Validation of Jugular Venous Flow as an Index of Total Cerebral Blood Flow

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Abstract:
Values of total cerebral blood flow in man measured by the indicator dilution method are compared with values of total internal jugular venous flow measured by the thermal dilution method. Except in the case of an extremely labile cerebral hemodynamic state, the results agree within the accuracy of the two methods, suggesting that for the supine patient total internal jugular venous flow provides a good index of total cerebral flow.

The relatively short measurement time associated with nondiffusible indicators (dye or thermal dilution) facilitates detection of transient changes in total CBF or differential jugular flow that would tend to be averaged out with diffusible indicator methods.

A mathematical analysis of the potential errors in the computation of total flow using the average of bilateral jugular venous dilution curves from a unilateral internal carotid injection is presented. This error can be partially corrected if the ratio of flow in one internal jugular to total flow is known.

An analysis of potential computational errors under nonsteady state flow conditions (change in flow during the period between alternate carotid injections) is presented. Such flow changes can effect substantial errors in the computation of individual hemispheric or internal jugular flow and smaller errors in the computation of total flow.

Introduction

The local thermal dilution method permits frequently repeatable measurements capable of detecting relatively rapid phase changes in jugular venous outflow. The methodology and application to physiological study has been described in two preceding publications.1,2

In viewing this measurement as a possible index of total cerebral blood flow, the need to validate it by comparison with an independent measurement simultaneously performed has been recognized. This is the subject of the present report. It will be seen that in the present small series of patients there is good agreement between total cerebral blood flow, as determined by intracarotid injection of a nondiffusible indicator, and bilateral jugular venous outflow. Further, it will be seen that the estimation of total cerebral blood flow as bilateral jugular venous outflow has the advantage of rapidly repeatable accurate measurements in the face of rapidly changing volume of total cerebral blood flow or direction of predominant jugular venous outflow. These nonsteady state conditions would preclude accurate measurements based on carotid injection in some circumstances. Finally, although this method—as any other total or average

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Supported in part by National Heart Institute Grant HE-10618 and National Institutes of Neurological Diseases and Stroke Grant NS-08802.

300

Stroke, Vol. 3, May-June 1972
blood flow measurement method—has substantial limitations in providing data on regional circulatory abnormalities as in cerebral infarction, it can provide valuable supplemental information about the presence or absence of steady state conditions which are a requisite for the measurement of hemispheric blood flow and metabolism by intracarotid injection of indicator.

In establishing the validity of comparison between the two methods and particularly to conduct an error analysis, a model of cerebral circulation and cerebral flow equations were developed (included in the Appendix). An analysis of these shows that under certain conditions (i.e., negligible crossover at the circle of Willis and steady state flow), a reasonable estimate of individual right and left hemispheric flow can be obtained. With a significant crossover at the circle of Willis, although individual hemispheric flow cannot be obtained, total cerebral flow can be measured. The computation of total cerebral flow based on a single carotid injection and an average of dye concentrations in the two internal jugular veins can result in relatively large errors except under certain restricted conditions discussed later. The magnitude of errors that can be obtained with bilateral internal jugular sampling following alternate internal carotid injection under nonsteady state conditions is discussed.

Methods

The patients selected had severe clinical disorders requiring cerebral angiography for clinical evaluation. The significant clinical and angiographical findings are summarized in table 1. In each case the predominant venous drainage was via the superior sagittal sinus and deep cerebral veins, torcular, lateral sinuses, and jugular bulbs. The predominant direction of venous drainage on arteriogram is not considered significant in view of the rapid phasic shifts which may occur as revealed in the flow measurements. Thermistor-catheter assemblies are inserted percutaneously into each internal jugular vein as previously described. Under fluoroscopic visualization the catheter is advanced until its distal end lies in the jugular bulb. As shown in figure 1 the catheter is connected by means of a three-way stopcock to a bolus injector for thermal dilution measurements and to a densitometer and withdrawal pump for the dye dilution measurements. This arrangement not only permits rapid switching from one type of measurement to the other but also facilitates flushing the catheter or densitometer. The catheter arrangement is duplicated for the opposite side. Several thermal dilution flow measurements are then made in order to insure proper thermistor positioning and to provide baseline flow values.

An arterial catheter (o.d. 1.9 mm) is then placed into one common carotid artery via a percutaneous insertion through a femoral artery. Biplane single films of the common carotid artery, its bifurcation and the vessels distal to the bifurcation are obtained by injecting 8 cc of contrast material (Renografin 60 or Hypaque 60).
TABLE 1
Summary of Clinical and Angiographical Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Clinical diagnosis</th>
<th>Angiographical findings</th>
<th>Distribution of contrast from carotid artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.S.</td>
<td>69</td>
<td>M</td>
<td>B</td>
<td>Right hemiplegia, aphasia</td>
<td>L. frontotemporal intracerebral hematoma, intracranial atherosclerosis</td>
<td>L + + +</td>
</tr>
<tr>
<td>L.L.</td>
<td>40</td>
<td>F</td>
<td>W</td>
<td>R. hemiparesis, status epilepticus 1 week prior to study</td>
<td>Normal</td>
<td>L + + +</td>
</tr>
<tr>
<td>I.M.</td>
<td>49</td>
<td>F</td>
<td>W</td>
<td>Alzheimer's disease (brain biopsy)</td>
<td>Enlarged ventricles</td>
<td>L + + +</td>
</tr>
<tr>
<td>W.B.</td>
<td>62</td>
<td>M</td>
<td>B</td>
<td>Quadriplegia, obtundation, subarachnoid hemorrhage</td>
<td>Intracranial atherosclerosis</td>
<td>L + + +</td>
</tr>
<tr>
<td>L.E.</td>
<td>17</td>
<td>F</td>
<td>W</td>
<td>Delirium, obtundation, unknown cause</td>
<td>Normal</td>
<td>L + + +</td>
</tr>
<tr>
<td>M.V.</td>
<td>33</td>
<td>F</td>
<td>W</td>
<td>Dementia, intractable seizure disorder</td>
<td>Normal</td>
<td>L + + +</td>
</tr>
<tr>
<td>S.H.</td>
<td>59</td>
<td>M</td>
<td>B</td>
<td>Dementia</td>
<td>Branch occlusion LMCA</td>
<td>L + + +</td>
</tr>
</tbody>
</table>
VALIDATION OF JUGULAR VENOUS FLOW

