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Convenient Automated Conductance Volumetric System

Kazunori UEMURA*, Masaru SUGIMACHI*, Toshiaki SHISHIDO*, Toru KAWADA*, Masashi INAGAKI*, Can ZHENG*,†, Takayuki SATO‡, and Kenji SUNAGAWA*

* Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Suita, 565–8565 Japan;
† Japan Space Forum, Minato-ku, Tokyo, 105–0013 Japan; and
‡ Second Department of Physiology, Kochi Medical School, Nankoku, 783–8505 Japan

Abstract: Conventional conductance volumetric systems require *ex-vivo* calibrations for blood conductivity and parallel conductance. It is often impractical to repeat blood sampling and hypertonic saline infusion for these calibrations. To overcome these limitations, we developed a useful, self-calibrating conductance volumetric system that does not require *ex-vivo* calibrations. On a conventional 6-electrode catheter, we added an extra electrode close to one of the recording electrodes to estimate blood conductivity. These two electrodes were placed close (0.5 mm) enough so that conductance between them reflected only blood conductivity regardless of cardiac volume. We estimated parallel conductance by the dual-frequency excitation (2 and 20 kHz) method. In 18 anesthetized rabbits, blood conductivity (σ_{est}) thus estimated agreed well with that (σ_{conv}) measured by the conventional *ex-vivo* blood sampling method ($\sigma_{est}=1.04\sigma_{conv}-0.25$, $R^2=0.98$, SEE=0.01 mS/cm, 1.2% error). Parallel conductance ($G_{p\,est}$) estimated by dual-frequency excitation also agreed well with that ($G_{p\,conv}$) estimated by the saline injection method ($G_{p\,est}=0.95G_{p\,conv}+4.25$, $R^2=0.87$, SEE=4.0 mS, 6.0% error). Estimated ventricular volume (V_{est}) by our system agreed reasonably well with that (V_{conv}) by the conventional method ($V_{est}=0.93V_{conv}+0.01$, $R^2=0.86$, SEE=0.22 ml, 14.7% error). The fact that this self-calibrating conductance volumetric system drastically simplifies volume measurement makes it an attractive tool for the assessment of cardiac function where significant changes in blood conductivity and parallel conductance are inevitable, such as in cardiac surgery. [Japanese Journal of Physiology, 52, 497–503, 2002]

Key words: conductance catheter, blood conductivity, parallel conductance.

The conductance catheter technique, a real-time ventricular volumetry method, is essential in the experimental and clinical application of the ventricular pressure–volume relationship framework [1–7]. The principles of conductance volumetry are described extensively elsewhere [1, 2]. The sum (G) of ventricular conductance signals between electrode pairs can be converted to the absolute ventricular volume (V) by the formula

$$V=\frac{1}{\alpha}\cdot\frac{L^2}{\sigma}(G-G_p),$$

where α is a volume calibration factor, L is the distance between the recording electrodes, σ is the blood conductivity, and G_p is the conductance resulting from the surrounding structures (i.e., parallel conductance).

Although the volume calibration factor is reported to be relatively constant [8], excessive changes in plasma electrolyte concentration, hematocrit, or tissue fluid contents, which are often observed during cardiac surgery, can alter blood conductivity and parallel conductance. This is also the case with the progression of chronic heart failure. Therefore, for the accurate estimation of ventricular volume, it is necessary to repeat calibrations for these quantities by blood

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Correspondence should be addressed to: Masaru Sugimachi, Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, 5–7–1, Fujishirodai, Suita, 565–8565 Japan. Tel: +81–6–6833–5012 ext 2426, Fax: +81–6–6835–5403, E-mail: sugimach@ri.ncvc.go.jp

sampling and injection of hypertonic saline [1, 2, 6, 7]. Needless to say, frequent blood samplings or saline injections are troublesome and mostly impractical during cardiac surgery as well as during chronic experiments in small animals. These manipulations are likely to alter hemodynamics and possibly exert cardio-depressive effects [9–11].

