference, and for the cardiac output. Duplicate readings of the oxygen content of the arterial blood were available in 61 of the 167 cases. Thus the reproducibility of the oxygen content of mixed venous blood and of the oxygen consumption was tested in the entire series of 167 cases, while that of the arterial oxygen saturation, of the arteriovenous oxygen difference and of the cardiac output was tested in 61 cases. The reproducibility was measured by determining the "relative error" of the duplicate determination, which is defined as the ratio of the difference between the two readings to their average and is expressed as per cent.

Table 1 presents a comparison of the median relative errors for the component measurements used in the Fick equation in each of the 4 groups of patients. The median relative error was computed from tables such as table 2, prepared for each of the variables. The median error for oxygen consumption is 6.08 per cent, meaning that in half of the cases duplicate determinations differed less, and in half more than 6.08 per cent. The median error for oxygen consumption does not differ significantly in the 4 groups. The median error for duplicate determinations of mixed venous blood is considerably lower, namely 1.9 per cent, also showing no significant variation among groups of patients. The median error for the duplicate determi-
CARDIAC OUTPUT BY FICK PRINCIPLE

Table 1.—Median Relative Errors* in Duplicate Determinations of Component Measurements of the Determination of Cardiac Output in Four Classes of Patients Expressed as Per Cents

<table>
<thead>
<tr>
<th>Component</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(a)</td>
<td>(b)</td>
<td>(c)</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>7.6</td>
<td>6.06</td>
<td>4.96</td>
</tr>
<tr>
<td>Oxygen content of mixed venous blood</td>
<td>1.5</td>
<td>1.64</td>
<td>2.42</td>
</tr>
<tr>
<td>Arteriovenous oxygen difference</td>
<td>1.6</td>
<td>1.39</td>
<td>2.32</td>
</tr>
</tbody>
</table>

* Relative error of 2 measurements is defined as their difference expressed as percentage of their average.

The patient classes are as follows: Group A, arterial oxygen saturation at or above 90 per cent, (a) with normal cardiac output; (b) with moderately reduced cardiac output; (c) with severely reduced cardiac output. Group B, cases with anoxemia (arterial oxygen saturation lower than 90 per cent.

Table 2.—Relative Error Found in Duplicate Determinations of Cardiac Output in 61 Patients

<table>
<thead>
<tr>
<th>Relative error (%)</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 to 1.0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1.1 to 3.0</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3.1 to 5.0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5.1 to 7.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7.1 to 9.0</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>9.1 to 11.0</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>11.1 to 13.0</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>13.1 to 15.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15.1 to 17.0</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>17.1 to 19.0</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>over 19.0</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

Median error 8.54% 9.20% 2.44% 9.20% 8.60%

nations of oxygen content of arterial blood is 1.76 per cent. The over-all median error for the determination of the arteriovenous oxygen difference is 4.78 per cent; however, the median error for the arteriovenous difference in case of group B is 8.20 per cent. This is a significant difference at the 2 per cent level by the application of Wilcoxon's test.

Table 2 presents the relative error found in the determination of cardiac output (oxygen consumption divided by the arteriovenous oxygen difference). The median error for the series is 8.6 per cent and no difference is seen among the 4 groups.

Figure 1 shows the graphic presentation of the difference between the duplicate determination of mixed venous blood. Figure 2 shows a graph representing that difference for the arteriovenous oxygen difference.

DISCUSSION

In evaluating the findings of this study, three variables have to be taken into consideration: (a) the error of the methods of determination, of the various procedures; (b) variation of the oxygen content of arterial and mixed venous blood caused by phasic changes and by laminar flow; and (c) deviation from the truly basal condition of the pa-
patients resulting in an actual change in cardiac output between the 2 determinations.

