
Radionuclide Assessment of Peripheral Hemodynamics: A New Technique for Measurement of Forearm Blood Volume and Flow

Yasuhiro Todo, Masaho Tanimoto, Tadao Yamamoto, and Tadaaki Iwasaki

First Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

A new peripheral hemodynamic measurement system using ^{99m}Tc -labeled red blood cells has been developed. This method was carried out on 22 normal subjects, 29 with coronary artery disease, and two with dilated cardiomyopathy. Peripheral hemodynamic indices obtained from this method included forearm blood volume (FBV), venous capacity (FVC), venous capacity index (VCI), blood flow (FBF), and vascular resistance (FVR), and were compared with the central hemodynamic parameters of left ventricular filling pressure (LVFP), cardiac output (CO), and total systemic vascular resistance (TSVR) obtained with an invasive technique. The normal values were FBV 8.54 ± 2.04 ml/100 ml; FVC 4.54 ± 1.23 ml/100 ml; VCI $65.5 \pm 3.8\%$; FBF 4.26 ± 0.56 ml/100 ml/min; and FVR 20.9 ± 4.4 mmHg/ml/100 ml/min. These values were in good agreement with the values reported using conventional plethysmography. The 16 patients with congestive heart failure (NYHA Class II or III) showed significantly lower FBV, FVC, and FBF values and significantly higher VCI and FVR values than the healthy subjects. Capacitance vessel parameters (FBV, FVC, and VCI) and LVFP, FBF and CO, and FVR and TSVR each showed significant correlation; reproducibility was also good. The advantages of this method are (a) the detector does not come in contact with the region being measured; (b) it is possible to ascertain the absolute quantity of blood in the tissue; (c) extravasation of the plasma component can be ignored; and (d) data processing is simple.

J Nucl Med 27:192-197, 1986

Peripheral capacitance and resistance vessels act as preload and afterload for the heart and influence cardiac function. Accordingly, evaluation of the condition of both sets of peripheral vessels is indispensable for an understanding of integrated cardiac function. Venous occlusion plethysmography is a conventional, noninvasive method for measuring peripheral hemodynamics; the water-filled method (1), strain-gauge method (2-5), and impedance method (6-10) are commonly used. However, these methods have drawbacks, such as requiring application of the detector directly to the area being measured and not revealing the absolute volume of blood in this area. Clements et al. (11) devised a new technique for measuring peripheral hemodynamics

that involves using technetium-99m- (^{99m}Tc) labeled red blood cells, widely used in nuclear cardiology, to evaluate changes in peripheral blood volume from changes in radioactivity. Based on the method of Clements et al. we have developed a method of peripheral hemodynamic measurement appropriate for clinical application. The purpose of this study was to evaluate the clinical usefulness of this method. We used this method to calculate mean values for each peripheral hemodynamic index in normal subjects and patients with congestive heart failure, and the results were compared with those obtained by invasive methods.

MATERIALS AND METHODS

Subject Population

Relevant data on the 53 patients entered in this study are summarized in Table 1. The normal subjects were

Received Feb. 27, 1985; revision accepted Nov. 7, 1985.

For reprints contact: Yasuhiro Todo, MD, Hyogo College of Medicine, First Department of Internal Medicine, 1-1 Mukogawa-cho Nishinomiya-shi HYOGO 663 Japan.

TABLE 1
Subject Population

Item	Number of cases	Mean age	Sex (M:F)	Cardiac catheterization
Normal	22	50.1 ± 12.4	15:7	7
CAD*	29	55.1 ± 10.0	24:5	29
DCM†	2	47.0 ± 5.0	2:0	2

* CAD: Coronary artery disease.

† DCM: Dilated cardiomyopathy.

selected on the basis of clinical history and physical findings. Among 31 patients with cardiac abnormality, 16 patients showed the symptoms of congestive heart failure (CHF) (New York Heart Association Class II in ten patients, III in six patients).

Method of Measurement

In vivo ^{99m}Tc -labeled red blood cells were prepared according to the method of Pavel et al. (12) using Techne-Pyrophosphate Kits,* pyrophosphate 20 mg/vial, SnCl_2 4 mg/ml. The contents of the kit were dissolved in 5 ml saline, and then 0.2 mg/kg pyrophosphate was administered intravenously; 30 min later an i.v. injection of [^{99m}Tc]pertechnetate 5mCi was given. ECG-gated cardiac blood-pool image detection was conducted from a modified 40° LAO position, and then the peripheral hemodynamic measurement technique was implemented. Figure 1 outlines the method.

