Measurement of Aortic Regurgitation
by Upstream Sampling with
Continuous Infusion of Indicator

By MARTIN J. FRANK, M.D., PABLO CASANEURA, M.D.,
MANOCHEHR NADIMI, M.D., ANGELO J. MIGLIOI, M.D.,
AND GILBERT E. LEVINSON, M.D.

ALTHOUGH many techniques have been proposed or utilized for the semi-quantitative or quantitative assessment of aortic regurgitation, the most direct approach involves measurement of the regurgitant flow by the recording of indicator concentrations from the left ventricle following injection into the aortic root. This method is theoretically valid and had been applied to aortic regurgitation in man and to experimental aortic regurgitation in dogs, utilizing the sudden indicator injection technique. Attempts to use this technique in our laboratory, however, yielded erratic results. It was reasoned that if the defect in the method was primarily due to the critical dependence of indicator distribution on the timing of the injection or to a beat-to-beat variation in forward or regurgitant stroke output, these difficulties could be overcome by using a continuous infusion of indicator. Therefore, the measurement of aortic regurgitation in man by the upstream sampling method was evaluated by use of both the sudden injection and the continuous infusion techniques.

Methods

Measurements were performed in 18 patients with clinical evidence of aortic regurgitation in whom cardiac catheterization was indicated. Patients were studied in the resting steady state under mild barbiturate sedation and local procaine analgesia. A closed-tip catheter with multiple side holes (NIH), to facilitate mixing and prevent direct ventricular injection, was placed just distal to the aortic valve through a right brachial arteriotomy. The left heart was entered by the transseptal technique, and a catheter with multiple side holes was placed in the left ventricular apex. A thin-walled 17-gauge Cournand needle was placed in the left brachial artery. The pulmonary artery was entered through a right antecubital vein. Appropriate pressures and valve gradients were measured as described elsewhere.

In all 18 patients regurgitant flow was measured by the continuous indicator-infusion technique. In eight patients upstream and downstream dilution curves were recorded in rapid succession with the same densitometer, and in 10 patients curves were recorded simultaneously with two densitometers. In 10 patients measurements by continuous infusion were compared with alternate measurements after sudden injection of indicator. The timing of sudden injections was random with respect to the cardiac cycle. To test the adequacy of aortic root mixing in aortic regurgitation, forward flow measurements by continuous infusion into the aortic root and brachial artery sampling were compared in seven patients with paired measurements of forward flow from sudden injection of indicator into pulmonary artery and aortic root sampling. In 14 patients, estimates of the regurgitant fraction of total aortic valve flow were compared with semiquantitative estimates by aortic valvulography.

Dilution curves were obtained by using

From the Division of Cardiovascular Diseases, Department of Medicine, New Jersey College of Medicine, and the Thomas J. White Cardiopulmonary Institute, B. S. Pollak Hospital for Chest Diseases, Jersey City, New Jersey.

Presented in part at the Annual Meeting of the American Federation for Clinical Research, Atlantic City, New Jersey, April 1963, and at the Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 1964.

Supported in part by Program Project Grant HE-06578 and by Grant 5TI HE-5510, from the National Heart Institute, U.S. Public Health Service, and in part by the Union County (New Jersey) Heart Association.

Work done while Dr. Casanegra was a Fellow of the Rockefeller Foundation and Drs. Nadimi and Migliori were Research Fellows of the Union County (New Jersey) Heart Association.
indocyanine-green dye, Gilford densitometers, Harvard infusion-withdrawal pumps, and a recorder (Electronics for Medicine). Calibration was by the integrated sample technique. Dye was introduced into the aortic root either by continuous infusion of a 1 mg/ml solution at constant rates of 30 to 75 ml/min, or by sudden injection of 6.6 mg from a calibrated pipette. When curves were recorded simultaneously, blood was withdrawn at a constant rate of 0.7 to 2.0 ml/sec from the left ventricle and brachial artery. When curves were recorded nonsimultaneously, both upstream and downstream curves were recorded from the left ventricle, the latter after sudden injections into the pulmonary artery, with an interval of less than 3 minutes between the two curves. For the calculation of regurgitant flow, each upstream curve, by either sudden injection or continuous infusion, was matched with the downstream curve closest in time.