Gawne *et al.* estimated parallel conductance with the dual-frequency excitation method and successfully avoided saline injection [12]. Gopakumaran *et al.* attempted to measure blood conductivity with electrodes on the conductance catheter [13]. However, the electrode spacing was not close enough to ensure precise blood conductivity measurement in their catheter. To overcome this limitation and to make neither *ex-vivo* calibration necessary, we developed a conductance volumetric system in which these calibration methods are combined and improved.

The results indicate that the developed, self-calibrating conductance volumetric system can estimate ventricular volume with acceptable accuracy without tedious *ex-vivo* calibrations in rabbits.

MATERIALS AND METHODS

Calibration system for blood conductivity and parallel conductance. Blood conductivity (σ) is conventionally measured by an external cuvette after blood sampling. We have developed a system to measure σ using two closely spaced electrodes on the conductance catheter. These two electrodes are used for current injection and voltage sensing simultaneously. Conductance between electrodes mainly reflects that within a limited volume (hereafter denoted as effective sample volume). If the sample volume is large, the injected current can leak from the ventricular blood pool in this setting, and the resultant voltage signal is dependent on both ventricular volume and blood conductivity. If the two electrodes are placed close together and the effective sample volume is confined to within the ventricular blood pool throughout the cardiac cycle [13, 14], however, the voltage signal is only dependent on blood conductivity.

We determined the effective sample volume of conductance catheters designed for rabbit left ventricle experimentally. We placed catheters with two electrodes (0.5 mm width, platinum) at various inter-electrode distances (0.5, 1.5, and 3.0 mm) at the center of plastic syringes of various sizes filled with diluted saline. Saline conductivity was matched to that of the blood (6.6 mS/cm). A constant current (20 kHz, 0.03 mA root-mean-square) was injected between the electrodes. The resultant voltage was converted to conductance (current/voltage). With the increase in syringe diameter, conductance between electrodes increased and reached a plateau (Fig. 1A). This implied that most of the current was confined to within the cylindrical diameter with which conductance reached the plateau (i.e., effective sample volume). The narrower the inter-electrode distance, at the smaller diameter, conductance reached a plateau. At the 0.5-mm inter-electrode distance, conductance reached at least $>95\%$ of the plateau at diameters of 5 mm. This means that the effective sample volume for a 0.5-mm inter-electrode distance is kept within a diameter of about 5 mm around the catheter. Left ventricular inner diameters were 15 ± 2 mm at end-diastole, and 9 ± 2 mm at end-systole in rabbits by ultrasound cardiography [15]. Consequently, when a catheter with two electrodes of 0.5-mm inter-electrode distance is centered in the rabbit left ventricle at its largest diameter, the effective sample volume is limited to within the

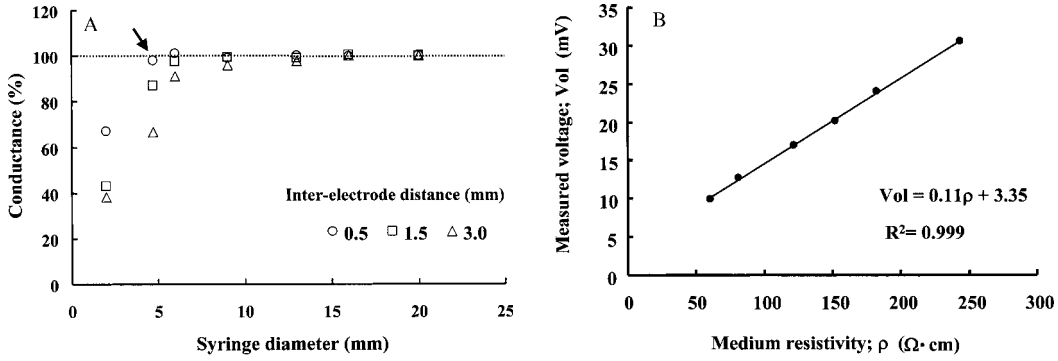

Fig. 1. A: Determination of effective sample volume of conductance catheter. Relationships between syringe diameter and conductance (normalized by its maximal value) are shown for catheters with 0.5, 1.5, and 3.0-mm inter-electrode distance. Conductance reaches a plateau at a 5-mm diameter (arrow) with a catheter having a 0.5-mm inter-electrode distance. This indicates that effective sample volume of a catheter with a 0.5-mm inter-electrode distance is confined to within a 5-mm diameter around the catheter. **B: Relationship between the voltage between the two electrodes and medium resistivity.**

ventricular blood pool throughout the cardiac cycle.

