Bull. Tokyo Med. Dent. Univ., 33: 41–48, 1986

DEFINITION OF MIXING RATE OF INDICATOR BY INDICATOR DILUTION METHOD: EVALUATION OF RELATIONSHIP BETWEEN MIXING RATE OF INDICATOR AND CARDIAC OUTPUT DETERMINATION

BY

Kuichi TANIGUCHI, Hajime KIRIGAYA, Haruki ITOH, Toshihiko TAKAMOTO, Yoshito IESAKA and Jugoro TAKEUCHI[1)]

ABSTRACT

It is generally agreed that complete mixing of the indicator is one of the most important factors of the indicator dilution method, however, no clear definition of the mixing state has been established. We established a formula for the mixing rate of the indicator by the indicator dilution method, using the concept of entropy in the information theory, and compared the mixing rate of indocyanine green in one mixing chamber (left ventricle) with that in the two mixing chamber system (including the aortic system). The mixing rate of the indicator (M) is shown as $M(\%)=100\ H/Hcm=-100\ (l\mathrm{k}\ \Sigma_{i=1}^{n}\ C_i \log C_i+\log k)$ (l & k: correction factors in each dye dilution curve, C: mean concentration of the indicator in the region).

Left heart and aortic catheterizations by retrograde femoral and carotid artery approach were performed in five anesthetized dogs. Simultaneous dye dilution curves were recorded at the aortic root and at the bifurcation of the abdominal aorta, following the injection of indocyanine green (2.5 mg/1ml of indocyamine green for each injection) by impulse into the left ventricle at the endsystole, triggered on the R wave of ECG, using the automatic injector devised by the authors. Twenty-five pairs of dye dilution curves were obtained by simultaneous recording in the aortic root and the abdominal aorta under several hemodynamic conditions, and the cardiac output, mean circulation time and the mixing rate of the indicator were determined.

The mixing rate of the indicator obtained in the aortic root (mean±SE:M=78.7±3.43%) was observed to be significantly greater ($P<0.01$) than in the abdominal aorta (mean±SE:M=70.0±3.51%).

Taking the mixing rate of the indicator into consideration, the cardiac output determination by the indicator dilution method is more sensitive to the changing hemodynamic conditions when determined in the aortic root than in the abdominal aorta.

Key words: 1) Indicator dilution method, 2) Mixing rate of indicator, 3) Entropy in the information theory, 4) Cardiac output determination

INTRODUCTION

Complete mixing of the indicator in a mixing chamber is one of the most important factors of the indicator dilution method[1)~3)]. No clear definition of the degree of mixing, however, has been established. Therefore, a clear definition of the mixing rate of the indicator by the indicator dilution technique is now re-

*1 谷口興一，伊東春樹，家坂義人，桐ケ谷　肇，高元俊彦，武内重五郎: The 2nd Department of Internal Medicine (Chief: Prof. J. TAKEUCHI), Faculty of Medicine, Tokyo Medical and Dental University (Tokyo Ika Shika Daigaku)

Received for publication, September 2, 1985.

quired. Considering that the mixing phenomenon of the indicator is equivalent to the distribution of the indicator in a solid mixing chanber, it is appropriate to apply the concept of entropy in the information theory in order to establish a definition of the mixing rate, because entropy is a non-dimensional value that represents a measure of uniformity of mixing quality in a system. Ogawa & Itoh[4),5)] applied the concept of entropy in the information theory to establish a definition of the mixing rate and developed a new concept of mechanism of mixing in chemical engineering.

It is the purpose of this paper to present a clinically available formula of the mixing rate of the indicator by the indicator dilution method by applying their definition of mixing rate[4),5)] and to evaluate the relationship between the mixing rate of the indicator and cardiac output determination in one mixing chamber (left ventricle) with that in two mixing chamber system (involving the aortic system).