using a pressure injector. This visualization permits evaluation of the arteries to determine whether the catheter can be advanced into the internal carotid artery. If feasible, the catheter is advanced. Serial biplane studies are then performed. These consist of ten films in each plane (four films during the first two seconds followed by six films at one-second intervals) using 7 cc of contrast material delivered by a pressure injector. Bilateral thermal measurements are repeated to insure that flow exists in both veins. A 4 cc bolus containing 2 mg of cardiogreen dye is then rapidly injected by hand into the internal carotid artery and dye dilution curves are obtained from both internal jugular veins. The blood-dye mixture is withdrawn at a rate of about 6 cc/min. Three or four pairs of measurements are made on each side. The blood withdrawn for each measurement is reinfused to the patient. Blood samples are then withdrawn for dye calibration and for arterial and bilateral jugular venous gas analysis. Several thermal measurements are made before retracting the arterial catheter. The procedure is then repeated for the other side.

The studies were performed under local anesthesia utilizing sedation with 1 mg hydromorphone, 100 mg phenobarbital, 25 mg hydroxyzine hydrochloride and 0.4 mg atropine given about one hour prior to initiation of the studies. This usually resulted in mild drowsiness. Frank Cheyne-Stokes breathing did not occur in any patient. Variation in rate and depth of respiration occurred from time to time during the course of study, although these were not monitored.

Computations

Flow computations based on injection of dye into alternate internal carotid arteries and simultaneous bilateral jugular venous samplings were made using the following equations. These equations are derived in the Appendix based on a cerebral vascular model described therein. Left and right internal jugular venous flows, $F_{LJ}$ and $F_{RJ}$, are given by

$$F_{LJ} = q \frac{C_{LJ,R} - C_{LJ,L}}{C_{LJ,R} C_{LJ,L} - C_{LJ,R} C_{LJ,L}}$$

(1)

$$F_{RJ} = q \frac{C_{RJ,R} - C_{RJ,L}}{C_{RJ,R} C_{RJ,L} - C_{RJ,R} C_{RJ,L}}$$

(2)

where $q$ = amount of dye injected (bolus) and

$$C_{RJ,R} = \int_0^t C_{RJ,R} \, dt$$

(3)

where $C_{RJ,R}$ refers to the concentration of dye (mg/cc) in the right internal jugular vein as a function of time following right internal carotid injection, $C_{RJ,L}$ is the dye concentration in the right jugular following left carotid injection and similarly for the other subscripts. Right and left hemispheric flows, $R$ and $L$, are given by

$$R = q \frac{C_{RJ,R} - C_{RJ,L}}{C_{RJ,R} C_{LJ,L} - C_{RJ,R} C_{LJ,L}}$$

(4)

$$L = q \frac{C_{RJ,R} - C_{RJ,L}}{C_{RJ,R} C_{LJ,L} - C_{RJ,R} C_{LJ,L}}$$

(5)

and total flow, $F_T = F_{RJ} + F_{LJ} = R + L$ (See Assumptions in Appendix), is given by

$$F_T = q \frac{C_{RJ,R} - C_{RJ,L} + C_{LJ,R} - C_{LJ,L}}{C_{RJ,R} C_{LJ,L} - C_{RJ,R} C_{LJ,L}}$$

(6)

Equations 1, 2, 4, 5, and 6 are equivalent to Appendix equations 18A, 19A, 23A, 24A, and 25A, and are similar to those used by Meyer. In the two cases in which injections were restricted to one internal carotid artery, say the right internal carotid, total flow, $F_{TR}$, is computed from an average concentration and is given by

$$F_{TR} = \frac{2q}{C_{RJ,R} + C_{LJ,R}}$$

(7)

(equivalent to 30A). The application of these equations requires that steady state flow conditions obtain between alternate carotid injections. Computations for internal jugular venous flow by thermal dilution were based on equations previously described.

Results

Measurements of cerebral blood flow by internal carotid injection of Indocyanine green dye compared with measurements of internal jugular flow by local thermal dilution have been made in a total of ten patients. The patients ranged in age from 17 to 69 with an average age of 49. In eight of these patients the method previously described was employed with an average of 3.3 carotid injections per side and an average of 11 pairs of thermal dilution curves per patient. In two patients severe carotid disease at the bifurcation (e.g., extreme tortuosity, atheromatous plaques, etc.) precluded bilateral internal carotid catheterization, and thus limited the dye to unilateral studies. In these cases, total flow was computed by the method of average concentration. The correction factor of equation 33A was not applied to these computations because the internal jugular venous flows were approximately equal and the correction would be less
than 10%. The data from two patients are not included in the results because of totally unsatisfactory dye curves (perhaps due to substantial reflux of dye into the external carotid). The procedure was started in two patients (exclusive of the ten) but not completed because of inability to catheterize both internal jugular veins.

Figure 2 shows the range of the ratios of right jugular flow to total jugular flow as well as the ratio of average $F_{RU}$ to average $F_T$ for eight patients in this study. The data from an additional four patients are taken from our previous study. These demonstrate the large differential shifts that can occur during flow studies.

Figure 3 shows the comparison of total flow measured by thermal dilution with total flow measured by carotid dye injection. For each patient the range, mean value and standard deviation for thermal dilution measurements are plotted with the average total flow determined by dye injection superimposed. When injections could be made alternately into each carotid, equation 6 was used (modified by equations 8A and 9A as previously explained to account for the bolus injection). The C (concentration) values used represented the average of the areas in sec-mg/cc for the several injections made into one carotid, etc. Where the dye measurements were restricted to unilateral injections (patient H.H.), equation 7 was used. The data for most (seven) of these patients show that the average measurements by dye dilution and thermal dilution differ by less than 12%, or approximately within the basic accuracies of the two methods. No systematic error between the two methods was observed. Figure 3 also shows the range of measurements by the dye method obtained by applying equation 6 to each combination of pairs of right carotid injection areas and left carotid injection areas. Close agreement is seen between the average total flows as well as the range of total flow by the two methods, except for S.H.

