Quantitation of Valvular Regurgitation from Multiple Indicator-Dilution Curves

By Ramon L. Lange, M.D., and Hans H. Hecht, M.D.

Dye-dilution curves obtained simultaneously from the pulmonary artery and from the femoral artery following an intravenous injection of T 1824 or Indocyanine Green in normal subjects and in patients with nonregurgitant heart disease yielded a similar contour. This suggested that in the absence of regurgitation the parameters of the distal (arterial) curve can be predicted from the proximal (pulmonary artery) curve. The distortion of the arterial curve by regurgitation can therefore be compared with the undistorted pulmonary artery curve. To the extent that 2 identifiable and measurable flow rates exist between the sites of sampling, a theoretical basis for quantitation of the degree of valvular regurgitation may be derived.

Severe instances of pure stenosis and pure regurgitation can usually be recognized with little equivocation by clinical methods. However, the diagnosis of "predominance" of one type of valvular deformity over the other is of considerable practical importance when surgical intervention is contemplated, since clinical findings may be misleading. Some examples of pure stenosis may even appear with signs commonly associated with regurgitation. The combined use of right heart, left heart and aortic catheterization has permitted a precise analysis of pure obstructive valvular disease, but equally satisfactory methods for the estimation of valvular regurgitation are not as yet available.

Few quantitative attempts to estimate aortic incompetence in man have been made. The procedure of Braunwald and co-workers and that of Warner and Toronto are the only recent attempts to assess aortic regurgitation. For mitral insufficiency, several approaches have been tried: 1. Attempts have been made to correlate the size of the left atrial (LA) or pulmonary wedge (PA-W) pressure pulses with the degree of regurgitation, and the detailed aspects of one or the other of the recorded parameters of the contour of the pressure curve have been used. In some instances vasoconstrictor drugs, which are said to unmask or to accentuate apparent diagnostic changes in pulse form, have been used in addition. Data obtained in this way, however, have in general been unreliable because information concerning (a) the forward nonregurgitated flow and (b) the volume of the receptacle into which regurgitation occurs has not been available.

2. On the other hand, shunting of blood away from the forward path in examples of congenital heart disease has been quantitated by the use of indicator substances whose path could be traced within the central circulation. Empirical analysis of such curves has allowed a certain quantitation of left-to-right shunts that agrees with estimations made from blood gas analyses and oxygen consumption. If congenital "regurgitation" of atrial, ventricular or great vessel defects is qualitatively similar to acquired regurgitation, the same general concept should apply in an analysis of the latter. Attempts have been made in the case of mitral regurgitation to obtain quantitation by injecting an indicator substance into the left ventricle through a trans-thoracic puncture, left atrial blood being sampled simultaneously. It was thought that the retrograde appearance of any indicator, before recirculation, should be proportional to the amount of blood regurgitated. This method is sensitive to the catheter position within the ventricle, and therefore the as-


**Table 1.—Normal or Nonregurgitant Heart Disease**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Degree of heart failure</th>
<th>Chamber enlargement</th>
<th>$\Delta MCT$ (sec.)</th>
<th>$\Delta AT$ (sec.)</th>
<th>$\Delta T$ (sec.)</th>
<th>Qr L/min.</th>
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<td>AS</td>
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<td>LA, 2+</td>
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<td>11.0</td>
<td>1.0</td>
<td>4.7</td>
</tr>
</tbody>
</table>

*Dye injection into right atrium.

**METHODOLOGY**

**Human Subjects**

The experiments were carried out on 9 normal subjects, 6 patients with heart disease and no

**METHOD**

**Human Subjects**

The experiments were carried out on 9 normal subjects, 6 patients with heart disease and no
regurgitation, and 31 patients with valvular regurgitation (tables 1 and 2). The observations were made with the patient in a steady resting state, and net forward cardiac output \( (Q_F) \) was determined by the Fick principle with use of oxygen consumption and oxygen arteriovenous difference, and by dye-dilution curves in the usual manner, but with direct recording cuvet oximeters.\(^2\) Pressures were recorded by means of an optimally damped catheter strain gage system. A catheter remained in the pulmonary artery (PA) throughout the test period. Three to 5 ml of a 1 per cent solution of T 1824 \(^\circ\) were injected and "flushed" into a peripheral vein (occasionally into the superior vena cava or right atrium) during a period not exceeding 1 second. Simultaneous sampling from the catheter and from a needle in a femoral artery was accomplished by means of a device that moved the plungers of matched 50-ml syringes in tandem by a constant-speed motor-driven worm-gear drive at 0.5 to 1.0 ml per second (fig. 1). The blood was drawn through equisensitive direct-recording Wood oximeters. The procedure was generally duplicated and bracketed between Fick output determinations. The catheter transit time for blood was measured separately.