Definition of Mixing Rate of Indicator by Indicator Dilution Method

Considering that there is a mixing chamber in a circulatory system (Fig. 1), the circulation time distribution curve of the indicator can be determined by recording at the exit of the chamber when the indicator is injected by impulse into a steady flow system at the chamber entrance. The circulation time distribution function is shown as a curve in Fig. 2 and is given by the equation $C(t)=-\exp(t)$. Generally, the circulation time distribution function $C(\tau)$ has the following characteristics (Fig. 2):

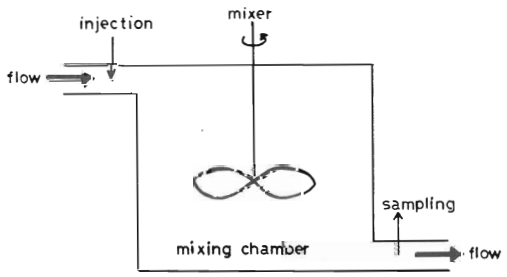


Fig. 1. Mixing of indicator injected by impulse into a mixing chamber in a steady flow system.

$$\int_0^\infty C(\tau)d\tau=\sum_{i=1}^{n} C_i\Delta\tau=1 \qquad (1)$$

$$\int_0^\infty C(\tau)\tau d\tau=\sum_{i=1}^{n} C_i\tau_i\Delta\tau=1 \qquad (2)$$

where τ and $C(\tau)$ denote the non-dimensional values. However, t and C(t) in the actual indicator dilution curve denote the dimensional values, and the equations (1) and (2) can be expressed as:

$$\sum_{i=1}^{n} C_i\Delta t=\int_0^\infty C(t)dt \qquad (1')$$

$$\sum_{i=1}^{n} C_i t_i\Delta t=\int_0^\infty C(t)tdt \qquad (2')$$

where t and Δt ($\Delta t=1$) denote the time and the minute time interval, respectively. Because $C(\tau)$ and τ are the non-dimensional values normalized by the correlation factors k and l, respectively, the above two equations (1) and (2) can be normalized by the insertion of these correction factors:

$$\sum_{i=1}^{n} (kC_i)(l\Delta t)=lk\sum_{i=1}^{n} C_i=1 \qquad (3)$$

$$\sum_{i=1}^{n} (kC_i)(lt_i)(l\Delta t)=kl^2\sum_{i=1}^{n} C_i t_i=1 \qquad (4)$$

Then, the correction factors are obtained by solving the equations (3) and (4) as follows:

$$k=\frac{\sum_{i=1}^{n} C_i t_i}{(\sum_{i=1}^{n} C_i)^2}, \qquad l=\frac{\sum_{i=1}^{n} C_i}{\sum_{i=1}^{n} C_i t_i} \qquad (5)$$

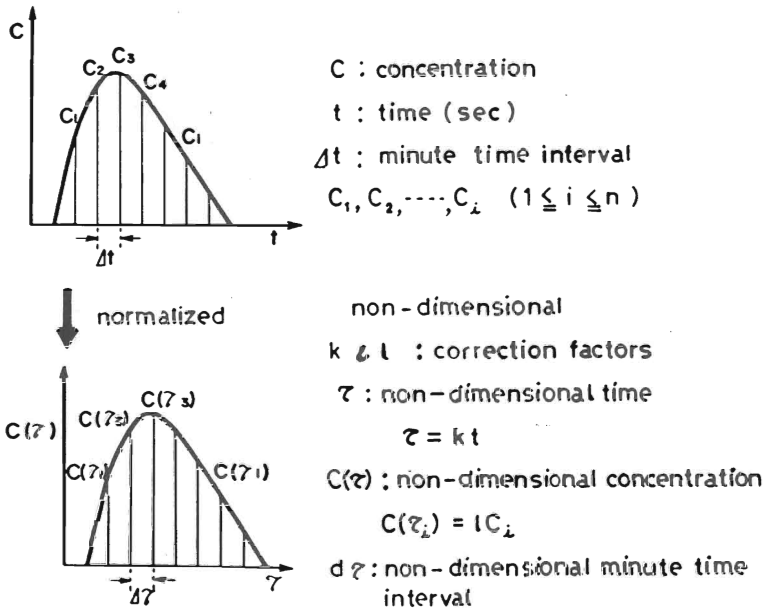


Fig. 2. Above: An indicator dilution curve in the circulatory system is divided into small areas at minute time interval (t) with C and t denoting concentration of indicator and time, respectively. Below: An indicator dilution curve normalized by the correction factors k and *l*.

