Clinical Tests of the Simple Method of Estimating Cardiac Stroke Volume from Blood Pressure and Age

By Isaac Starr, M.D.

The results secured by the simple method of estimating cardiac output, described in the previous paper, have been applied to data already in the literature. Hundreds of comparisons are possible between estimates of cardiac output made by our blood pressure method from values given by the authors, and the results of estimates of cardiac output by some other well known method employed at the same time. The correlations between the results secured by our method and those obtained by Fick, acetylene, ethyl iodide, and nitrous oxide methods are often surprisingly good. There is an unexplained difference in level between the Fick and blood pressure estimates, but not between the blood pressure estimates and those of the three older methods.

As a next step in the investigation of our simple method of estimating cardiac output from blood pressure and age, by formulas derived from experiments in cadavers, it seemed necessary to subject it to test in the clinic. But experiments designed especially for this purpose seemed unnecessary, for a large number of estimates of cardiac output, made by the many methods in use during the last 30 years, have already been reported together with the blood pressures and pulse rates of the subjects tested. Indeed, over 500 instances have been discovered in which it is possible to compare values for cardiac output estimated by our formula from blood pressure measurements made by the authors themselves, with estimates of cardiac output made by some other method. However, one aspect of the situation made me hesitate to undertake this study. Most of the authors have reported the blood pressures of their subjects only incidentally, to indicate whether the subjects suffered from hypertension or not, and so one might properly wonder whether these measurements were made with the care requisite to the use to which we now proposed to put them. Indeed, one does not always know whether the blood pressures recorded were taken under circumstances identical with those under which the cardiac outputs were estimated, or not. And in some reports there is a distressing tendency for the figures given for blood pressure to end in such digits as 0 or 5, a tendency the author finds, alas, in reviewing some of his own work, and which certainly indicates that the highest accuracy was not sought. But despite these difficulties, it seemed wiser to take the data already in the literature at their face value and proceed with a comparison between estimates made by the different methods, especially since the result would be so completely free of bias. From data already in the literature we have estimated stroke volume by our blood pressure method in over 400 instances in which the results of comparable estimates of cardiac output by another method were recorded, and a summary of these results will be given here.

Certainly one might properly have misgivings that our simple scheme of estimating cardiac stroke volume from blood pressure, although working well in cadaver experiments, would work equally well throughout the far greater range of physiologic and pathologic variations to be encountered in the clinic. To use a formula which does not include pulse wave velocity as a measure of the elasticity

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of the compression chamber at the time of the test is to adopt an unorthodox view. This I was prepared to do, for results secured in cadavers seemed inconsistent with the compression chamber theory as it is usually understood. And it was equally surprising to me to find that the size of the subject, or of his aorta, made so little difference. But preconceived conceptions should have no standing if opposed to the cold logic of the results secured in the cadaver experiments, where stroke volume could be measured with high accuracy, and where both it and blood pressure were recorded directly by methods of a high order of merit. So our formulas for estimating stroke volume, unlike the previous methods proposed for relating blood flow to blood pressure, were not based on a theory but on a demonstration. And the fact that the relations proved simpler than had been anticipated, was, after my surprise had subsided, a cause for rejoicing. Nevertheless, it seemed necessary to undertake the clinical study in the hope of learning what we could of the limitations of the simple ideas developed in the cadaver experiments and of discovering the clinical situations in which these limitations were to be expected.

It was also evident that there were at least two places of weakness in the data from which our blood pressure method had been built up in the cadaver experiments. The first was the lack of data in young persons. When applied to blood pressure measurements taken on young persons the results given by our cardiac output formula are based on an extrapolation from data secured in older subjects. A secondary deficiency was the small number of systoles conducted at high hypertension in the experiments in which blood was used as perfusing fluid, and we were well aware of the lack of agreement between actual and estimated stroke volume in the systoles conducted at very high hypertension, or when pulse pressure was very large, in the experiments in which water was used. So it was hoped that comparison with results secured by other cardiac output methods would throw light on these problems, and help to define the limitations of the method.

Comparisons between Estimates of Cardiac Output from Intra-arterial Blood Pressure and from Other Methods

Comparisons with the Results Secured by the Fick Method

Data secured from Stead's laboratory are particularly suited to this purpose because in these reports blood pressures were secured by an optical manometer connected with a needle in the femoral artery; and thus it is proper to employ our formula 59, first to estimate stroke volume from the pressures recorded, and then, by multiplying the result by the pulse rate, to estimate cardiac output per minute.

A comparison of the results secured in healthy subjects is given in figure 1A. In 21 healthy subjects at rest Stead and his co-workers obtained an average cardiac index of 3.98 liters per minute per square meter by the Fick method, with a standard deviation about the mean of 1.36 liters per minute, a coefficient of variation of 34 per cent. Using his blood pressure data and our formula 59, one estimates an average cardiac index of 2.7 liters per minute per square meter, and a standard deviation of 0.50 liters per minute, so that \( v = 19 \) per cent. The mean of our estimates of basal cardiac output from blood pressure is, therefore, much lower and our data much less scattered than in results secured by the Fick method; but despite these differences the correlation between the two sets of results is highly significant.

In the experiments of Brannan and associates the effect of anemia was investigated, and the relation between the results secured by the two methods is shown in figure 1B. Again the estimate from blood pressure is consistently smaller than the Fick estimate, the mean difference being 1.6 liters per minute per square meter. Nevertheless, there is obvious correlation between results secured by the two methods which would be reasonably good were it not for four divergent points, marked with crosses on the dot diagram, each pertaining to a result secured in a case of anemia (hemoglobin 8.6; 10.7; 5.1 and 8.8 Gm.)
which showed an abnormally high cardiac output as estimated by the blood pressure method, but gave values within the normal range by the Fick method, judging by the results secured in the normal subjects described in the preceding paragraph. In favor of the greater correctness of the blood pressure estimate one could point out that the heart rates of three of these four cases were elevated, 100, 94 and 100 per minute; that of the last being 84. Indeed, the blood pressure results suggest that the cardiac output rises much more consistently in anemia than do the Fick results.

