 VALIDATION OF REGIONAL FLOW METHOD/Pepine et al.  795

In Vivo Validation of a Thermodilution Method to Determine Regional Left Ventricular Blood Flow in Patients with Coronary Disease

CARL J. PEpine, M.D., Jawahar Mehta, M.D., W. W. WEBSTER, Jr., B.S., M.E., and W. W. Nichols, Ph.D.

SUMMARY Several methods have been used to measure left ventricular regional blood flow in humans. However, limitations and lack of validation in patients are major problems. A continuous thermodilution technique to measure regional left ventricular blood flow in patients with coronary disease was validated in vivo. This technique permits simultaneous assessment of venous blood flow draining predominantly from the anterior wall and of the total left ventricular effluent. Thermodilution measurements with simultaneous electromagnetic flowmeter recordings from anterior descending vein grafts were compared in patients with occluded or subtotally occluded anterior descending coronary arteries. The thermodilution method yielded values for both absolute anterior regional blood flow and changes in anterior regional flow that compared closely to anterior descending bypass graft flow measured independently. The multifluid technique may be useful in monitoring flow effects of regional coronary disease over time, as well as in studies of agents purported to alter regional blood flow.

MEASUREMENTS OF REGIONAL blood flow are clinically desirable for evaluating the coronary hemodynamic significance of segmental coronary artery abnormalities. Such measurements would also be helpful in assessing the effects of various interventions on the distribution of regional blood flow. Although these measurements are available by several techniques in animal models, application to human studies has been limited by costly equipment, the necessity for direct coronary artery injection and other problems.1

A relatively simple technique, applicable for use in human studies to measure coronary sinus blood flow as an index of total left ventricular flow, was advanced by Ganz and coworkers.2 This method has the advantage, in addition to its relative simplicity and safety, of offering continuous measurements so that changes in flow can be rapidly detected. Thus, the technique has been useful in evaluating the effect of agents on the changes in coronary flow that occur with interventions like tachycardia stress.3,6 Although adequate mixing of blood with the indicator is a fundamental assumption, accuracy of the method as an index of total left ventricular flow has been demonstrated in vitro and also in an animal model.3,7 Ganz and co-

workers also applied an additional thermistor to the coronary sinus thermodilution technique and measured great cardiac vein flow (GCVF). The ability of the method to simultaneously measure two different blood flows was confirmed in animals. However, in vivo validation by an independent method in patients with coronary disease has not been described.

To determine the validity of the multisensor thermodilution method in assessing regional left ventricular blood flow, we studied patients undergoing coronary revascularization. Simultaneous coronary venous and arterial graft blood flows were recorded in patients with occlusion of the anterior descending branch of the left coronary artery (LAD). The GCVF and coronary sinus flow (CSF), measured by thermodilution, were compared with blood flow to the anterior myocardial wall measured by electromagnetic flow probe on the anterior descending bypass graft.

Methods

Catheter Design and Construction

Based on pilot observations with multiple catheter designs, different thermistor arrangements and distal diameters were tested. Tips of two of these catheters are shown in figure 1. These catheter arrangements are slightly modified from the catheter described by Ganz and coworkers, but allow for simultaneous measurement of indicator temperature and the temperatures of great cardiac vein and coronary sinus blood.

