Quantitation of Aortic Valvular Insufficiency Using Radioactive Tracers: An Experimental Study In Vitro

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An Experimental Study In Vitro

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A method has been developed in vitro *for quantitation of aortic valvular insufficiency (AI) based on the use of radioactive tracers to generate graphic recordings of the movement of blood out of the ventricle and back again. The regurgitant fraction of stroke volume (percent of AI) is read from this recording. The method was evaluated in a mechanical heart model by comparing AI values read from the istope recordings and AI values determined volumetrically. The recordings gave excellent agreement with the volumetric results (Corr. Coeff. .9). These* in vitro *results are of such quality that clinical trials seem justified.*

Although aortic valvular insufficiency (AI) can usually be detected by physical examination and phonocardiography, crude estimates of its extent can be obtained by simple angiographic procedures. [1,2] Quantitative measurements are possible, although cumbersome, with indicator dilution techniques [3-13] and biplane angiocardiography. [14,15] In recent years, the need has grown for a simple, safe but accurate method of measuring AI because of the advent of surgical techniques which require preoperative knowledge of the amount of AI.

Our study introduces such a method. It was undertaken to develop a method of quantitation of AI which would surpass other routine clinical methods in safety, ease of performance and accuracy. It is similar in principle to that introduced by Folse and Braunwald[16] for the measurement of ventricular end-diastolic and end-systolic volumes. Radioactive material is injected into the left ventricle, and a detector over it observes the subsequent ejection and regurgitation of the blood containing the radioactivity. The ratio between the rise in activity during regurgitation and the preceding decline during systole is then equal to the amount of AI, expressed as a percent of stroke volume. No other measurements, such as cardiac output, are necessary.

Principle of the Method

Radioactive tracer is introduced into the left ventricle at some time during diastole, either by direct injection into the left ventricle or by injection just distal to the aortic valve with subsequent backflow. Over a span of several heart beats, a detector placed over the precordium measures the activity in the

entire ventricular volume on a fast (0.05 to 0.1 second) time scale. A graphic record of the count-rate *vs* time is obtained on a strip chart recorder.

To illustrate how we can read the ratio of regurgitated volume to stroke volume (ie, the percent regurgitation) directly from such a recording, we may adopt a highly simplified picture of the heart in which we assume

(1) that the tracer is uniformly mixed in the ventricle by the time each systole occurs,

(2) that all regions of the ventricle are counted with about the same efficiency,

(3) that this efficiency is not substantially altered during the heart cycle by motion of the heart or changes in the amount of intervening tissue,

(4) that counting of both direct and scattered radiations originating outside the ventricle can be avoided,

(5) that there is not extensive aortic mixing of the blood ejected during systole with blood already present in the aorta, and

(6) that there is no retention of tracer on the ventricular walls.

Given the above idealization and a normal aortic valve, the variation of count rate during several beats is as shown in Figure 1. The tracer enters the left ventricle at some time (t_o) during diastole. The count-rate (which is proportional to the total amount of radioactivity in the ventricle) remains constant at A_o until the onset of systole, decreases during systole, then levels off and remains constant at A_1 throughout diastole, and begins to fall again when the next stroke begins. This stepwise washout continues, $A_2 \ldots \ldots$,

until the left ventricle is cleared of tracer. We can write:

$$\frac{B_0}{A_0} = \frac{B_1}{A_1} = \frac{B_2}{A_2} = \cdot\cdot = \frac{B_n}{A_n} = \frac{SV}{EDV} \quad (1)$$

A_n is the height (counting rate) of the $n th$ plateau, B_n is the total fall during the $n th$ systole, SV is the stroke volume, and EDV is the end-diastolic volume. In the example shown in Figure 1, SV/EDV is 0.5.