Curves obtained with sudden injections were plotted semilogarithmically and extrapolated to 1% of peak concentration. Areas were obtained by summation of the concentrations at 1-second intervals. Forward flow was calculated according to the method of Kinsman and co-workers. Aortic regurgitant flow was calculated according to the following formula:

\[ \dot{Q}_R = \frac{\dot{Q}_F}{(A_f/A_r) - 1}, \]

where \( \dot{Q}_R \) = regurgitant flow, \( \dot{Q}_F \) = effective forward flow, \( A_f \) = the area under the upstream dilution curve, and \( A_r \) = the area under the downstream dilution curve (fig. 1). Total flow \( (\dot{Q}_F) = \dot{Q}_R + \dot{Q}_F \), and the regurgitant fraction of total aortic valve flow = \( \dot{Q}_R / \dot{Q}_F \).

During continuous indicator infusion, left ventricular and brachial arterial indicator concentrations were seen to rise to equilibrium plateaus, followed by recirculation (fig. 2). The equilibrium plateau indicates a steady state in which all blood free of indicator has left the vascular bed between injection and collection sites and in which the amount of indicator

Circulation, Volume XXXIII, April 1966
leaving this bed per unit of time is equal to the amount infused per unit of time. The height of the plateau above the baseline of the arterial dilution curve = \( A_f \), and the height of the plateau above the base line of the left ventricular dilution curve equals \( A_r \). Forward flow was calculated as

\[
\dot{Q}_F = \frac{\text{Indicator concentration} \times \text{Infusion rate} \times \text{Calibration factor}}{A_f}
\]

(2)

and aortic regurgitant flow according to formula 1. When nonsimultaneous curves were recorded, the expected \( A_r \) if \( \dot{Q}_F \) had been measured simultaneously by continuous infusion was calculated by rearrangement of formula 2, as

\[
A_r = \frac{\text{Indicator concentration} \times \text{Infusion rate} \times \text{Calibration factor}}{\dot{Q}_F}
\]

(3)

In the patients on whom angiography was performed, 85% diatrizoate sodium (Hypaque) was injected into the ascending aorta just distal to the aortic valve by Gidlund syringe through a closed-tip catheter with side holes (NIH). Cinefluorography, at 32 or 64 frames/sec, was performed with the patient in the 60°, left anterior oblique position during deep inspiration. Regurgitation was graded 1+ (mild), 2+ (moderate), 3+ (moderately severe), or 4+ (severe), by the following criteria, adapted from those used by investigators47 employing Schonander angiography. With mild regurgitation, a small amount of contrast material is seen in the outflow tract of the left ventricle during diastole but disappears

\[
\begin{align*}
A_f &= 470 \text{ mm} \\
A_r &= 28.2 \\
\text{CALIBRATION FACTOR RATIO} &= 0.781 \\
\dot{Q}_F &= \frac{32 \text{ mg} \times 6.94 \text{ m m}^{-1} \text{ mg/L}}{47.0} = 4.81 \text{ L/min} \\
\dot{Q}_R &= \frac{4.81}{\left( \frac{470}{28.2} \times 0.781 \right) - 1} = 15.92 \text{ L/min}
\end{align*}
\]

Figure 2

Measurement of aortic regurgitation by the upstream sampling method with use of continuous infusion of indicator. Abbreviations are defined in the text and used in figure 1. The onset and termination of continuous infusion into the aortic root are indicated on the horizontal line at the top of the record. \( A_f \) and \( A_r \) are the heights of the equilibrium plateaus of the BA and LV curves above their respective base lines. In this patient, total flow was 20.73 L/min, and the regurgitant fraction was 76.8%.
from the ventricle during systole. With 2+ regurgitation, a moderate amount of contrast material refluxes beyond the outflow tract into the body of the left ventricle during diastole, and opacification persists during systole. With 3+ regurgitation, increasing amounts of regurgitated contrast