Thin-wall flow catheters (United States Catheters, Inc) were constructed from woven Dacron (fig. 1). All catheters had a nylon tube floating within the external catheter shell with injection orifice (jet) reduced to 0.5 mm diameter and located 0.5 cm from the tip. The floating nylon tube prevented heat transfer between the indicator and dilution thermistors. An indicator thermistor was located proximal to the jet orifice. The great cardiac vein (distal external dilution) thermistor was located 1 cm proximal to the jet. The coronary sinus (proximal external dilution) thermistor and pacing electrode location varied. The tip of the first catheter design tested appears in figure 1, top panel. A #7 French catheter with a #6 French soft tip 5 cm long was used. Separation of great cardiac vein and coronary sinus thermistors was 4.5 cm, and the second pacing electrode was 1 cm distal from the coronary sinus thermistor and distal electrode. The injection lumen was 0.8 mm in diameter. Next, the entire catheter was increased to #7 French without a soft tip, and the proximal pacing electrode was moved 4 cm proximal to the coronary sinus thermistor/distal electrode. These changes were done to reduce distal stiffness. The indicator lumen was increased to 1 mm diameter to permit infusion of indicator at an increased rate and to improve sampling. Then the catheter size was increased to #8 French with a #7 French soft tip, 15 cm long, to maintain distal flexibility. Spacing between the great cardiac vein and coronary sinus thermistors was reduced to 3.5 cm to ensure that the coronary sinus thermistor sampled within the midsinus in smaller hearts. The coronary sinus thermistor was rotated 90° laterally, from the inside of the curve of the preformed tip, to ensure that this bead did not become imbedded against the wall of the coronary sinus. The final design used in these studies (fig. 1B) was the same as the latter, except that

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** A) Basic design of multithermistor regional flow catheter tip. See text for details. The catheter contains two platinum electrodes. Just after the distal electrode (clear arrowhead), the catheter narrows to #6 French. Near the proximal pacing electrode, a thermistor bead is mounted externally to measure coronary sinus blood temperature (TCS). A second externally mounted thermistor measures great cardiac vein temperature (TGV). An internally mounted thermistor is located at the orifice of the lumen 5 mm from the catheter tip to measure temperature of the indicator jet (TT). B) The basic catheter was modified to permit more distal flexibility by increasing the distance between the pacing electrodes and the bond to a smaller tip was moved. These modifications positioned the rigid electrodes and bond to the right atrium, so that the distal part of the catheter is more flexible to conform to the coronary venous system. In this modification, the distal pacing electrode marks the coronary sinus thermistor (arrow).
the proximal electrode was moved to 2 cm proximal from the coronary sinus thermistor/distal electrode to improve right atrial pacing.

All thermistors (Thermometrics, Inc, Edison, NJ) were in a resistance range from 5,000-8,000 ohms at 37ºC and had a linear resistance (R)-temperature (T) function (\( R = KT + C, \frac{dR}{dT} = \text{constant} \)). The catheters were preshaped by baking them with a hollow Teflon tip-forming tool in place. After each use the catheters were flushed with 3% hydrogen peroxide, dried and sterilized in gas. The tip-forming tool was left in place.

**Patient Selection**

Patients scheduled to undergo bypass graft surgery of the LAD were studied after informed consent was obtained. On the basis of preoperative coronary angiograms, six patients were selected who had total or subtotal occlusion (99% diameter narrowing) of the LAD. Other criteria were that the LAD, filled by collaterals, was at least 1.5-2 mm in diameter and free of significant distal narrowing. Finally, each patient included had a patent anterior descending graft verified by postoperative angiography. Angiographic and other patient data are summarized in table 1.

**Catheterization Technique**

Just before surgery, each patient was taken to the catheterization laboratory. Cannulation of the coronary sinus and great cardiac vein was performed under image intensification fluoroscopy as the catheter was advanced from an antecubital vein. Pressure at the catheter port and surface electrocardiogram were monitored continuously as the catheter was introduced into the right atrium and coronary sinus. This avoided unnecessary manipulation in the right ventricle and the tendency to evoke ventricular extrasystolic beats. When the catheter appeared to be in the coronary sinus, 2 ml of Renographin 76 (meglumine diatrizoate) was injected to verify its position. The catheter was then advanced so that the flexible tip and distal thermistor were well within the great cardiac vein (fig. 2). The location of the proximal thermistor was identified by a platinum pacing band. Catheter position was adjusted so that the proximal thermistor was 1 cm within the right atrial-coronary sinus junction (fig. 2). Catheter stability was confirmed by angiography and recording a consistently uniform temperature, approximately 1.5ºC above the fluctuating right atrial temperature which is characteristically respiration-related. The catheter lumen was filled with heparin solution, and the patients were taken to the operating suite where coronary revascularization was accomplished.

