ASSESSMENT OF SEVERITY OF TRICUSPID REGURGITATION BY ANALOG COMPUTER ANALYSIS OF DILUTION CURVES RECORDED BY SCINTILLATION CAMERA

YUTAKA KONISHI, M.D., NORIKAZU TATSUTA, M.D., YORINORI HIKASA, M.D.
NAGARA TAMAKI, M.D.*, YASUSHI ISHII, M.D.*, AND KANJI TORIZUKA, M.D.*

To estimate the severity of tricuspid regurgitation, we developed a new mathematical model of the circulatory system, in which the right atrium and the right ventricle were represented by a single mixing chamber and tricuspid regurgitation was expressed as a reverse flow from the right ventricle to the right atrium with a time delay equivalent to one cardiac cycle. The actual dilution curves obtained from the right atrium and the right ventricle following rapid intravenous injection of Technetium-99m-macroaggregated human albumin were fitted to the theoretical curves based on the above-described model. The use of macroaggregated albumin avoided the contamination of the dilution curves by radio-activity from the left heart or by the recirculation of the tracer due to left to right shunt. Mean transit times and percentage of regurgitation, as given by the ratio of regurgitant flow to total outflow from the right ventricle, were determined by an analog computer.

The correlations of these results with the findings of other examinations, including contrast echocardiography, demonstrated that the present method may be useful in detecting tricuspid regurgitation and in grading its severity.

EVALUATION of the severity of tricuspid regurgitation is difficult. Angiocardiography can provide quantitative information about mitral or aortic regurgitation. With regard to tricuspid regurgitation, however, it is frequently inconclusive because right ventriculography has a potential source of artifact regurgitation due to the presence of a cardiac catheter across the tricuspid valve. Contrast echocardiography¹

and doppler echocardiography² have been shown to be useful in the detection of tricuspid regurgitation but not in determining its severity. Recently several radionuclide techniques³⁻⁵ have been reported for assessing valvular regurgitation, although these are mostly limited to the measurement of left-sided valvular regurgitation. In 1967 Kuwahara, Hirakawa and their associates⁶ proposed a mathematical model of the circulatory system and its analog simulation circuit for the quantitative analysis of radiocardiograms. Subsequently they expanded this model for the quantification of aortic regurgitation^{7,8}

With further modification of this model, we

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The Second Department of Surgery and *Department of Radiology and Nuclear Medicine, Faculty of Medicine, Kyoto University, Kyoto, Japan

Address for correspondence: Yutaka Konishi, M.D., The Second Department of Surgery, Kyoto University Hospital, Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606, Japan

have tried to quantify the severity of tricuspid regurgitation.

MATERIALS AND METHOD

A total of 25 patients with or without tricuspid regurgitation were studied and their data was compared with that obtained by physical examination, cardiac catheterization or contrast echocardiography performed within 2 to 3 weeks before or after radionuclide study. During this interval, there were no significant changes in clinical condition.

The reproducibility of this technique was examined in randomly-selected patients. First, the same dilution curves were independently analyzed by two operators. Second, two successive tests in the same patients were analyzed by one operator. The differences between these two performances were assessed statistically.

With the patient lying supine, a large-field-of-view gamma camera (Searle) with a high resolution collimator was positioned in the anterior projection and 3 to 5 mCi of Technetium-99m-macroaggregated human albumin (MAA) in a volume of less than one ml was injected into the antecubital vein, followed by 10 ml of a saline flush solution. The passage of the tracer through the heart was recorded on a 64 x 64 matrix at 10 frames/sec for 20 sec by a computer (DEC; PDP 11/60). The areas representing the superior vena cava, the right atrium and the right ventricle were selected as the regions of interest on the radionuclide angiocardiographic image, and time-activity curves of these regions were obtained. By an analog simulation technique described later, these curves were analyzed to quantify tricuspid regurgitation.

Mathematical Model of the Circulatory System

The right atrium and the right ventricle were represented as a single mixing chamber, and tricuspid regurgitation was expressed as a reverse flow from the right ventricle to the right atrium with a transport delay equivalent to one cardiac cycle (Fig. 1). As the administration of radioisotope is done by peripheral venous injection, a further assumption is necessary for the process of the injection and the transportation of the tracer to the right atrium. Therefore, the injection compartment, defined as a small mixing chamber, is added. The transportation process of the injected radioisotope through the right heart is shown by the following equations:

Fig. 1. Model of the circulatory system. Two tanks represent the right atrium (RA) and the right ventricle (RV) as mixing chambers. Tricuspid regurgitation is expressed as a reverse flow from RV to RA with a transport delay. The injection compartment is not shown in this figure.