In the experiments of Warren and his colleagues the effect of hemorrhage was investigated. In these data the correlations between the estimates of cardiac output made by the two methods is excellent, r = 0.86, although the same difference in level appears. There is one interesting difference in result, subject E. S., the only subject to show a substantia

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**Fig. 1.** Comparisons of estimates of cardiac output per minute per square meter, made from the blood pressure, and by other methods. The horizontal coordinates define cardiac output per minute as estimated by our blood pressure method and the pulse rate; the vertical coordinates define cardiac output per minute as estimated by the Fick or dye method.

(A) Data of Stead and his colleagues, a study of normal subjects. Cardiac output estimates were estimated from femoral intra-arterial blood pressures by formula 59; and by the Fick method. The correlation is significant r = 0.62. (B) Data of Brannon and co-workers, a study of the effect of anemia. The estimates of cardiac output were made as in A. Points marked with a cross are especially commented upon in the text. (C) Data of Warren and his associates, a study of the effect of hemorrhage. Estimates as in A. Note the strong correlation, r = 0.91. (D) Data of Cathcart and co-workers, a clinical study concerned with the evaluation of Nickerson's ballistocardiographic method. Cardiac outputs were estimated from auscultatory blood pressures, using the point of muffling as diastolic pressure, by our formula 68, and by the Fick method. Duplicate estimates are joined by lines. The correlation is significant, r = 0.47 after correction for attenuation. (E) Data of de Wardener and colleagues, a study of the effect of hemorrhage on anesthetized subjects. Cardiac outputs were estimated from femoral intra-arterial blood pressures by formula 59; and by Hamilton's dye method.
increase of cardiac output after hemorrhage by the Fick method, shows a negligible increase in the estimate from blood pressure, a finding consistent with the results secured after hemorrhage in the other subjects. But it should be emphasized that the unexpected finding of this paper, and the chief conclusion of Warren and associates, that a subject could be bled to the point of collapse without a material decrease in his cardiac output, is altogether supported by the blood pressure data.

Other data secured in Stead’s laboratory do not lend themselves so well to our purpose, although they deserve mention. The ample data of Hickam and Cargill on the effects of exercise cannot be used because pulse rates are not given, but, with the knowledge that the heart rate can be expected to rise during exercise, inspection of the data indicates that correlation between estimates from blood pressure and from the Fick method is to be expected. On the other hand, when one inspects the data on the effects of tilting given by Hickam and Pryor, although the results secured by the two methods of estimating cardiac output cannot be directly compared as the height and weight of the subjects are not given, it is easy to see that the agreement would be very poor. The average of both methods indicates a diminished stroke volume on tilting to 60 degrees, but the diminution is much larger in the Fick estimates. As the position of the subject approached the vertical, the output per minute fell in 17 of 18 tests according to the Fick results, while it diminished in only 8 of the 18 tests according to the estimates made from blood pressure.

Comparisons with Results Secured by the Dye Method

The data of de Wardener and coworkers permit 14 comparisons between estimates made from intra-arterial blood pressure by formula 59 and by Hamilton’s dye method of estimating cardiac output. These results were secured in experiments on the effects of hemorrhage during anesthesia, and figure 1D shows the results. Again the blood pressure estimates are at a lower level. What would be good correlation is spoiled by two extremely divergent points. According to the results secured by the dye method, the cardiac output per minute of each of these subjects at this time was much larger than any other value found in the rest of the experiments, despite the fact that the pulse rates were only 55 and 47 per minute. Indeed, these two stroke volumes, as estimated by the dye method, are so huge, 220 and 320 cc., that one is inclined to bet on the greater accuracy of the estimates from blood pressure, which give results at a level consistent with that found under similar conditions in the other experiments of this series.

Comparisons between Estimates of Cardiac Output Made from Blood Pressures Taken by the Auscultatory Method, with Those Made by Various Other Cardiac Output Methods

Comparisons with Results Secured by the Fick Method

As soon as the ordinary clinical method of taking blood pressure is used as the basis for an estimation of cardiac output from our formula, a much larger error must be expected, but it seemed proper to make further tests of our method in the ample data already in the literature in which auscultatory blood pressures were recorded in conjunction with estimations of cardiac output by some other method. Almost ideal for this purpose is the splendid body of data compiled by Cathcart and associates, the qualification being inserted solely because blood pressures were taken in conjunction with the ballistocardiograms—blood pressure being employed in Nickerson’s formula for measuring cardiac output from these records—rather than under the exact conditions in which the blood and gas samples required for the Fick estimate were secured. In presenting this comparison here we shall consider only the 46 results in 23 cases in which duplicate estimations are reported, because this feature, so seldom accomplished by those working with the Fick method, seems so vitally necessary not only to permit detection of technical errors, but also to demonstrate that the subject is actually in the steady state.
that is essential for accuracy of the results, despite the character of the experiment, which, requiring cardiac catheterization, arterial puncture and breathing through a mask, seems certainly sufficient to disturb most conscious patients.

Figure 1D shows the results of such a comparison. The correlation is highly significant, \( r = 0.44 \), while a value of 0.291 is significant for \( p = 0.05 \), though the agreement is certainly not of a high order. The agreement of duplicates by both methods is unusually good, the test-retest correlation coefficients being 0.91 for the Fick duplicates and 0.96 for those estimated from blood pressure. Correcting for the variation inherent in each method as judged by the deviation of duplicates—called by the statisticians correcting for attenuation—the correlation between the results secured by these two methods rises from \( r = 0.44 \) to \( r = 0.47 \).*

Comparing the stroke volume as estimated by the two methods, one finds that the standard deviation about the regression which minimizes the Fick values is 21 cc. This is to be compared with the value of 10 cc., which is our estimate of the maximum standard deviation if an accurately measured stroke volume, as in the cadaver experiments, could be estimated from blood pressures determined by the auscultatory method; so apparently each method contributes about the same amount to the differences between the results.