<table>
<thead>
<tr>
<th>Patient, age, sex</th>
<th>BSA*</th>
<th>Cine†</th>
<th>HR‡</th>
<th>QF§</th>
<th>QF∥</th>
<th>QT**</th>
<th>Qt†</th>
<th>HR</th>
<th>Qt</th>
<th>Qt</th>
<th>Qt</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.M. 22 M</td>
<td>1.79</td>
<td>3+</td>
<td>87</td>
<td>6.80</td>
<td>8.90</td>
<td>15.70</td>
<td>55.7</td>
<td>84</td>
<td>6.47</td>
<td>9.89</td>
<td>16.36</td>
</tr>
<tr>
<td>A.V. 45 F</td>
<td>1.56</td>
<td>3+</td>
<td>70</td>
<td>4.04</td>
<td>9.64</td>
<td>13.68</td>
<td>70.5</td>
<td>70</td>
<td>3.74</td>
<td>8.59</td>
<td>12.33</td>
</tr>
<tr>
<td>P.G. 64 M</td>
<td>1.61</td>
<td>4+</td>
<td>78</td>
<td>2.25</td>
<td>4.41</td>
<td>6.66</td>
<td>66.2</td>
<td>81</td>
<td>2.35</td>
<td>10.65</td>
<td>13.00</td>
</tr>
<tr>
<td>B.S. 29 F</td>
<td>1.37</td>
<td>3+</td>
<td>71</td>
<td>2.73</td>
<td>3.44</td>
<td>6.17</td>
<td>55.7</td>
<td>76</td>
<td>2.72</td>
<td>4.80</td>
<td>7.52</td>
</tr>
<tr>
<td>H.J. 56 F</td>
<td>1.53</td>
<td>3+</td>
<td>72</td>
<td>2.45</td>
<td>1.56</td>
<td>4.01</td>
<td>38.9</td>
<td>75</td>
<td>2.45</td>
<td>2.36</td>
<td>4.81</td>
</tr>
<tr>
<td>D.A. 61 M</td>
<td>1.81</td>
<td>1+</td>
<td>73</td>
<td>6.71</td>
<td>0.36</td>
<td>7.07</td>
<td>5.1</td>
<td>73</td>
<td>6.71</td>
<td>1.07</td>
<td>7.78</td>
</tr>
<tr>
<td>E.K. 17 M</td>
<td>1.73</td>
<td>2+</td>
<td>74</td>
<td>5.33</td>
<td>2.98</td>
<td>8.31</td>
<td>35.8</td>
<td>73</td>
<td>4.74</td>
<td>3.70</td>
<td>8.44</td>
</tr>
<tr>
<td>J.R. 45 F</td>
<td>1.54</td>
<td></td>
<td>74</td>
<td>5.35</td>
<td>7.59</td>
<td>12.94</td>
<td>58.6</td>
<td>74</td>
<td>4.74</td>
<td>4.62</td>
<td>9.36</td>
</tr>
<tr>
<td>J.S. 53 M</td>
<td>1.72</td>
<td>1+</td>
<td>78</td>
<td>5.44</td>
<td>0.56</td>
<td>6.00</td>
<td>9.4</td>
<td>75</td>
<td>5.44</td>
<td>1.21</td>
<td>6.65</td>
</tr>
</tbody>
</table>

*BSA = Body surface area, in m².
†Cine = Cinefluorographic grade of the severity of aortic regurgitation.
‡HR = Heart rate, in beats/min.
§QF = Effective forward flow, in L/min.
∥QF = Regurgitant flow, in L/min.
**QT = Total aortic valve flow, in L/min.
††QF = Regurgitant fraction of total aortic valve flow, expressed as a percentage.
### Patients with atrial fibrillation; all others had a regular sinus rhythm.