Equation (1) demonstrates that the circulation time distribution function can be considered as the probability density distribution function. Therefore, the entropy for indicator mixing by the indicator dilution method can be defined in the information theory (Shannon's equation).

$$H = -\int_0^\infty C(\tau) \log C(\tau) d\tau \qquad (6)$$

Then, equation (6) can be rewritten by substituting the correction factors as:

$$H = -lk \sum_{i=1}^{n} C_i \log C_i \qquad (7)$$

In the completely mixed state, the entropy for mixing (Hcm) defined in equation (7) becomes the maximun value (Hmax) which is proved mathematically, as shown in the following equation:

$$Hcm = Hmax = 1 \qquad (8)$$

On the contrary, the entropy for the unmixed state of the indicator (Hum) shows the minimum value (Hmin) to be

$$Hum = Hmin = 0 \qquad (9)$$

Therefore, when an indicator is injected by impulse by the indicator dilution method, the mixing rate of the indicator (M) is consistent with the ratio of the entropy for indicator mixing at an arbitrary time (H) to that in the completely mixed state (Hcm). In conclusion, the mixing rate of the indicator by the indicator dilution technique can be defined by the following equation:

$$M(\%) = 100 \times H/Hcm = -100(lk \sum_{i=1}^{n} C_i \log C_i + \log k) \qquad (10)$$

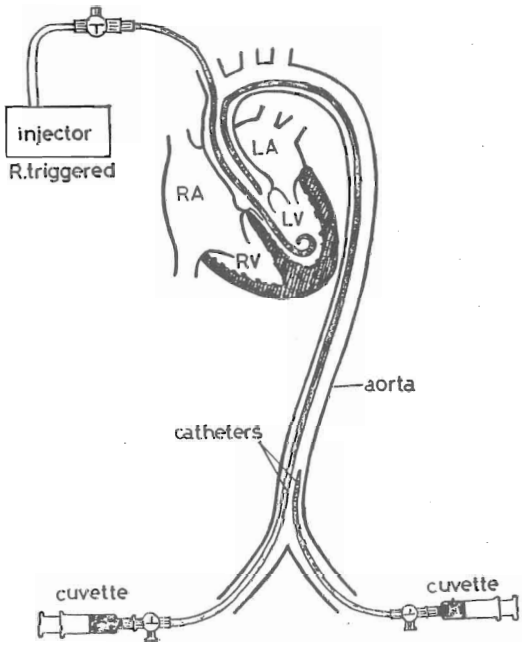
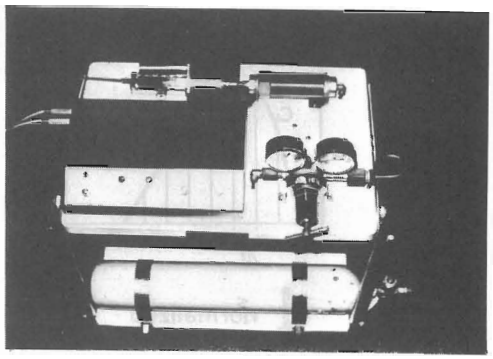


Fig. 3. Schema of the experimental procedure showing placement of multi-side hole catheters in the left ventricle, in the aortic root and at the bifuraction of the abdominal aorta. Following injection of indicator in the left ventricle, simultaneous indicator dilution curves were recorded in the aortic root and abdominal aorta.