Despite this fairly satisfactory correlation, the marked difference in the level of the results, encountered in comparisons made from data secured in Stead's laboratory\(^1\), \(^2\), \(^3\) persists in these data also. In the comparison permitted by the data of Cathcart and coworkers\(^4\) there is an additional factor which might make the results of the estimate of cardiac output from blood pressure too low; by using formula 68 we have assumed identity of radial and femoral pulse pressures while the scanty data\(^5\) on the subject, too few we believed to base a satis-

* It is of interest that if one omits the data from the 6 pairs in which the duplicate Fick estimates diverge most widely, the correlation of the remaining 34 estimates rises to \( r = 0.57 \), without correction for attenuation.

factory correction upon, indicated that the femoral pulse pressure was actually somewhat larger. But we can correct our formula by the means of the data available securing:

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\text{Stroke Volume (cc.)} = 93 + 0.62 \text{ pulse pressure (mm. Hg)} - 0.45 \text{ diastolic pressure (mm. Hg)} - 0.61 \text{ age (years)} \] (76)

When this formula is applied to the data of Cathcart and associates, the estimates of stroke volume from blood pressure are a little larger, but the gross difference between these and the Fick estimates persists, the average value of the former being almost exactly two thirds of the average of the Fick estimates. It is perhaps of interest that this lower level corresponds closely to that of the average of estimates of stroke volume made by Catapart and colleagues\(^6\) from the formula Nickerson employs for this estimate from his ballistocardiograms, and it was in conjunction with the taking of the ballistocardiograms that the blood pressure was determined. But our estimates of cardiac output from blood pressure correlate much better with the Fick results than with the estimates of cardiac output made by Cathcart and co-workers\(^8\) using Nickerson's methods, and the chief conclusion of this paper, that the latter are of no value for estimating cardiac output in clinical work, is supported by our data.

Comparisons with Results Secured by the Acetylene Method

Figure 2F and G are concerned with Grollman's experience\(^10\) with two subjects at sea level, during a stay at Pike's Peak and after returning to the base of the mountain. The agreement between results secured by the two methods is striking. Both methods give extremely consistent values at sea level, those of the acetylene method being slightly more so. On reaching the top of Pike's Peak the basal cardiac output increased, as is shown by both methods, but after a few days residence on the peak it diminished somewhat, as both methods show. At the base of the mountain the results were closely similar to those at sea level.

The greater changes in cardiac output produced in one subject by breathing low
oxygen mixtures in a series of experiments are plotted in figure 2H, where the correlation between results secured by blood pressure and acetylene methods is impressive, \( r = 0.85 \).

Unfortunately, in much of the rest of Grollman's data\(^1\) the ages of the subjects are not given. I have, however, used his data on the effects of typhoid vaccine\(^2\) by assigning to the medical students used as subjects the age of 23 years, which is the average age in our school of the class Grollman taught in Johns Hopkins.

Obviously to be wrong by a few years would make little difference in the results. The comparison is shown in figure 2I. Again there is impressive similarity between the magnitude of cardiac output estimated by acetylene and blood pressure methods when the subjects are at rest and afebrile. Both methods show the increase of cardiac output when fever developed but there is somewhat more scatter, and there is one marked divergence of result, the blood pressure method indicating a great increase.

![Graph](image)

**Fig. 2.** Comparisons of estimates of cardiac output per minute made from blood pressure (horizontal coordinates) and by two of the other cardiac output methods (vertical coordinates).

\((F)\) Grollman's data,\(^1\) basal cardiac outputs of subject A. G. Dots, from results at sea level; crosses, results secured on the top of Pike's Peak; z's, after return to the base of the mountain. Cardiac output per minute was estimated from auscultatory blood pressures and formula 68; and by the acetylene method. \((G)\) Grollman's data,\(^6\) subject L. C. G. at sea level, on Pike's Peak, and at the base of the mountain. Methods and symbols as in \(F\). \((H)\) Grollman's data,\(^6\) subject A. G. in a series of experiments at sea level concerned with the effect of breathing gas mixtures low in oxygen. Methods as in \(F\). Note the excellent correlation between the two methods, \( r = 0.85 \). \((J)\) Grollman's data,\(^7\) experiments concerned with the effect of fever, induced by typhoid vaccine, on healthy medical students. Methods as in \(F\). Estimates made while the subjects were febrile are marked with crosses. \((K)\) Data of the author and his collaborators.\(^1\) Estimates from auscultatory blood pressures and formula 68; and by the improved ethyl iodide method. Dots, results secured on healthy persons; X's, results secured on hospital patients judged to have normal circulations; crosses, results secured on cases of hyperthyroidism. \((K)\) Data of the author,\(^1\) effect of injection of epinephrine on hospital patients. Dots, results secured before and crosses, results secured during the action of the drug. Results secured on the same subject are joined by lines.
in cardiac output while the acetylene method shows no increase over basal values. Interestingly enough the subject at the time of these estimates had the highest temperature and the fastest pulse rate encountered in the series of experiments, so we have another instance in which, when the blood pressure estimate of cardiac output disagrees with that of a more elaborate and difficult method it is the former that is more consistent with the rest of the data.

The results of this set of comparisons can be summarized only by saying that in Grollman's data the two sets of results are extraordinarily similar.

**Comparison with Estimates by the Ethyl Iodide Method**

The improved ethyl iodide method was the first cardiac output method which could be applied to subjects without requiring their intelligent and skilled cooperation, so it was the first method to be widely employed in the clinic and comparisons between its results and those secured by the blood pressure method can be made in several hundred instances. A sample of over 50 of these was taken for study.

Figure 2 shows comparisons of results secured by both methods in a group of healthy persons, a group of hospital patients with circulations judged to be normal from clinical data, and in 10 cases of hyperthyroidism. The average levels of the two sets of results secured in healthy persons are very similar, the mean difference being only 2.8 cc., but the scatter is larger than in the comparison with the acetylene method. The root mean square of the deviations from the mean difference is 23 cc. In results secured in pa-

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**Figure 3.** Comparisons of estimates of cardiac output per minute made from blood pressure (horizontal coordinates); and by the nitrous oxide method of Krog and Lindhard, (vertical coordinates). Data of Liljestrand and Zander; the subjects sat on a bicycle ergometer or rode at various levels of work. Estimates of cardiac output were from auscultatory blood pressures and formula 68.

(L) Subject G. L., a normal subject. Note the surprising correlation, $r = 0.95$. (M) Subject K. E. Ek, a case of heart block; $r = 0.97$. (N) Subject U. von E., a normal subject; $r = 0.88$. (O) Subject H. B., a normal subject; $r = 0.93$. 