Circulation, Volume XXXIII, April 1966
material accumulate in the left ventricle on successive cycles, and the entire left ventricle is filled. With 4+ regurgitation, the left ventricle is completely filled by refluxed contrast material during the first complete diastole following injection, and the density of opacification in the ventricle approaches that in the aorta. The results of the study were evaluated by the conventional statistical techniques for small samples. The reproducibility of repeated measurements of $Q_T$, $Q_R$, and $Q_R/Q_T$ by each method in individual patients was analyzed by means of the coefficient of variation and, on the assumption that all variation might be attributable to error, was expressed as a percentage error of estimate at 95% confidence limits. The relationship between the regurgitant fraction $Q_R/Q_T$, measured by each of the dye techniques, and the angiographic grade of severity of aortic regurgitation was expressed by the correlation ratio eta ($\eta$), which is applicable whether or not the relationship is linear.

Results

The results of this study are presented in tables 1 through 3 and in figures 3 through 8.

Measurement of Aortic Regurgitation by Continuous Indicator Infusion

Aortic regurgitant flow, based on the mean of the two or more measurements in each of the 18 patients, ranged from 0.8 to 30.0 L/min. Total aortic valve flow ranged from 3.0 to 36.0 L/min and the regurgitant fraction from 12 to 85.5% of total aortic valve flow. Detection of regurgitant stroke volumes as small as 8 ml/beat indicates the sensitivity of the method.

Reproducibility was excellent and was not impaired by nonsimultaneity of upstream and downstream curves (fig. 3). For the eight patients (the first eight of table 1) with non-

<table>
<thead>
<tr>
<th>Patient, age, sex</th>
<th>BSA</th>
<th>Cine</th>
<th>HR</th>
<th>$Q_T$</th>
<th>$Q_R$</th>
<th>$Q_T/Q_R$</th>
<th>$Q_P$</th>
<th>$Q_R$</th>
<th>$Q_T$</th>
<th>$Q_T/Q_R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.S.</td>
<td>1.66</td>
<td>2+</td>
<td>83</td>
<td>3.85</td>
<td>1.27</td>
<td>5.12</td>
<td>24.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 M</td>
<td>84</td>
<td>4.29</td>
<td>4.08</td>
<td>1.55</td>
<td>5.63</td>
<td>27.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85</td>
<td>4.70</td>
<td>4.43</td>
<td>1.75</td>
<td>6.18</td>
<td>28.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H.C.</td>
<td>1.83</td>
<td>2+</td>
<td>57</td>
<td>4.55</td>
<td>3.86</td>
<td>2.15</td>
<td>6.01</td>
<td>35.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 M</td>
<td>54</td>
<td>4.30</td>
<td>3.80</td>
<td>2.57</td>
<td>6.37</td>
<td>40.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F.M.</td>
<td>1.76</td>
<td>4+</td>
<td>82</td>
<td>4.76</td>
<td>25.71</td>
<td>30.47</td>
<td>84.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 M</td>
<td>88</td>
<td>5.79</td>
<td>5.30</td>
<td>31.55</td>
<td>36.85</td>
<td>85.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N.K.</td>
<td>2.12</td>
<td>54</td>
<td>5.11</td>
<td>2.42</td>
<td>7.53</td>
<td>32.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46 M</td>
<td>53</td>
<td>5.13</td>
<td>5.24</td>
<td>2.37</td>
<td>7.61</td>
<td>31.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.C.</td>
<td>1.98</td>
<td>3+</td>
<td>60</td>
<td>4.68</td>
<td>13.48</td>
<td>18.16</td>
<td>74.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52 M</td>
<td>61</td>
<td>4.61</td>
<td>16.41</td>
<td>21.02</td>
<td>78.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>4.81</td>
<td>15.92</td>
<td>20.73</td>
<td>76.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.C.</td>
<td>1.69</td>
<td>2+</td>
<td>123</td>
<td>4.82</td>
<td>2.90</td>
<td>7.72</td>
<td>37.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 M</td>
<td>123</td>
<td>5.67</td>
<td>2.75</td>
<td>8.42</td>
<td>32.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>5.36</td>
<td>5.50</td>
<td>3.20</td>
<td>8.70</td>
<td>36.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.C.</td>
<td>1.62</td>
<td>4.36</td>
<td>4.09</td>
<td>7.06</td>
<td>11.15</td>
<td>63.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 M</td>
<td>68</td>
<td>4.21</td>
<td>7.58</td>
<td>11.79</td>
<td>64.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>4.44</td>
<td>8.33</td>
<td>12.77</td>
<td>65.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.P.</td>
<td>1.39</td>
<td>95</td>
<td>7.10</td>
<td>7.09</td>
<td>3.03</td>
<td>10.12</td>
<td>29.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33 F</td>
<td>98</td>
<td>7.57</td>
<td>2.70</td>
<td>10.27</td>
<td>26.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>7.87</td>
<td>3.02</td>
<td>10.89</td>
<td>27.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations and units of measurement are the same as in table 1.

