Measurement of Mitral Regurgitation in Man
by the Upstream Sampling Method Using
Continuous Indicator Infusions

By Martin J. Frank, M.D., Manouchehr Nadimi, M.D.,
Khaldoon I. Hilmi, M.D., and Gilbert E. Levinson, M.D.

SUMMARY
The upstream sampling method for measuring mitral regurgitation was evaluated in 19 patients during retrograde left ventricular and transseptal left atrial catheterization. Measurements obtained by using continuous infusions of indicator were compared, in all patients, with those obtained by using sudden single injections and, in 14 patients, with semiquantitative estimates by mitral valvulography. The mean values for regurgitant flow, total flow, and the regurgitant fraction did not differ significantly for the two dilution techniques. However, measurements of forward flow following sudden injections into the left ventricle were significantly larger than those following sudden injection into the pulmonary artery, while the latter differed insignificantly from measurements during continuous infusions into the left ventricle. Although neither technique had excellent reproducibility, the continuous-infusion method was clearly superior in this respect. The authors concluded that (1) a single measurement of mitral regurgitation by upstream sampling has a probability of large error, (2) continuous infusions in place of sudden injections give more reliable estimates, but (3) continuous infusion measurements are reliable only for mean values from replicate determinations.

Additional Indexing Words:
Cardiac catheterization

Since the introduction of the upstream sampling method for the measurement of mitral regurgitation by Wood and associates1 10 years ago, the technique has been evaluated in hydraulic models2 and in acute and chronic animal preparations3–5 and has been used in man.6–10 Sinclair and co-workers4 demonstrated good agreement in dogs with experimental mitral regurgitation between measurements of regurgitation by upstream sampling and values calculated by the hydraulic formula of Gorlin and Dexter.11 In the studies in man, a relationship was demonstrable between the calculated values of regurgitant flow and clinical or surgical estimates of the severity of insufficiency. However, in the series of Levinson and associates,8 in which duplicate measurements were obtained, the reproducibility of results was poor, and they concluded that, with conventional indicator-dilution techniques, this theoretically sound approach was not a dependable quantitative method. The difficulties in that series may be attributable to an uncontrollable sampling position, since the atrium was entered by the dorsal percutaneous approach. Lacy and co-workers2 had postulated and

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.

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Sinclair and co-workers\(^4\) had demonstrated that the left atrial catheter should be located just proximal to the mitral valve. Jose and Bernstein\(^5\) used an atrial sampling needle introduced by the transseptal route and reported a better agreement between duplicate measurements. However, in our laboratory, using the transseptal technique, the method continues to yield measurements which are poorly reproducible and occasionally manifestly incorrect in the light of clinical, hemodynamic, cinefluorographic, and surgical evidence.

We have previously effected a substantial improvement in the measurement of aortic regurgitation in man by substituting continuous infusions of indicator for sudden single injections\(^1\)\(^2\) and have shown that this method provides accurate measurements in dogs with simulated aortic regurgitation.\(^3\) The present investigation was undertaken, therefore, to determine whether the continuous-infusion technique would effect a comparable improvement in the measurement of mitral regurgitation.

**Methods**

Measurements were performed in 19 patients with clinical evidence of mitral 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\(^\text{a}\)), to facilitate indicator dispersion and prevent direct atrial injection, was placed in the apex of the left ventricle by the retrograde approach. The left atrium was entered by the transseptal technique, and a catheter with multiple side holes was placed just proximal to the mitral valve following withdrawal from the left ventricle. A thin-walled 17-gauge Courand needle was placed in the left brachial artery. In some patients, blood was sampled directly from the needle, while in others polyethylene tubing was advanced to the aorta by the Stille technique. The pulmonary artery was entered through a right ante-cubital vein. Appropriate pressures and valve gradients were measured as described elsewhere.\(^4\)

In all patients both sudden single injections and continuous infusions of indicator were used for measurements of regurgitant flow. The timing of sudden injections was random with respect to the cardiac cycle. However, Sinclair and associates\(^4\) have found this variable to be unimportant in the measurement of mitral regurgitation after sudden injection. In 13 patients measurements of forward flow obtained with continuous infusions and sudden injections into the left ventricle were compared with measurements obtained with sudden injections into the pulmonary artery. In 14 patients measurements of the regurgitant fraction of total mitral valve flow were compared with semiquantitative estimates by mitral valvulography.