**Blood Flow Measurements**

After cardiopulmonary bypass was terminated, LAD graft flow was measured by appropriately sized electromagnetic flow probe transducers (Model 400H, Carolina Medical Electronics, King, NC). Each transducer was connected to a square wave flowmeter (Model 601D, Carolina). The great cardiac vein and coronary sinus thermistors were connected to resistance bridges (Model CBA-210, Webster Laboratories, Altadena, CA) that had self-contained, solid state preamplifiers. The off-balance thermistor signals were recorded simultaneously with the flowmeter signal on a multichannel recorder (DR 12, Electronics for Medicine, White Plains, NY) as room temperature saline was infused at 53-56 ml/min with a Harvard pump. The exact infusion rate was determined at the end of each study using the same pump, connecting tubing, and catheter by timed volumetric collection. At the beginning and end of each measurement, the position of the coronary venous flow catheter was verified by palpation. Recordings were analyzed only when the catheter position was stationary throughout all recording periods.

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**Table 1. Patient Data and Angiography Results**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Class</th>
<th>Old MI</th>
<th>Left ventricle</th>
<th>Coronary arteries, diameter narrowing</th>
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<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>III</td>
<td>Yes</td>
<td>Inferior akinesis</td>
<td>100% LAD, 100% RCA</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>IV</td>
<td>No</td>
<td>Anterior hypokinesis</td>
<td>100% LAD, 80% LCX, 50% RCA</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>M</td>
<td>II</td>
<td>Yes</td>
<td>Inferior and apical hypokinesis</td>
<td>99% LAD, 100% RCA</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>III</td>
<td>No</td>
<td>Normal</td>
<td>99% LAD, 80% RCA</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>IV</td>
<td>No</td>
<td>Normal</td>
<td>99% LAD, 50% RCA, 100% LCX</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>F</td>
<td>III</td>
<td>No</td>
<td>Anterior hypokinesis</td>
<td>100% LAD</td>
</tr>
</tbody>
</table>

Abbreviations: Class = New York Heart Association functional classification; MI = myocardial infarction; M = male; LAD = left anterior descending; RCA = right anterior descending; LCX = circumflex coronary anterior; F = female.
All thermistors and electromagnetic flow probes were calibrated before each study, and calibrations were rechecked immediately after the study. Thermistors were calibrated in a saline bath. Resistance-temperature plots were generated at 2–4°C increments between 20–40°C. Electromagnetic flow probes and flowmeters were calibrated using the method outlined by Van Heerden et al.8 Since the blood hematocrit has an important influence on electromagnetic flowmeter measurements of blood flow, probe calibration factors were determined for each hematocrit value. In the present study the hematocrit was obtained just before the LAD graft flow recording.

Experimental Design

Experiments were designed to permit comparison of the blood flows in the LAD bypass graft and great cardiac vein during two periods. These consisted of a period when bypass graft flow was relatively stable (± 10%) for 3–5 minutes and an interval when graft flow was changing. The latter included recordings during reactive hyperemia after release of a 20-second complete graft occlusion and catecholamine administration as required by the clinical status of some patients. Two patients sustained brief atrial tachyarrhythmias as the atria were manipulated. Blood flows were again measured during tachycardia in both

Figure 2. A) Position of catheter in great cardiac vein and coronary sinus. An additional catheter has been advanced to the proximal coronary sinus to inject contrast material and sample and to illustrate the location of the thermistor bead relative to the coronary sinus orifice. This bead senses coronary sinus temperature (arrow). B) Contrast material has been injected into the indicator port, outlining the position of the great cardiac vein thermistor bead (arrow).
patients. Measurements were made with the other vein grafts occluded.