Circulation, Volume XXXIII, April 1966
simultaneous curves, the error of estimate at 95% confidence limits was 8.2% for $Q_R/Q_T$, 22.1% for $Q_R$, and 14.5% for $Q_T$. For the 10 patients on whom simultaneous curves were recorded (the last two of table 1 and the eight of table 2), the comparable errors of estimate were 8.8, 18.7, and 12.2%, respectively.

**Comparison of Continuous Indicator Infusion with Aortography**

Ranking of patients by the magnitude of $Q_R$ and $Q_T$ did not correspond to ranking by the angiographic criteria of severity, since concomitant valve lesions and myocardial failure limited the prevailing forward and total flows. On the other hand, ranking by regurgitant fraction corresponded completely with that by aortography, and the correlation, in the 14 patients in whom aortography was performed, between angiographic grade of severity and $Q_R/Q_T$, was excellent ($\gamma = 0.998$), indicating that the regurgitant fraction is the most meaningful expression of severity.

In the cases in which aortic valvulography was performed, mild aortic regurgitation was equivalent to a regurgitant fraction of $< 25%$; moderate regurgitation to a regurgitant fraction of 25 to 50%; moderately severe regurgitation to a regurgitant fraction of 50 to 75%; and severe regurgitation to a regurgitant fraction of $> 75%$.

**Measurements of $Q_F$ by Continuous Infusions of Indicator Into the Aortic Root**

Measurements of systemic flow by continuous infusion technique exhibited excellent reproducibility and good agreement with measurements obtained by sudden injections of indicator into the pulmonary artery. In 27 measurements, in 10 patients, the error of estimate at 95% confidence limits for measurements of $Q_F$ by continuous infusions was 8%. In 10 pairs of measurements, obtained in seven patients (table 2), the mean algebraic difference between values obtained by continuous infusion and those obtained by sudden injection was $+ 0.08 \text{ L/min}$, which is statistically insignificant ($P > 0.3$), and the correlation coefficient $r$ was 0.93.
MEASUREMENT OF AORTIC REGURGITATION

Figure 4
Reproducibility of measurements by the upstream sampling method: Comparison of continuous infusion and sudden injection techniques for measurements of $Q_r$. In this figure, and in figures 5 and 6, each measurement in each patient (observation X) is plotted against the measurement which immediately followed (observation X + 1). From these data, the calculated error of estimate at 95% confidence limits is 92% of a measurement for the sudden injection technique and 22% for the continuous infusion technique.

Figure 5
Reproducibility of measurements by the upstream sampling method: Comparison of continuous infusion and sudden injection techniques for measurements of $Q_r$. The errors of estimate at 95% confidence limits are 54% for data obtained with sudden injection and 13% for data obtained with continuous infusion.