These data are further described in table 2, which shows a comparison of average right and left jugular flows obtained by thermal dilution with those obtained by dye dilution using equations 1 and 2 (the areas used in the equation are the average of all areas from one

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**FIGURE 2**

Range of ratio of right jugular flow to total jugular flow by the thermal dilution method. The data for the last four patients are taken from the preceding study.8
VALIDATION OF JUGULAR VENOUS FLOW

**FIGURE 3**

Comparison of total internal jugular flow by the thermal dilution method with "total cerebral flow" by the dye dilution method. The range, mean value and standard deviation are shown for thermal dilution. The average dye value is computed by taking the average of the ipsilateral areas and the average of the contralateral areas for both right and left carotid injections. These four averages are then applied in equation 6. The range of dye values is obtained by applying equation 6 to each combination of pairs of right and left areas. The flow values for patient H.H. should be multiplied by 2. The dye measurements were unilateral only for this patient.

The generally good agreement of average total flows by the two methods and the poorer agreement in individual jugular flows and unrealistic hemispheric flows lend clinical support to the theoretical analysis that nonsteady state flow conditions can cause small errors in total flow and much larger errors in individual jugular or hemispheric flow computations. The nonsteady state of cerebral hemodynamics of some of these patients in terms of jugular outflow is illustrated in figure 2, showing the differential changes in jugular outflow, and in figure 3, showing changes in total jugular flow by thermal dilution. This nonsteady state character is re-emphasized in
TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>FRJ cc/min</th>
<th>FLJ cc/min</th>
<th>R cc/min</th>
<th>L cc/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.S.</td>
<td>(Dye) 370</td>
<td>770</td>
<td>620</td>
<td>530</td>
</tr>
<tr>
<td></td>
<td>(Th.) 415</td>
<td>645</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.L.</td>
<td>(Dye) 705</td>
<td>33</td>
<td>310</td>
<td>430</td>
</tr>
<tr>
<td></td>
<td>(Th.) 345</td>
<td>440</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.M.</td>
<td>(Dye) 320</td>
<td>100</td>
<td>160</td>
<td>260</td>
</tr>
<tr>
<td></td>
<td>(Th.) 280</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W.B.</td>
<td>(Dye) 315</td>
<td>205</td>
<td>290</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>(Th.) 370</td>
<td>140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.E.</td>
<td>(Dye) 240</td>
<td>325</td>
<td>320</td>
<td>245</td>
</tr>
<tr>
<td></td>
<td>(Th.) 275</td>
<td>360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.V.</td>
<td>(Dye) 360</td>
<td>220</td>
<td>-140</td>
<td>720</td>
</tr>
<tr>
<td></td>
<td>(Th.) 350</td>
<td>195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.H.</td>
<td>(Dye) 180</td>
<td>160</td>
<td>80</td>
<td>260</td>
</tr>
<tr>
<td></td>
<td>(Th.) 540</td>
<td>130</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3, in which the percentage variation in dye dilution curve areas from the mean is shown. The period between dye injections on any one side was about one to two minutes. For patient S.H. (59 NM) the dye method showed a substantially lower flow than the thermal. If the “dye flow” were higher than thermal, this discrepancy could be accounted for by either large nonjugular outflow, or by loss of dye indicator input through leakage or reflux into the external carotid. The most plausible explanation for the discrepancy is in a combination of errors due to differential and total flow changes occurring between right-side and left-side injections. This seems probable because of the flow patterns depicted in figure 4. The data from this patient provided an example of flow correction based on equation 33A for the average flow method. If the thermal flow measurements are taken to represent the true ratio of right or left jugular flow to total flow, then we can approximate the ratio which would obtain at the time of a unilateral dye measurement as the mean of the thermal ratios immediately before and after the dye measurement. Thus, in figure 4 the mean of $F_{TL}/F_T$ for left carotid injection is 0.18. If we assume $K_L$ (crossover fraction R to L—see equation 4A) to be 0.3 then the ratio of $F_{TL}$ to $F_T$ is about 0.5 or $F_T$ (corrected) = $F_{TL}/0.5$. The average of three pairs of dye curves yielded $F_{TL} = 340$ cc/min ($F_{TLr} = 310$, $F_{Tlr} = 340$, $F_{TLr} = 370$). Therefore, the corrected value for $F_T$ from left dye injection is 680, which compares favorably with the average from the two thermal values of 730. A similar calculation for corrected flow for the right injection yields a value of 525 (with $F_{rl}/F_T = 0.85$) versus a mean thermal value of 700. The larger discrepancy here may result in the uncertainty in estimating the value $K_R$ (crossover fraction—L to R—equation 5A) and large variation in correction factor with a change in $K_r$.

Figure 5 shows a comparison of right and left internal jugular venous flow determined by

TABLE 3
Summary of Dye Curves Percent Variation (From Mean) of Dye Areas

<table>
<thead>
<tr>
<th>Patient</th>
<th>RR</th>
<th>LR</th>
<th>LL</th>
<th>RL</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.H.</td>
<td>-10.8</td>
<td>-27.8</td>
<td>only</td>
<td></td>
</tr>
<tr>
<td>R.S.</td>
<td>-16.0</td>
<td>-19.7</td>
<td>+ 0.6</td>
<td>+ 6.8</td>
</tr>
<tr>
<td>L.L.</td>
<td>-14.7</td>
<td>-11.5</td>
<td>0</td>
<td>+ 4.8</td>
</tr>
<tr>
<td>L.M.</td>
<td>-0.3</td>
<td>-27.9</td>
<td>-4.9</td>
<td>- 38.1</td>
</tr>
<tr>
<td>W.B.</td>
<td>+ 9.2</td>
<td>+17</td>
<td>+ 1.2</td>
<td>+ 6.0</td>
</tr>
<tr>
<td>M.V.</td>
<td>+ 9.0</td>
<td>+29.1</td>
<td>+13.2</td>
<td></td>
</tr>
<tr>
<td>S.H.</td>
<td>+18.0</td>
<td>+17.7</td>
<td>- 8.2</td>
<td>- 9.7</td>
</tr>
</tbody>
</table>

$RR = Area$ from right jugular with right carotid injection.
$LL = Area$ from left jugular with right carotid injection.
$% = Area-mean area \times 100 \over Mean area$
VALIDATION OF JUGULAR VENOUS FLOW

Graph of a series of thermal dilution measurements of internal jugular venous flow for patient S.H. Note the large variations in total flow (shown as top of rectangle) and variation in differential flow (right jugular flow shown as bottom of rectangle). The relative time of injection of contrast material and of dye dilution measurements is shown. See text for further discussion.

thermal dilution with flow determined by dye dilution for patient R.S. (69 NM). The dye dilution values are obtained by applying equations 1 and 2 to each combination of areas from a single right carotid injection and a single left carotid injection. Thus the first dye dilution measurement (R1/L1) is obtained from the dilution curves from the first right injection and the first left injection, etc. A relatively good steady state flow is observed in both the dye dilution and thermal dilution values. A similar behavior was noted in the computations for hemispheric flow (range for right hemisphere 550 to 690 cc/min and for left hemisphere 680 to 490 cc/min). As seen in figure 3 the total flow comparison shows good agreement.