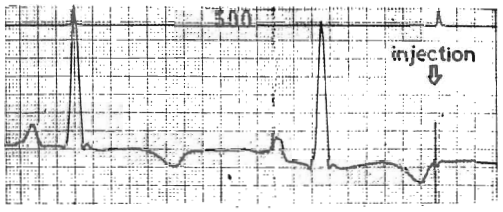


Fig. 4. R-triggered injector devised by the authors. Dye was injected at the endsystole, as is indicated on the electrocardiogram.

Method

Left heart and aortic catheterization by the retrograde femoral and carotid artery approach was performed in five pentobarbital anesthetized dogs. Multi-side hole catheters were placed in the left ventricle, in the aortic root at the level of the aortic cusps and at the bifurcation of the abdominal aorta, and the proximal portion of the catheters were fixed on to the skin with a stitch (Fig. 3). The indicator dilution method was performed using the Erma-Kogaku Quvette dye densitometers with a Towa-Denpa Two-channel Recorder. Following the injection of indocyanine green by impulse into the left ventricle, simultaneous dye dilution curves were recorded in the aortic root and at the bifurcation of the abdominal aorta in various hemodynamic conditions by the bloodletting or blood transfusion technique. Injections of the dye (2.5 mg/1 m*l* of indocyanine green for each injection) were done automatically at the endsystole, triggered on the R wave of ECG, using the injector devised by the authors (Fig. 4). Cardiac output and mean circulation time were calculated by the method of Lilienfield & Kovach[6] and Hamilton[1]. The mixing rate of the indicator was determined by the above-mentioned eqaution. The position of each catheter, the time in the cardic cycle when the injection were performed and the injection speed were all constant throughout the experiment.

Result

Twenty-five pairs of dye dilution curves were obtained by simultaneous recordings in the aortic root and the abdominal aorta under several hemodynamic conditions. A pair of dye dilution curves