In the carrying out of these procedures several additional points had to be considered. 1. The presence of reduced hemoglobin in the PA sample could distort a dye-dilution curve when compared with the fully oxygenated arterial sample. When tracings with uneven baselines were rejected this was found to be not a significant factor. Several PA samples obtained with Iodocyanine Green ("Cardio-Green"), \(^2\) a substance with infrared absorption, independent of hemoglobin concentration, yielded identical data. 2. "Smearing" of the PA dye curves sampled through a long catheter, as compared to a femoral sample obtained by needle puncture, was found to be negligible when sampling was accomplished through the syringe puller. This was tested in several experiments on dogs with the equipment described above. No difference could be seen in dye-dilution curves sampled in this manner through catheter or needle (fig. 2). 3. Skewing of dye curves due to the distorting effects of the peripheral arterial vascular bed\(^2\) was avoided by sampling from the femoral artery exclusively and disturbing flow as little as possible.

Model Experiments

The observations on human subjects were complemented by models in an attempt to construct a simple system yielding similar dye curves. The model consisted of 2 "ventricles" with a matched pulsatile flow provided by a Sigma finger pump. The dye mixture was injected proximally to the right ventricle and arrived well mixed. Simultaneous sampling from the right and from the left ventricular outflow was accomplished by using the same oximeter sampling device discussed above. Single or multiple connections between the 2 chambers constituted "the lung." Left ventricular "regurgitation" was produced by increasing the left ventricular stroke volume and allowing the excess volume to recirculate (fig. 7). For reasons to be discussed, the proximal sample was taken as close as possible to the regurgitant system.

\(^*\)Courtesy of Warner-Chilcott Laboratories.

\(^2\)Courtesy of Hynson, Westcott, & Dunning.
RESULTS

Observations on Normal Subjects, on Patients with Nonregurgitant Heart Disease, and on Models.

With use of the technic described above, an interesting similarity involving all parameters of the curves could be demonstrated in all 9 normal subjects and in 6 patients with heart disease but without regurgitation. The similarity was observed to be independent of chamber size, cardiac output, or the presence of congestive failure (table 1, fig. 3). The well-known difference in the appearance of a congestive failure curve with that of a normal dye-dilution curve was, of course, recognized, but this was present to an equal degree in the PA sampled and femoral artery (FA) sampled curves (fig. 3).

When in the model an attempt was made to simulate conditions that would yield a set of nearly identical curves, it was noted that only a direct connection, consisting of a single tube between right and left ventricle, would reproduce such curves. The model and data from a single tube "lung" experiment are reproduced in figures 4 and 5.

The observations of human subjects without regurgitation, and of the nonregurgitant model demonstrating near identity of the curves, strongly suggest that all pathways between the 2 sampling sites are traversed with essentially equal speed. Thus the time it takes for any given particle of dye to travel from one site to the other would be similar and the points on the 2 curves that define this particle would occupy the same relative position on each curve.

Fig. 2. A series of single arterial dilution curves sampled by needle (N) and catheter (C) from same site. Rate of sampling is of order usually used. Note absence of effect on C curve due to catheter passage.

Fig. 3 Top. Unretouched dye-dilution curves in young normal resting adult male (subject no 5 of table 1), sampled from pulmonary artery (PA) and femoral artery (FA). Note similarity in all parameters of 2 curves. Sampling rates cause delay in inscription of PA curve of 4 seconds due to volume of catheter sampling system. "True" PA curve corrected for delay in catheter system is indicated by dashed line. In subsequent figures curves are corrected by adjustment of the "injection time" forward by an interval equal to the catheter delay. The disappearance slopes (in8) of the 2 curves are nearly identical. Bottom. Curves obtained as in A from 56-year-old man in heart failure due both to emphysema heart disease and to arteriosclerotic heart disease with generalized chamber enlargement (patient 10, table 1). Despite longer passage time of both curves, delay of disappearance of slopes, and absence of a discrete recirculation deflection, relationships are similar to normal subject (A) and both curves are nearly identical.
QUANTITATION OF VALVULAR REGURGITATION

Fig. 4. Diagram of a hydraulic model of 2 ‘‘ventricles’’ in series. The lung is a single tube. Curves from ‘‘PA’’ and ‘‘arterial’’ sites are traced. $S.V.$, stroke volume; $C.O.$, output; $Q_f$, forward flow; $Q_r$, total flow.