Figure 6 shows a similar plot for patient M.V. (33 WF). In contrast to the steady state condition for R.S., although the total flow remained relatively constant and showed good agreement between the two methods (see figure 3), marked differential shifts are noted in both the thermal and dye dilution measurements. The computation of hemispheric flows from these same data yielded an obviously spurious negative value for the right hemisphere.

Figure 7 shows a similar plot for patient L.L. (42 WF). Larger variations in differential flow are noted yielding negative values for the computation of individual jugular flow by dye dilution despite relatively good agreement in total flow between the thermal and dye dilution methods. The computed values for right hemispheric flow ranged from 250 to 400 cc/min and for left hemispheric flow from 330 to 250 cc/min.
Discussion

The major objective of this phase of the study was to develop a means by which "total cerebral flow" as measured by bilateral internal jugular venous thermal dilution could be compared with total cerebral flow as measured by an independent means. Our results tend to indicate that in most cases the average flows determined by the two methods are equal within about 15%, or within the limits of accuracy of the two methods, with no systematic error observed. This is in agreement with other data in which internal jugular flow measured with an electromagnetic flowmeter and extrapolated to flow per unit mass compared with predicted values from the nitrous oxide method. The results further suggest that venous outflow via the emissaries and vertebral venous plexus in these patients was relatively small. This is in contrast to the work of Epstein,7 who by angiographical studies demonstrated a substantial outflow in the vertebral venous plexus in upright Rhesus monkeys and to that of Eckenhoff8 who made similar observations in man. However, both pointed out that this outflow was reduced in the supine position (patients were supine in all of our studies).

The thermal dilution studies reported here confirm our earlier findings of marked short-term change in total jugular venous flow as well as marked differential changes in the ratio of right to left jugular flow. Similar short-term variations in total CBF were observed by Reinmuth9 using iodoantipyrine.191. The differential flow changes may have occurred in part because of changes in head position, despite the fact that some degree of head restraint was usually employed. The patients were sedated, but not infrequently somewhat
Our earlier studies have shown the desirability of bilateral jugular venous flow measurements as opposed to unilateral measurements coupled with contralateral venous compression because: (1) total flow during compression may be significantly below the precompression total, and (2) it is difficult to establish that venous occlusion is complete without possibly significantly reducing flow in the adjacent carotid.

The analysis of total flow based on an average of bilateral venous concentrations following one arterial injection of an indicator (equation 33A) shows the possibility of significant error unless the venous crossover fractions are known. This potential error has been noted qualitatively by others. Based on limited observations in these and in our previous studies, relative equality of jugular venous flow seems considerably less likely than marked disparity of flow (fig. 2). If the assumption is made that the venous crossover fraction K is in the range 0.2 to 0.4, and if it happens that the agitated with highly irregular rates and depth of respiration. These respiratory irregularities and the concomitant large changes in intrathoracic pressure may account for part of the observed changes in total flow, since the thermal dilution curve, extending over some two to three seconds, occupies a small fraction of the respiratory period.

On the other hand, the dye curves, extending over some 25 to 35 seconds, would tend to damp respiratory flow variations. The relative agreement in average total flow obtained by the two methods offers some clinical support to the validity of the methods for this total flow measurement. However, the transient variability of both total and differential flow from thermal measurements and the spurious results (negative flows) for hemispheric and individual jugular flows suggest that the cerebral hemodynamic state in these patients was far from steady state. Any derived information such as hemispheric metabolic rate for oxygen would be similarly in error.
arterial injection is made on the side of lower venous outflow, and if the flow ratio is established by some other means, then a reasonable estimate of total flow can be made. If the injection happens to be on the side of predominant flow, an error correction cannot be applied because of the marked dependence of the error (sign and magnitude) on small variations in the unknown K. In neither case would it appear that a valid estimate of hemispheric flow can be obtained from one unilateral injection.

The estimation of hemispheric flow based on indicator injections into alternate internal carotid arteries with bilateral internal jugular venous sampling for each is similar to the work of Meyer. His development was based on the use of a diffusible indicator (hydrogen-saturated saline) and weight-normalized flows (ml/100 mg/sec), whereas ours is based on a nondiffusible indicator (Cardiogreen) and actual flows (ml/sec). The hydrogen method has much to recommend it, particularly in that blood withdrawal is not required. However, since it is a diffusible indicator, the washout curves require some ten minutes for completion. This requires constant hemispheric blood flow during the measurement. Although several investigators have shown average cerebral flow to be relatively constant over long periods, our work and that of others have shown significant transient changes in total internal jugular venous flow despite an apparent steady state patient condition. Whether these transient changes reflect actual changes in HBF (which would be filtered out because of the long time associated with the washout method) and whether the transient venous flow changes averaged over successive ten-minute intervals would remain constant, or whether

FIGURE 7
Similar graph for patient L.L. Despite relatively good agreement in total flow (see fig. 3), large differential shifts noted by thermal dilution yield unrealistic computation of right and left jugular flow by dye dilution.
VALIDATION OF JUGULAR VENOUS FLOW

they reflect changes in flow diverted to nonjugular channels, is yet uncertain.

The effects of transient changes in flow tend to be damped in the washout method by the diffusion process in the brain tissue and to be damped in both the washout and dye dilution methods by dispersion in the withdrawing catheters. Moreover, dispersion in the catheter can create distortion in the dilution or washout curves which would cause an error in the computation of mean transit time and in other derived data.