The subject lay in the supine position for 5 min at room temperature (18°–22°C) with the left upper limb slightly away from the body at the level of the mid-axillary line. An arterial occlusion cuff was placed around the arm just above the wrist joint and a venous occlusion cuff just above the elbow joint. A scintillation detector (equipped with a flat-field collimator) to measure dynamic functions was positioned as close to the forearm as possible. The end of the collimator was rectangular (11 × 7 cm). The detector-ratemeter was connected to a chart pen recorder for monitoring and to a computer. The arterial occlusion cuff was inflated to 200 mmHg and, after it had been confirmed that the radioactivity in the area to be measured was stable, measurement began. Arterial occlusion was maintained throughout the study. Sampling time was 5 sec. One minute after commencement of measuring, the venous occlusion cuff was rapidly inflated to 40 mmHg. Radioactivity in the area being measured started to increase immediately after inflation of the venous occlusion cuff, and finally reached a plateau usually in 3 to 5 min, after which the venous occlusion cuff was deflated. Measurement was concluded when radioactivity returned to the baseline at which time the arterial occlusion cuff was deflated. Five to seven minutes are required for one measurement. The results of measurement were stored in a computer. During this time, blood

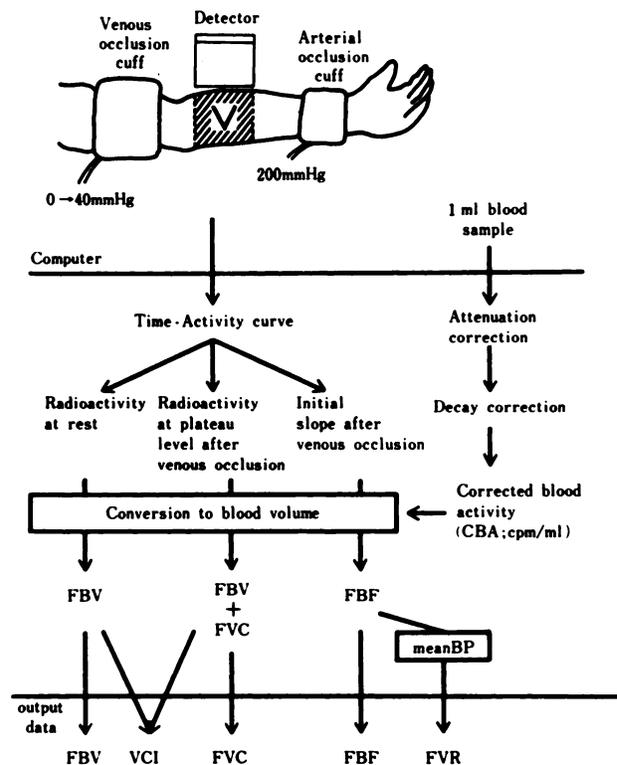


FIGURE 1

System of radionuclide measurement of peripheral hemodynamics. Five indices obtained from this system are: forearm blood volume (FBV), venous capacity (FVC), venous capacity index (VCI), blood flow (FBF), and vascular resistance (FVR)

pressure was recorded every minute by an automatic blood pressure recorder on the opposite arm. When measurement is completed, a 1-ml sample of blood was taken and positioned near the detector to measure the radioactivity. The volume of the monitored area of the left forearm was measured using a large capacity measuring cylinder.

Data Processing

In order to ascertain the volume of blood actually contained in the tissue, it is necessary to consider the attenuation of radioactivity by the tissue. Accordingly, we used water, which has an attenuation rate equal to that of body tissue, and 1 ml of ^{99m}Tc -labeled blood to make a 50-ml solution. This solution was then increased to 500 ml in 50-ml increments. Radioactivity of each volume was measured using the same detector to obtain an attenuation correction rate with changes in volume (Fig. 2). The results showed that the greater the volume of aqueous solution, the greater the attenuation of the radioactivity. We were able to draw a reference curve for attenuation correction (Fig. 2) which is approximated by a quaternary function. We used this function to obtain attenuation corrections for the volume of the measured part in each of the subjects and took a 1-ml