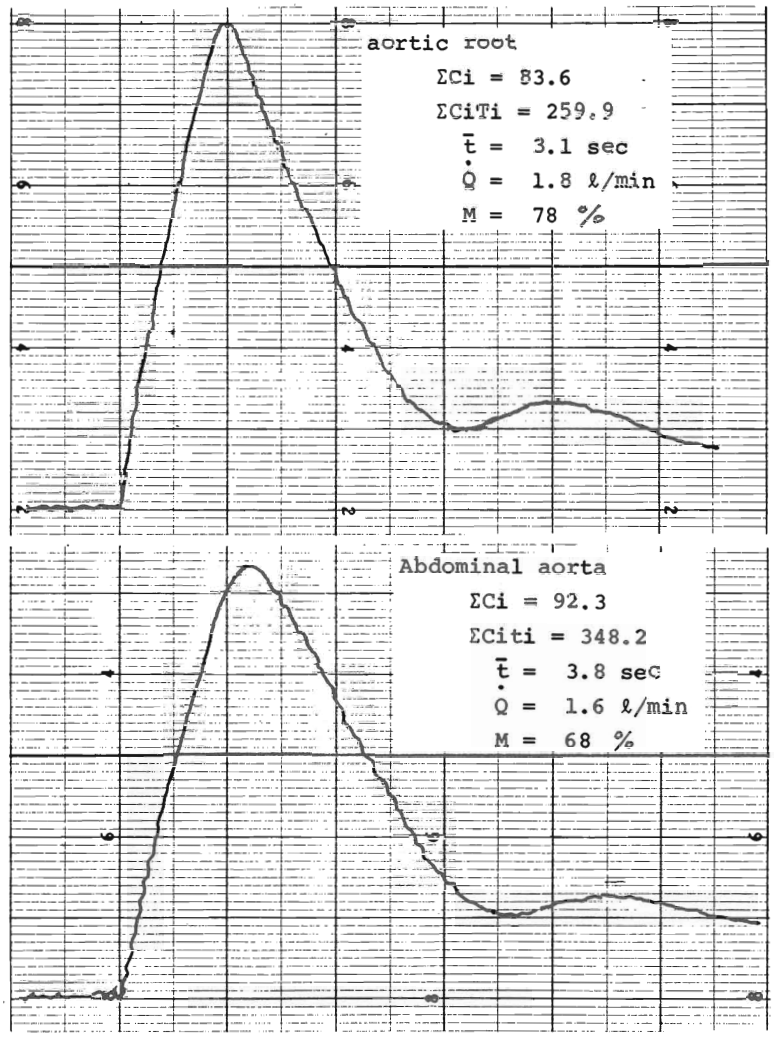


Fig. 5. Dye dilution curves obtained by simultaneous recordings in the aortic root and the abdominal aorta after injection of dye in the left ventricle.

Table 1. Cardiac output ($\dot{Q}$), mean circulation time ($\bar{t}$) and mixing rate of indicator (M) determined in the aortic root and the abdominal aorta

	$\dot{Q}$ (*l*/min)	$\bar{t}$ (sec)	M (%)
Aortic root	1.25~2.96(1.98±0.44)	3.12~4.22(3.76±0.25)	73.5~85.5(78.7±3.43)
Abdom. aorta	1.09~2.24(1.65±0.39)	3.62~4.56(4.1 ±0.23)	62.8~75.4(70.0±3.51)

* $p<0.01$ (m±S.E.)

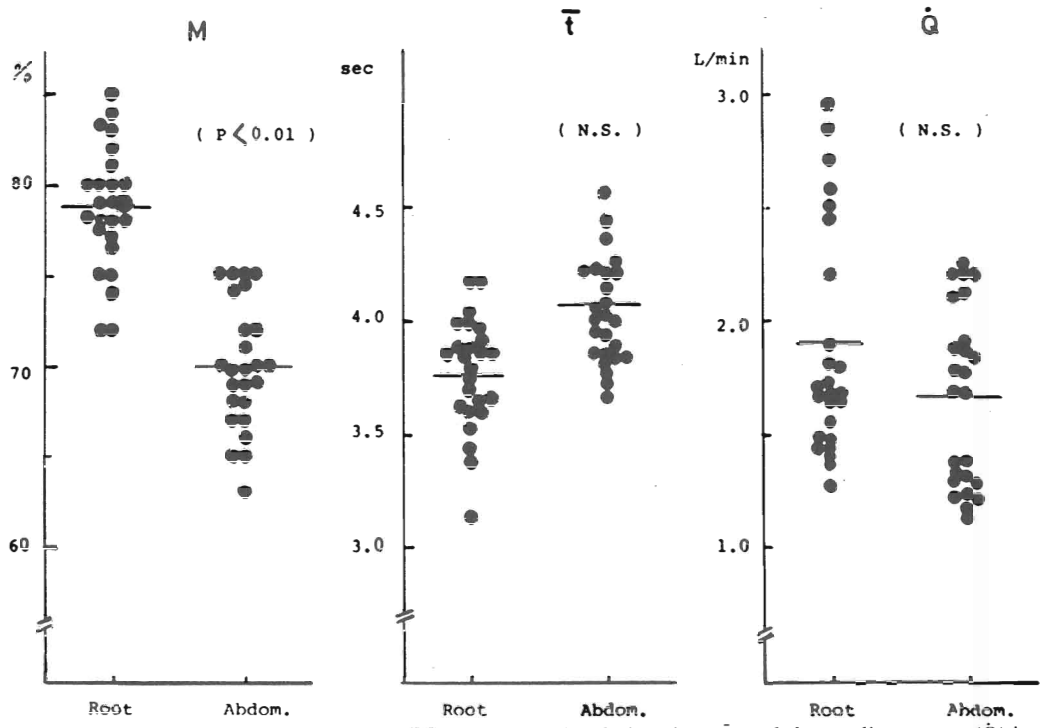


Fig. 6. The mixing rate of indicator (M), the mean circulation time ($\bar{t}$) and the cardiac output ($\dot{Q}$) in the aortic root and abdominal aorta. Note that the mixing rate of the indicator is significantly higher ($P<0.01$) in the aortic root than in the abdominal aorta.

shown in Fig. 5 were simultaneously recorded in the aortic root and the abdominal aorta.