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patients with hyperthyroidism the scatter is still larger. In four of these patients the results secured by both methods indicated a cardiac output within the normal range, in two patients the cardiac output was judged to be far in excess of normal by both methods, so in these six the agreement between results secured by the two methods is reasonably good. But in four cases of hyperthyroidism the circulation was judged to be normal by the ethyl iodide method, but to be clearly greater than normal by the blood pressure estimates. So here again we have a situation in which the blood pressure estimates are more in line with expectations from other sources.

In figure 2K have been placed results secured when adrenaline was given to six subjects. The increased circulation occurring after adrenaline is shown clearly in every case by both methods. Both methods yield quite similar results if the data secured before adrenaline is averaged, and also if that secured after adrenaline is averaged, but in most individuals the result of the two methods agree poorly.

Comparison with Estimates Made by the Krogh and Lindhard Method

The four exercise experiments made by Liljestrand and Zander were ideal to compare results secured by the two methods and the data for each of the four subjects has been plotted in figure 3. The correlation in each case is so unexpectedly good that the author was taken by surprise. The results secured by the two methods agree closely as to the resting level of cardiac output in one of the three healthy subjects, but in the other two the results secured by nitrous oxide average a little larger, but the use of formula 76, which allows for possible differences between femoral and brachial pressures brings the levels together. The difference in level is more noteworthy in the patient with heart block, K. E. Ek., who, with a pulse rate in the thirties, was estimated as having a normal resting cardiac output per minute by the nitrous oxide method and a somewhat subnormal output by the blood pressure method. But it need hardly be repeated that the correlation is extraordinary for the subjects individually; and \( r = 0.94 \) for the group of three healthy persons taken together, while a value of \( r = 0.29 \) is significant for \( p = 0.05 \).

To summarize all the foregoing findings, the data has been presented in a somewhat different light in table 1. Correlation coefficients have been included in the foregoing discussion because they seemed appropriate, and to be expected, but in many ways they constitute an inferior method of investigating the relation

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<tr>
<th>Data</th>
<th>Regression Equation</th>
<th>( \sigma_{yx} )</th>
<th>V</th>
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<tbody>
<tr>
<td>Starr et al. (Cadaver exp.; formula 59)</td>
<td>S.V. (measured directly) = 91 + 0.54 P.P. - 0.57 D.P. - 0.61 Age</td>
<td>6</td>
<td>13%</td>
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<tr>
<td>Starr et al. (Cadaver exp. results adjusted for the auscultatory B.P. method. Diastolic pressure at muffling of sounds; formula 68)</td>
<td>S.V. = 93 + 0.54 P.P. - 0.47 D.P. - 0.61 Age</td>
<td>10</td>
<td>16%</td>
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<tr>
<td>Warren et al. (Hemorrhage exp.)</td>
<td>S.V. (Fick method) = 1.5 S.V. (formula 59) + 8.9</td>
<td>20</td>
<td>19%</td>
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<tr>
<td>Cathcart et al. (Resting patients)</td>
<td>S.V. (Fick method) = 1.02 S.V. (formula 59) + 20.6</td>
<td>21</td>
<td>22%</td>
</tr>
<tr>
<td>Grollman (Breathing air and low oxygen mixture)</td>
<td>S.V. (Acetylene method) = 0.45 S.V. (formula 68) + 43</td>
<td>10</td>
<td>14%</td>
</tr>
<tr>
<td>Liljestrand and Zander (3 normal subjects at rest and during exercise)</td>
<td>S.V. (Nitrous oxide method) = 1.81 S.V. (formula 68) - 25.9</td>
<td>21</td>
<td>20%</td>
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S.V. = stroke volume in cc.; P.P. = pulse pressure in mm. Hg; D.P. = diastolic pressure in mm. Hg; age in years. \( \sigma \) = the standard deviation about the regression minimizing the deviations of the results of the elaborate methods. V = \( \sigma \) divided by the mean value of the elaborate method.
of the results of one method to those of another, and indeed, they may mislead the unwary. Therefore, confining our attention to the data best suited to the purpose, the regression equations for stroke volume and the standard deviations around the regression, given (under \( \sigma \)) in absolute values and (under \( V \)) in percentage of the mean estimate made by the elaborate method, are given in table 1.

At the head of table 1 is given the scatter of the estimates of cardiac output from blood pressure and age about the true values found in the cadaver experiments, below have been placed the scatter of the blood pressure estimates about the results of four elaborate cardiac output methods. A comparison of the magnitude of these standard deviations is most illuminating. One sees at once that our results correspond most closely to those of the acetylene method in the experiment studied, the scatter about the regression being similar to that which was estimated for our method from theoretical conceptions. However, in this experiment \(^\text{10} \) Grollman used only one subject, himself, and undoubtedly this fact has greatly reduced the scatter. Indeed, in the data shown in figure 2 it is obvious that the scatter increases when additional subjects are employed, so these results do not mean that the acetylene method is necessarily superior to the other methods which were used on a number of subjects in the experiments analyzed. Nevertheless, the agreement between the results of our method and those of the acetylene method in this experiment is nothing short of remarkable. Grollman's method required trained cooperation of the subject, and undoubtedly he himself was most adept at it.

Table 1 shows that the Fick and nitrous oxide methods gave almost identical scatter about the regression, which is about twice the amount we estimate to be inherent in the blood pressure cardiac output method when the auscultatory method of taking blood pressure is used.\(^\text{1} \) This increase is to be attributed to the errors inherent in the elaborate methods themselves; indeed this difference is of the order of magnitude of the "accuracy" of the Fick procedure as defined by duplicate estimations.