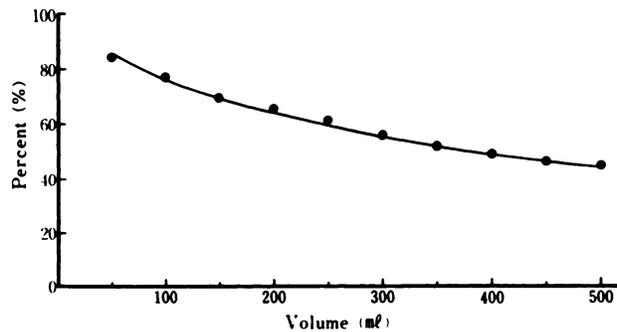


FIGURE 2
Reference curve of attenuation. Volume of measured forearm segment (ml), on abscissa, and percent of attenuation (%), on ordinate. $Y = Ax^4 + Bx^3 + Cx^2 + Dx + E$; $A = 1.04 \times 10^{-9}$; $B = -1.126 \times 10^{-6}$; $C = 6.43 \times 10^{-4}$; $D = -2.38 \times 10^{-1}$; $E = 0.95 \times 10^2$

blood sample for radioactivity compensation. Moreover, we compensated for radioactive decay during the time lag between measurement of the radioactivity in the forearm and that in the sample blood, calculated the corrected blood activity (CBA: cpm/ml) and, based on this CBA, made the conversion from radioactivity to local blood volume. These data were stored in a computer. The various peripheral hemodynamic indices were obtained from these data (Fig. 3).

Forearm blood volume (FBV; ml/100 ml) shows the volume of blood per 100 ml of tissue (prior to venous occlusion) in the measured arm. Forearm venous capacity (FVC; ml/100 ml) represents the increased volume of blood after venous occlusion. The venous capacity index (VCI; %) is expressed as the percentage of FBV to the volume of blood at the point where the plateau is reached after venous occlusion (FBV plus FVC). Forearm blood flow (FBF; ml/100 ml/min) indicates the volume of blood flow per min in the same region, and forearm vascular resistance (FVR; mmHg/ml/100 ml/min) is calculated by dividing the mean arterial pressure (diastolic pressure plus one-third of pulse pressure in mmHg) by forearm blood flow.

Examination of Validity

In order to examine the reproducibility of this method, each measurement was conducted twice at 15 to 30-min intervals under the same conditions on 15 subjects. Furthermore, two observers independently processed the data from 15 subjects, selected at random, and interobserver agreement of the indices calculated was examined. Similarly, the same examiner processed the data for 12 cases twice, 1 wk apart, and intraobserver agreement was examined.

Furthermore, cardiac catheterization was performed on seven normal subjects and 31 cardiac patients during the period when their clinical symptoms were stabilized

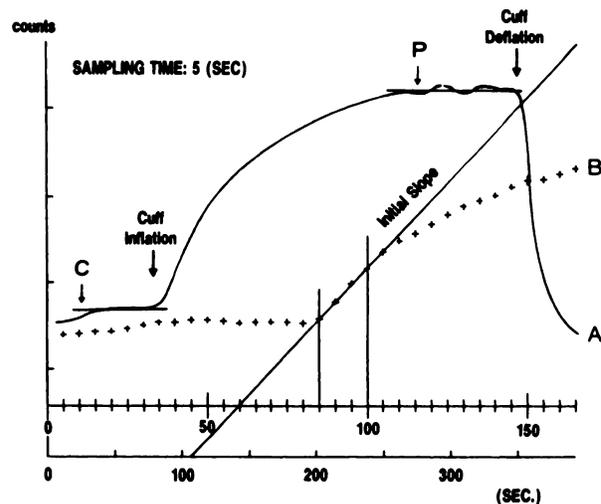


FIGURE 3
Indices of peripheral hemodynamics by means of radionuclide measurement. Curve A (solid line) indicates time-activity curve throughout entire period of one measurement. First half of Curve A is enlarged and shown in same figure as Curve B (dotted line) in order to clearly observe portion of slope at which linear increase occurred immediately after venous occlusion. Arrows C and P indicate radioactivity at rest and at plateau level after venous occlusion. With CBA the corrected blood activity, and V volume of measured forearm segment: Forearm blood volume [(FBV):ml/100ml] = C (cpm)/CBA (cpm/ml) $\times 100/V$ (ml); Forearm venous capacity [(FVC):ml/100ml] = $P - C$ (cpm)/CBA (cpm/ml) $\times 100/V$ (ml); Venous capacity index [(VCI):%] = $FBV/(FBV + FVC) \times 100$; Forearm blood flow [(FBF):ml/100 ml/min] = Initial slope (cpm/min)/CBA (cpm/ml) $\times 100/V$ (ml); Forearm vascular resistance = [(FVR):mmHg/ml/100ml/min] = mean BP (mmHg)/FBF.