The resultant voltage signal is converted to σ by a conversion formula (Fig. 1B). We determined the conversion formula experimentally. We first examined the relation between measured voltage between the two electrodes and medium resistivity (reciprocal of conductivity). We placed a catheter with a 0.5-mm interelectrode distance at the center of a plastic syringe with a 9-mm diameter. Diluted saline of various resistivities from 61 to 243 Ω·cm, spanning the reported range of blood resistivity, were filled in the syringe. Constant current (20 kHz, 0.03 mA root-mean-square) was injected between the electrodes. We checked the relationship of the measured voltage (Vol; mV) and saline resistivity (ρ; Ω·cm). They strongly correlated in linear regression analysis (Fig. 1B, Vol=0.11ρ+3.35, R^2=0.999). We adopted this regression line as the conversion formula from measured voltage to blood resistivity (reciprocal of σ).

Blood essentially has a constant conductivity over the range of frequencies from 2 to 100 kHz [16]. On the other hand, cardiac muscle is more conductive with higher frequencies when examined at around 10 kHz [17]. Based on the knowledge that the cardiac muscle of the ventricular wall contributes to the largest part of parallel conductance (G_p), Gawne *et al.* [12], and Georgakopoulos *et al.* [10] developed a dual-frequency excitation method for the estimation of G_p. In accordance with their data [10], the difference between conductance signals at two different frequencies around 10 kHz was proportional to the G_p estimated by the saline method using a proportionality constant:

$$G_{p\,conv}=\kappa\times\Delta G_{20-2},$$

where $G_{p\,conv}$ is G_p by the conventional saline method, ΔG_{20-2} is the average difference in ventricular conductance signal over the cardiac cycle between 2 and 20 kHz excitation frequencies, and κ is an experimentally derived constant. Once κ is determined, G_p can be estimated with the conductance difference alone, without the necessity of saline infusion.

Volume calibration factor. In a preliminary study, we evaluated volume calibration factor, α, in 10 rabbits by comparing conductance-derived stroke volume with an ultrasound-flowmeter (4SB640, Transonics, Ithaca, NY, USA) to derive stroke volume. Mean α was 1.03 (±0.12). Therefore, α is assumed to be 1.0 in this study [3, 18, 19].

Conductance catheter and analog signal generator/processor. Figure 2 illustrates the conductance catheter designed for rabbits. It has seven platinum electrodes. An extra electrode is added 0.5 mm proximal to the distal third electrode. These two electrodes (two arrowheads) serve as both excitation and recording electrodes for σ measurement.

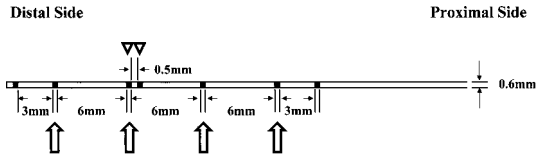

Fig. 2. A schematic illustration of the custom-made conductance catheter. Two arrowheads indicate electrodes for conductivity measurement. Four arrows indicate recording electrodes for volumetry. The two outermost electrodes are current-injection electrodes for volumetry.

We custom-made electronic circuits for both excitation and recording. The circuits are capable of simultaneously delivering 2- and 20-kHz currents (0.03 mA root-mean-square) for volumetry, and a 20-kHz single current for σ measurement. We separated volume conductance signals for each frequency with analog filters.