Selecting arbitrarily (a) the shortest observed transit time of dye particles, characterized by the beginning of the inflection of the 2 curves and designating these ‘‘appearance times’’ as $\Delta T_{PA}$ and $\Delta T_{FA}$ respectively, and (b) designating the average particle circulation time that elapses between all points as ‘‘mean circulation time’’ $MCT_{PA}$ and $MCT_{FA}$ respectively, we find that in the normal subjects and in patients without regurgitation the 2 sets of measurements are nearly identical. In consequence, the differences in the 2 appearance times $\Delta T_{PA}-\Delta T_{FA}$ (henceforth to be called $\Delta \Delta T$), and the differences in the 2 mean circulation times $MCT_{PA} - MCT_{FA}$ (henceforth to be called $\Delta MCT$) are similar. The small systematic difference between these (called $\Delta T$) averaged 0.6 second (table 1). This small difference could not be correlated with any known parameter, and must be considered a characteristic of the non-regurgitant system under these circumstances. It is applied as a correction factor, as seen in table 2.

Observations on Subjects with Regurgitation and on the Insufficiency Model

Figure 6 illustrates examples of valvular regurgitation of varying severity. The difference between the 2 simultaneously recorded curves is at once apparent and contrasts with the extreme similarity of all parameters of the 2 curves in the nonregurgitant system of figures 3 and 5. As seen alone, the distal curves of figure 6 might be considered normal in the first case (top) but not in the second case (bottom). However, the distal curve in the second case, of figure 6, might be confused with that observed in severe heart failure, which it closely resembles. In both instances the distal curves can be interpreted only in the light of their deviation from the proximal curve. Table 2 summarizes the data on cases of valvular regurgitation analyzed in this manner.

The changes in the relation of the 2 simultaneously inscribed dye-dilution curves were always of a similar kind: while $\Delta AT$, the difference between the 2 appearance times, was of the same order of magnitude seen in the normal controls, the changes in $\Delta MCT$, the differences in the respective mean circulation times, were larger. This essentially describes a change in the variance and in the disappearance slope of the dye curve obtained from the regurgitant system. Observed alone and of itself, it has no apparent advantages over direct slope measurements, or the reciprocal

Fig. 5. Dye-dilution curves obtained from model of figure 4 with injection at site indicated in figure 4. Note essential similarity of PA and FA curves, which reproduces a set of tracings such as illustrated in figure 3.
thereof, as used by Woodward and co-workers\textsuperscript{15} or by Korner and Shillingford,\textsuperscript{17} except that it is measured with respect to a "predicted" curve in the same individual. However, it alone does not discriminate between effects of volume, heart failure and other related parameters. Yet from a comparison of $\Delta AT$ and $\Delta MCT$ and from the difference, $\Delta T$, a value is measured which, we believe, is primarily dependent on the regurgitant flow.

Upon introduction of a left ventricular bypass into the model, as seen in figure 7, a similar relationship can be readily demonstrated.

**Calculations**

Apparently, with use of the technics described and in the absence of regurgitation, by the time dye injected into the peripheral venous system reaches the PA, the curve inscribed is insensitive to subsequent dilution in volumes encountered in health or disease. This is not to say, however, that there is no mixing in the subsequent chambers. The observations simply indicate that the curve is not significantly changed by such further mixing.

Consider the case of regurgitation as the result of 2 extremes of flow, (a) the total flow ($Q_T$), and (b) the regurgitant flow ($Q_R$). In the intact organism, they cannot be determined directly. Recall that $Q_T - Q_R$ equals the net forward flow ($Q_F$). If any 2 can be determined the other can be calculated. $Q_F$ can be obtained by the Fick principle; therefore, if either $Q_T$ or $Q_R$ can be described in terms of $Q_F$, quantitation of the regurgitation should be possible.