With regurgitation, the recording from the idealized heart is as shown in Figure 2. From t_o until the end of the first systole the recording is identical to that obtained from a normal heart. However, shortly after the next diastole begins, the count-rate begins to rise again as radioactive blood regurgitates into the ventricle from the aorta, and continues rising until the end of diastole. We can write:

$$\frac{RgV}{SV} = \frac{C_0}{B_0} = \frac{C_?}{B_1} = \cdot\cdot = \frac{C_n}{B_n} \quad (2)$$

Here, RgV is the regurgitated volume, SV is the stroke volume, B_n is the total fall in count-rate during the $n th$ systole, and C_n is the subsequent increase to the $(n+1) th$ peak. In the example given in Figure 2 RgV/SV is 0.5 (ie, there is 50% regurgitation), and SV/EDV is 0.5 as before. This kind of behavior has been observed and explained qualitatively earlier.[16]

It is essential to note that the only quantities that are significant are the fall (B_n) and the subsequent rise (C_n) between peaks and troughs, and not the actual peaks and troughs. (The scale of measurement of B_n and C_n is arbitrary, since one is concerned only with their ratio). Consequently, even large baseline shifts do not affect the results. In particular, a gradual increase in the background count-rate,

as recirculated blood arrives in the heart, will not introduce a systematic error even in data taken from the later heart beats. A baseline shift taking place in a very short time interval compared to one heart cycle would affect only a single B_n or C_n value. The effects of such shifts, as might occur for example with a very sudden onset of recirculation, should be detected and/ or suppressed by the usual practice of taking and averaging as many readings as possible before the curve becomes lost in the random statistical counting fluctuations.

The real heart does not warrant these simplifications, of course. It is known that mixing in the normal ventricle is incomplete.[17,18] There is certainly substantial variation of counting efficiency over the ventricular volume. The counting of radiations originating outside the ventricle (especially radiations originating from the aorta) can be effectively suppressed by suitably placed shielding, by detector placement, and by rejection of scattered radiation through energy selection. The counting of radioactivity in the coronary circulation or in recirculated blood cannot be avoided. However, the recordings can be completed in a few seconds, ie, in a short time compared to that required for recirculation, and
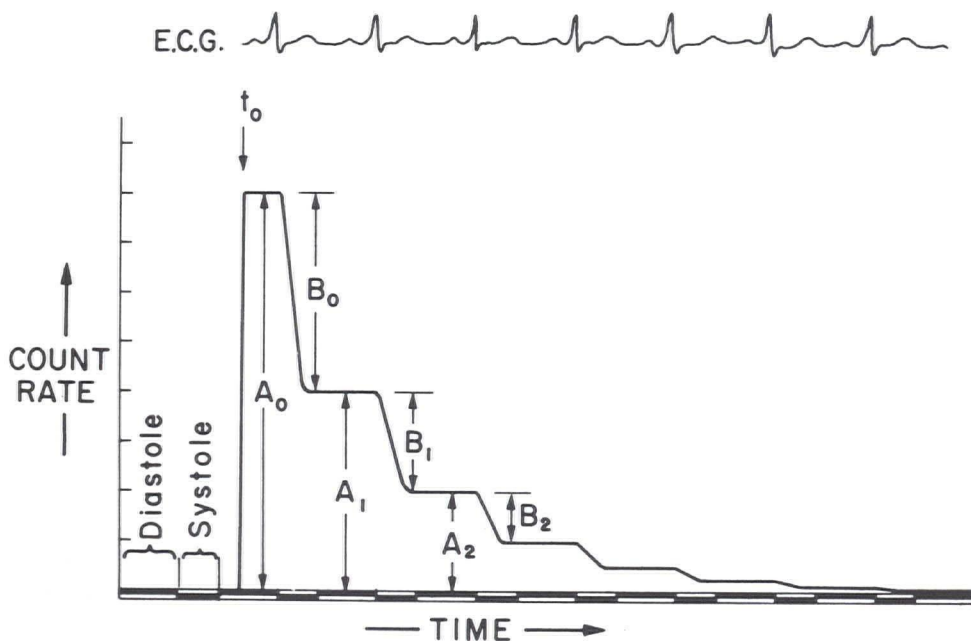
Figure 1