Dilution curves were obtained with use of indocyanine-green dye, Gilford densitometers, Harvard infusion-withdrawal pumps, and a photographic recorder (Electronics for Medicine). Calibration was by the integrated sample technique.\(^5\) Dye was introduced into the left ventricle either by continuous infusion of a 1 mg/ml solution at constant rates of 30 or 75 ml/min, or by sudden injection of 6.6 mg from a calibrated pipette.\(^6\) Blood was withdrawn simultaneously at a constant rate of 0.8 to 2.0 ml/sec from the left atrium and downstream site.

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-sec intervals. Forward flow was calculated according to the method of Kinsman and co-workers.\(^7\) Mitral regurgitant flow was calculated according to the following formula:\(^1\)\(^8\)

\[
Q_R = \frac{Q_F}{(A_f/A_r - 1)}
\]  

where \(Q_R\) = regurgitant flow, \(Q_F\) = 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 \((Q_T) = Q_R + Q_F\), and the regurgitant fraction of total mitral valve flow = \(Q_R/Q_T\).

During the continuous infusion of indicator, the resultant left atrial and downstream dilution curves were seen to rise to equilibrium plateaus and were followed by recirculation (figs. 2 and 3). 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 leaving this bed per unit of time is equal to the amount delivered per unit of time. The height of the plateau above the base line of the arterial dilution curve is \(A_r\) and the height of the plateau above the base line of the left atrial dilution curve is \(A_f\). Forward flow was calculated as:

\[
Q_F = \frac{\text{Indicator concentration} \times \text{Infusion rate} \times \text{Calibration factor}}{A_f}
\]
and mitral regurgitant flow according to formula 1.

In the patients in whom mitral valvulography was performed, 85% diatrizoate sodium (85% Hypaque) was injected into the left ventricle by Gidlund syringe through a closed-tip catheter with multiple side holes (NIH). Cinefluorography, at 32 or 64 frames per second, was performed with the patient in the 45° right 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 investigators employing Schonander angiography.19–22 With mild regurgitation, a small amount of contrast material is seen to enter the left atrium which is not filled completely. During this time, the aortic arch and descending aorta are densely opacified. With 2+ regurgitation, a moderate amount of contrast material refluxes and eventually outlines the entire left atrium, while the aortic arch is filled more rapidly and to a greater density. With 3+ regurgitation, increasing amounts of regurgitated contrast material enter the left atrium which fills to the same or slightly greater density and more rapidly than the aortic arch. With 4+ regurgitation the left atrium is filled to a greater density and much more rapidly than the arch of the aorta.

The results of the study were evaluated using conventional statistical techniques for small samples. The reproducibility of repeated measurements of $Q_F$, $Q_R$, $Q_D$, 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 $Q_R/Q_T$, as measured by each of the dye

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**Figure 1**

Measurement of mitral regurgitation by the upstream sampling method using sudden injection of indicator. $A_F$, the effective forward flow area, is the area under the curve recorded from the brachial artery (BA); $A_R$, the regurgitant flow area, is the area under the curve recorded from the left atrium (LA). The calibration factor ratio corrects for the differences in sensitivity of the two recording systems. The vertical lines represent 1-second time intervals. The time of injection into the left ventricle is indicated by the interruption of the horizontal signal at the top of the record. In this patient, total flow = 13.58 L/min, and the regurgitant fraction = 69.7%.
MEASUREMENT OF REGURGITATION

![Graph](image)

\[ A_f = 49.0 \text{ mm.} \]
\[ A_r = 17.5 \text{ mm.} \]

CALIBRATION FACTOR RATIO = 1.284

\[
\frac{60 \text{ mg.}}{\text{min.}} \times 4.04 \text{ mm.} = 4.95 \text{ L./min.}
\]

\[
\dot{Q}_F = \frac{49.0 \text{ mm.}}{4.95} = 1.91 \text{ L./min.}
\]

\[
\dot{Q}_R = \frac{49.0}{17.5} \times 1.284 - 1
\]

Figure 2

Measurement of mitral regurgitation by the upstream sampling method using continuous infusion of indicator. All abbreviations are as defined in the text and used in figure 1. The onset of continuous infusion into the left ventricle is 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 LA curves above their respective base lines. In this patient, total flow = 6.86 L/min and the regurgitant fraction = 27.8%.

Techniques, and the angiographic grade of severity of mitral regurgitation was expressed by the correlation ratio, \( \eta \), which is applicable whether or not the relationship is linear.\(^{23} \)

Results

The results of this study are illustrated in tables 1 and 2 and figures 4 through 6.