within 2 wk before or after application of this method. The relationship between the invasive hemodynamic parameters and the indices obtained by this method was examined. The following hemodynamic parameters were obtained based on invasive methods: cardiac output (CO: l/min), left ventricular filling pressure (LVFP: mmHg), total systemic vascular resistance (TSVR: dyne-sec-cm⁻⁵) = (mean aortic pressure—right atrial pressure)/CO $\times 80$.

RESULTS

Comparison Between Normal and CHF

Mean values (\pm s.d.) in the normal subjects and the patients with congestive heart failure are shown in Table 2. The CHF patients showed significantly lower FBV, FVC, and FBF values and significantly higher VCI and FVR values than the healthy subjects.

Determination of Reproducibility

Good correlations were observed in the resulting co-

TABLE 2
Mean Values in Normal Subjects and Patients with CHF* (\pm s.d.)

Item	Normal subjects	Patients with CHF	p
Forearm blood volume (ml/100 ml)	8.54 \pm 2.04	6.87 \pm 2.97	<0.05
Forearm venous capacity (ml/100ml)	4.54 \pm 1.23	3.05 \pm 2.41	<0.05
Venous capacity index (%)	65.5 \pm 3.8	69.3 \pm 4.5	<0.01
Forearm blood flow (ml/100 ml/min)	4.26 \pm 0.56	3.40 \pm 1.18	<0.01
Forearm vascular resistance (mmHg/ml/100 ml/min)	20.9 \pm 4.4	30.3 \pm 11.4	<0.01

* CHF: Congestive heart failure.

efficients of correlation between the two testing intervals, as shown in Fig. 4. Interobserver and intraobserver agreement results also evidenced coefficients of correlation of at least 0.98.

Comparison with Invasive Methods

Figure 5 shows the correlation between LVFP and FBV, FVC, and VCI. The correlation between TSVR and FVR and between CO and FBF is shown in Fig. 6.

DISCUSSION

Several investigators (11,13,14) have estimated the volume of blood in peripheral tissues using ^{99m}Tc -labeled red blood cells, but they did not attempt to convert the radioactivity in the measured body part into a volume of blood. When measuring the radioactivity of the blood distributed in body tissue from the surface of the skin, accurate compensation must be made for attenuation by the tissue. We converted the radioactivity to the blood volume using a previously established formula for correction of attenuation.

There is considerable disparity between the various reports with regard to forearm vascular capacity (FVC) in normal subjects; Mason et al. (15) reported 9.5 ± 1.6 ml/100 g, and Vyden et al. (16) 4.0 ± 0.3 ml/100 ml (mean \pm s.e.e.). We obtained a value of 4.5