Circulation, Volume XXXIII, April 1966
Comparison of the Continuous Infusion and Sudden Injection Techniques

Although mean values by these two techniques, for \( Q_R \), \( Q_T \), and \( Q_R/Q_T \), did not differ significantly \((P > 0.25\) in all instances\), measurements obtained by the sudden injection technique were clearly less reliable (figs. 4 through 8 and table 3). In figures 4 to 6, the excellent agreement between sequential measurements for the continuous infusion technique and the poor agreement for the sudden injection technique are shown for measurements of \( Q_R \), \( Q_T \), and \( Q_R/Q_T \). That these comparisons were performed during a comparable steady state was confirmed by a heart rate variation of less than 10% in all 10 patients and a cardiac output variation of 10% or less in nine patients and less than 20% in one patient throughout the entire series of measurements. Comparison of the quantitative measurements of aortic regurgitation by the two indicator techniques with semiquantitative estimates obtained by aortography (figs. 7 and 8) demonstrates the clearly superior correlation of results obtained by continuous infusion \((\eta = 0.997)\) over those obtained with sudden indicator injection \((\eta = 0.894)\). The greater scatter among multiple measurements in individual patients and the marked overlap between radiographically distinct grades, for the sudden indicator injection technique (fig. 8), are in striking contrast to the small scatter and appropriately small overlap obtained with the continuous infusion technique (fig. 7).

Table 3 summarizes the unequivocal statistical superiority of the continuous infusion technique over that of randomly-timed sudden indicator injections. Despite the statistically insignificant difference between the two techniques for the mean values of \( Q_R \), \( Q_T \), and \( Q_R/Q_T \), the range of values for replications was strikingly smaller for the continuous infusion technique and, on the assumption that all variation is due to error, the percentage error of estimate at 95% confidence limits, for all three variables, was approximately four times smaller for the continuous infusion technique.

Discussion

The fundamental Stewart-Hamilton equa-
MEASUREMENT OF AORTIC REGURGITATION

Figure 7

Relation between measurements of $Q_{p}/Q_{a}$ by the upstream sampling method and semiquantitative estimates by angiography: Results of using continuous infusions of indicator. Different symbols over a given angiographic grade represent different individual patients; the repetition of a symbol over that grade represents the replicate measurements in that patient.

Figure 8

Relation between measurements of $Q_{p}/Q_{a}$ by the upstream sampling method and semiquantitative estimates by angiography: Results of using sudden injections of indicator. The same nine patients are represented as in Figure 7.

Zierler\textsuperscript{24} has pointed out that, if flow is not constant, the sudden injection method fails to measure flow correctly while the continuous infusion method is less vulnerable to error under these circumstances. This situation is the rule rather than the exception in man in whom stroke volumes may vary with the phases of the respiratory cycle. Furthermore, variation in the length of systolic and diastolic intervals associated with the inconstant R-R interval of sinus arrhythmia or atrial fibrillation may result in striking beat-to-beat differences in both the forward and regurgitant stroke volumes. In addition, the timing of sudden injection is critical for measurements of aortic regurgitation. Sudden single injections made in late systole and early diastole may result in an overestimate of backflow, while injections made in late diastole and early systole would be expected to result in an underestimate of backflow.\textsuperscript{25}

For these reasons it was hypothesized that continuous indicator infusions would be superior to random sudden injections for the specific circumstances surrounding aortic regurgitation. The results of the present study confirm the difficulties arising from the variation in forward stroke volume, regurgitant stroke volume, and injection timing and demonstrate...
that these are overcome by continuous indicator infusion.

The validity and accuracy of the upstream sampling method for the measurement of aortic regurgitation depend on the adequacy of indicator mixing in the aortic root and left ventricle. Recent studies by Freis and Heath,26 utilizing thermodilution, revealed no significant differences in mean temperatures, degree of temperature fluctuation, or rate of temperature change across the diameter of the aortic root, both near the walls and in the central stream, during continuous infusion of cold saline 1 to 2 cm proximal to the detector site. They suggested that the narrow inlet of the valve orifice projecting into a tube of much larger diameter (the aortic bulb) acts as a hydrodynamic diffuser, promoting mixing by producing vortices which need not depend entirely on turbulence for their effect. In addition, Peterson and co-workers,27 using a catheter-producing, radially directed jet during continuous infusions of Evans blue (T-1824) into the ascending aorta, found practically complete mixing. Armelin and co-workers14 demonstrated that, although withdrawal of the infusion catheter from its location just distal to the aortic valve results in a reduction in the amount of aortic regurgitation measured, little variation occurs when injections are made within the first 2 cm distal to the valve. (In the present study, the position of neither the injection nor sampling catheters could influence the result in regard to the superior reproducibility of the continuous infusion method, since the sudden injection and continuous-infusion techniques were employed alternately and by use of the same catheters in identical locations.) The demonstration in the present study of insignificant differences between cardiac outputs measured on continuous infusion into the aortic root and on sudden injection into the pulmonary artery contributes additional evidence for the presence of aortic root mixing.