Representation of a recording of radioactive tracer count rate vs time, for a heart with a normal aortic valve. The radiation detector is placed over the left ventricle and tracer is introduced instantaneously into ventricle at time t_o. The ordinate is proportional to the amount of radioactivity in the ventricle. The ratios $B_o/A_o = B_1/A_1 = \ldots = B_n/A_n$ are equal to SV/EDV, ie, to the ratio between stroke volume (SV) and end-diastolic volume (EDV). This particular figure has been drawn to correspond to the case SV/EDV = 0.5. For reference, an electrocardiogram has been added along the top.
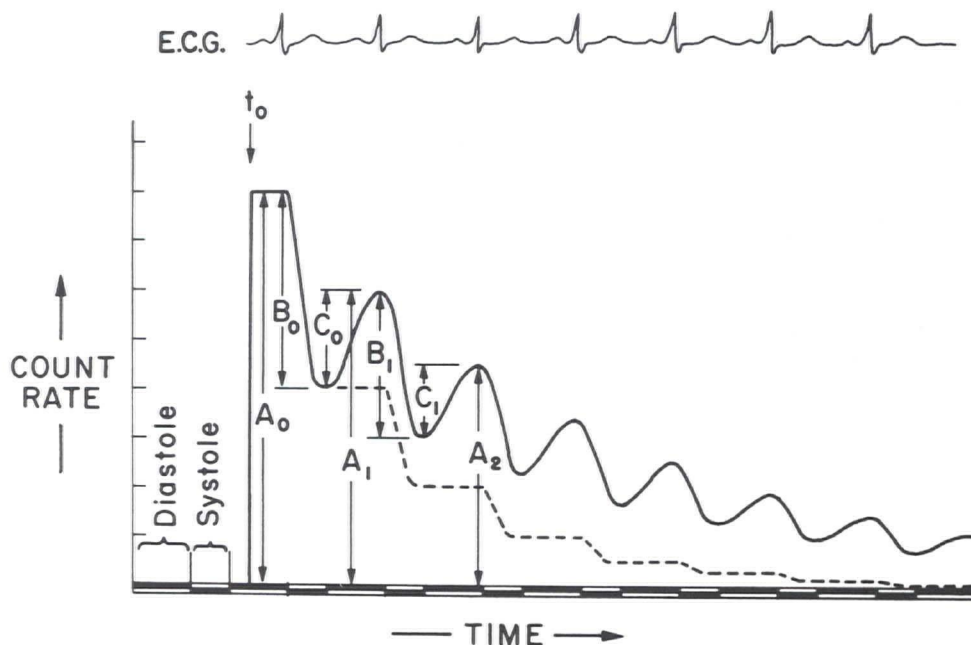
Figure 2

Idealized representation of a recording of count rate vs time, for a heart with an aortic valve through which regurgitation is taking place. Detector is placed over left ventricle and tracer is introduced instantaneously at time t_o. The ratios $C_o/B_o = C_1/B_1 = \ldots = C_n/B_n$ are equal to RgV/SV, ie, to ratio between regurgitated volume (RgV) and stroke volume (SV). This figure has been drawn to represent a case of 50% regurgitation (RgV/SV = 0.5) and SV/EDV = 0.5. An electrocardiogram has been added for reference along the top. The dashed curve is the normal-valve recording from Figure 1.

a *gradual* increase or decline of extraneous activity (gradual baseline shift) has no effect on the results.

It is known that mixing occurs in the aorta.[19] However, for the present purpose it is not necessary to assume that there is no mixing of blood ejected from the heart with blood already present in the aorta. But, it *is* necessary to assume that whatever blood is

to regurgitate should not have been mixed in the aorta. Our experiments question whether this simplified picture offers a good enough approximation to test the feasibility of the proposed method. The work of Folse and Braunwald[16] was subject to these same problems, except that of aortic mixing, and their discussion deals with several of these matters.

Experiments

Mechanical Model

The mechanical model for these experiments consisted of a pulse duplicator (Fig 3) designed to simulate left ventricular function. Basically, this was a pump composed of a piston and
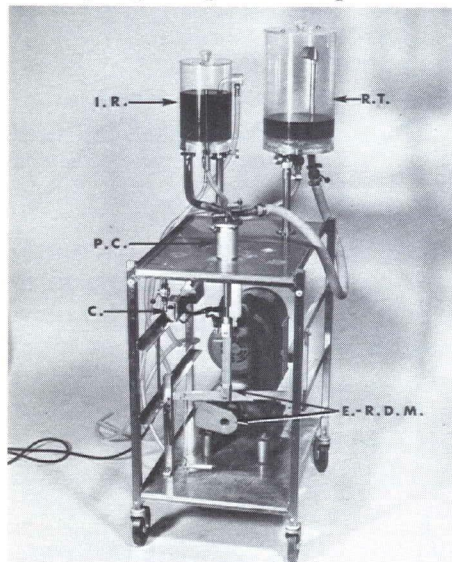