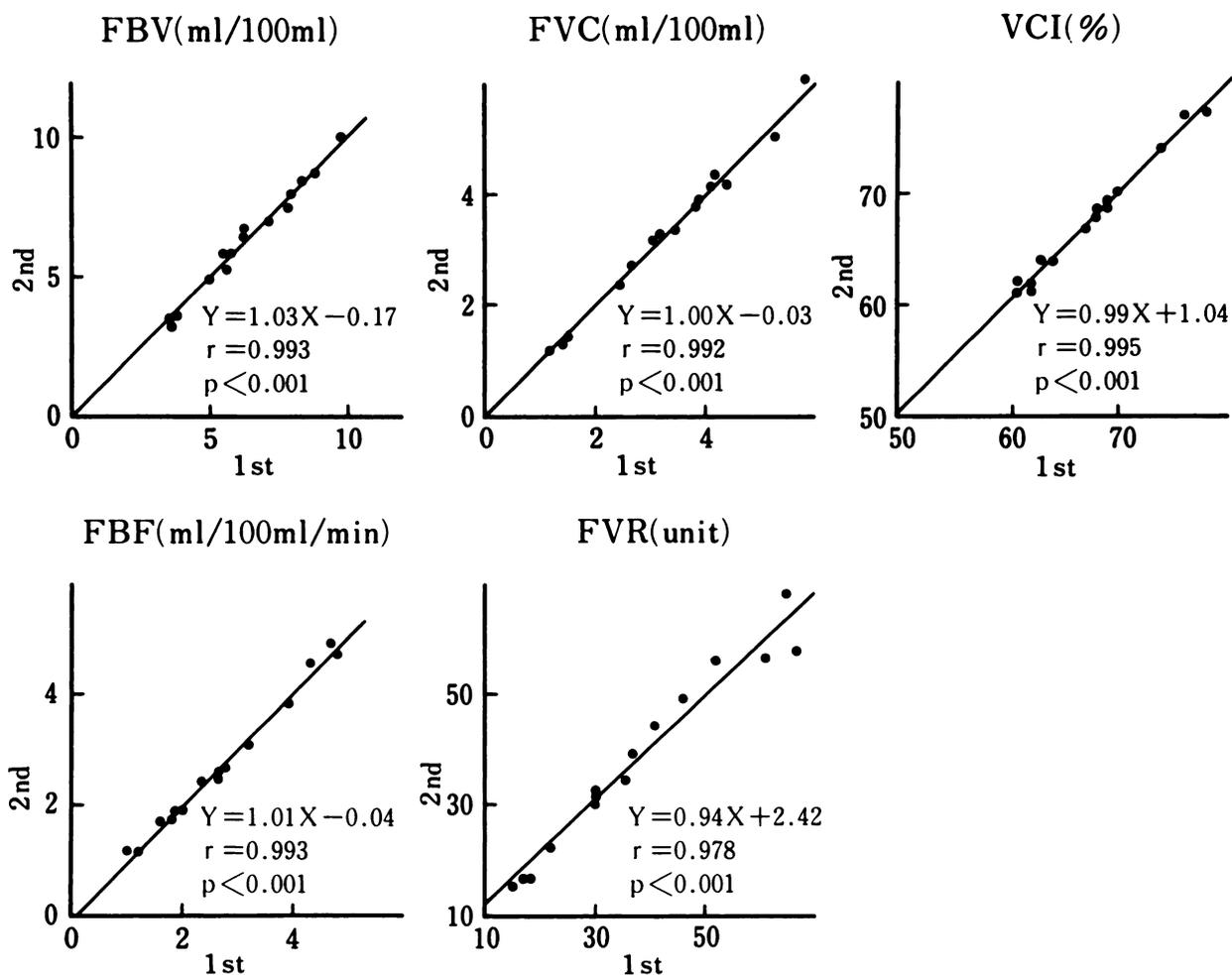


FIGURE 4
Analysis of reproducibility in each index, $n = 15$

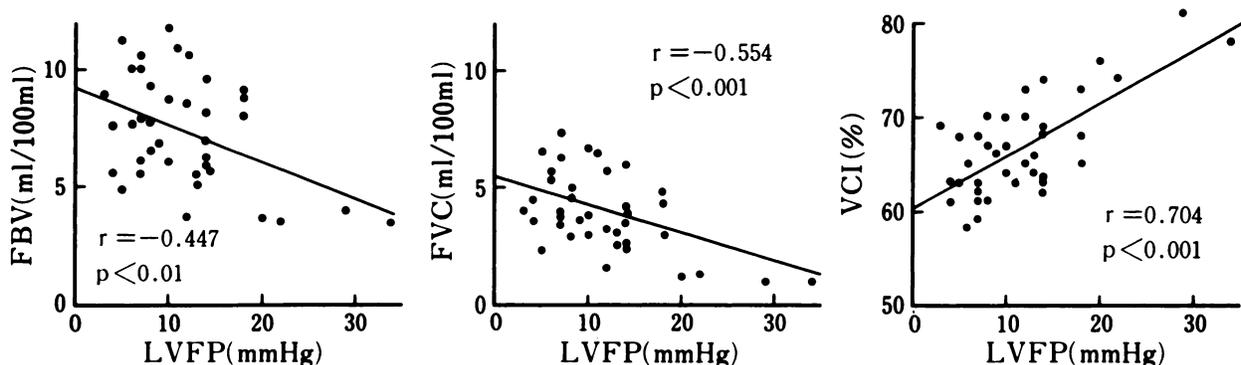


FIGURE 5
Relationship of indices of capacitance vessel to left ventricular filling pressure (LVFP), $n = 38$