1) Mixing rate of indicator (M) (Table 1)

The mixing rate of the indicator in the aortic root ranged from 73.5% to 85.5% (mean±S.E.=78.7±3.43), while that in the abdominal aorta ranged from 62.8% to 75.4% (mean±S.E.=70.0±3.51). Note that the M in the aortic root was significantly higher than the M in the abdominal aorta ($p<0.01$), as shown in Fig. 6.

2) Cardiac output ($\dot{Q}$) and mean circulation time ($\bar{t}$) (Table 1)

Cardiac output as determined in the aortic root varied within a relatively wide range from 1.25L/min. to 2.96L/min. (mean±S.E.=1.98±0.44), whereas those in the abdominal aorta remained within a relatively narrow range from 1.09L/min. to 2.24L/min. (mean±S.E.=1.65±0.39). The mean value in the aortic root was slightly larger than in the abdominal aorta (Fig. 6). Cardiac output as determined in the aortic root was more sensitive to the changing hemodynamic conditions.

The mean circulation time (Fig. 6) in the aortic root ranged from 3.12 seconds to 4.22 seconds (mean±S.E.=3.76±0.25), while in the abdominal aorta it varied from 3.62 seconds to 4.56 seconds (mean±S.E.=4.1±0.23).

Discussion

This study establishes a formula for the mixing rate of the indicator by the indicator dilution method, using the entropy in the information theory. Indica-

tor dilution curves were recorded simultaneously in the aortic root and the abdominal aorta following the injection of the dye by impulse at the endsystole into the left ventricle in the anesthetized dogs. It is generally recognized that the indicator dilution curves are affected by the site of injection and recording, the function of the mixing chamber and the injection speed. Such conditions were fixed throughout the experiment. In addition, the part of the cardiac cycle in which the injections are performed has an important influence on the indicator mixing. Therefore, an automatic injector triggered on the R wave of ECG was used as stated above. Cardiac output, mean circulation time and the mixing rate of the indicator were calculated from the simultaneous recordings obtained in the aortic root and the abdominal aorta. Several differences were noted in the data from these two recording sites. For example, the mixing rate of the indicator in the aortic root was significantly higher than that in the abdominal aorta ($P<0.01$). Certain anatomical factors exist to explain these differences. For the indicator dilution curves obtained from the aortic root, the mixing chamber consisted of the left ventricle and a small area of the proximal aortic root. For the abdominal aortic recordings, however, the mixing chamber for the indicator was consider-