Since the dye dilution curve measures average cerebral flow over a 20-second to 30-second period, transient changes would be more discernible and the time period over which constant flow is requisite is markedly reduced. The obvious disadvantage of blood withdrawal and reinfusion might be eliminated by the use of fiberoptic catheters. Neither method appears optimal in terms of ease of calibration. The flow equations developed here do depend on flow during the right-side injections being equal to flow during the left-side injections. The degree to which flow on a given side does remain constant from one dye measurement to another can be readily determined by interspersing thermal dilution measurements. Observed changes in relative venous flow can then be partially corrected by changes in head position.

The angiographical procedure itself may have contributed to flow changes between right and left carotid injections. It was necessary to slide the patient several feet from the fluoroscopic visualization area to the serial x-ray area and back. This could have altered differential flow. More importantly, the injection of contrast material has been observed to alter total cerebral flow.

The adequacy of mixing of indicator with blood is a problem common to all indicator dilution methods for measuring flow rates or volumes. The assumption that at any instant of time there is a uniform concentration of indicator throughout the cross-section at the sampling site may be only partially true because of laminar flow. It is less true for dye dilution than thermal dilution because the former results from particle mixing only, whereas the latter results from heat conduction in addition to particle mixing. A second problem of mixing relates to preferential gain or loss of indicator relative to the vascular bed in which flow is being measured. That is, if there were an inflow at point B in figure 8 proximal to the sampling site S, and if mixing occurred between B and S, then the computed \( F_{R2} \) (or \( F_{L2} \)) would include the flow at B. If this flow were of noncerebral origin (e.g., mastoid emissary), then the total and individual flows would be in error by that amount. If it were of basilar origin and bypassed any hemispheric mixing (e.g., via inferior cerebellar vein), then \( F_{R2} \), \( F_{L2} \) and, hence, total cerebral flow (i.e., cerebellar plus cerebral) can be computed by equations 1 and 2. It can be shown, however, that the computation of hemispheric flow by equations 4 and 5 will be in error. Since this type of input is probably quite small compared to total flow, the error is considered negligible. If there is an outflow at point B (e.g., mastoid emissary) and if uniform concentration exists through a cross-section at this point, then the equations for hemispheric and jugular venous flow will still be correct. In this case, however, jugular flow measured by thermal dilution will be less than that obtained by dye dilution by the amount of outflow.
If an occlusion or congenital absence of one or more arterial pathways exists such that some fraction, say $k_4$, of indicator crosses to the contralateral hemisphere via the anterior communicating artery, the equations for $F_{HJ}$ and $F_{LJ}$ are still valid. Hence, total cerebral flow can be obtained. In this case, however, the addition of the constant $k_4$ precludes computation of $R$ and $L$ hemispheric flow individually.

Conclusions

Values of “total cerebral blood flow” as determined by the dye dilution method using alternate internal carotid injection generally agree with values of total internal jugular venous flow as determined by local thermal dilution within the accuracy of the two methods if the cerebral hemodynamics are in a relatively stable state. This suggests that vertebral venous outflow and emissary venous outflow are small in these supine patients. Relatively large errors can occur in the computation of total CBF based on unilateral carotid injection unless the two internal jugular flows are relatively equal. A correction for this error can be made if the percentage of total flow carried by one internal jugular is known by some independent method.

If the cerebral hemodynamic state is relatively unstable (i.e., changes occur in either total CBF and/or differential changes in internal jugular venous flow), a mathematical analysis shows that relatively large errors can occur in the computation of individual hemispheric or internal jugular flow based on alternate carotid injection. This analysis was confirmed in our studies on patients in which a labile hemodynamic state was observed by the thermal dilution method. It would appear that similar errors would occur in the computation of hemispheric gas concentrations based on bilateral jugular blood gas measurements if the cerebral hemodynamic state were unstable. Since the duration of a measurement using a nondiffusible indicator is relatively short, a nonsteady hemodynamic state is more readily detected than with diffusible indicators. On the other hand the use of the latter may tend to average out computational errors. The analysis and experimental results indicate that during nonsteady conditions the computation of total flow is much less subject to error than the computation of individual hemispheric and internal jugular flow.
VALIDATION OF JUGULAR VENOUS FLOW

mean transit time-dye dilution method. J Appl Physiol 21: 1637-1641 (Sept) 1966


Appendix
AN ANALYSIS OF INDICATOR DILUTION METHODS IN THE MEASUREMENT OF CEREBRAL BLOOD FLOW

A two-dimensional representation of cerebral vascular paths presents a formidable task. Major arterial inflow can be reasonably depicted as shown in figure 9. Because of common drainage channels, confluent and interconnected sinuses and anastomotic vessels as well as substantial biological variation, venous outflow is somewhat more complex. Figure 10 depicts normal major cerebral venous drainage. Referring to figures 9 and 10 in tracing the course of blood containing no dye and the blood-dye mixture following dye injection into one internal carotid, it is evident that several principal types of flow patterns are present (assuming zero flow in the anterior and posterior communicating arteries, the dye is confined to the ipsilateral hemisphere—assume right [R] carotid injection):

**Principal Flow Paths.** 1. R hemispheric mixing—mixture to common channels. (R carotid plus part basilar via R posterior cerebral artery to small branches of major cerebral veins and via anastomoses [e.g., Trolard, Rolandic, etc.])

2. R hemispheric mixing—mixture to R transverse sinus and R sigmoid sinus—not commingled with contralateral flow. (R middle cerebral vein to R transverse sinus via superior petrosal sinus and anastomotic veins [Labbé], and inferior petrosal sinus to R sigmoid sinus.)

3. R hemisphere—Nonmixing. (R vertebral plus part basilar arteries via R posterior inferior and anterior inferior cerebellar arteries to R inferior cerebellar vein to R transverse sinus.) (Mixing does occur in ipsilateral transverse sinus.)

4. Interhemispheric mixing: (A) Common vessels or sinuses. Great cerebral vein (Galen), straight sinus, superior sagittal sinus, occipital sinus. (B) Interconnecting sinuses. (Intercavernous sinus, basilar plexus.) (C) Sinus confluens (Torcular herophili).