Figure 3

Pulse duplicator used for *in vitro* experiments. I.R., inflow reservoir; R.T., receiving tank; P.C., pump chamber; E.-R.D.M., engage-release drive mechanism; C., counter (mechanical register) for counting the number of machine strokes.

cylinder (left ventricle) with spring-loaded, one-way valves for inflow (mitral valve) and outflow (aortic valve). An unseating pin was incorporated into the housing of the outflow valve to make the valve "insufficient". Stopcock ports were installed in the cylinder and downstream 1 cm from the outflow valve to provide access for pressure monitoring and injection of radioactive tracer. Pulse rate, stroke volume, residual volume and degree of insufficiency were all independently adjustable over a wide

range. By proper choice of static pressure head, dimensions and elasticity of outflow hose (aorta), it was a simple matter to produce pressure curves which duplicated those in the human system (Fig 4) over the whole range of speeds, volumes and degrees of insufficiency tested.

Counting Equipment

Gamma-ray scintillation counting was employed, using as the detector thallium-activated sodium iodide [NaI(th)] crystal 1.75 inches in diameter by 2 inches thick and placed a few cm away from the pump chamber. Figure 5 shows block diagram of the instrumentation. The output pulses from the EMI 9536 phototube were sent through conventional amplifying circuitry to a single-channel pulse height analyzer, the output of which was fed into a periodic integrator (see below) whose output went into a strip-chart recorder. A scaler connected to the amplifier or the single-channel analyzer was used as an aid in making and checking settings, measuring dosage and as a general check to see that the apparatus was operating properly.

The periodic integrator designed for these experiments[20] has some advantage over that of Donato et al[21-24] in writing-speed requirements and switching speeds. The linearity of the periodic integrator output is believed to be better than $\pm$ 1% of full scale. The chief source of inaccuracy is probably the temperature drift, which is about 0.03% of full scale per 1°C temperature change.

Method

For these experiments a few microcuries of the tracer sodium-24 (as aqueous Na_2CO_3) were injected at one
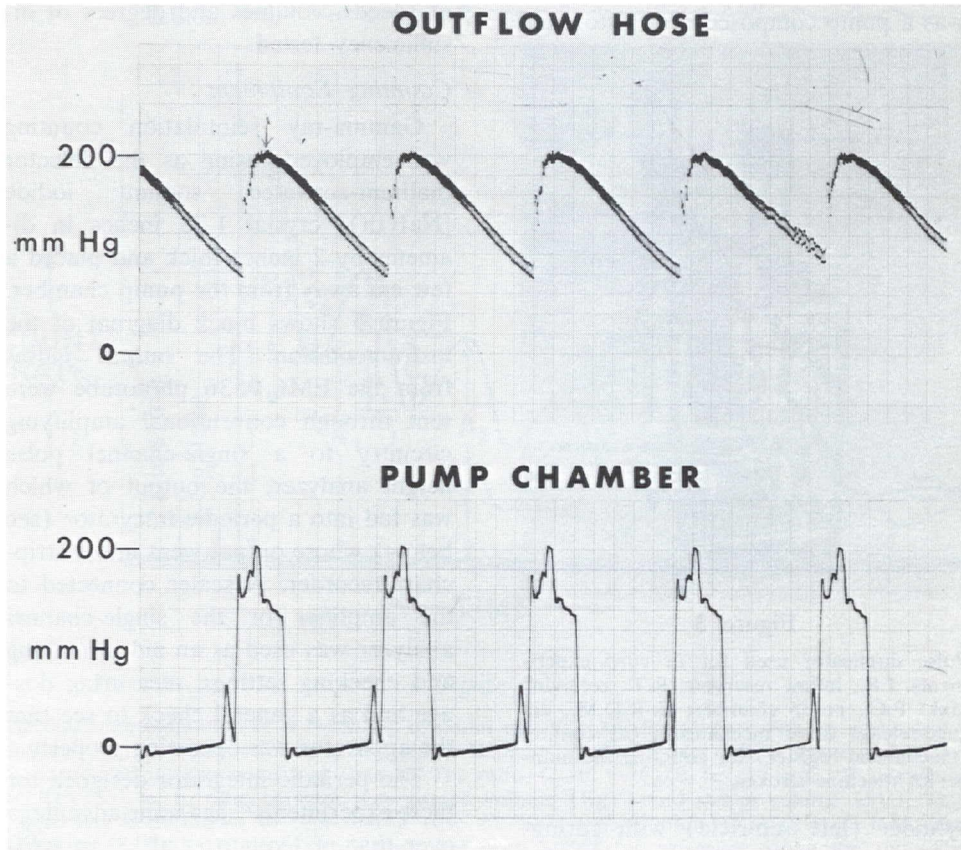
Figure 4

Representative pressure curves for outflow hose (aorta) and pump chamber (left ventricle) obtained from pulse duplicator with out-flow valve in the fully seated position and with stroke volume 87 ml. Chart speed is 25 mm per second (each heavy or fifth line being 5 mm or 0.2 second).