It is of interest to point out that the taking of intra-arterial femoral blood pressures in the experiments of Warren and his colleagues\(^\text{1} \) has not led to the expected diminution in the scatter; a possible reason for this may be that the tip of the cardiac catheter was not advanced beyond the tricuspid valve in the experiments from Stead's laboratory, while in the experiments of Cathcart and co-workers,\(^\text{8} \) the tip was in the pulmonary artery, which should secure a better mixed sample and so greater accuracy. Perhaps in the experiments from Stead's laboratory the gain in accuracy of the blood pressure method from intra-arterial measurements was cancelled by the diminished accuracy of the Fick estimate; but, in any event, while the slopes of the regressions are somewhat different, the scatter of our estimate about the results of both versions of the Fick method is very similar. The larger correlation coefficient pertaining to the data of

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<td>Warren et al.(^\text{4} )</td>
<td>C.O. (Fick) L./min./M.(^2 ) = 1.91 (S.V. by formula 59) \times P.R. - 0.68 \text{ body surface area}</td>
<td>0.8 L./min./M.(^2 )</td>
<td>19%</td>
</tr>
<tr>
<td>Catcchart et al.(^\text{8} )</td>
<td>C.O. (Fick) L./min./M.(^2 ) = 0.58 (S.V. by formula 68 \times P.R.) + 2.5 \text{ body surface area}</td>
<td>0.6 L./min./M.(^2 )</td>
<td>16%</td>
</tr>
<tr>
<td>Grollman(^\text{10} )</td>
<td>C.O. (Acetylene) L./min. = 1.08 (S.V. by formula 68 \times P.R.) + 0.2 \text{ body surface area}</td>
<td>0.88 L./min.</td>
<td>17%</td>
</tr>
<tr>
<td>Liljestrand and Zander(^\text{16} )</td>
<td>C.O. (Nitrous oxide) L./min. = 1.92 (S.V. by formula 68 \times P.R.) - 2.63</td>
<td>1.36 L./min.</td>
<td>14%</td>
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Data as in table 1. C.O. = cardiac output. S.V. = stroke volume in cc. P.R. = pulse rate per minute. \( \sigma \) and \( V \) as in table 1.
Warren and associates\(^4\) is due to the fact that, in these experiments, the range of values is much greater than in the Cathcart data, which dealt altogether with resting subjects.

Finally, in table 2 have been placed the regression equations for cardiac output applicable to the data given in certain of the figures.

**DISCUSSION**

These studies leave little room for doubt that results secured by our blood pressure method of estimating cardiac output, conceived and designed as a rough method, correlate well with those obtained by many other methods under a wide variety of conditions. Indeed, it seems evident that, in every one of the series illustrated in the figures, the same conclusions must be drawn when cardiac output is estimated from the blood pressure measurements by our formula as were indeed drawn by the authors from the results secured by the elaborate cardiac output methods they employed. But despite this surprising correlation there are some conspicuous differences in results which must be pointed out and discussed.

The goal of a cardiac output method useful in the clinic can be properly approached from two directions. In one, everything is sacrificed to the aim of securing the highest accuracy obtainable, and this has been the philosophy inspiring those who, with great skill and boldness, have developed the Fick method, by means of cardiac catheterization, to its present usefulness\(^17\); and a much similar aim has also inspired those who labored with the many difficult and time consuming cardiac output methods employed in the past. But there is a second approach which has always seemed equally proper to the author; that of first designing methods so innocuous that they do nothing to disturb the subject, and so simple and practicable that any physician can operate them, and then searching for their limitations. Obviously, our method of estimating cardiac output from blood pressure and age belongs in the latter category, and a chief aim of this study was to compare the results secured by our simple method with those obtained by much more elaborate procedures in the hope that the limitations inherent in the former method could be defined. The accomplishment of this aim would have been simple enough if one had knowledge that the accuracy of the elaborate methods was clearly superior to that of the simple method. But do we have this knowledge? With the results before me, I am by no means certain that we do. The situation, as I see it, is as follows.

When the wide spread of the data favors such investigations there is always significant correlation between results of our estimates of cardiac output per minute from blood pressure, age, and heart rate, and the results of cardiac output estimates made by the Fick, acetylene, ethyl iodide and nitrous oxide methods. In some of these situations the correlation is amazingly good, especially when one recalls that the blood pressure data were collected without knowledge of the purpose to which they have been applied in this paper.

There is, however, a very marked difference in level when estimates of cardiac output made from blood pressure are compared with the results secured by the Fick method, or by the dye method. When compared with results secured by acetylene, ethyl iodide and nitrous oxide methods, this difference is absent or minimal; so, completely to the surprise of the author, the results support the cardiac output levels for resting subjects characteristic of the older, rather than of the newer, technics. But unable to point with certainty to a defect in the Fick procedure to which the difference can be attributed, one must first do some searching of soul regarding the accuracy of the blood pressure procedure. Certainly it is accurate enough in the cadavers, in experiments in which cardiac output could be measured with exactitude, but would it be as accurate when applied to the living?

It is often the philosophic dilemma of quantitative scientific work that, in order to make the accurate measurements we require, we must create conditions different from those in which we plan to apply our method. Thus our blood pressure method is based on experiments made in cadavers, because in these the
cardiac output and many other cardiac functions could be measured with an accuracy not to be approached in experiments on living men or animals. Also in favor of this means of attack is the anatomic similarity of the conditions of our tests to those in which we plan to work, and one would certainly expect that the forces required to accelerate the blood column and the resistance due to pressure and friction would be similar in both the living and the recently dead. Physiologists have not hesitated to apply the results of measurements of arterial elasticity made on aortic rings removed from the animal to conditions existing in the aorta during life; indeed, muscular contraction is readily demonstrated in such rings. Similarly, signs that all vital activity had not ceased were sometimes encountered in our experiments. In addition, surgeons have successfully used as arterial grafts pieces of aorta taken at necropsy many days previously. But despite these aspects favorable to our preparation, the question must be raised; does not some vasomotor effect, ceasing at death, so change the distensibility of the compression chamber during life, that a given stroke volume delivered during life causes a smaller increment of pulse pressure than a similar stroke volume delivered after death? In favor of an affirmative answer one notes that Alexander has found that adrenaline caused increased tone of the intrinsic muscle in the aorta of dogs, and that when this muscle contracted the distensibility of the aorta was increased, a finding which certainly permits the view that aortic distensibility might decrease at death when the muscles relaxed and let the aortic wall expand until it rested on the less vital elastic fibers.