Fig. 2. Analog computer simulation circuit for analysis of dilution curves derived from injection site, RA and RV.

Injection site (superior vena cava):

$$V_i C_i(t) = \int_0^t i(t) dt - F_i \int_0^t C_i(t) dt$$

$$i(t) = \begin{cases} I/\tau, & 0 \leq t \leq \tau \\ 0, & t > \tau \end{cases}$$

$$\int_0^\infty i(t) dt = I$$

Right atrium:

$$V_{ra} C_{ra}(t) = F_i \int_0^t C_i(t) dt - F \int_0^t C_{ra}(t) dt + K F \int_0^t C_{rv}(t - \tau_R) dt$$

Fig.3. Changes of dilution curves with variations of each parameter. Influences of time required for injection (τ) and time constant (T_i) on the curve of injection compartment (superior vena cava) (upper panel). Influence of time constant (T_{ra}) on the curve of the right atrium (middle panel). Influence of percentage of regurgitation (K) on the curves of RA and RV (lower panel).

Fig.4. Analog simulation results of a patient without tricuspid regurgitation. This 22-year-old female had had surgery to close an atrial septal defect one month earlier. No sign of tricuspid regurgitation was found at operation. MTT = mean transit time; PR = percentage of regurgitation.

Right ventricle:

$$V_{rv}C_{rv}(t) = F \int_0^t C_{ra}(t)dt - F \int_0^t C_{rv}(t)dt$$

In these equations, subscripts i, ra and rv denote the injection compartment, the right atrium and the right ventricle, respectively. I , $i(t)$ and τ represent the total amount of injected tracer, injection speed and time required for injection, respectively. V is an equivalent mean volume of each compartment, and $C(t)$ is the concentration of radioisotope in each compartment at time t . The mean blood flow in the right heart is represented by F , and the flow back from the right ventricle to the right atrium is represented by

TABLE I REPRODUCIBILITY OF THE METHOD

Parameter	Curve-fittings by two operators, A and B (n = 10)		Two successive examinations* analyzed by one operator (n = 5)	
	Correlation coefficient	B/A × 100 (mean ± SD)	Correlation coefficient	2nd/1st × 100 (mean ± SD)
Mean transit time				
Right atrium (RA)	0.991	102.8 ± 12.6	0.893	126.6 ± 26.2
Right ventricle (RV)	0.951	103.2 ± 12.8	0.944	131.8 ± 28.3
RA/RV ratio	0.959	100.8 ± 16.3	0.983	97.2 ± 13.8
Percentage of regurgitation	0.974	98.2 ± 12.4	0.983	102.8 ± 12.3

* Two examinations were performed with an interval of 2 to 3 weeks because the use of macroaggregated human albumin made it difficult to do the two successive trials in a short period. The great difference of mean transit time between the 1st and 2nd examinations was probably due to the difference of the cardiac output (blood flow) between the two performances. The ratio of RA to RV which should be constant showed reasonable agreement.

Correlation coefficients in the left column are highly significant ($p < 0.001$), and in the right column are also significant ($p < 0.05$).