Animal preparation. *In vivo* validation of the volumetry system was performed in 18 Japanese White rabbits (both sexes, weighing 3–4 kg). Care of the animals was in strict accordance with the "Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences," approved by the Physiological Society of Japan. Rabbits were anesthetized with sodium pentobarbital (35 mg/kg, I.V.), tracheotomized, intubated, and mechanically ventilated with oxygen-enriched room air. Additional doses of α-chloralose (40 mg/ml) were injected as necessary for appropriate anesthesia. Three-French silicon catheters were inserted into the right jugular vein and right femoral artery for hypertonic saline injection and blood sampling, respectively. The left ventricular (LV) apex was exposed through the anterior mediastinum. The conductance catheter was inserted into the LV cavity through the apex and was advanced toward the aortic valve along the longitudinal axis of the LV cavity. After confirming that the tip of the conductance catheter was positioned in the ascending aorta, we withdrew the conductance catheter so that the three segmental volume signals were in phase and the output voltage between the conductivity measurement electrode pair was lowest, showing virtually no change during the cardiac cycle. The latter guaranteed the appropriate positioning of the catheter at the center of the ventricle. We also inserted a 3-French catheter tip micromanometer (SPC330A, Millar Instruments, Houston, TX, USA) into the LV cavity from the apex. The surgical wound was closed layer by layer, leaving the thorax almost intact. After

preparing the instrumentation, the conductance catheter was connected to our custom-made electronic circuit. We digitized the intraventricular ECG, LV pressure, and three segmental conductance signals for each of 2- and 20-kHz excitation at 1,000 Hz (AD12-16D-98H, Contec, Osaka, Japan) using a dedicated laboratory computer (PC9801FA7, NEC, Tokyo, Japan). We stored the obtained data on a hard disk for offline analysis.

Experimental protocol. We measured blood conductivity both by the conventional method (σ_{conv}), with an external cuvette, and our intraventricular measurement method (σ_{est}). Measured voltage signals between electrodes on the catheter, for conductivity measurement, were averaged over 10 cardiac cycles. This was converted to σ_{est} according to the conversion formula.

We estimated parallel conductance (G_p) using both the conventional hypertonic saline method ($G_{p\,conv}$) and the dual-frequency excitation method ($G_{p\,est}$) [2, 10, 12].

To obtain $G_{p\,conv}$, we injected 0.2 ml of saturated saline into the superior vena cava with continuous data acquisition at 20-kHz excitation. We performed a single saline injection [10]. We selected only the ascending portion of the saline wash-in into the LV. The intersection between the linear regression line between end-diastolic (at R wave of ECG) and end-systolic (minimal) conductance and the line of identity yielded $G_{p\,conv}$ [2].

To obtain $G_{p\,est}$, we delivered 2- and 20-kHz excitation simultaneously and calculated the conductance difference (ΔG_{20-2}) between 2 and 20 kHz. The difference in values was averaged over 10 cardiac cycles. We randomly selected 9 rabbits (group A) to determine the proportionality constant (κ). The ratio of $G_{p\,conv}$ to ΔG_{20-2} was calculated in each animal. We used the mean value of the ratio as κ. We obtained parallel conductance by the dual-frequency method ($G_{p\,est}$) with this constant, κ, using the following formula,

$$G_{p\,est} = \kappa \times \Delta G_{20-2},$$

for group A as well as the 9 remaining rabbits (group B).

We also compared end-diastolic and end-systolic volume determined by the conventional method (V_{conv}), with σ_{conv} and $G_{p\,conv}$, and by the system we developed (V_{est}), with σ_{est} and $G_{p\,est}$, assuming α to be unity. All data were acquired while ventilation was temporarily suspended at end-expiration. We confirmed that the effect of lungs on parallel conductance was negligible in preliminary studies. Our catheter was designed so that the most apical electrode was placed within the ventricular blood [10]. Our interelectrode distance may be a little bit smaller than commercially available catheters, making lung influence negligible.