**Calculation and Data Analysis**

Blood flows in the great cardiac vein, the coronary sinus, and the LAD bypass graft were determined using the mean (electronic filtration) signals from at least 10 consecutively recorded beats. Volume of blood flow per minute for both the coronary sinus and the great cardiac vein was computed from the formula used by Ganz et al.²

This blood flow, in ml/min from the respective veins, was determined as

\[ CSF = F_1 \times 1.08 \times \frac{(T_B - T_1)}{(T_B - T_{MCS}) - 1} \]

and

\[ GCVF = F_1 \times 1.08 \times \frac{(T_B - T_1)}{(T_B - T_{MCGV}) - 1}. \]

F₁ is the volume flow of indicator per minute. T B, T₁, T MCS, and T MCGV are the temperatures of the blood, indicator, and the mixture of blood and indicator in the coronary sinus and great cardiac vein, respectively. Each thermistor used in this study had a linear calibration over the temperature range employed; therefore the temperature changes T B − T₁, T B − T MCS, and T B − T MCGV were determined to simplify calculations.

Both the absolute flow measurements and changes in flow induced by the various interventions were submitted to statistical analysis. Mean values and standard error of the mean were calculated. Correlation coefficients, simple equations, and linear regression lines were determined. Certain data were also compared by use of the t test.

**Results**

**Comparison of Anterior Regional Blood Flow Measurements During a Stable Hemodynamic Period**

Twenty to 30 minutes after termination of cardiopulmonary bypass when anterior descending graft flow was stable, 12 simultaneous pairs of flow recordings were made. These results are summarized in table 2. During these periods when LAD graft blood flow was relatively constant (± 10%) and averaged 49 ± 5 ml/min (mean ± 1 SEM). Thermobilation measurements of GCVF and CSF were 44 ± 4 ml/min, and 14 ± 6 ml/min, respectively. The difference in blood flow between LAD graft and the great cardiac vein averaged 7.7 ± 1.2 ml/min. Anterior regional flow measured by thermobilation from the great cardiac vein did not differ significantly from electromagnetic flow probe measurements made from the LAD graft (table 2 and fig. 3). Blood flow in the great cardiac vein was highly correlated (r = 0.89) with LAD graft flow, although GCVF slightly underestimated LAD flow. With LAD graft flow used as a reference, anterior wall blood flow or GCVF averaged approximately 89% of LAD graft flow. No other systematic difference was apparent.

**Table 2. Comparison of Simultaneously Obtained Blood Flow**

<table>
<thead>
<tr>
<th>Pt no</th>
<th>GCVF</th>
<th>CSF</th>
<th>LAD</th>
<th>Arterial pressure</th>
<th>Intervention</th>
<th>Altered graft flow (n = 20)</th>
<th>Change in blood flow with intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>115</td>
<td>59</td>
<td>106/88</td>
<td>Cathelic stimulation</td>
<td>90 211 102</td>
<td>120/92 40 96 43</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>80</td>
<td>29</td>
<td>125/90</td>
<td>LAD graft occlusion</td>
<td>5  65  0</td>
<td>120/95 43 45 52</td>
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<tr>
<td>3</td>
<td>63</td>
<td>140</td>
<td>78</td>
<td>115/80</td>
<td>Cathelic stimulation</td>
<td>104 228 123</td>
<td>150/90 47 107 59</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>128</td>
<td>50</td>
<td>140/90</td>
<td>Cathelic stimulation</td>
<td>12 90  0</td>
<td>140/90 29 38 50</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>126</td>
<td>40</td>
<td>100/70</td>
<td>Cathelic stimulation</td>
<td>73 210 85</td>
<td>127/95 32 82 35</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>141</td>
<td>42</td>
<td>110/90</td>
<td>Cathelic stimulation</td>
<td>56 200 60</td>
<td>150/95 25 95 32</td>
</tr>
<tr>
<td>Mean</td>
<td>44</td>
<td>114</td>
<td>49</td>
<td></td>
<td>Cathelic stimulation</td>
<td>8  145  0</td>
<td>145/92 48 55 60</td>
</tr>
</tbody>
</table>

Blood flow in ml/min. Arterial pressure in mm Hg measured from the radial artery.