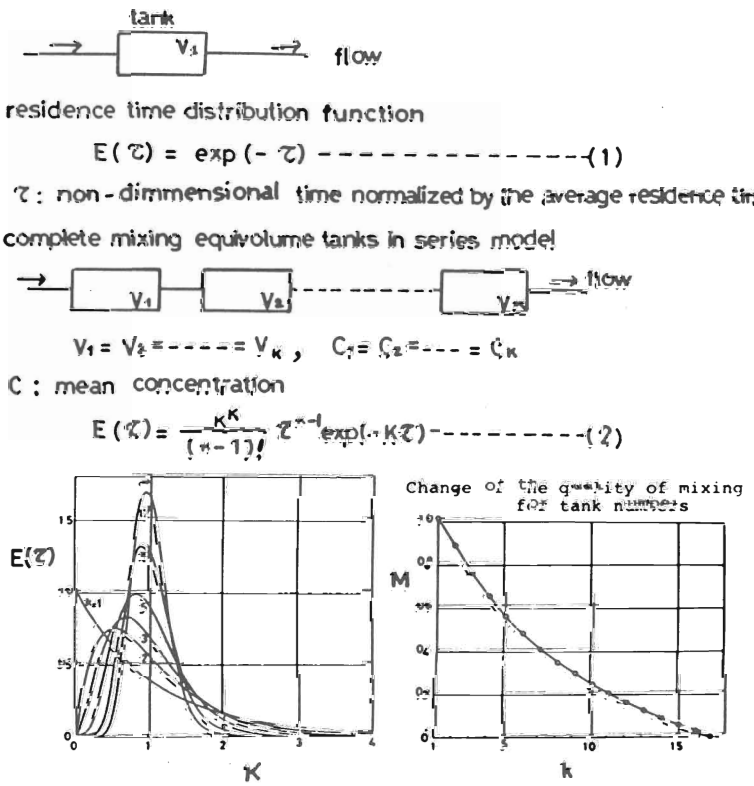


Fig. 7. Residence time distribution function and the degree of indicator mixing in the completely mixed equivolume tanks in series. This graph shows that the degree of indicator mixing decreases with increasing number of tanks (k) (Ogawa, K., & Itoh, S.: J. Chem. Engin. Japan, 8: 148, 1975).

ably larger, including the left ventricle plus the entire aortic system. Thus, significant differences in the volume and function of the mixing chamber occurred between these two aortic recording sites, although no statistical difference was noted in the mean circulation time. According to the previous studies by the impulse response method, the residence time distribution function in the completely mixed equivolume tanks in the series is shown as:

$$E(\tau)=\frac{k^k\tau^{k-1}}{(k-1)!}\exp(-k\tau).$$

(τ: non-dimensional time normalized by the average residence time complete mixing equivolume tanks in the series model.)

The varying degree of the indicator mixing for the different numbers of mixing tanks (k) is shown in Fig. 7 (lower right). It is apparent from this graph that the mixing rate of the indicator decreases with the increasing number of tanks.

In reference to the present study, this concept explains that a more complete mixing of the indicator in the aortic root than in the abdominal aorta results from a smaller number of tanks in the mixing chamber of the proximal aortic site than that in the abdominal aorta. This observation means that the determination of the cardiac output by the indicator dilution method is more accurate and reflective of the hemodynamic changes in the circulatory system with a more complete degree of mixing that occurs in the aortic root than with a lesser degree of indicator mixing in the abdominal aorta.

Acknowledgement

We thank Associate Professor Ogawa of the Department of Chemical Engineering of the Tokyo Institute of Technology for his suggestion with respect to the fundamental theory of indicator mixing.

References

1) Kinsman, J. M., Moore, J. W., and Hamilton, W. F.: Studies on the circulation. I. Injection method: Physical and mathematical considerations. Am. J. Physiol., 89: 322, 1929.
2) Newman, E. V., Merrell, M., Genecin, A., Monge, C., Milnor, W. R., and Mckeever, W. P.: The dye dilution method for describing central circulation. An analysis of factors shaping the time-concentration curves. Circulation, 4: 735, 1951.
3) Folse, R., and Braunwall, E.: Determination of fraction of left ventriclar volume ejection per beat and of ventriclar end diastolic and residual volumes. Experimental and clinical observations with a precordial dilution technique. Circulation, 15: 674, 1962.
4) Ogawa, K., and Itoh, S.: A definition of quality of mixedness. J. Chem. Engin. Japan, 8: 148, 1975.
5) Ogawa, K., Itoh, S., and Matsumura, Y.: Mixing rate in a stirred vessel. J. Chem. Engin. Japan, 13: 324, 1980.
6) Lilienfield, L. S., and Kovach, R. S.: Simplified method for calculating flow, mean circulation time and downslope from indicator dilution curves. Proc. Soc. Biol. Med., 91: 595, 1956.