The total forward flow $Q_T$ moves along the path of flow, and, since there is net forward flow, no matter how great the regurgitation, one may assume that some particles of the indicator will not be regurgitated but move along as a measure only of $Q_T$. Such a behavior characterizes the most rapid traversal possible for a given volume and is expressed by the difference in appearance times at the 2 sites, $\Delta AT$. Thus equation I:

$$\Delta AT = \frac{\Delta V}{Q_T} ; \quad Q_T = \frac{\Delta V}{\Delta AT}$$

$Q_F$, the effective net forward output ($Q_T - Q_R$), on the other hand, is characterized by the time elapsed between the passage of the centroid of the dilution curve at each site. This is simply an application of calculation of forward flow-volume relation by the technic of Hamilton and his associates.\textsuperscript{20} The measured
Quantitation of Valvular Regurgitation

Quantitative differences between the 2 curves are defined as $\Delta MCT$. Then, equation 2:

$$\Delta MCT = \frac{\Delta V}{Q_f}$$

$$Q_f = \frac{\Delta V}{\Delta MCT}$$

If one now assumes that the volume traversed by the fastest moving dye (which gave $Q_f$) is equal to the volume traversed by the average particle (which gave $Q_r$), the equality of $\Delta V$ in equations 1 and 2 is established. Recalling that $Q_r = Q_f - Q$, equation 3:

$$\frac{\Delta V}{Q_r} = \frac{\Delta MCT - \Delta AT}{\Delta V \cdot \Delta AT \cdot \Delta MCT}$$

which states that the ratio of regurgitant to net forward flow can be determined from the differences of 2 dye-dilution curves.

The $\Delta V$ used in these equations needs further definition because the assumed identity of $\Delta V$ in equation 1 and equation 2 may not be readily apparent. We have chosen a sample in equation 1 which escapes regurgitation; it is made up of smaller samples which may have taken various pathways (of nearly equal transit time) through a given volume between the 2 sites. The only requirement made of these particles is that they move only forward through this volume. In equation 2 the volume is the same, but the particles of indicator may traverse it only once or many times (as in regurgitation). The average traversal time yields the net forward flow through the volume between sampling sites. There is no reason why $\Delta V$ should not be the same in both equations.

These calculations allow a quantitative expression of the regurgitation in per cent of the forward flow. The model demonstrates that these calculations agree well with a known degree of shunting under the circumstances (fig. 7). Table 2 and figures 6 and 8 have used these calculations for quantitating the degree of regurgitation in human subjects.

Discussion

The foregoing method has been developed for quantitating valvular regurgitation relatively simply with little danger to the patient and by the use of commonly available technics.

It was thought that 2 dye curves being inscribed simultaneously, one proximal and one distal to the regurgitation, the effects of flow and volume on the one hand and of regurgitation on the other could be determined separately. This method yielded the information that, once a dilution curve is established in the nonregurgitant human subject (that is to say, once passage through the first mixing chamber has occurred), the effects of subsequent chambers cannot be discerned. This constant finding in a variety of flow and volume situations, with various combinations of chamber enlargement but in the absence of regurgitation, allows the use of the proximal PA curve as an internal "control" against which the effects of regurgitation further "downstream" may be checked. The essential identity of curves sampled from PA and from a peripheral arterial site has also been noted by others.

The comparison of 2 dye curves in regurgitation then suggested that some quantitation might be possible. The ratio obtained from equation 3 cannot be tested easily in the intact organism, though correlation of estimated regurgitation at surgery was good. This is not considered as support for the method but rather a lack of adverse evidence. In 3 cases, table 2, patients 4, 7 and 13, and figure 6 (top), the degree of mitral insufficiency was thought to be minimal or virtually absent by clinical criteria, but at surgery a degree of regurgitation through the mitral valve compatible with the predicted amount was found.