Abbreviations: GCVF = great cardiac vein flow; CSF = coronary sinus flow; LAD = left anterior descending.
Comparison of Anterior Regional Blood Flow Measurements During Intervals When Graft Flow Changed

Simultaneous measurements were made during 20 separate intervals. The relationship between changes in simultaneously obtained GCVF and LAD graft flow after various interventions is illustrated in figure 4. The association between the change in LAD and GCVF was highly significant ($P < 0.001$). The data points were only moderately scattered, and the correlation coefficient was 0.86. Again, GCVF was systematically lower than LAD graft blood flow (mean 45 ± 4 and 51 ± 5, respectively). This discrepancy did not appear to be related to coronary anatomy, and the type of intervention (reactive hyperemic, catecholamine administration, or atrial tachycardia) could not be implicated.

Discussion

Comparison studies of a relatively simple thermodilution technique for obtaining estimates of anterior regional left ventricular blood flow were made by simultaneously measuring great cardiac vein
and LAD graft (electromagnetic flowmeter) flows. Our results showed that blood flow to the anterior wall, as reflected in the great cardiac vein effluent, can be estimated with relative ease using a thermodilution approach. Furthermore, these venous flow measurements related closely to blood flow delivered via the graft to the occluded LAD. Changes in GCVF also closely reflected changes induced in LAD graft flow. Although the correlation coefficients were good with the use of the thermodilution technique to estimate either absolute blood flow or flow changes, some systematic deviation occurred. Measurements of GCVF underestimated (mean 11%) blood flow in the LAD graft.

It is conceivable that the anterior regional flow might also represent a contribution of collateral flow and some antegrade flow, even though the LAD appeared totally or subtotally occluded at angiography. This is unlikely with an unobstructed bypass graft and a GCVF that actually underestimated LAD graft flow. The latter suggests that some of the bypass graft flow might drain through other venous channels. In this regard, Nakazawa et al. have proposed that a small portion of the LAD flow of normal dogs may drain to the coronary sinus through circumflex venous branches rather than through the great cardiac vein. In man, venous drainage other than to the great cardiac vein, either directly or as a result of collateral flow to regions drained by veins not emptying into the great cardiac vein, could account for this systemic discrepancy. This does not seem to be a serious limitation in the patients studied. However, the contribution of flow from the graft to the GCVF might be proven by adding an indicator, such as an isotope, in the saphenous vein graft with great cardiac vein sampling.

The indicator injection rate is important to insure adequate mixing of blood and indicator. Ganz et al. found indicator injection rates of 35–55 ml/min were the minimal rates necessary for accurate measurements of blood flow to 300 and 500 ml/min, respectively. In preliminary experiments using tygon tube we found that similar injectate rates provided accurate blood flow measurements. We did not vary the injectate rate during this study due to the limited time available for measurements in the operative setting. The blood flows measured were < 300 ml/min so the 53–56 ml/min injectate rate should have provided adequate mixing.

This method of grossly estimating regional blood flow has several advantages. Studies may be performed in awake subjects at the time of coronary angiography with little additional risk to the patient other than a slight increase in catheterization time. Since the arterial catheters can be removed, this is not translated to prolonged “arterial time.” Expensive equipment, isotopes, and assumptions relative to washout and overlap are unnecessary. Data are recorded on an analog recorder and provide constant reference. Infusion can be prolonged to determine acute changes “on line.”