The decisive experiment on this point, made to permit one to compare the pulse wave velocity of a single subject in health and after death, would be obviously very difficult to accomplish, and one doubts whether a comparison made between this velocity during one's last illness and after death would give a conclusive answer. But the less direct evidence does not support the view that the changes occurring at death have a noteworthy effect on the pressure-flow relationship. The reasons for this belief are: First, the changes in elasticity on death, if any are present, seem to be small; for the pulse wave velocity of our cadavers is of the order of magnitude expected in patients of similar age tested during life; thus while a small change at death might well have been missed, a large change in pulse wave velocity would have surely been detected. Second, and more important, threefold, indeed, almost fourfold changes in the distensibility of the compression chamber, as measured by pulse wave velocity, changes much greater than could have occurred at death without our detecting them, were produced experimentally in our cadavers without any important interference with the pressure-flow relationship. Third, when volunteers were bled in the experiments of Warren and co-workers, one must believe that vasoconstriction occurred, but the correlation between the cardiac output estimates made by the Fick method and those made from blood pressure remained excellent. And lastly, adrenaline given in experiments on man, while producing marked changes in blood pressure, caused similar increments in the estimates of cardiac output both from blood pressure and from ethyl iodide methods. Apparently, therefore, either vital phenomena such as vasoconstriction have less effect on the relationship between flow and pressure in the great vessels than has been ordinarily believed, or this effect, by causing a change of diastolic pressure, is compensated by the resulting change in the term for diastolic pressure in our equations. We certainly have not discovered any reason for believing that the blood pressure method of estimating cardiac output will not work as well in living subjects as it does on the cadavers.

Having given the basis for our viewpoint, let us now enquire concerning the evidence for the accuracy of other cardiac output procedures, confining our attention chiefly to the Fick method, because it is thought of by many as providing a standard by which other methods should be judged.

Most authors in discussing the "accuracy" of the Fick method in their hands have had the deviation of the duplicate estimates in mind, and knowledge of the scatter of these,
while of the greatest importance to the proper interpretation of changes in the measurements, is not to be compared with the knowledge of absolute accuracy permitted by our cadaver experiments. Thus McMichael's estimate of an accuracy of 6 per cent is based on the standard error calculated from the deviations found in 100 consecutive cardiac output determinations, in which paired samples of venous blood were taken from the right auricle or right ventricle, within five minutes of one another, and simultaneous duplicate estimations of oxygen uptake were made, while the subjects were in a steady state. In these experiments, where subjects were normal, a fixed 95 per cent arterial oxygen saturation was assumed, and in patients only one sample of arterial blood was taken, so the errors of these estimates are not included in the scatter of the duplicate. Duplicating the arterial blood samples as well as the other items, Donald and co-workers got a value of 8.1 per cent for the standard error of estimates made by the Fick method in the supine position.

A value of 9 per cent for "accuracy" has been based on the data of Harvey and associates and was derived from the limiting values of the range of a small series of duplicate estimations, a far less useful statistic. At a symposium on recent advances in cardiovascular physiology and surgery, held in September, 1953, under the auspices of the Minnesota Heart Association, those present seemed to agree that the accuracy of the Fick method as applied to man should be rated at approximately 15 per cent or 20 per cent, this value meaning simply that when one estimate differed from another by less than this amount the difference should not be regarded as significant, but the exact means of arriving at the figure, and the level at which significance was placed, were not clearly defined. In any event it should be emphasized that all these studies on "accuracy" are in reality studies on consistency of performance, and that they contribute nothing towards an explanation of the difference in level of cardiac output as estimated by the Fick method and by our formulas. Indeed, if one is to judge solely by such tests, I am tempted to point out that, in the data of Catheart and colleagues, the "accuracy" of cardiac output estimates from blood pressure might be judged greater than that of the Fick method, for the test-retest correlation coefficient of the former is larger but, to tell the truth, the difference is too small to be significant.

The lack of satisfactory data concerning absolute accuracy of the Fick method in man has led to the search for this information in animal experiments, and the first investigation to furnish data from which this information could be obtained, that of Bohr and Henriques, deserves mention for its historical interest. The methods available in 1897 would be considered crude today, and while the average of the Fick estimates was high in comparison with measurements made by a mechanical flowmeter, the individual results scattered widely.

It was not until 1950 that this difficult experiment was repeated by modern methods, and in that year Seely, Nerlick and Gregg compared estimates of cardiac output made by the Fick method with measurements made by a rotameter placed in the pulmonary artery of anesthetized dogs with the chest open. Such experiments are of great technical difficulty, and it should occasion no surprise that, of the 40 experiments started, only 20 were completed; and in only 12 of these were the results considered reliable. Calculating the coefficient of variation from the data of the 12 best experiments, one gets a value of 7 per cent; obviously, the agreement between results secured by the two methods was excellent. However, one is concerned that the results of only 12 of the 20 completed experiments were accepted, and we seriously question whether a better estimate of the accuracy usually secured in the clinic would not be obtained by including at least some of the other results, for some were discarded because of the detection of a type of error—duplicate estimations of oxygen in arterial blood failed to agree—which would pass unnoticed in the great bulk of the clinical work reported, for duplicates have seldom been taken.

In the same year, a somewhat larger series of
comparisons, 36 tests in 10 dogs, were reported by Huggins, Smith and Sinclair.\textsuperscript{27} In these experiments Fick estimates could be compared with measurements of cardiac input made by placing a rotameter in the great veins, and the coefficient of variation was 13 per cent, but a reasonable allowance for the coronary circulation, missed by the rotameter, would reduce this value.

Obviously, one has no assurance that an estimate of the accuracy of any methods made in animals under special experimental conditions will apply exactly when the method is used under the great variety of conditions existing in clinical work. Indeed, by using an anesthetized animal to compare results secured by the Fick and those obtained by a mechanical method, one has avoided a difficulty that in the clinic may well be a major source of error, the hazard that the arduous nature of the experiment will of itself alter the cardiac output in a manner varying with the temperament of each subject, so that the results secured will be but a poor measure of the state of the circulation characteristic of the clinical situation in which one is interested.