The question of the variability of technic is minimized to an appreciable extent by the fact that 2 of the 3 determinations involved in the Fick formula are direct measurements, the accuracy of which can be controlled by requiring close checks of 2 independent determinations. The third factor, oxygen consumption, is a two-step procedure, therefore less accurate than the determination of oxygen content of blood samples. One part of the determination of oxygen consumption, the analysis of the expired air, is satisfactorily controllable by drawing and analyzing 2 separate samples from the air-collecting container and requiring the results to check closely. The second part, however, the determination of the minute volume of ventilation, cannot be performed in duplicate, and is the least accurate part of the measurement of cardiac output. Here the error of a single determination is compounded by unavoidable error caused by occasional small leaks of air around the mouthpiece. Therefore the reproducibility of oxygen consumption is only about one-third as accurate as that of the other 2 determinations, which is evident from table 1.

The problem of the variation in oxygen content of arterial or mixed venous blood depends on an exaggeration of the potential error caused by nonhomogeneity of mixtures of bloods differing in oxygen content. Physiologically the 3 principal sources of blood combining into mixed venous blood (inferior caval, superior caval and coronary sinus) differ in oxygen content, but are assumed to become homogeneous within the lower part of the right atrium. Under abnormal conditions, in the presence of a low cardiac output or in anoxemia, the exaggerated difference between the 3 types of blood could, in the presence of laminar flow, affect the accuracy of blood sampling even if the samples were withdrawn from the pulmonary artery, where mixing is expected to be more perfect, and if samples were drawn very slowly, which also reduces the possibility of error. Visser and Johnson4 based their criticism of the method on the magnitude of the error which could be caused by a phasic variation of oxygen content in acute anoxia, implying that such an error could arise in other pathologic conditions as well. The oxygen content of arterial blood is more stable than that of mixed venous blood, although it is also nonhomogeneous in its origin, containing mixtures of poorly oxygenated blood from less efficiently ventilated alveoli, Thebesian vessels and physiologic shunts. Here, too, the presence of anoxemia could introduce a significant error by improper mixing of the fully and poorly oxygenated bloods, even at the level of peripheral arteries.

The third variable, changes of cardiac output caused by deviation from the basal state, are primarily due to the patients' apprehension, for other conditions of the "basal state" can easily be controlled. Experience in this laboratory suggests that apprehension of the patients can be reduced significantly by the "priming" procedure described by reason of which the patient comes to the laboratory well acquainted with the various steps of cardiac catheterization. In spite of such preparation, however, some individuals show such apprehension that a suitable steady state cannot be attained. In some of these cases, this was evident at the time of the study, in spite of which they were included in the series.

It is seen from table 1 that the reproducibility of the oxygen content of the 2 determinations of arterial and of mixed venous blood is very satisfactory, showing a median error for each procedure of less than 2 per cent, which means that half of the pairs of determinations in each series agreed to within 2 per cent. Only minor differences are noted between cases with normal and low cardiac output and those with normal and subnormal oxygen saturation, which are statistically not significant.

The reproducibility of the arteriovenous oxygen differences shows lower accuracy for 2 reasons: in the first place, the errors of 2 independent determinations may be additive. In the second place, inasmuch as the absolute values of the oxygen content of mixed venous blood and of arterial blood are much larger than those of arteriovenous oxygen difference (normal average: A = 18; V = 14; A-V = 4
vol. per cent), the percentage variation of blood oxygen content appears more accurate than it is in reality. Thus, a 10 per cent variation in normal cardiac output, manifesting itself as 0.4 vol. per cent change in arteriovenous oxygen difference, will be shown as a 3 per cent change in oxygen content of mixed venous blood. In abnormal conditions, where the arteriovenous oxygen difference is wide and the oxygen content of mixed venous blood is low, this difference is less pronounced, and becomes less significant with low levels of cardiac output.

The fourth line of table 1 shows the difference in reproducibility of the arteriovenous oxygen difference between group B and the whole series. It also demonstrates the fact that in group A, the accuracy increases with the fall in cardiac output, as was to be anticipated. The question as to whether the lower accuracy of reproducibility of the anoxicemic group is related to variation in oxygen content in arterial and mixed venous blood in the presence of anoxemia, or is due to other factors cannot be answered from the available data. However, if phasic variation of oxygen content were the principal factor, one would have expected to find a significant difference in reproducibility between anoxicemic and normoxicemic cases in other parameters than the arteriovenous oxygen difference as well.