It is possible to consider an individual with a left-to-right shunt within the central circulation, such as may occur in patent ductus arteriosus as a form of left ventricular regurgitation. By sampling mixed blood proximal and distal to such a shunt, the present method could be checked against shunt estimations derived by the Fick principle of using "mixed" venous blood from areas involved in the shunt
FIG. 7. Diagram of a 'regurgitation' model and dye curves obtained by this arrangement. The left ventricular bypass (50 ml./min.) represents regurgitant flow ($Q_R$). Representative dye curves are sketched below each ventricle. Lower figure. Actual dye curves from model with total flow ($Q_T$) of 250 ml./min. and measured regurgitation ($Q_R$) of 50 ml. Three sets of dye curves shown, with calculated $Q_T$ of 52, 46 and 52 ml. respectively.

vs. 'unshunted' venous blood. Two patients were selected who had uncomplicated patent ductus arteriosus and in whom mixing of shunted blood seemed fairly constant in various branches of the pulmonary artery. Dye curves were recorded from the right ventricle and from the femoral artery and also from the main PA and femoral artery. 'Regurgitation' (left to right shunt) was estimated by dye curves 60 per cent and by oxygen anal-
Fig. 8. Top curves from patient 21, table 2 with mitral stenosis and mitral insufficiency and fixed cardiac output. Comparison of PA and FA curves (upper record) show calculated regurgitation of 1.3 forward flow. Below are curves from PA and LA with presumably same cardiac output. PA curves of both records nearly identical, suggesting equal rates of net forward flow. However (lower curves) difference between LA and PA curves is much less striking than in upper tracing. The calculated $Q_R/Q_F$, however, is same in both sets because of proportionate decrease of both ($\Delta MCT - \Delta AT$) and $\Delta AT$. This supports assumption that in the regurgitant segment multiple sampling sites would show that the most rapid rate and the average rate of movement of indicator substances observe a constant ratio. Equation 3 may therefore be applied to any 2 sites in system. (Indocyanine Green, 5 mg., i.v.)

ysis 48 per cent in one, and 38 per cent and 32 per cent respectively in the second case (table 3).

Another internal check is provided if the sampling site of the distal curve is moved, for instance from LA to FA. Naturally, the appearance time $\Delta T$ is later in the FA curve than in the LA curve, and $\Delta AT$ of equation 3 will be larger. If the ratio $Q_R/Q_F$ measures insufficiency, it must remain constant, since it should not be influenced by the sampling site. $\Delta MCT - \Delta AT$ of equation 3 must therefore increase if the distal sampling site is moved farther downstream. Figure 8 indicates that this is clearly the case.

Using the method of Korner and Shillingsford, we found poor agreement with our own estimation, the method of the British investigators yielding consistently higher values for regurgitation than our own (fig. 9). The recent experimental approach of Sarnoff and his associates might offer an independent check on these methods, and will be the subject of further investigations.
Table 2.—Mitrail or Aortic Regurgitation with and without Heart Failure

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<th>Patient</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Failure</th>
<th>ΔMVT (ms)</th>
<th>ΔAT (ms)</th>
<th>ΔT (sec)</th>
<th>Qa</th>
<th>Qp</th>
<th>Qp(L) (L/min)</th>
<th>QL (L/min)</th>
<th>QL (L/min)</th>
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(Continued on next page)
The method, of course, suffers from errors possible in all dilution technics that have recently been reviewed by Dow. These mainly are related to the presence of short segments of laminar flow, the response time of the recording instrument and the possibility of alteration of flow during a given curve. Specific factors peculiar to our modification deal with the accurate recording of true appearance time at the 2 sites; conceivably the more sensitive instrument will record an earlier ΔT but this is seldom likely to be more than a fraction of a second. Equation 3 suggests that all errors in measurement diminish in importance with an increase in the absolute value of the denominator, ΔAT; thus, with high flow rates, accuracy may be less than at low flow rates. Besides, for accuracy, the nonregurgitant curve should be obtained from a site extremely close in time to the regurgitant receptacle. In the case of mitral regurgitation the PA site is probably less than a second in time from the LA, which receives the regurgitation, and therefore introduces a small systemic error which decreases as the denominator of equation 3 increases. This is insignificant, as indicated by the consistently close agreement between the fraction of regurgitation as estimated from PA and LA curves (with a ΔAT of only a few seconds) and from PA and FA curves with a ΔAT considerably increased (table 2, patients 21, 22, 25, 27, 28, 30).