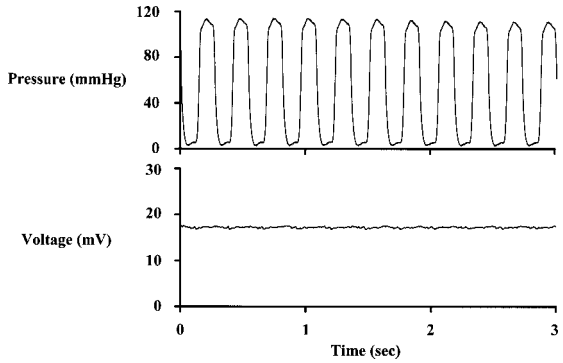

Fig. 3. An example of voltage waveform between electrodes for conductivity measurement during cardiac cycles. The signal was almost flat with minimal fluctuation. Mean voltage was 17.13 mV. Estimated blood conductivity (σ_{est}) from this value was 7.06 mS/cm. Blood conductivity (σ_{conv}) measured in a cuvette was 6.86 mS/cm in this case.

Statistics. Data are expressed as means±SD. A linear regression analysis using the least-squares method was used to determine the relationship between σ_{conv} and σ_{est}, between $G_{p\,conv}$ and $G_{p\,est}$, and between V_{conv} and V_{est}.

RESULTS

Intraventricular blood conductivity measurement

A representative example of the changes in voltage signal between electrodes for conductivity measurement is presented in Fig. 3. The voltage signal showed little fluctuation with the cardiac cycle, indicating that the effective sample volume was completely confined to within the ventricular blood pool. Conductivity measured by the method we developed (σ_{est}) correlated well with that by the conventional method (σ_{conv}) (Fig. 4, $\sigma_{est}=1.04\sigma_{conv}-0.25$, $R^2=0.98$, SEE=0.01 mS/cm, 1.2% error). The slope and the intercept were not significantly different from unity and zero, respectively.

Parallel conductance estimation with the dual-frequency excitation method

There were no significant differences between group A and B with respect to body weight and hemodynamics. A representative example of conductance signals obtained by excitation with each 2 and 20 kHz is shown in Fig. 5. The ventricular conductance signal

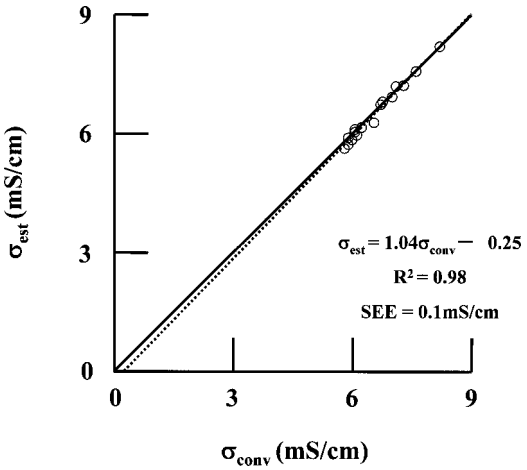

Fig. 4. Relationship between blood conductivity (σ_{conv}) measured in a cuvette and that (σ_{est}) estimated by the catheter. Dashed line, regression; solid line, identity line.

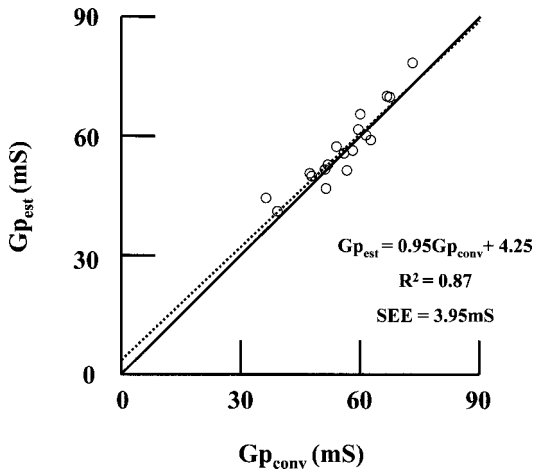

Fig. 6. Relationship between parallel conductance ($G_{p\,conv}$) estimated by the saline infusion method and that ($G_{p\,est}$) by the dual-frequency excitation method for all animals. Dashed line, regression; solid line, identity line.