Whether left ventricular mixing is complete is a matter of controversy.28, 29 However, evidence for the adequacy of left ventricular mixing in aortic insufficiency has been presented by Armelin et al.14 who demonstrated similar areas under two dilution curves recorded simultaneously from the left ventricle at different sites during sudden injections of indicator into the aortic root in dogs with experimental aortic regurgitation. Discordant results were obtained on only one occasion, in which one of the ventricular catheters was lying in the outflow tract of the left ventricle, immediately beneath the defect in the aortic valve. Although ventricular mixing is, therefore, probably adequate in most cases of clinical aortic regurgitation, data are lacking to establish whether or not this is true in the markedly dilated left ventricle seen in some patients with severe aortic regurgitation.

In this connection, it is important to note that our method and the method of Sandler and co-workers,13 based on Arvidson's angio-graphic technique for measuring ventricular volumes which does not depend on uniform mixing, provide entirely comparable estimates of the regurgitant and total flows prevailing in all grades of clinical aortic regurgitation. Since these methods differ conceptually and technically, such agreement constitutes a strong criterion of mutual validation. It is evident, however, in the present study, as in all clinical investigations of techniques for measuring valvular insufficiency, that direct evidence can be obtained only in regard to validity, sensitivity, and reproducibility, but not accuracy, since demonstration of accuracy requires a simultaneous and independent measurement by a method of proven accuracy, which is not presently available in man.

The accuracy of the upstream sampling method has been investigated in dogs by Malooly and associates15 with experimentally induced aortic regurgitation, and by ourselves with an aortico-left ventricular shunt.30 Malooly et al. found a good correlation (r = 0.91), but a systematic difference between measurements by flowmeter and measurements by dye dilution after sudden injections. We found a good correlation (r = 0.95), with no systematic discrepancy, between measurements by rotameter and measurements by dye dilution with continuous infusion. Al-
though the two studies differed in the animal preparation as well as in the technique of dye administration, both provide evidence of an acceptable accuracy for the upstream sampling method; the differences between them, in our opinion, are due, at least in part, to the demonstrated defects in the sudden injection technique.

Among the other methods used to measure aortic regurgitation, those which analyze downstream dilution curves have been shown merely to reflect changes in mixing and to be invalid as measures of backward flow. Theoretically valid approaches have been offered by Warner and Toronto, and Braunwald and Morrow, using optical indicators, and by Arcilla and associates, employing radiopaque indicators, to measure the relative degree of forward travel and backward travel of dye in the aorta. To translate results into quantitative terms, investigators using optical indicators must make an assumption as to the volume of the various aortic segments, or use a radiographic technique to measure these volumes as Armelin and associates have done. When radiopaque indicators alone are used, the technique is complicated by changing aortic volumes during ejection and poor definition of moving boundaries in the presence of laminar flow. Moreover, a significant centripetal movement of blood occurs in some patients with normal aortic valves. The method of Sandler and co-workers is also theoretically valid, but presents major difficulties as compared with the upstream sampling method using continuous infusion. The required geometric assumptions may be false in the presence of pathological alterations in ventricular configuration. In combined mitral and aortic regurgitation, only total regurgitant flow across the two valves is measured, while the upstream sampling method should measure the aortic regurgitation correctly in the presence of mitral insufficiency. In addition, basal measurements of forward stroke volume must be related to angiocardiographic estimates of total stroke volume. This requires the assumption that the radiopaque medium has no effect on left ventricular function, which is not the case. Moreover, repeated measurements are progressively hazardous. Finally, the method is difficult or impossible to apply when heart rates are rapid or rhythm irregular or when transient dysrhythmias are produced by the injection of contrast medium. The dilution technique, however, is applicable under these circumstances, provided upstream and downstream curves are recorded simultaneously.