Measurements of Mitral Regurgitation During Continuous Indicator Infusion

Mitral regurgitant flow, based on the mean of the two or more measurements for each of the 19 patients, ranged from 0.22 to 32.46 L/min. Total mitral valve flow ranged from 4.17 to 37.82 L/min and the regurgitant fraction of total mitral valve flow from 4.9% to 85.6%. Regurgitant stroke volumes as small as 1 ml per beat were detected, indicating the sensitivity of the method. The error of estimate at 95% confidence limits was 14.1% for \( \dot{Q}_F \), 40.8% for \( \dot{Q}_R \), 22.1% for \( \dot{Q}_T \), and 24.8% for \( \dot{Q}_R/\dot{Q}_T \). None of the measurements was mathematically impossible or physiologically incredible. The mean errors of estimate for patients with normal sinus rhythm did not differ significantly from those with atrial fibrillation.

Comparison of Continuous-Infusion and Sudden-Injection Techniques and of Both with Cinefluorography

Although mean values by the two techniques for \( \dot{Q}_R \), \( \dot{Q}_T \), and \( \dot{Q}_R/\dot{Q}_T \) did not differ significantly, measurements obtained by the sudden-injection technique were clearly less reliable (figs. 4 through 6 and table 2). The
### Table 1

**Measurements of Mitral Regurgitation by the Upstream Sampling Method: Comparison of the Sudden-Injection and Continuous-Infusion Techniques**

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Measurements of Regurgitation

Abbreviations: BSA = body surface area, in m²; Cine = cinefluorographic grade of the severity of mitral regurgitation; H.R. = heart rate, in beats/min; $Q_F$ = effective forward flow, in L/min; $Q_R$ = regurgitant flow, in L/min; $Q_T$ = total mitral valve flow, in L/min; and $\frac{Q_R}{Q_T}$ = regurgitant fraction of total mitral valve flow expressed as a percentage.

*Patients with atrial fibrillation; all others had a regular sinus rhythm.
mean error of estimate at 95% confidence limits was 27.2% for \( Q_F \), 99.6% for \( Q_R \), 58.0% for \( Q_T \), and 51.3% for \( Q_R/Q_T \). In addition, several measurements using sudden injections were mathematically absurd or physiologically incredible. Examples of the former are two of the six measurements in patient S.E., in which \( A_t/A_r \) was less than one, yielding a \( Q_R \) exceeding \( Q_T \); examples of the latter are the total flows of 95 L/min in one of S.E.’s measurements and of 100 L/min and 544 L/min in the two measurements in patient F.A. In figure 4, the good agreement between sequential measurements for the continuous-infusion technique and the poor agreement for the sudden-injection technique is illustrated for measurements of \( Q_R/Q_T \). Measurements using sudden injections were no more

### Table 2

<table>
<thead>
<tr>
<th>Sudden injection</th>
<th>Error of estimate at 95% confidence limits</th>
<th>Continuous infusion</th>
<th>Error of estimate at 95% confidence limits</th>
</tr>
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<tbody>
<tr>
<td>( Q_F )</td>
<td>2.46—6.53 L/min</td>
<td>2.61—6.03 L/min</td>
<td>14.1%</td>
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<td>( Q_R )</td>
<td>0.30—316.66 L/min</td>
<td>0.22—32.46 L/min</td>
<td>40.8%</td>
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<tr>
<td>( Q_T )</td>
<td>3.32—322.05 L/min</td>
<td>4.17—37.82 L/min</td>
<td>22.1%</td>
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<td>( Q_R/Q_T )</td>
<td>3.2—96.8%</td>
<td>4.9—85.6%</td>
<td>24.8%</td>
</tr>
</tbody>
</table>

Abbreviations are as in table 1.
MEASUREMENT OF REGURGITATION

Figure 4

Reproducibility of measurements by the upstream sampling method: Comparison of continuous-infusion and sudden-injection techniques for measurements of $\dot{Q}_R/\dot{Q}_T$. Each measurement of $\dot{Q}_R/\dot{Q}_T$ in each patient (observation x) is plotted against the measurement that immediately followed (observation x + 1). The errors of estimate at 95% confidence limits are 51% and 25% for sudden injection and continuous infusion, respectively.