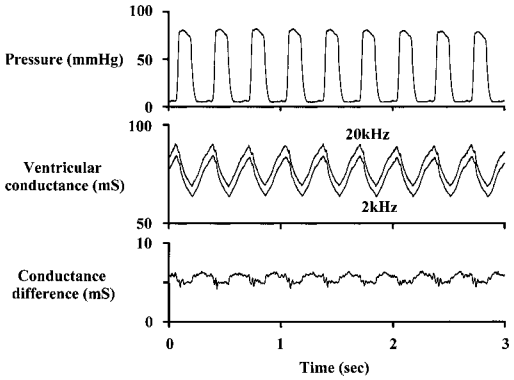

Fig. 5. An example of ventricular conductance waveforms as a function of time obtained by 2- and 20-kHz excitation in one animal. The difference between these signals is also shown at the lowest value. Average conductance difference was 5.501 mS in this case.

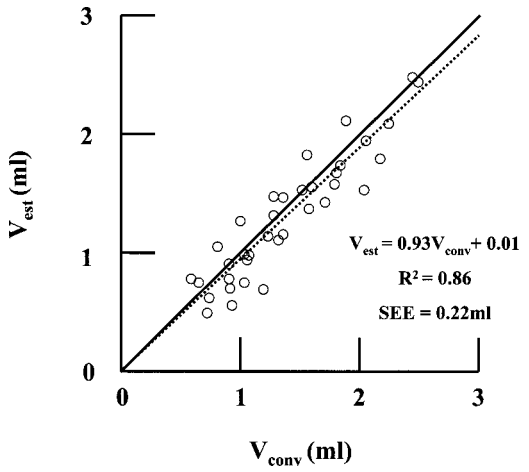

Fig. 7. Relationship between ventricular volume (V_{conv}) calibrated with $G_{p\,conv}$ and σ_{conv} and that (V_{est}) calibrated with $G_{p\,est}$ and σ_{est}. Dashed line, regression; solid line, identity line.

at 20-kHz excitation was consistently larger than that at 2 kHz. The conductance difference (ΔG_{20-2}) between 2- and 20-kHz excitation averaged over 10 cardiac cycles was 5.501 mS in this example. With hypertonic saline, $G_{p\,conv}$ was measured as 47.92 mS, resulting in the ratio of $G_{p\,conv}$ to ΔG_{20-2} as 8.71. In group A the ratio was 9.14±0.56 on the average. Because the ratio was rather constant (coefficient of variation: 6.2%) over a wide range of $G_{p\,conv}$ (39.3–67.6 mS), we used the average ratio for the empirical constant, κ. As shown in Fig. 6, parallel conductance estimated with this constant ($G_{p\,est}$) correlated well with $G_{p\,conv}$ in the 18 rabbits of groups A and B combined ($G_{p\,est}=0.95G_{p\,conv}+4.25$, $R^2=0.87$, SEE=4.0 mS, 6.0% error). The slope and intercept were not significantly different from unity and zero, respectively.

Accuracy of ventricular volume estimation

Figure 7 depicts the relation between V_{conv} and V_{est}. Volume measurements of both ESV and EDV are pooled. These correlated reasonably well ($V_{est}=0.93V_{conv}+0.01$, $R^2=0.86$, SEE=0.22 ml, 14.7% error). The slope and intercept were not significantly different from unity and zero, respectively.

DISCUSSION

We have developed a convenient automated conductance volumetric system requiring no *ex-vivo* procedures for calibration of blood conductivity or parallel conductance. We demonstrated that these two quantities, as estimated by our system, agree well with those

estimated by the conventional method. Resultant ventricular volume using our system agreed reasonably well with that estimated by the conventional method.

Conventionally, blood electrical conductivity is measured in an external cuvette with sampled blood. Frequent blood sampling is troublesome, and in small animals, this can induce anemia. While intraventricular blood is warm (i.e., body temperature) and continuously stirred, blood in an external cuvette is cool (i.e., room temperature) and stationary. The differences have been reported to cause additional errors in blood conductivity measurement (decrease of about 10%) [1]. Our system eradicates such concerns.