TABLE II COMPARISON OF DATA OF SIMULATION METHOD WITH THOSE OF OTHER EXAMINATIONS

Case No.	Diagnosis (Operation performed)	% of TR by simulation method	Contrast echocardiography for TR	TR at operation	Murmur suggestive of TR	CTR	Hepato-megaly (cm)	RA mean pressure (mmHg)
1	(MVR+TAP)	70	+	+++	+	0.81	5	18
2	MVD	60	+	+++	+	0.74	5	27
3	MVD+ADV	55	+	++	+	0.66	3	
4	MVD	50	+	++	+	0.67	6	14
5	ASD	50	+	++	+	0.68	3	22
6	MVD	45	+	++	+	0.55	3	17
7	(OMC)	45	+		—	0.71	5	
8	(MVR+AVR+TAP)	40	+		+	0.60	2	9
9	MVD	40	+	++	—	0.63	2	8
10	(OMC)	40	+		+	0.56	6	12
						0.66±0.88*	4±2**	16±7
11	MVD+AVD	35	—	++	—	0.75	2	7
12	(AVR+OMC)	35	+		+	0.57	5	2
13	MVD	30	—	++	+	0.59	0	2
14	(MVR+TAP)	30	—		—	0.68	1	8
15	(MVR+TAP)	30	—		—	0.46	0	7
16	Clotted valve (TVR)	30	+	+	—	0.62	2	
17	MVD+AVD	25	—	+	—	0.44	0	9
18	ASD	25	+	+	+	0.60	1	13
19	(AVR+OMC)	20	—		—	0.52	0	7
20	(MVR+TAP)	20	—		+	0.61	0	
						0.58±0.09	1±2	7±4
21	MVD+AVD	0	—	—	—	0.68	0	14
22	MVD	0	—	—	—	0.68	4	12
23	ASD	0	—	—	—	0.62	0	7
24	ASD	0	—	—	—	0.50	0	4
25	(Repair of ASD)	0			—	0.50	0	
26	(TVR)	0	—		—	0.54	0	8
27	(Repair of ASD)	0			—	0.50	1	
28	(MVR+TVR)	0	—		—	0.70	2	18
29	(MVR)	0			—	0.48	0	
30	(OMC+TAP)	0	—		—	0.52	0	
						0.56±0.08	1±1	11±5

Numbers 1 and 28, 3 and 8, 6 and 15, 17 and 19, and 24 and 25 were pre- and post-operative data for the same patients. Grade of TR at operation: Negative (—), mild (+), moderate (++) and severe (+++).

* = $p < 0.05$, ** = $p < 0.001$, when compared with the group without regurgitation.

Abbreviations: ASD = atrial septal defect; AVD = aortic valve disease; AVR = aortic valve replacement; CTR = cardiothoracic ratio; MVD = mitral valve disease; MVR = mitral valve replacement; OMC = open mitral commissurotomy; RA = right atrium; TAP = tricuspid annuloplasty; TR = tricuspid regurgitation; TVR = tricuspid valve replacement.

KF. Therefore, the outflow from the right ventricle towards the lung compartment is (1-K)F. Transport time delay due to regurgitation is

represented by τ_R . The time-activity curves, $r(t)$, obtained from the areas representing the superior vena cava, the right atrium and the right

Fig.5. Data of a patient with severe tricuspid regurgitation.

- a: Right ventriculography intensely opacified the huge right atrium. This tricuspid regurgitation appeared to be significant, even considering the artificial regurgitation due to a cardiac catheter (left). No significant regurgitation was demonstrated postoperatively (right).
- b: Contrast echocardiography after peripheral venous injection of 10 ml of saline demonstrated that microcavitations (as a cloud of echoes) moved back and forth across the tricuspid valve over a number of successive cardiac cycles. Arrows show reverse flow of the injectate during systole (left). No regurgitation was revealed after surgery (right).
- c: With the use of analog simulation analysis, a diagnosis of severe tricuspid regurgitation (left) disappeared after tricuspid annuloplasty using Carpentier ring (right). The curves of the superior vena cava are not shown in this figure. MTT = mean transit time; PR = percentage of regurgitation.

ventricle can be expressed as follows:

$$r_i(t) = G_i \cdot V_i C_i(t)$$

$$r_{ra}(t) = G_{ra} \cdot V_{ra} C_{ra}(t)$$

$$r_{rv}(t) = G_{rv} \cdot V_{rv} C_{rv}(t)$$

where G is a constant or gain-factor which depends on the counting efficiency of the gamma camera and on the monitored volume for each compartment. The parameters for each compartment which correspond to potentiometers on the computer control represent time constant ($T = V/F$), regurgitation fraction (K) and gain-factor (G) (Fig. 2).

The model curves obtained from the analog simulation circuit with the variations of the parameters are shown in Fig. 3. The actual curves are fitted to the model curves of the computer in the order of the transportation processes of the injected tracer by selecting the optimal parameters iteratively on the computer. The time constant (mean transit time) is selected from the upslope of the curves, or the time to the peak, and the percentage of regurgitation from the degree of the downslope of the curves.