Figure 5

Block diagram of counting equipment. Scaler is connected to analyzer or amplifier as appropriate. Recorder trace produced by periodic integrator is represented at upper right.

of the two injection sites during early diastole or at the end of systole. Lead was used as shielding between the detector and those areas beyond the ventricle where there could be activity, particularly the aorta. The detector location was varied somewhat over the course of the experiments in order to ascertain optimum placement and the extent of the effects produced by such variations.

Each experiment consisted of two parts. (1) With the valve normal (able to seat), the output of water from a convenient number of strokes was collected and weighed, and from this the

Figure 6

Sample recording from experiment with aortic valve normal. Activity is injected into left ventricle at time t_0 indicated. Systolic and diastolic portions of cycle are denoted by symbols S and D, respectively. Note the elevated initial baseline; this represents activity in the needle in the aorta prior to injection. A rise accompanies injection as activity appears in ventricle. Sudden drop in count rate represents activity being largely removed from detector's field of view during first systole. Pump speed is 72 beats per minute. Chart speed is 50 mm per second (each heavy or fifth line being 5 mm or 0.1 second).

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stroke volume was calculated. Sometimes, while the water was being collected prior to weighing, sodium-24 tracer was injected at one of the two injection sites and a strip-chart recording was obtained of count-rate *vs* time (Fig 6). (2) With the outflow valve made incompetent (unseated), the output of water was measured again and, simultaneously, a recording of count-rate *vs* time was obtained (Fig 7) from which the *tracer* percent insufficiency was calculated, using equation 2.

Throughout each experiment all parameters remained constant except for seating of the valve. Consequently, the reduced volume delivered per stroke when the valve was unseated is the final regurgitant volume per stroke. Dividing this by the normal stroke volume (the volume per stroke delivered before unseating the valve) gives the *volumetric* percent insufficiency which is then compared for each experiment with the *tracer* per cent insufficiency.

Results

Table I summarizes the results. In these runs, injections were made both into the mechanical aorta and ventricle. Generation of a recording which reflects the washout of activity from the ventricle necessitates that some regurgitation be present if isotope is injected into the aorta. In cases where AI is mild or absent, only a small amount of activity is observed. This activity arises from scatter from the aorta or minimal reflux into the ventricle. Therefore, it is useful to know what approximate order of magnitude of activity is expected when AI is present. Then, the dose of isotope and recorder sensitivity can be roughly adjusted and

TABLE I

DATA IN VITRO

PERCENT INSUFFICIENCY

(I) VOLUMETRIC	(II) TRACER	(II-I) ERROR
0.0	6.3	6.3
0.0	7.5	7.5
0.0	-1.2	-1.2
0.0	0.0	0.0
0.0	0.0	0.0
0.0	0.0	0.0
5.6	7.3	1.7
11.5	15.9	4.4
18.1	13.5	-4.6
24.0	22.8	-1.2
31.9	31.5	-0.4
33.0	21.5	-11.5
35.2	29.2	-6.0
42.4	33.4	-9.0
43.8	35.0	-8.8
44.6	46.8	2.2
45.5	40.3	-5.2
45.4	53.6	8.1
49.0	44.5	-4.5