Thus, the accuracy of the arteriovenous oxygen difference is considerably lower than that of the oxygen content of the arterial and of mixed venous blood. It compares with the accuracy of oxygen consumption. The reproducibility of the determination of cardiac output is the lowest of all because the errors of oxygen consumption and of arteriovenous oxygen difference are compounded. The median error for the determination of cardiac output is 8.6 per cent.

The principal objective of this study was to determine whether a carefully performed determination of cardiac output, using the Fick principle in an average laboratory, is reliable under a variety of normal and abnormal conditions. A corollary of this objective is to find out whether patients during the performance of the long and involved, perhaps even frightening cardiac catheterization study, are capable of reaching a satisfactory steady state so as to approach a basal level of cardiac output. On the basis of the findings of this study, one is justified in accepting an affirmative answer to these 2 questions. The facts that 2 determinations of cardiac output, separated by no less than a 10 min. period, differ in the majority of cases by less than 10 per cent and that the arteriovenous oxygen differences of these 2 determinations differ in the majority of cases by less than 5 per cent suggest that the method is fully acceptable and its accuracy compares favorably with many other biologic measurements. It should be emphasized that this study involved a consecutive series which included a number of patients in whom it was obvious that apprehension prevented their reaching a steady state. The elimination of such cases would have materially increased the accuracy of the determination.

The demonstration of a significant difference between the reproducibility of the arteriovenous oxygen difference and of the cardiac output justifies furthermore the use of the former in the setting of normal and abnormal standards and in observing the effects of various factors upon the cardiac output. Thus, in expressing the changes in cardiac output as a variation in arteriovenous oxygen differences rather than as cardiac index, the accuracy may be increased; this is permissible, owing to the fact that in resting individuals oxygen consumption is, as a rule, well regulated and minute-to-minute changes in cardiac output are likely to be mirrored by alterations in arteriovenous oxygen difference.

**SUMMARY**

In a series of 167 unselected cardiac catheterization studies in patients with normal cardiovascular systems and those with a variety of cardiopulmonary abnormalities, 2 separate determinations of cardiac output using Fick’s formula were performed in the resting state within a 15 min. time period.

The reproducibility of the oxygen content of mixed venous blood tested in 167 cases and that of arterial blood in 61 cases showed a high degree of accuracy, the median error
being, in both, under 2 per cent. Oxygen consumption was found to be less reliable, with a median error of 6 per cent. The arteriovenous oxygen difference showed a median error of 4.8 per cent and was more accurate than the cardiac output, in which the median error was 8.6 per cent.

Cases were divided according to whether normal and subnormal arterial oxygen saturation was present. The accuracy of the component measurements in the 2 groups showed no difference, although the arteriovenous oxygen difference appeared more variable in the anoxic group than in cases with normal oxygen saturation.

The satisfactory reproducibility of the measurements in the vast majority of cases is interpreted as demonstrating that the potential error due to phasic variation of blood oxygen content is of no major importance in the determination of the basal cardiac output; and that in spite of the complexity of the procedure of cardiac catheterization, a satisfactory steady state occurs in the majority of patients.

Acknowledgments

The authors are indebted to Dr. Lincoln E. Moses, Associate Professor of Statistics, Stanford University, who has supplied the statistical evaluation of the data.

Summario in Interlingua

In un serie de 167 non-seligite studios de catheterisation cardiac in patientes con normal systemas cardiovascular e in patientes con un varietate de anormalitates cardiopulmonar, duo separate determinaciones del rendimento cardiac esseva effectuate per medio del principio de Fick, ambes intra un periodo de 15 minutas e con le subjectos in stato de reposo.

Le determinaciones del contento de oxygeno de sanguine venose mixte in 167 casos e de sanguine arterial in 61 casos se provava altemate reproducibile. In ambe series le error median esseva infra 2 pro cento. Esseva trovate que le determination del consumption de oxygeno esseva minus accurate. Pro illo le error median esseva 6 pro cento. Le differ-
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