In view of the limitations of the radiographic technics described, and of the other methods cited, we conclude that the upstream sampling method during continuous indicator infusion, because of its validity, sensitivity, excellent reproducibility, and applicability to multiple measurements during departures from the steady state, appears to be the most useful method for quantifying aortic regurgitation in man.

**Summary**

A direct and theoretically valid method for the measurement of aortic regurgitation involves the recording of indicator concentrations from the left ventricle and a downstream site through aortic root injection. However, this method has yielded erratic results when applied to man in our laboratory when using the sudden injection technique. Moreover, others have found a systematic overestimate of backflow when the sudden injection technique was compared with flowmeter measurements in dogs with experimental aortic regurgitation. If defects in the method are due primarily to a critical dependence of indicator distribution on the timing of injection or to beat-to-beat variations in the forward or regurgitant stroke volumes, these difficulties could conceivably be overcome by substituting continuous infusion of indicator for sudden single injections. Therefore, the upstream sampling method, using continuous infusion of indicator, was evaluated in 18 patients with aortic regurgitation during retrograde aortic and transseptal left ventricular catheterization. The continuous infusion technique was compared with
the technique of sudden injection in 10 patients and with aortic valvulography in 14 patients.

Measurements of forward flow obtained with continuous infusions into the aortic root were not significantly different from measurements obtained with sudden injections into the pulmonary artery. Recordings of indicator concentrations from the left ventricle, during continuous infusions into the aortic root, demonstrated readily evident equilibrium plateaus. The resultant measurements of regurgitant flow were highly reproducible and not impaired by nonsimultaneity of upstream and downstream sampling. The percentage error of estimate at 95% confidence limits was 22% of the measurement for regurgitant flow, 13% for total flow, and 9% for the regurgitant fraction of total flow. The corresponding errors of estimate for the sudden injection technique were four times larger.

Regurgitant flow by the continuous infusion method ranged from 0.8 to 30.0 L/min, total flow from 3.0 to 360 L/min, and the regurgitant fraction of total flow from 12 to 86%. Ranking of patients by the magnitudes of regurgitant and total flow did not correspond to ranking by angiographic criteria of severity. However, an excellent correlation prevailed between angiographic grade and the regurgitant fraction of total flow, demonstrating that this variable is the most meaningful expression of severity. The correlation (0.997) between the angiographic grade and the regurgitant fraction measured by the continuous infusion technique was clearly superior to that obtained with the sudden injection technique (0.894). Mild regurgitation was equivalent to a regurgitant fraction of <25%, moderate regurgitation to a fraction of 25 to 50%, moderately severe regurgitation to a fraction of 50 to 75% and severe regurgitation to a fraction of >75%.

It is concluded that the upstream sampling method during continuous infusion of indicator, because of its sensitivity, reliability, applicability to multiple measurements, and validity in the presence of mitral regurgitation, is the most useful method for quantifying aortic regurgitation in man.

Acknowledgment

We are pleased to acknowledge the assistance in the catheterization laboratory of Mrs. Carol Speckart, Mrs. Jacqueline Czerniakowski, and Miss Georgina Abich, and the technical assistance of Miss Sharon Malone, and to thank Mrs. Phyllis Moschos for the preparation of the manuscript.

References


Measurement of Aortic Regurgitation by Upstream Sampling with Continuous Infusion of Indicator

MARTIN J. FRANK, PABLO CASANEGRA, MANOUCHEHR NADIMI, ANGELO J. MIGLIOI and GILBERT E. LEVINSON

Circulation. 1966;33:545-557
doi: 10.1161/01.CIR.33.4.545

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/33/4/545

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/