In aortic regurgitation, the distance of the PA site from the regurgitant system may be more important, and either the LA should be used as the proximal site or, if this is not possible, the PA curve should be shifted for-
Two cases of patent ductus arteriosus as a special form of "regurgitation." There is reasonably close agreement between values obtained by direct blood gas analysis and the degree of "regurgitation" predicted from the dye method.

\[
\begin{align*}
Q_F & = \text{Fick output, systemic.} \\
Q_{L-R} & = \text{L - R shunt from blood gas data.} \\
Q_{F}^{\text{regurgitation}} & = \text{"Regurgitant" flow - L - R shunt by dye method.} \\
Q_P & = \text{Pulmonary flow from blood gas data. (Should equal } Q_T \text{ from dye method.)} \\
Q_T & = \text{Total flow (pulmonary flow from dye method).}
\end{align*}
\]

ward an appropriate time interval (usually 2 to 3 seconds).

The method applies equally well to mitral and aortic regurgitation, although, in the latter, proximal sampling from LA seems preferable to sampling from the PA site (for reasons mentioned). There is some information also concerning the differential quantitation of simultaneous mitral and aortic regurgitation. For this, 3 dye curves obtained from PA, LA and FA are needed. The difference between PA and LA curve indicates the degree of mitral, the difference between LA and FA, of aortic incompetence. Further data, however, are needed to clarify these relationships. Patient 28, table 2, is an example of such a case.

**Summary**

1. A method has been described that attempts to quantitate valvular regurgitation on the basis of 2 simultaneously recorded dye-dilution curves, one sampled from the pulmonary artery and one from the arterial circulation.

2. With this technic in normal subjects and in patients with heart disease without regurgitation, the 2 curves are nearly identical in spite of the variable volume present between the proximal and distal sampling sites.

3. In regurgitation, the distal curve is altered, and by comparing the differences in

---

**Table 3.—Patent Ductus Arteriosus**

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<tr>
<th>Patient</th>
<th>Name</th>
<th>Dye Qr/QF</th>
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<th>QL-R</th>
<th>Q&quot;r&quot;</th>
<th>Qp</th>
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</table>

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**Fig. 9.** 31 cases of single or multiple left-sided valvular regurgitation. In mitral insufficiency total left ventricular output \( Q_r \) seldom over 7 L./min, although \( Q_e/Q_r \) may exceed unity. This in contrast to results obtained by Korner-Shillingford application to similar group reported by Dexter and co-workers.\(^7\) \( Q_r \) in aortic insufficiency is quite large, although \( Q_e/Q_r \) is relatively small in this group.
appearance times and in mean circulation times in the 2 curves the ratio of regurgitant to nonregurgitant flow may be obtained.

4. The calculated value agreed with surgical estimations and other independent internal checks. A simple hydraulic analog demonstrated that the calculated values agreed with the known forward and regurgitant flow.

5. The method is simple and appears adequate to separate mitral from aortic regurgitation when these occur in combination.

ACKNOWLEDGMENT

The authors are particularly indebted to Mr. Robert P. Carlisle for his invaluable technical assistance.

SUMMARIO IN INTERLINGUA

1. Es descrive un metodo que viso a quantitare le regurgitatio valvular super le base del registration simultanee de 2 curvas de dilutio tinctural, le un ab le arteria pulmonar e le altere ab le circulation arterial.

2. In subjectos normal e in subjectos con morbo cardiaca sin regurgitatio le curvas producute per le metodo es quasi identice in despecto del differentias de volumine inter le sito proximal e le sito distal.

3. In casos de regurgitatio, le curva distal es alterate, e per comparar le differentias inter le 2 curvas quanto al tempore del apparition e quanto al tempore circulatori medi, il es possibile obtenere le proportion inter le fluxo regurgitante e le fluxo non-regurgitante.

4. Le valores assi calculate se trovava de acordo con estimationes chirurgica e con altere independente estimationes interne. Un simple analogo hydraulico demonstrava que le valores calculate essava de acordo con le cognosita magnitude del fluxo in avante e del fluxo regurgitante.

5. Le metodo es simple e pare esser adequate pro separar regurgitatio mitral ab regurgitatio aortic quando le duo occurre in combination.

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Quantitation of Valvular Regurgitation from Multiple Indicator-Dilution Curves
RAMON L. LANGE and HANS H. HECHT

Circulation. 1958;18:623-636
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