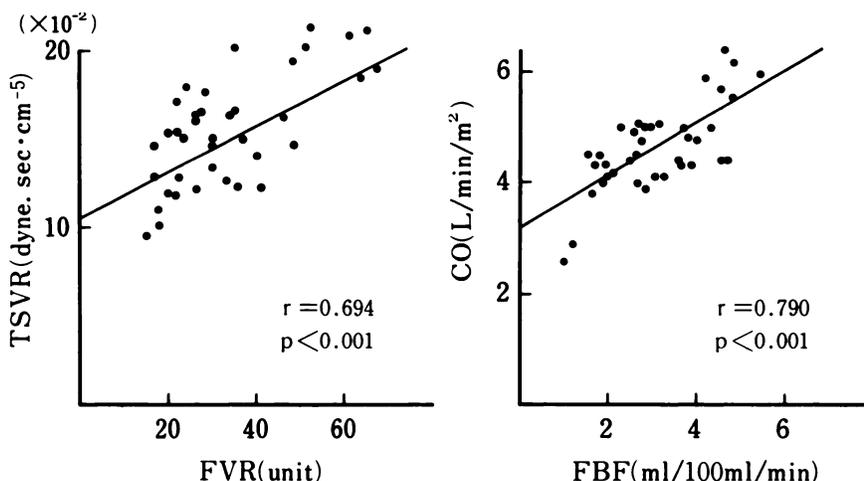


FIGURE 6
Relationship of total systemic vascular resistance (SVR) to forearm vascular resistance (FVR) and of cardiac output (CO) to forearm blood flow (FBF), $n = 38$

± 0.3 ml/100 ml (mean \pm s.e.e.), almost the same value as Vyden et al. With regard to forearm blood flow (FBF) and vascular resistance (FVR), our results are very similar to the values reported elsewhere (4,15,16).

To assess the reproducibility of this measurement method, we performed measurements twice and compared the results. A high level of reproducibility was attained ($p < 0.001$) for all indices. Moreover, at the data processing stage, observers must set the level of radioactivity prior to vascular occlusion and set the linear-increase-interval after venous occlusion and the plateau level. Investigation of intra- and interobserver agreement showed a high level of correspondence ($p < 0.001$ in both cases). This demonstrates the repeatability of our method.

One of the advantages of this method is that by performing measurement following the detection of an ECG-gated cardiac blood-pool image, both cardiac function and peripheral hemodynamics can be evaluated at the same time. Moreover, unlike peripheral hemodynamic measurement by venous occlusion plethysmography, there is no distortion of results by pressure from the detector, because the detector does not come

in contact with the body part being measured. Extravasation of the plasma component caused by venous occlusion can be ignored, because the method involved labeling red blood cells. Postmeasurement data processing is easily performed by computer. However, the method is not suitable for bedside measurement, and the operating cost is high. The latter problem can be solved by combining evaluation of cardiac function using the conventional cardiac blood-pool images.

In venous occlusion plethysmography, the venous capacity of the forearm or lower leg has been the only index of capacitance vessel parameters. By ascertaining with our method the volume of blood prior to venous occlusion and at maximum volume after occlusion, we have added two new capacitance vessel indices: forearm blood volume (FBV) and venous capacity index (VCI).

FBV is the volume of blood contained in a unit of tissue in the resting state and, because most of the blood is normally contained in the capacitance vessels, this is regarded as an index of these vessels. VCI represents the percentage of volume of blood at rest to the maximum volume of blood after venous occlusion. In other words, it is a relative index that shows the proportion of

the capacity at rest, with the maximum capacity of the capacitance vessels being regarded as 100. While FBV and FVC showed great variation among subjects, there was relatively little deviation in VCI. When we examined the correlation between LVFP, an index of the preload in invasive testing, and FBV, FVC and VCI, VCI showed the closest correlation. This indicates that VCI is more appropriate than FVC when comparing the level of preload by a noninvasive method.

Furthermore, both cardiac output and FBF as well as peripheral vascular resistance (TSVR) and FVR showed significant correlations, suggesting that this method is also useful as a noninvasive index of cardiac function or afterload level.