The importance of the problem of potential catheter motion should be emphasized. At the beginning of each study the position of the catheter is adjusted, during continuous infusion, so that respiratory-related changes in temperature, recorded at both the external thermistors, are not observed. Such changes occur when either external thermistor moves across a venous side branch draining into the major coronary sinus — great cardiac vein system. In an occasional patient we have had to replace the catheter used in this study (3.5 cm spacing between great cardiac vein and coronary sinus thermistors) with another catheter having a thermistor spacing of 4.5 or 5 cm. After these preliminary adjustments, catheter position is then controlled by reference to a videotape or video disc recording stored at the beginning of the procedure. In our experience these regional flow catheters are not subject to as much movement as the catheters used to measure only coronary sinus blood flow. The extension positioned in the great cardiac vein tends to help stabilize catheter position. With interventions that might alter heart size or function, the potential for movement of the catheter might increase. We also film the venous phase of the coronary angiogram so that the thermistors can be precisely localized to indicate the venous regions sampled. Previous limitations relative to the use of these techniques in animals where there are multiple small veins entering the proximal coronary sinus have been described elsewhere. Additionally, others have recently suggested that patients with very high atrial pressures during ventricular pacing may have reflux back to the midcoronary sinus. Finally, it is not certain that equally good correlations can be found under catheterization laboratory or cardiac care unit conditions. Although similar validity testing cannot be done in these other patient care settings, it may be possible to compare thermodilution measurements to regional flow derived by another method (i.e., isotopes).

No difficulties or complications were encountered in selective cannulation of the great cardiac vein and coronary sinus. In subsequent clinical studies we have used this technique successfully in 64 of 67 patients without serious complications. In one of these patients, transient atrial fibrillation developed but reverted spontaneously after the catheterization procedure. In the other two patients the distal thermistor bead could not be advanced beyond the midcoronary sinus. No cardiac perforation, tamponade or serious arrhythmias occurred.

Since the pathophysiologic consequences of obstructive coronary artery disease are nonuniform and result in regional maldistribution of blood, a need exists for regional blood flow evaluation. Simultaneous assessment of regional myocardial metabolic function could be clinically helpful. Herman et al. used serial sampling of blood from various cardiac veins to evaluate regional myocardial metabolism relative to coronary artery obstructive lesions. Recently, Chatterjee et al. suggested a technique for selective simultaneous investigation of regional (anterior) and global left ventricular myocardial metabolism in man. Further studies in a much larger number of patients will be needed to establish the
TABLE 3. Percent Prediction Limits for Anterior Regional Flow (ml/min) Derived from Individual Great Cardiac Vein Flow Measurements

<table>
<thead>
<tr>
<th>GCVF</th>
<th>LAD</th>
<th>Predicted anterior regional flow</th>
<th>95% prediction limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>59</td>
<td>57.5</td>
<td>54.3 61.2</td>
</tr>
<tr>
<td>48</td>
<td>52</td>
<td>54.6</td>
<td>51.4 58.0</td>
</tr>
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<td>57</td>
<td>64</td>
<td>67.3</td>
<td>64.1 71.0</td>
</tr>
<tr>
<td>25</td>
<td>29</td>
<td>22.2</td>
<td>16.9 26.8</td>
</tr>
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<td>28</td>
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<td>22.7 29.8</td>
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<td>47.6</td>
<td>44.3 50.9</td>
</tr>
<tr>
<td>50</td>
<td>42</td>
<td>57.5</td>
<td>54.3 61.2</td>
</tr>
</tbody>
</table>

Predicted anterior regional flows estimated from least squares equation (GCVF − 9.21)/0.71.1

Abbreviations: GCVF = great cardiac vein flow; LAD = left anterior descending graft flow; LPL = lower prediction limit; UPL = upper prediction limit.

clinical value of this type of investigation. However, the potential for combining gross estimates of regional flow, measured by this technique, and regional metabolic assessments is apparent. Also, if the goal is to assess the significance of a particular LAD lesion, it is important that a percentage possible error for an individual be known. Then it would be possible to predict the expected change in LAD flow from measurements of GCVF with stress or intervention in more precise terms. Expressions for the upper and lower 95% prediction limits about the estimated values of anterior regional flow (LAD flow) are given in table 3.1

In conclusion, this study provides in vivo comparison of a technique to measure regional venous flow with flow independently recorded in a graft to this region in selected patients with coronary disease. The thermodilution method used yielded results that closely correlated with coronary artery graft flow to the anterior region measured by electromagnetic flowmeter. Further studies are warranted to assess the potential usefulness of this type of investigation in evaluating procedures thought to alter regional coronary flow.

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