$$\frac{\sum (II-I)}{19} = -1.2$$

$$\left[\frac{\sum (II-I)^2}{18}\right]^{\frac{1}{2}} = 5.7$$

Table I

Data from experiments performed through the use of a mechanical pulse duplicator. Values given are regurgitant flow expressed as a percent of stroke volume. *Volumetric per-cent insufficiency* represents regurgitant flow measured from output of a mechanical pulse duplicator. *Tracer percent insufficiency* represents experimental results obtained from isotope dilution curves. *Error* is the arithmetical difference between the volumetric and tracer values.
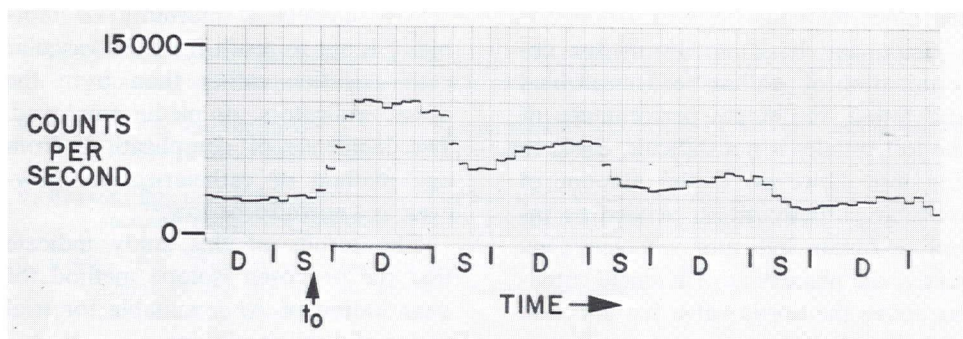
Figure 7

Sample recording from experiment with aortic valve insufficient. Activity is injected at time t_o into aorta and enters ventricle with onset of diastole. Counting rate arising from radioactivity in needle just prior to injection can be seen at left. Systolic (S) and diastolic (D) portions of cycle are denoted by symbols. Initial rise signifies activity being swept into ventricle as part of the regurgitant stream. Wave pattern is seen to be the same as that predicted for the idealized case (Fig 2). Pump speed is 72 beats per minute. Chart speed is 50 mm per second (each heavy or fifth line being 5 mm or 0.1 second). Periodic integrator period is 0.05 seconds. AI read from this recording, using equation 2, is 37%.

total runs kept at a minimum. Injection of isotope into the ventricle provides good recordings, even when no AI is present and allows easy standardization of total dose. The first six entries of Table I show what happens when this is ignored. In the three earliest ones, spurious results were obtained, partly because of improper detector placement. The next three readings indicate that correct results (AI=O) can be obtained with proper alignment, even on recordings generated by spurious radiation. Nevertheless, because of the poor counting statistics and relatively prominent secondary effects, injection directly into the ventricle would be preferable for measuring AI when it is small or absent.

On the average, the *tracer* insufficiency reads 1.2% lower than the *volumetric* insufficiency, without significant dependence on the level of insufficiency. The standard deviation is 5.7%. The best (least-squares) straight-line fit to the data is:

$$T = 1.81 + 0.87\,V \quad (3)$$

Here T is the *tracer* percent insufficiency and V is the *volumetric* percent insufficiency. The correlation coefficient is 0.96 (or, if the six normal-valve cases are ignored, 0.92).

Discussion

Most methods of grading AI have not been compared with known values. Aortic valvulography, which expresses degree of AI on a 1 to 4+ scale, offers only a gross estimate. However, experimental results with known values from mechanical models have been compared in several studies.[5,10,26] Comparison of our results with these reports is difficult because of the manner in which some of their data were handled. Nevertheless, we believe that the accuracy of the tracer method pre-

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sented here equals or exceeds that of the other methods.

Once any basic apparatus for determination of AI has been assembled and tested, the actual performance of the test usually is not difficult. Basic to any test, however, is the amount of vascular catheterization needed to inject or obtain indicator samples. Certainly, the placement of a single catheter above the aortic valve for injection of radioactivity or contrast medium is less difficult than the multiple vessel-and-heart-chamber catheterization required for other indicator-dilution methods. Moreover, in ordinary indicator-dilution techniques, the timing of the injection is critical and the dosage must be accurately known. In the method described here, injection of *any* reasonable amount of radioisotope during *any* portion of diastole is adequate. Also, the interpretation of isotope recordings is not liable to the subjective interpretation inherent in contrast aortography. Both of these are also probably far easier to perform and analyze than the indicator-dilution or the biplane, angiographic, ventricular volumetric methods.

Any coincident mortality or morbidity is apt to result from the vascular catheterization rather than from the drugs, indicators, or media employed. The incidence of complications from any method of catheterization, however, is known to be low.[27]

The results of this study indicate that the proposed isotope method for quantitation of AI is suitable for trial under clinical conditions.

Acknowledgements

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