Comparison of the quantitative measurements of mitral regurgitation by the two upstream sampling techniques with semiquantitative estimates obtained by mitral valvulography (figs. 5 and 6) demonstrates the superior correlation of results obtained with continuous infusions (eta = 0.98) over those obtained with sudden indicator injections (eta = 0.92). The greater scatter among multiple measurements in individual patients and the marked overlap between radiographically distinct grades for the sudden-injection technique (fig. 5) are in striking contrast to the small scatter and appropriately small overlap obtained with the continuous-infusion technique (fig. 6). Moreover, a number of measurements of the regurgitant fraction using the sudden-injection method were clearly not compatible with cinefluorographic estimates. Measurements of the regurgitant fraction by the continuous-infusion technique were compatible in every instance. Mild mitral regurgitation was equivalent to a regurgitant fraction less than 20%; moderate regurgitation to a fraction of 20 to 40%; moderately severe

erratic in patients with atrial fibrillation than in those with regular sinus rhythm.

Figure 5

Relation between measurements of $\dot{Q}_R/\dot{Q}_T$ by the upstream sampling method and semiquantitative estimates by angiography: Results using sudden injections of indicator. The different symbols over a given angiographic grade represent individual patients; the repetition of a symbol over that grade represents the replicate measurements in that patient.

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regurgitation to a fraction of 40 to 70%; and severe regurgitation to a fraction greater than 70%.

For the entire group of 19 patients, mean $Q_F$ obtained with sudden injections into the left ventricle significantly exceeded mean $Q_F$ obtained with continuous infusions (mean difference = +0.26 L/min, $P < 0.05$). In 17 instances, both of these were compared with $Q_F$ obtained from arterial dilution curves following sudden injections into the pulmonary artery. All three measurements were made at similar heart rates and over a period of less than 15 minutes. Measurements of systemic flow during the continuous infusion of indicator into the left ventricle exhibited excellent agreement with those obtained from arterial dilution curves following sudden injection into the pulmonary artery (mean difference = +0.04 L/min, $P < 0.7$). However, forward flows obtained with sudden injection into the left ventricle significantly exceeded those obtained after pulmonary artery injection (mean difference = +0.39 L/min, $P < 0.01$).

Table 2 summarizes the unequivocal superiority of the continuous-infusion technique over that of sudden-indicator injection. Despite the statistically insignificant difference between the mean values for $Q_R$, $Q_T$, and $Q_R/Q_T$ by the two techniques, the range of values for replications was strikingly smaller for the continuous-infusion technique and, on the assumption that all variations were due to error, the percentage error of estimate at 95% confidence limits, for all four variables, was approximately half that for the sudden-injection technique.

**Discussion**

Many methods have been proposed for the hemodynamic assessment of mitral regurgitation. Some of these are semiquantitative. Others, which attempt quantification, have been shown merely to reflect changes in mixing and to be invalid as measurements of backflow. Only three techniques are valid and potentially quantitative: (1) the peeling of downslopes of aortic or ventricular dilution curves after ventricular dye injection, as described by McClure and co-workers; (2) quantitative angiography, as employed by Sandler and co-workers; and (3) the upstream sampling method. The method of McClure and associates is theoretically sound and has been shown in our laboratory to be empirically valid in a limited series of patients. However, its stringent mixing and recording requirements have precluded our reliance on its application as a quantitative technique. Quantitative angiography presents certain major difficulties which we have previously pointed out in connection with aortic regurgitation.

The principal limitation to the upstream sampling method, as shown previously and in the present study, is the poor reproducibility of measurements when dye is introduced into the left ventricle by sudden injection. The results of this study demonstrate that an appreciable improvement is effected by substituting continuous infusions for sudden injections. This improvement, we believe, results in large part from a specific advantage of continuous infusion over sudden injection, inherent in the methodology itself, pertinent to all measurements by indicator dilution, and independent of considerations of mixing. This advantage, as Zierler has pointed out and,
as we have discussed in reference to aortic regurgitation, consists of less vulnerability to error in the presence of inconstant forward and regurgitant stroke volumes.