Using these principal flow patterns, the partially reduced flow model of figure 11 can be established for a unilateral dye injection. Because of vertebral and basilar artery input to the cerebellum and cerebellar drainage which is commingled with cerebral drainage, the term “total cerebral flow” as heretofore and subsequently used is taken to mean cerebral plus cerebellar and brain stem flow.

At this point three additional assumptions are invoked. First, that bypass flow (flow path #3) via the cerebellum is small compared to total cerebral flow. Second, that emissary flow, parietal, occipital, and mastoid, is also small in comparison to total flow. And thirdly, that vertebral venous plexus outflow is small compared to total internal jugular flow in the supine patient. Discussion of these assumptions is made later. Recall also that arterial crossover is assumed negligible. With these assumptions the simplified flow model of figure 12 can be obtained.

The flow equations for this model are:

\[ F_C = k_1 R + k_2 L \]  
(1A)

\[ F_{13} = k_1 F_0 + R(1 - k_1) = R(1 - k_1 + k_1 k_3) + L k_2 k_3 \]  
(2A)

\[ F_{12} = (1 - k_3) F_0 + L(1 - k_2) = R(k_1 - k_1 k_3) + L(1 - k_3) \]  
(3A)
Diagram of major cerebral and cerebellar arteries.

Diagram of major cerebral and cerebellar veins and sinuses.
VALIDATION OF JUGULAR VENOUS FLOW

HEMISPHERIC FLOW DIAGRAM — TYPES OF FLOW PATHS

C = COMMON CHANNELS (SUP & INF. SAG SINUS, STRAIGHT SINUS, OCCIP. SINUS, INTERCavernous SINUS, BASILAR PLEXUS)
V = VERTEBRAL VENOUS PLEXUS
T = TORCULAR (SINUS CONFLUENS)
A = ANASTOMOTIC VEIN (LABBE'), SUP PETROSAL SINUS, INF. PETROSAL SINUS.

FIGURE 11
Hemispheric flow diagram showing major types of flow paths.

R = RIGHT HEMISPHERIC FLOW
FRB = BASILAR FLOW TO R HEMISPHERE
FRC = R CAROTID FLOW
FMC = R COMMON VESSEL FLOW
FRA = R INTERNAL JUGULAR FLOW
L = LEFT HEMISPHERIC FLOW
k1 = FRACTION OF R FLOW TO COMMON CHANNELS
k2 = FRACTION OF L FLOW TO COMMON CHANNELS
k3 = FRACTION OF TORCULAR FLOW TO R TRANSVERSE SINUS

If we let \( K_2 = k_2 k_3 \)  
and \( K_1 = k_1 - k_1 k_3 \)  
then \( F_{12} = R(1 - K_1) + L K_2 \)  
\( F_{12} = R K_1 + L(1 - K_2) \)

From equations 6A and 7A the simplified flow model of figure 8 can be obtained. This model is similar to one given by Meyer.5

Considering now the general relationship between dye concentration and flow rate, if a q mg bolus of dye is injected into a stream the flow rate f is given by

\[
f = \frac{q}{c t} \int_0^\infty \text{cdt}\]

Where c is the concentration of dye as a function of time measured downstream from the site of injection. If the indicator is introduced as a continuous infusion at a constant rate, A mg/sec, then the flow rate, F, is given by

\[
F = \frac{A}{c}\]

FIGURE 12
Reduced hemispheric flow diagram.

Stroke, Vol. 3, May-June 1972
where $C$ is the downstream concentration after equilibrium has been reached.

In the equations subsequently developed the form of equation 9A is used to avoid repetitive writing of the integral. The C of equation 9A is equivalent to $\int_{0}^{\infty} c \, dt$ of equation 8A if a rate input $A$ is substituted for a bolus quantity input $q$ and vice versa.

Referring to figure 2 with a right carotid infusion of $A$ mg/sec the rate of dye entry into the right internal jugular vein (RJ) equals $A(1-K_1)$ and the rate into LJ equals $AK_1$. Similarly for a left infusion the rate into the LJ equals $A(1-K_2)$ and into the RJ equals $AK_2$. Thus the relationship between concentration and flow are given by

$$C_{RJ,R} = \frac{A(1-K_1)}{F_{RJ}} \quad (10A)$$

$$\frac{A}{C_{RJ,R}} - \frac{A}{C_{IJ,L}} = R \left[ \frac{1-K_1}{K_2} - \frac{K_1}{1-K_2} \right] = R \left[ \frac{C_{RJ,R}}{C_{IJ,L}} - \frac{C_{RJ,L}}{C_{IJ,R}} \right] \quad (22A)$$

where $C_{RJ,R}$ is RJ concentration for an R carotid infusion, etc. By eliminating $F_{RJ}$ from equations 10A and 13A and $F_{LJ}$ from equations 11A and 12A, we have

$$K_2 = (1-K_1) \frac{C_{RJ,R}}{F_{RJ}} \quad (14A)$$

and

$$K_1 = (1-K_2) \frac{C_{IJ,L}}{F_{RJ}} \quad (15A)$$

from which

$$K_1 = \frac{C_{IJ,R}}{C_{IJ,L}} \frac{C_{RJ,R} - C_{RJ,L}}{C_{RJ,R} - C_{RJ,L}} \quad (16A)$$

and

$$K_2 = \frac{C_{RJ,L} - C_{IJ,R}}{C_{RJ,L} - C_{IJ,R}} \quad (17A)$$

Substituting equation 16A into equation 11A (or 17A into 12A) yields

$$F_{LJ} = A \frac{C_{RJ,R} - C_{RJ,L}}{C_{RJ,R} - C_{RJ,L}} \quad (18A)$$

and substituting 16A into 10A (or 17A into 13A) yields

$$F_{RJ} = A \frac{C_{IJ,L} - C_{IJ,R}}{C_{IJ,L} - C_{IJ,R}} \quad (19A)$$

Eliminating $F_{RJ}$ from equations 6A and 13A yields

$$L = \frac{A}{C_{IJ,R}} - R \left( \frac{1-K_1}{K_2} \right) \quad (20A)$$

and eliminating $F_{LJ}$ from equations 7A and 12A yields

$$L = \frac{A}{C_{IJ,R}} - R \left( \frac{K_1}{1-K_2} \right) \quad (21A)$$

Equating 20A and 21A and simplifying yields

$$\frac{F_{RJ} + F_{LJ}}{R + L} = A \frac{C_{RJ,R} - C_{RJ,L} + C_{IJ,L} - C_{IJ,R}}{C_{RJ,R} - C_{RJ,L}} \quad (25A)$$

Thus, if dye injections are made sequentially into each internal carotid and dye concentrations measured bilaterally in the internal jugular veins for each injection, individual hemispheric and jugular flows and, of course, total flow can be computed subject to the assumptions heretofore stated. The validity of the equations also assumes a steady-state condition for flow, i.e., there is no appreciable change in flow between right and left injections. The equations given thus far are similar to those used by Meyer and Nylin based on a mathematical derivation by Andersson. They are included in some detail here in order to provide a basis for the subsequent error analysis.