RESULTS

The reproducibility of this method appears to be satisfactory for clinical use because the values obtained fall predominantly within approximately $\pm 15\%$ agreement (Table I).

Analog simulation data of a patient without tricuspid regurgitation are shown in Fig. 4. This is a good example of the normal dilution curves of the right heart. Another patient who had mitral valve disease was revealed to have severe tricuspid regurgitation by right ventriculography and contrast echocardiography as well as the radionuclide method, but the regurgitation disappeared after mitral valve replacement and tricuspid annuloplasty (Fig. 5-a, b and c).

Comparison between the data of the simulation method and that of other examinations is summarized in Table II. A significant tricuspid regurgitation of more than 40% by the simulation method was usually associated not only with positive echocardiographic findings of tricuspid regurgitation but also with clinical evidence suggesting tricuspid regurgitation, such as cardiac murmur, cardiomegaly or hepatomegaly. On the other hand, clinical and echocardiographic findings were not characteristic when regurgitation was less than 40%. Some patients underwent

surgery following the radionuclide examination. At operation, tricuspid regurgitation was diagnosed by inspection or palpation of the tricuspid valve and its severity was arbitrarily graded by the same surgeon: negative (—), mild (+), moderate (++) and severe (+++). Patients with more than 40% regurgitation by the simulation method were always revealed to have moderate to severe regurgitation at operation.

DISCUSSION

The contours of indicator-dilution curves of the right atrium and the right ventricle are affected not only by variations in cardiac output and blood volume but also by the presence of left to right (or right to left) shunt or tricuspid valvular incompetence. Since the influences of left to right shunt and recirculation of the tracer are avoided by the use of MAA in this study, a disproportionate prolongation of the disappearance slope is produced exclusively by tricuspid regurgitation. This is used to estimate the severity of the regurgitation. Other hemodynamic changes associated with valvular incompetence, such as stroke volume or heart rate, are neglected for simplification of the model. For instance, atrial fibrillation itself does not affect the result unless cardiac output or blood volume changes, but it may actually alter the dilution curves, especially due to alteration of streaming or mixing of the tracer. At present these problems remain unsolved.

The present model consisting of a series of first order lag system is simple and practical. The clinical usefulness of this approximation has been reported in the analysis of the dilution curves recorded not only by a single probe, the so-called radiocardiogram^{9,10} but also by scintillation camera^{11,12}. Perhaps the most critical assumption in the model is that a tracer entering a chamber mixes instantaneously with all the blood in that chamber. Although this assumption has been refuted by several studies,^{13,14} indicator-dilution techniques, such as dye-dilution and thermodilution, have become widely accepted for clinical use and demonstrated that ventricular mixing is adequate for the measurement of cardiac output, chamber volume and ejection fraction. In the right atrium, which is just distal to an injection site, however, tracer mixing seems to be incomplete¹⁵ and the calculated values for this chamber may be unreliable. However, the curves of the atrium as an input for the ventricle

must be simulated because of the sequential input-output relationship of the model. Of the two values for the percentage of regurgitation, one obtained from the atrial curves and the other from the ventricular curves, the latter was preferentially adopted, although the difference between these values was 10% or less.

The selection of region of interest is an important part of this procedure. Variations in radioactivity in different areas of a chamber caused by uneven mixing of the tracer¹⁴ might be eliminated or averaged if the selected area representing the chamber is large enough to cover the entire chamber. The contamination of the dilution curves by radioactivity from the left heart or by recirculation of the tracer due to left to right shunt can be avoided by the use of MAA because these particles are all trapped in the pulmonary capillaries and unable to reach the left heart. However, the slight contamination frequently seen in the last portion of the curves, which probably originated from activity in the lung, obscured trivial changes in the curves and made it difficult to detect and quantify regurgitation of less than 20%. This is a major limitation of this technique. Furthermore, the method is not valid for the diagnosis of tricuspid regurgitation combined with a reverse (right to left) shunt.

Since there is no perfectly reliable standard of reference for quantification of tricuspid regurgitation, it is impossible to discuss the discrepancy between the actual rate of the regurgitation and the value obtained by the simulation method. However, the present method appears to be useful in detecting tricuspid regurgitation and at least in grading its severity. Further study, including animal experiments, will be needed to quantify the accurate tricuspid regurgitant flow.

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