Therefore, to the author the distance from an anesthetized, open chested dog, subjected to a long and difficult operative procedure, to a living man is a long one. In the early days of cardiac output work, methods which gave results agreeing with the Fick estimates in animal experiments sometimes yielded very different results when applied to man; it was this finding that inclined me away from using the Fick method in animal experiments as a standard by which to judge methods designed for application to man. But technical perfection in animal experiments has increased since that time, and it may be further increased in the future until the difficulties are altogether overcome. The fact is that the two methods of attack, both starting from accurate measurements of cardiac output, the one made in anesthetized dogs, and the other in cadavers, once more have not yielded similar results when applied to man, and the reason for this discrepancy is by no means certain. For those convinced of the absolute accuracy of the Fick results, as the method is performed at present in man, I have supplied the regression equations given in tables 1 and 2 by which one would convert the blood pressure results to the level of the Fick results.

But the author will not advise this conversion on the basis of the present evidence. The results of the new blood pressure method agree too well with those of the older group of methods as to the general level of the cardiac output of resting subjects. Indeed, the correlation of the results secured by the blood pressure method with those of the acetylene and nitrous oxide methods in a variety of conditions is surprisingly good. The author's own ethyl iodide method plainly does not come out so well; the averages agree closely with those of estimates of cardiac output from blood pressure; the difference between the mean stroke volume estimated in 34 healthy persons at rest by both methods is only 2.8 cc., but the difference between the two estimates in many persons is large. Fortunately, in drawing conclusions from results secured by the ethyl iodide method in the past, it was the statistical analyses of the data that were stressed, so proper allowance was made for this variability and the conclusions concerning the major changes in cardiac output to be found in clinical conditions have been largely supported by later work. But it was obviously no mistake to abandon the ethyl iodide procedure 18 years ago.

The average level of basal cardiac output found in healthy young adults by these older methods was about 4 liters per minute, but in similar subjects the Fick method with cardiac catheterization gives greater values, about 6 liters per minute. The reason for this discrepancy has been debated, those partial to the older methods contending it was the excitement inherent in venous and arterial puncture, and in the catheterization, that caused the difference, while the adherents of the Fick method deny this, citing the basal levels of pulse rate and metabolic rate that they so often secure despite the rigors of their method, and they attribute the discrepancy to errors in the design of the older methods. My own opinion is that excitement plays more part than some authors are willing to admit, but I fully
concede that there may well be other factors still unidentified.

However, the unexplained differences in level are not likely to be of great practical importance, for the utility of any method in the clinic lies in its ability to detect differences, to make distinction between the amount of the circulation in health and disease, and to distinguish various clinical and physiologic states from one another. In such tests the blood pressure method has come out well; certainly its ability to detect changes in cardiac output such as those occurring during exercise, after adrenaline and hemorrhage, during fever and anoxemia, and in thyrotoxicosis is evident from the data given in the figures. The important question is, will it make such distinctions as well as the more elaborate methods? And let us not forget that a simple method might make such distinctions with greater accuracy, for the elaborateness of a method, far from guaranteeing its accuracy, introduces errors at every step, and any procedure which may disturb the subject inserts an unpredictable disturbing factor into the results.

In a few instances described in this paper the more elaborate cardiac output methods yielded results differing markedly from those calculated from the blood pressure. Certainly the elaborate methods are subject to the errors inherent in several analyses and measurements of volume and, all but the dye method, also to errors due to leakage from masks, tubing and containers of the gases resired; so an occasional aberrant result is to be expected solely from the effect of chance on the cumulation of these errors. Common experience with the estimation of basal metabolic rates in the clinic illustrates well one source of error, for in the Fick, acetylene and nitrous oxide methods an estimation of metabolic rate is an integral part of the estimation of cardiac output, and the error of the latter estimate cannot be less than the errors occurring in the former. In the absence of duplicate estimations many errors are likely to escape detection. So it is not surprising that, when results obtained by elaborate methods have deviated markedly from those secured by the blood pressure method, it has usually been the latter results that were consistent with the rest of the data. So it was the simple method which made the clinical distinctions most consistently.

Another feature of the results deserves comment. In some comparisons in which correlation is good the slope of the regression exceeds one, so that the blood pressure method exhibits smaller increments than the other methods as cardiac output increases. I have no explanation for this, but it should be realized that in the Fick, acetylene and nitrous oxide methods the estimation of cardiac output is derived from the size of the difference between two samples; as the circulation increases this difference becomes smaller, so that as cardiac output increases the normal errors of analysis cause increasingly greater errors in the estimate. But with the blood pressure method the contrary is true, for as stroke volume increases pulse pressure increases also, so the normal errors of estimating blood pressure cause diminishing errors in the estimate as cardiac output increases. Nevertheless, our blood pressure method has not been standardized in the cadavers against such large stroke volumes as may occur in exercise, anoxemia, or after hemorrhage; nor, of course, have results secured by other methods been subjected to such a test.

Therefore, doubt as to the accuracy of other methods of estimating cardiac output has handicapped the search for limitations in our blood pressure method. We were anxious to scrutinize our results, especially in young people and in the presence of high hypertension, but we have little to report at present. In a child, the cardiac output estimated by the ethyl iodide method differed greatly from the result of the estimate from blood pressure and, obviously, the latter method should certainly not be used on children in its present form without further study. In young adults, tested by each of the methods, we note no greater tendency for the blood pressure estimate to deviate from results secured by other cardiac output methods than is the case in persons within the older age range of our cadavers.1 In the data of Cathcart and associates8 results secured in two cases of hypertension deviate
from the run of the data, but in other cases the agreement is excellent and the removal of all cases of hypertension from the series does not improve the correlation between blood pressure and Fick estimates. The large body of data on hypertensive patients studied by the ethyl iodide and acetylene methods have been inspected carefully, but the data are too scattered to be of help. So we have as yet found no basis for a conclusion that the estimate of stroke volume from blood pressure was erroneous in subjects with severe hypertension.

However, a significant difference of result does seem to have been present in tilting experiments where the average cardiac output per minute estimated by blood pressure is little changed by tilting, while the Fick results show a consistently smaller output after tilting. Here again results of the blood pressure estimates resemble more closely the results of older than those of more recent work. But this discrepancy raises the question whether it is proper to apply our formulas to data secured from subjects in the upright position, since all the cadaver experiments on which our method is based were conducted in the horizontal position, because there are such marked physiologic differences between the circulation of subjects in the horizontal and vertical positions. But the exercise experiments of Liljestrand and Zander were conducted with the subject upright, riding a bicycle ergometer, and in these the correlation between the two sets of estimates of cardiac output is excellent.

