Comparison of Central and Peripheral Injection Sites in the Estimation of Cardiac Output by Dye Dilution Curves

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In the measurement of cardiac output by indicator dilution methods, the indicator may be introduced either centrally or peripherally. It is clear that use of a peripheral vein, particularly in large animals such as man, may result in two major sources of error. a) Indicator may be trapped between the injection site and the central circulation resulting in a small primary curve and an overestimate of cardiac output. b) Slow release of indicator into the central circulation and modified recirculation of indicator may also interfere with the primary curve and lead to an underestimate of cardiac output. Comparisons of values obtained from central and peripheral injection sites in man have yielded conflicting results. Hetzel et al.\(^1\) reported that there was no significant difference while Crane et al.\(^2\) reported lower, and Gunnels and Gorten\(^3\) higher, values from the peripheral injection site.

One possible reason for this lack of agreement may lie in failure to standardize an important variable, the method by which the injection is made. While in our laboratory peripheral injections of indicator are invariably flushed into the circulation by an immediately consecutive injection of saline, this is not an invariable practice elsewhere. Furthermore it is frequently not stated whether this or some other maneuver designed to speed the injection into the circulation, such as elevation of the arm, has been employed or not. Neither theoretical speculation nor model experiments can solve this problem. A study was therefore designed with two objects; first, to test in man the validity of cardiac output values resulting from peripheral injections of indicator and second, to test the effect of flushing the peripherally injected dye into the circulation with an immediately consecutive saline injection.

**Methods**

Successive dye injections were given alternately into an antecubital vein and into the central circulation of 20 subjects ranging in age from 12 to 56 years. There were 10 cases of rheumatic, three cases of arteriosclerotic, and one of congenital heart disease (pulmonary stenosis with atrial septal defect and minimal left to right shunt). There were also one of each of the following conditions —gout, pulmonary emphysema, hepatic cirrhosis, anemia, thyrotoxicosis and cardiac neurosis. All subjects were fasting and lay quietly at rest for at least 20 minutes before the study was started. Central injections of dye were given either through a cardiac catheter into the pulmonary artery at the completion of a diagnostic study, or via a percutaneously inserted polyethylene catheter, the tip of which lay at the junction of the superior vena cava with the right atrium. The peripheral injections were given by means of an indwelling needle or short polyethylene tube into an antecubital vein with the arm lying in the same plane as the body with 45° abduction. The dye, 2% solution of Coomassie Blue*\(^4\) 0.4 mg/kg body weight was given every four to five minutes. No more than six injections were given to any one subject. Routinely both peripheral and central injections were instantaneously and forcefully flushed into the circulation with 12 ml isotonic saline.

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saline. In order to assess the value of the flushing maneuver 12 peripheral injections of dye (in five patients) were given without flush.

The concentration of dye in the circulating blood was measured by a modified ear oximeter\textsuperscript{4,5} attached to the vasodilated pinna of the ear. The cardiac output (plasma) was calculated from the area under the time-concentration curve with extrapolation of the declining slope of concentration according to Hamilton et al.\textsuperscript{6} Whole blood output was then obtained from the formula $Q = \frac{100 \times Q_{\text{plasma}}}{100 - 0.95 \times Ht}$ (where $Ht$ = venous hematoctit). For the time components of the curves the usual terminology\textsuperscript{7} is employed.

Nine curves which presented major irregularities in the base line or contour could not be read and were rejected. There were five such curves from 12 peripheral non-flushed injections, two from 35 peripheral flushed and two from 30 central injections. Furthermore most subjects were not sedated and were therefore apt to show the usual fluctuations in cardiac output which accompany such procedures. As the different site of injection might be falsely incriminated for such spontaneous fluctuations, it was decided at the beginning of the study to exclude pairs of curves when the difference in cardiac index from consecutive injections at the same site exceeded an arbitrary limit of 25%. This criterion necessitated the exclusion of four pairs of curves which were otherwise technically good, before consideration of the data.

\textbf{Results}

In table 1 average values for time components and cardiac index are compared according to injection site and technique. The more rapid time components observed with a veno caval (table 1b) rather than with a pulmonary arterial injection (table 1a), are the result of chance selection of cases with a higher cardiac output in the former series and are obviously unrelated to the injection technique. With the exception of recirculation times all the time components were significantly longer following flushed peripheral injections than following central injections. By contrast the corresponding values for cardiac index did not differ significantly (table 1a and b). When the values for all peripheral flushed injections were pooled and compared to the corresponding central injections there was no significant difference in mean cardiac index. The mean and standard deviation for values from central injections was $2.90 \pm 0.52$ liter per min/m$^2$ and from the peripheral flushed injections $2.85 \pm 0.51$ liter per min/m$^2$ ($r = 0.986$). In figure 1 each value derived from a peripheral flushed injection is compared to the value from the immediately preceding or following central injection giving in consequence a greater number of comparisons than in the table. There is no systematic difference. The standard deviation of the mean of the differences between the paired values, expressed as a percentage of the values for central injection is 5.7%.

As stated above, five of 12 injections made peripherally without saline flush were completely unreadable. Of the remainder the time components, with the exception of recirculation time, were significantly prolonged in comparison to the immediately consecutive flushed injections and the cardiac index values were significantly lower (table 1c).