Leithe et al. (17) and Seino et al. (18) used plethysmography to measure the peripheral hemodynamics of chronic congestive heart failure or acute myocardial infarction. They reported that blood flow and venous capacity were less and vascular resistance was greater than in normal subjects. Using plethysmography, Mason et al. (15) and Awan et al. (19) recently investigated the effects of some vasodilating agents, which are becoming a common treatment for heart failure. However, the peripheral hemodynamic state in congestive heart failure was not consistently proportional to the degree of decompensation in their patients. Moreover, as the various vasodilating agents currently used have their own mechanisms of action, it is desirable that peripheral hemodynamics be measured in every case of heart failure, and venodilating agents be selected for cases that show strain of the capacitance vessels while arteriodilating agents are selected for cases exhibiting strain in resistance vessels. The method we have discussed can simultaneously measure cardiac function and peripheral hemodynamics. It has the added advantages of being repeatable, because it is noninvasive and allows the absolute volume of blood in tissue to be ascertained. Accordingly, this method may be useful for the determination of peripheral hemodynamic characteristics in cases of heart failure and in the selection of the most appropriate medication for treatment.

FOOTNOTE

* Dai-ichi Radio-isotope Ltd.

REFERENCES

- Greenfield AD, Whitney RJ, Mowbray JF: Methods for the investigation of peripheral blood flow. *Br Med Bull* 19:101-109, 1963
- Mason DT, Braunwald E: A simplified plethysmographic system for the measurement of systemic arterial pressure and peripheral blood flow. *Am Heart J* 64:796-804, 1962
- Whitney RJ: The measurement of volume changes in human limbs. *J Physiol* 121:1-27, 1953
- Takeshita A, Imaizumi T, Ashihara T, et al: Limited maximal vasodilator capacity of forearm resistance vessels in normotensive young men with a familial predisposition to hypertension. *Circ Res* 50:671-677, 1982
- Hokanson DE, Sumner DS, Strandness DE: An electrically calibrated plethysmograph for direct measurement of limb blood flow. *IEEE Trans Biomed Eng* BME22:25-29, 1975
- Hill RV, Jansen JC, Fling JL: Electrical impedance plethysmography: a critical analysis. *J Appl Physiol* 22:161-168, 1967
- Yamakoshi K, Shimazu H, Togawa T, et al: Admittance plethysmography for accurate measurement of human limb blood flow. *Am J Physiol* 235:H821-H829, 1978
- Derblom H, Johnson L, Nylander G: Electrical impedance plethysmography as a method of evaluating the peripheral circulation. *Acta Chir Scand* 136:579-586, 1970
- Hill DW, Lowe HJ: The use of the electrical impedance technique for monitoring of cardiac output and limb blood flow during anesthesia. *Med Biol Eng* 11:534-545, 1973
- Nyboer J, Kreider NM, Hannapel L: Electrical impedance plethysmography: A physical and physiologic approach to peripheral vascular study. *Circulation* 2:811-821, 1950
- Clements IP, Strelow DA, Becker GP, et al: Radionuclide evaluation of peripheral circulatory dynamics: New clinical application of blood pool scintigraphy for measuring limb venous volume, capacity, and blood flow. *Am Heart J* 102:980-983, 1981
- Pavel DG, Zimmer AM, Patterson VN: In vivo labelling of red blood cells visualization. *J Nucl Med* 18:305-308, 1977
- Rutlen DL, Wakers FJ, Zaret BL: Radionuclide assessment of peripheral intravascular capacity: A technique to measure intravascular volume changes in the capacitance circulation in man. *Circulation* 64:146-152, 1981
- Fukuoka M, Kawakami K, Shimada T, et al: A new plethysmography for measuring limb blood flow using RI. *Iyodenshi To Seitaikogaku* 21:252-255, 1983
- Mason DT, Braunwald E: The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 32:755-766, 1965
- Vyden JK, Sellers A, Nagasawa K, et al: Peripheral hemodynamics in anephric patients with hypertension. *Am Heart J* 96:203-212, 1978
- Leithe ME, Margorien RD, Hermiller JB, et al: Relationship between central hemodynamics and regional blood flow in normal subjects and patients with congestive heart failure. *Circulation* 69:57-64, 1984
- Seino Y, Akaike M, Hayakawa K, et al: Changes of peripheral circulation in patients with acute myocardial infarction—Non-invasive observation by the lower limb venous occlusion plethysmography. *Kokyu To Junkan* 29:297-304, 1981
- Awan NA, Beattie JM, Evenson ME, et al: Importance of neuroendocrine regulators of vascular tone and integral adrenoreceptor interaction during oral vasodilator therapy of severe congestive heart failure with Prazosin. *J Cardiovasc Pharmacol (Suppl 1)* 4:S176-S180, 1982