Certainly limitations in a procedure as simple as ours are to be expected, and they should be diligently sought. It is to be hoped that every worker estimating the cardiac output by some other method will take, with all the care of which he is capable, a series of estimations of blood pressure under conditions identical with those in which the other method is employed and utilize the findings to compare results of the two estimates. But such a comparison must be assessed without the preconceived idea that the more elaborate the method the more correct the result.

However, despite our failure to get convincing evidence of the limitations of our method by studying data already in the literature, there are several clinical situations in which there is evidence that the auscultatory method of taking blood pressure leads to erroneous results, and so would lead to erroneous estimates of cardiac output if our formulae were employed. In aortic regurgitation intra-arterial pressures have proved to be poorly estimated by the auscultatory method in two series. In arms of unusual diameter the standard auscultatory method has given erroneous results unless a cuff of suitable breadth was employed. In arrhythmias the blood pressure may vary so that many estimates might be necessary before a satisfactory average could be secured. Any improvement in the standard method of taking blood pressure would improve the cardiac output estimate as well and there is already evidence that, by using the point of disappearance of sounds to indicate diastolic pressure, and our formula number 72, a small gain in accuracy would occur.

Therefore, although it seems proper to expect that limitations to our simple method will be encountered and that improvements will be suggested, it seems obvious that a rough cardiac output method is now available, so simple that it can be applied by any physician with the apparatus he now has, and that its results correlate reasonably well with those secured by the elaborate cardiac output methods in a wide variety of clinical and physiologic conditions.

While it is certainly to be hoped and expected that attempts to develop and employ cardiac output methods of the highest accuracy obtainable will be pursued despite technical difficulties, it is my opinion that the simpler methods such as this one will have a brighter future in the clinic. Now that a means of assessing their accuracy is at hand, one has every reason to believe that our simple method will suffice to measure cardiac output in most clinical conditions with an accuracy commensurate with our present ability to use this knowledge to the advantage of our patients. Indeed, our studies suggest that means are now available to make a rough estimation of cardiac output as a routine part of every examination of the patient, and that
physicians taking the blood pressure routinely can interpret their findings with greater insight into their physiologic meaning.

**Conclusion**

The simple formulas, relating cardiac stroke volume to pulse pressure, diastolic pressure and age, and derived from results secured in cadaver experiments in which stroke volume could be measured accurately, have been used as the basis for estimations of cardiac output from clinical data already reported in the literature.

Many instances have been found in which the results of estimates of cardiac output by well-known methods could be compared with estimates made by our formulas from blood pressures taken in conjunction with the other tests. A sample of about 400 such comparisons was taken for study, and in these, estimates of cardiac output from the blood pressures could be compared with estimates made by the Fick, dye, acetylene, ethyl iodide and nitrous oxide methods.

The estimation of cardiac output from blood pressure and age gives excellent duplicates in resting subjects, and one gets the impression that the cardiac output is a more stable and consistent physiological function than certain results secured by the Fick method suggest.

Examples have been found in which estimates of cardiac output from blood pressure correlate well with those of other methods in a wide variety of conditions; such as in resting subjects, during exercise, during anoxemia, after hemorrhage, after adrenaline and in thyrotoxicosis. Thus changes in cardiac output resulting from many experiments, or occurring in many clinical situations are as well shown by the blood pressure method as by the other methods.

The level of cardiac output estimated by the blood pressure method is distinctly below that given by Fick and dye methods, but it seems to be identical, or nearly so, with the levels given by the acetylene, nitrous oxide and ethyl iodide methods.

When the estimate of cardiac output from blood pressure diverges widely from that of another method, as occasionally happens, it is usually the estimate from the blood pressure that yields a result more consistent with the rest of the data.

It appears that a rough method of determining cardiac output is available which can be performed by any doctor with the apparatus he now has.

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**Sumario Español**

Las sencillas fórmulas relacionadas a volumen por contracción cardíaca, presión de pulso, presión diastólica y edad, derivadas de resultados obtenidos en experimentos en el cual el volumen por contracción se pudo medir con exactitud, han sido usadas como la base para estimados de producción total cardíaca de datos clínicos ya informados en la literatura.

Muchos casos se han encontrado en los cuales los resultados de estimados de producción total cardíaca por métodos bien conocidos pueden ser comparados con estimados hechos con esta fórmula de la presión arterial tomada en conjunción con las otras pruebas. Un grupo de aproximadamente 400 semejantes comparaciones fué tomado para estudio, y en estas, estimados de producción total cardíaca obtenidos de presiones arteriales pudo ser comparado con estimados hechos por los métodos de Fick, tinte, acetileno, ioduro etílico y óxido nitroso.

El estimado de producción total cardíaca de la presión arterial y la edad produce excelentes duplicados en sujetos durante el descanso, y uno obtiene la impresión que la producción cardíaca total es una función fisiológica más estable y consistente que ciertos de los resultados obtenidos por el método de Fick sugiere.

Ejemplos han sido encontrados en los cuales estimados de producción cardíaca total de la presión arterial correlacionan bien con aquellos por otros métodos en una variedad extensa de condiciones; como en sujetos durante el descanso, durante el ejercicio, durante la anoxemia, después de hemorragia, luego de la administración de adrenalina y en la tirophtoxicosis. De
manera que cambios en producción total cardíaca resultado de muchos experimentos, y ocurriendo en muchas situaciones clínicas son tan bien demostrados por el método de presión arterial como por otros métodos.

El nivel de producción cardiaca total estimado por el método de presión arterial es distingutivamente menor que aquel obtenido por el método de Fick y de tinte, pero parece idéntico, o aproximado, a los niveles obtenidos por los métodos de acetileno, óxido nitroso e ioduro etílico.

Cuando el estimado de producción cardiaca total obtenido por el método de presión arterial difiere marcadamente de otro método como ocasionalmente ocurre, es usualmente el estimado por presión arterial el que resulta más consistente con el resto de los datos.

Parece que hay un método tosco disponible para la determinación de la producción cardiaca total que puede ser usado por cualquiera médico con los aparatos que corrientemente el tiene en el presente.

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Clinical Tests of the Simple Method of Estimating Cardiac Stroke Volume from Blood Pressure and Age
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