\textbf{Discussion}

These data indicate that there is no systematic difference in the cardiac output values obtained from central injections of dye and from peripheral injections when the latter are flushed in, as described. Thus our findings
are essentially in agreement with those of Hetzel et al.\textsuperscript{1} Gunnels and Gorten,\textsuperscript{3} however, employing non-flushed peripheral injections, observed that these resulted in higher cardiac output values than their paired central injections, and thought that this was due to retention of dye in the peripheral veins. Five of 12 non-flushed peripheral injections in this study gave rise to extremely protracted uneven curves, which might have given erroneous values for cardiac output, had an attempt been made to read them. Although the possibility of retention of dye in the periphery cannot be excluded, it is likely that in the absence of flush, slow and irregular release of the dye into the central circulation produces such protracted and irregular curves, that calculation of them may give inaccurate values of cardiac output.

The unreliability of curves from peripheral non-flushed injections in man has been noted by other investigators who have suggested measures for their improvement such as reactive hyperemia,\textsuperscript{7} elevation of the arm\textsuperscript{8} or injection into the femoral vein in which the flow is larger and faster.\textsuperscript{9} The technique of vigorous flushing as applied in this study is probably the most convenient; furthermore it simplifies measurement of the amount of indicator as the dye from the dead space of the system is also injected.

The improvement in the characteristics of curves from peripheral injections by flushing has also been commented upon by Pritchard et al.\textsuperscript{10} The spreading and attenuation of curves from peripheral injections is not only determined by the greater volume between injection and sampling site and the longer path traversed by the indicator, but also by the slower entrance of the dye into the great veins which carry blood streams of high velocity. In this respect a peripheral injection might be simulated by a very slow one delivered centrally.\textsuperscript{11} By increasing the velocity of flow in the peripheral vein, as shown by the shorter appearance time, the vigorous saline flush delivers the injected dye as a more compact bolus into the central circulation, resulting in reduction of passage time. It should be noted, that the effect of flushing on the central injection is probably negligible because the indicator is mixed into a stream of high velocity and large volume which can hardly be influenced by the amount of injected saline.

Although the Hamilton extrapolation method theoretically excludes recirculation, the possibility of contamination of the primary

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curve by recirculating dye has been mentioned by several authors. Gerst et al.\textsuperscript{12} suggested that this may occur whenever indicator is injected proximal to the pulmonary artery and as stressed by Dow,\textsuperscript{13} "if recirculation is ever going to enlarge the curve area this should be expected to occur more frequently in the attenuated curves from peripheral injections."\textsuperscript{17} This problem was studied by Crane et al.\textsuperscript{2} who injected indicator into the pulmonary artery and sampled simultaneously from the brachial artery and right ventricle, the latter in order to detect recirculation. They found an average increment in the area of the primary curve due to recirculation of only 1.3%. They suggested, however, that admixture of recirculating dye was of higher order with peripheral injections since the cardiac output averaged 4.5% less than the paired estimates from central injections. The closer agreement between flow values from central and peripheral injections in our study may have been due to several reasons. Injection of dye in the superior vena cava in over half the number of the central curves should not be an important factor since it has been shown that curves from superior vena caval injection do not differ appreciably from those obtained after pulmonary arterial injection.\textsuperscript{1-14} It is perhaps more relevant that in the study of Crane et al.\textsuperscript{2} the peripheral injection was performed after an interval of about 15 minutes from the central, thus making possible a change in the physiological condition of the subjects. A diminution of cardiac output from the first to the second and subsequent injections, as the patients became more basal, has been observed by Bruce and Shillingford\textsuperscript{8} in a study of multiple determinations of output in the same subjects. Further, the smaller ratio of the average mean transit time of the curves from peripheral and pulmonary arterial injections in this study (1.41), as compared with the same ratio (1.67) calculated from the data of Crane et al.\textsuperscript{2} suggests that our curves were sharper, containing a smaller extrapolated area possibly due to more effective flush. The systematically lower values of cardiac output from peripheral non-flushed versus peripheral flushed injections on the other hand is not surprising: the curves from non-flushed injections were significantly prolonged when compared to their paired curves from flushed injections and thus would be liable to greater contamination by recirculating dye.

In conclusion it would appear from our data that the prolongation of indicator dilution curves which occurs when a peripheral injection site is used, does not result in any difference in the total area under the curve. Irregularities of the curves due to slow release of dye into the circulation may be prevented by immediately following the injection of dye with a vigorous saline flush. When this is done there appears to be no systematic difference between the values for cardiac output obtained from peripheral dye injections and those from paired central injections.

**Summary**

The validity of cardiac output values from injections of indicator into a peripheral vein was tested. Dye dilution curves resulting from injections of Coomassie Blue dye alternately from peripheral and central sites were obtained in 20 subjects. Peripheral injections in which the dye was not flushed into the circulation do not differ appreciably from those obtained after pulmonary arterial injection.\textsuperscript{1-14} It is perhaps more relevant that in the study of Crane et al.\textsuperscript{2} the peripheral injection was performed after an interval of about 15 minutes from the central, thus making possible a change in the physiological condition of the subjects. A diminution of cardiac output from the first to the second and subsequent injections, as the patients became more basal, has been observed by Bruce and Shillingford\textsuperscript{8} in a study of multiple determinations of output in the same subjects. Further, the smaller ratio of the average mean transit time of the curves from peripheral and pulmonary arterial injections in this study (1.41), as compared with the same ratio (1.67) calculated from the data of Crane et al.\textsuperscript{2} suggests that our curves were sharper, containing a smaller extrapolated area possibly due to more effective flush. The

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