Gopakumaran *et al.* reported an intraventricular conductivity estimation method [13]. They seemed to have underestimated the effective sample volume. Using a numerical analysis by the finite element method, they analyzed the relationship between inter-electrode distance and effective sample volume. They showed that most of the effective sample volume of a catheter with a 9-mm inter-electrode distance was within 20 mm in diameter (fig. 8 in Gopakumaran *et al.* [13]). In contrast, we have shown, with *ex-vivo* experiments, that the effective sample volume of a catheter with a 0.5-mm inter-electrode distance was 5 mm in diameter. We conjectured that our experimental results reflected the actual effective sample volume more accurately for the following reasons. First, the resistance signal measured for conductivity measurement with their catheters changed with cardiac contraction [13], suggesting that the sample volume size was likely to exceed the ventricular end-systolic volume. Second, numerical analyses by the finite element method suffer from errors introduced with discretization. It is well known that the nearer the element, the smaller it should be. From these considerations, we conclude that a closer inter-electrode distance than that suggested in the method of Gopakumaran *et al.* is needed for precise blood conductivity measurement and that appropriate spacing can be judged by examining cyclic changes in the conductance signal.

We used the dual-frequency excitation method for the estimation of parallel conductance. Unlike the saline injection method, this method does not affect hemodynamics [9, 10]. Chaturvedi *et al.* [6] using conductance volumetry, demonstrated mild deterioration in systolic function in patients with simple congenital heart defect after cardiac operation, even with its short bypass and cross clamp time. The dual-frequency excitation method without cardio-depressant saline infusion is beneficial for the assessment of cardiac function in cardiovascular surgery, where additional cardiac depression should be avoided as much as possible.

One preferable condition for the successful estimation of parallel conductance by the dual-frequency method is that myocardial tissue comprises almost the entire parallel conductance volume. This is the case in mice, in which the relative thickness of the ventricular wall to the ventricular cavity is large enough so that parallel conductance resides almost exclusively in the myocardial tissue, and estimation accuracy was reported as being reasonably good [10]. Blood in the right ventricle could contribute to parallel conductance more or less in rabbits and other larger animal species including humans [3]. Further studies are required to develop some compensation for those non-myocardial constituents of parallel conductance in order to improve estimation accuracy by the dual-frequency method.

We found the mean ratio of parallel conductance to the conductance difference to be 9.1 in rabbits. The ratio was reported to be 10.5 in mice [10]. As suggested in previous reports, this ratio might depend on the animal species or catheter design [10, 12]. This indicates that one has to determine the ratio κ for each animal species and catheter design. In addition, it has been reported that parallel conductance varies with drastic hemodynamic changes such as in inferior vena caval occlusion [20]. Further studies are required to examine if the dual-frequency method is capable of accurately estimating dynamic changes in parallel conductance during drastic hemodynamic changes. The state of the myocardium may influence κ. As reported previously, myocardial conductance varies after myocardial ischemia [21]. How changes in myocardial electrical properties affect the constant κ remains to be studied.

Conductance signals in Figs. 3 and 5 contained high-frequency components. Because the conductance signals are obtained through highly selective bandpass (2 and 20 kHz) filters, we do not think high-frequency signals arose from the contamination with electrocardiogram. In addition, the phase of the high-frequency signals does not match that of QRS complexes. We conjectured that the high-frequency signals in Figs. 3 and 5 arose from the changes in catheter position and/or from the motion of intraventricular structure, such as papillary muscle.

In conclusion, we have developed a convenient, fully automated conductance volumetric system. Estimated ventricular volume obtained by our system agreed reasonably well with that by conventional methods. With this system, a simple insertion of the conductance catheter enabled us to estimate calibrated ventricular volume with reasonable accuracy. This

system drastically simplifies volume measurement, thereby making it a very attractive tool in the assessment of cardiac function in clinical settings such as in cardiac surgery, as well as for chronic experiments in small animals where significant changes in blood conductivity and parallel conductance are inevitable.

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