However, the improvement achieved by substituting continuous infusions for sudden injections is substantially less in mitral regurgitation than in aortic regurgitation. This limitation, we believe, is related to the problem of unrepresentative sampling in the presence of incomplete mixing in cardiac chambers. As Levinson and associates have pointed out, complete mixing is not actually essential to the method. The fundamental requisite is that the masses of dye sampled from the ventricle by atrium and aorta, and the masses of dye sampled from the atrium by left ventricle and by the atrial catheter, be proportional to the volumes of blood sampled. Such proportionality is assured by complete mixing but is achievable in its absence by random distribution and representative random sampling. However, representativeness of sampling is a function of the ratio of sample size to population size. Thus, if forward and regurgitant flows are not small in relation to atrial and ventricular volumes, randomization of mixing and of sampling will fortuitously provide representative samples of ventricular dye to atrium and aorta and of atrial dye to the ventricle. However, the samples (flows) obtained through atrial catheters are small in relation to the populations (left atrial volumes) sampled. Thus, an additional advantage of continuous infusions over sudden injections may result from superior randomization of dye distribution within the left ventricle. However, since alteration of the injection mode can have little influence on events taking place in the atrium, a definite ceiling to improvement results from the limitation in atrial sampling.

This analysis indicates that the principal source of error lies in unrepresentative sampling from the left atrium in the presence of incomplete mixing of indicator with blood. The conclusion is supported by the data of Sinclair and co-workers who, in dogs with surgically produced mitral regurgitation, demonstrated that the timing and location of sudden injections into the left ventricle had little effect on the reproducibility of measurements, but that the results were profoundly influenced by the position of the atrial sampling catheter. In the present study, the difference in reproducibility between the continuous-infusion and sudden-injection methods is independent of atrial catheter position, since the position was not altered during the random intermingling of the two methods and corresponded throughout to the position recommended on theoretic and empiric grounds. The conclusion that the improvement effected by the use of continuous infusion results from less vulnerability to error in the presence of varying stroke volumes and from superior randomization of dye distribution within the ventricle is supported by the finding that forward flow measurements during continuous infusions into the ventricle agreed well with those obtained by sudden injections into the pulmonary artery but that forward flows measured with sudden injections into the ventricle did not.

Since mixing in the left ventricle and in the aortic root is undoubtedly superior to mixing in the left atrium, it is not surprising that the substitution of continuous indicator infusion for sudden single injection improved the reproducibility of measurements in aortic regurgitation substantially more than in mitral regurgitation. (In the former, the error of estimate at 95% confidence limits for the regurgitant fraction was reduced from 37% to 9% while the decrease in mitral regurgitation was only from 51% to 25%.) Nevertheless, this degree of improvement avoided measurements of mitral regurgitation which were mathematically absurd, physiologically incredible, or at variance with angiographic estimates of severity. Therefore, although a single measurement of mitral regurgitation, even using the continuous-infusion method, has a possibility of relatively large error, such measurements are reliable if mean values are obtained from replicate determinations.

It is of interest that the maximum left ventricular output (38 L/min) here reported for
mitral regurgitation, by upstream sampling during continuous dye infusions, is very similar to what we found for aortic regurgitation (36 L/min) on using the same method. Total flows of this magnitude should not be surprising since cardiac outputs as high as 30 L/min had been reported by Astrand and associates in male physical education students during maximum work on an upright bicycle ergometer. In addition, Binak and coworkers reported a resting cardiac output in excess of 40 L/min in a 31-year-old man with a popliteal arteriovenous fistula of 12 years' duration. It would appear that the capacity of the left ventricle to do volume work may be increased as much as tenfold by conditioning. The gradual development of severe valvular regurgitation over many years is equivalent to conditioning of the heart muscle to progressive volume loading without the necessity for an increase in total body oxygen requirements or a need for conditioning of skeletal muscle.

Conclusions

We believe that the superiority of the continuous infusion method results from a lesser vulnerability to error in the presence of varying forward and regurgitant stroke volumes and from superior randomization of dye distribution within the ventricle. However, since alteration of the injection mode can have little influence on atrial events, a definite ceiling to improvement results from limitations in atrial sampling. Thus, although the substitution of continuous infusions for sudden injections eliminated manifestly incorrect results and yielded a significantly improved reproducibility, the mean error of estimate at 95% confidence limits for a single measurement of the regurgitant fraction (±25%) was about three times larger than was the case when the continuous-infusion method was used in aortic regurgitation.

It must, therefore, be concluded (1) that a single measurement of mitral regurgitation by upstream sampling has a probability of large error, (2) that considerably more reliable estimates are obtained by employing continuous infusions in place of sudden injections, but (3) that measurements using continuous infusions can be considered reliable only if mean values are obtained from replicate determinations.

Acknowledgment

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Measurement of Mitral Regurgitation in Man by the Upstream Sampling Method Using Continuous Indicator Infusions

MARTIN J. FRANK, MANOUCHEHR NADIMI, KHALDOON I. HILMI and GILBERT E. LEVINSON

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