Stroke, Vol. 3, May-June 1972
VALIDATION OF JUGULAR VENOUS FLOW

If there is a significant arterial crossover via the circle of Willis as might be determined by angiographical or other means, individual hemispheric flow cannot be computed. However, since equations 10A through 19A can be developed without regard for arterial crossover (i.e., $K_1$ and $K_2$ could reflect arterial plus venous crossover instead of the latter only), $F_{RJ}$, $F_{LJ}$ and total flow can still be computed.

Another special case, which is perhaps of more mathematical than practical interest, arises when $C_{RJ,R} = C_{RJ,L}$. Since from equations 10A and 13A

$$C_{RJ,R} = \frac{A (1 - K_1)}{F_{RJ}} = C_{RJ,L} = \frac{A K_2}{F_{RJ}} \quad (26A)$$

it follows that $1 - K_1 = K_2$ or $K_1 + K_2 = 1$. \quad (27A)

Since from equations 11A and 12A

$$F_{RJ} = R (1 - K_1) + L K_2 = \frac{A K_2}{C_{RJ,L}} = R K_2 + L K_2 \quad (28A)$$

or

$$F_{TOTAL} = R + L = \frac{A}{C_{RJ,L}} \quad (29A)$$

Similarly, if $C_{RJ,R} = C_{LJ,R}$, it can be shown that $C_{RJ,L} = C_{LJ,L}$ or that $K_1 + K_2 = 1$ as in the preceding case. Since the crossover fractions $K_1$ and $K_2$ would normally

\[ \begin{align*}
\text{For Right Injection} \\
K &= K_1 \\
\text{Use } F_{RJ}/F_T \\
\text{For Left Injection} \\
K + K_2 &= 1 \\
\text{Use } F_{LJ}/F_T
\end{align*} \]

\[ \begin{align*}
F_{TR} &= \frac{2 F_{RJ} (1 - F_{RJ})}{1 - K_1 F_{RJ} (1 - 2 K_2)} \quad (28A) \\
F_{TOTAL} &= R + L = \frac{A}{C_{RJ,L}} \quad (29A)
\end{align*} \]

\[ \begin{align*}
\text{Graph of possible errors in computation of total flow based on unilateral carotid injection and average of dilution curve areas from both internal jugulars. The ordinate gives the ratio of computed total flow for a right carotid injection, } F_{TR}, \text{ to the actual total flow, } F_T.
\end{align*} \]
be in the range $0.1 \leq K \leq 0.4, 9, 10, 18, 20$ these two cases would not likely occur.

**Total Flow by Method of Average Concentration**

Total cerebral flow has been estimated by making a single bolus injection into one internal carotid and measuring the concentration in the two internal jugulars. 9, 4, 21 Again using the continuous infusion steady-state concentrations rather than the bolus time integral, it is interesting to compute the possible error with this method. In this method total flow is computed from the average of the two jugular concentrations. Thus, for a right injection, total flow, $F_{TR}$, is given by

$$F_{TR} = \frac{A A_{HJ, R} + A_{IJ, R}}{C_{HJ, R} + C_{IJ, R}} (30A)$$

To simplify the analysis, if we “normalize” the equation by keeping total actual flow, $F_T$, constant (arbitrarily unity), then

$$F_T = F_{RJ} + F_{IJ} = 1.0. (31A)$$

Substituting equations 10A and 11A in 30A yields

$$F_{TR} = \frac{2}{1 - K_1 + K_1} \frac{F_{RJ}}{F_{IJ}} (32A)$$

or from 31A and 32A

$$F_{TR} = \frac{2}{1 - K_1 + K_1} \frac{F_{RJ}}{1 - F_{RJ}} (33A)$$

A plot of the ratio $F_{TR}/F_T$ or the relative error of the average computed total flow versus true total flow as a function of $F_{RJ}$ for different values of $K_1$ is given in figure 13. When the two flows are equal ($F_{RJ} = 0.5$) the error is zero, independent of the value of $K$. When the flows are unequal, when the predominant flow is ipsilateral to the injection side, the error is less than 10% for an ipsilateral flow of 50% to 75% of total flow for $K = 0.2$ to 0.3. If $K = 0.1$ an error of less than 10% requires that ipsilateral flow be either 50% to 57% or 83% to 93% of total flow. If the contralateral flow is predominant, then a 10% error limit restricts the ipsilateral flow range to the range of about 45% to 50% of total flow. In view of the large disparity of flow between right and left jugular (see fig. 2 and accompanying text) which we have frequently observed, the error in this method can be appreciable.

**Errors Due to Change in Flow Between Injections**

A. Differential flow change with total flow constant. If the total flow remains constant between dye injections, but if the jugular venous outflow changes differentially (as observed by us a result of a change in head position), then relatively large errors in the individual computed flows can obtain.

Thus, if we assume an initial balance in jugular flow at the time of a right carotid dye injection, equations 10A and 11A would be

$$C_{HJ, R_1} = \frac{A (1 - K_{11})}{F_{RJ}} (34A)$$

and

$$C_{IJ, R_1} = \frac{A K_{11}}{F_{IJ}} (35A)$$

where the subscript refers to initial conditions in flow, concentration and crossover fraction. If a differential jugular flow change occurs prior to the left carotid injection, then equations 12A and 13A become

$$C_{IJ, L_2} = \frac{A (1 - K_{22})}{F_{IJ}} (36A)$$

and

$$C_{HJ, L_2} = \frac{A K_{22}}{F_{RJ}} (37A)$$

where the subscript refers to final conditions during left carotid injection. If equation 23A is now used for computed right hemispheric flow, $R_C$, we have

$$R_C = \frac{C_{LJ, I_2} - C_{RJ, I_2}}{C_{LJ, R_1} - C_{RJ, L_2} C_{LJ, I_2}} (38A)$$

or in terms of equations 34A to 37A.

$$R_C = \frac{1 - K_{22} - K_{22}}{F_{LJ} - F_{RJ} - F_{RJ} F_{IJ}} (39A)$$

If we let

$$F_{RJ} = k_1 F_{RJ_1} (40A)$$
VALIDATION OF JUGULAR VENOUS FLOW

and

\[ F_{L2} = k_2 F_{L1} \]  \hspace{1cm} \text{(41A)}

and recall that \( F_{R2} = F_{L2} \), equation 39A reduces to

\[ R_0 = A \left( 1 - \frac{K_{22}}{k_1} \right) \]  \hspace{1cm} \text{(42A)}

Under certain conditions the computed \( R_0 \) can indicate a negative flow (e.g., with \( K_{11} = 0.3, K_{22} = 0.1, k_1 = 0.15 \)!

The computed total flow, \( F_{TC} \), however, would be considerably less in error and under reasonable conditions would provide a good approximation to the average total flow \( F_T \), where

\[ F_{TC} = A F_{RJ1} \frac{k_1 (2 K_{11} - 1) + k_1 (3 - 4 K_{11}) - 2 K_{22}}{2 K_{11} K_{22} - K_{22} + K_{11} K_{22}} \]  \hspace{1cm} \text{(45A)}

A plot of the ratio of \( F_{TC} / F_T \) as a function of \( k_1 = F_{RJ1} / F_{RJ2} \) for several values of \( K_{22} \), with \( K_{11} \) assumed equal to 0.3, is given in figure 14. This shows, for example, that if \( K_{22} = 0.2 \) and if \( k_1 \) is greater than 0.35 (differential flow change of about 3 to 1), the computed total flow would be within 7% of the average true total flow.

(NOTE: Some caution should be exercised in arbitrarily assigning values to the various constants. An examination of figure 8 will show that \( K_{11} \) and \( K_{22} \) must be in the range 0 to 1.0, typically in the range 0.2 to 0.4. The general constraint on \( k_1 \) is \( 0 < k_1 < 2 \). A further constraint is that if hemispheric flows are assumed equal, if

\[ 0 < k_1 < 1 \], then \( k_1 > K_{22} \)

and if \( 1 < k_1 < 2 \), then \( 1 - k_1 < K_{22} \).

B. Total flow change with constant proportionality between right and left jugular flow.

If the total flow changes between injections, but if each internal jugular carries the same fraction of total flow, then relatively large errors in individual computed flows may obtain.

Thus if \( F_{R2} = K_0 F_{RJ1} \) \hspace{1cm} \text{(46A)}
then $F_{1,2} = K_3 F_{2,1}$

and $C_{1,2,1} = \frac{1}{K_3} C_{1,2,1}$

$C_{1,2,2} = \frac{1}{K_3} C_{1,2,1}$

where $C_{1,1,1}$ and $C_{R,1,1}$ are the concentrations which would have obtained for a left injection if no flow change occurred, and the two subscripts refer to observed concentrations.

Applying equations 48A and 49A to 19A yields a computed right jugular flow.

$F_{RJO} = A \frac{C_{1,2,2} - C_{1,2,1}}{C_{1,2,2} C_{1,2,1} - C_{1,2,1} C_{1,2,1}}$

If we let $C_{1,1,1} C_{R,1,1} = C_{R,1,1} C_{1,1,1} = D$

and apply 48A and 49A to 18A, 23A and 24A, then the remaining computed flows are given by

$F_{LJO} = A \frac{C_{R,2,1} C_{R,1,2} - C_{R,1,2} C_{R,1,1}}{D}$

$R_0 = R$

$L_0 = K_3 L$

and equation 51A

---

**FIGURE 15**

Graph of possible errors in computation of average total flow in nonsteady state condition. A change in total flow occurs between right and left carotid injections. The ratio of right and left jugular venous flow is assumed to remain constant.
VALIDATION OF JUGULAR VENOUS FLOW

\[ F_{12,0} = A \frac{C_{12,11} - K_3 C_{12,11}}{D}. \] (56A)

From an examination of equations 53A and 56A it is evident that negative values of flow can be computed for either right or left jugular flow. Equations 54A and 55A show that computed right hemispheric flow would equal the initial flow, \( R_i \), and computed left hemispheric would equal the final flow, \( L_f \).

Actual total flows are given by

- **Initial total** \( F_{T1} = R + L \) (57A)
- **Final total** \( F_{T2} = K_3(R + L) \) (58A)

and average total

\[ \bar{F}_T = \frac{1}{2}(F_{T1} + F_{T2}) = \frac{1}{2}(1 + K_3)(R + L). \] (59A)

The ratio, \( Y \), of computed average total to actual average total is given by

\[ Y = \frac{F_{70}}{\bar{F}_T} = \frac{2(R + K_3L)}{(R + L)(1 + K_3)}. \] (60A)

If \( R = L \), then \( Y = 1 \), or the computed average is equal to the actual average; but, if \( R \neq L \), then the computed average will be in error. The magnitude of this error can be determined by assigning a proportionality factor between \( R \) and \( L \) equal to \( K_4 \) such that

\[ L = K_4R. \] (61A)

then

\[ Y = \frac{2(R + K_3K_4R)}{(R + K_3R)(1 + K_3)} = \frac{2(1 + K_3K_4)}{(1 + K_3)(1 + K_4)}. \] (62A)

If \( Y \) is plotted as a function of \( K_3 \) for different values of \( K_4 \), the graph of figure 15 is obtained. For reasonable values, i.e., \( K_4 \approx 0.6 \) and \( K_3 \approx 0.5 \), then the computed total flow would exceed the average total flow by less than 9%.
Validation of Jugular Venous Flow as an Index of Total Cerebral Blood Flow
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Stroke. 1972;3:300-321
doi: 10.1161/01.STR.3.3.300
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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