an important role in the regulation of synaptic NE concentration in the SA node. Microdialysis is a powerful tool to assess the changes of synaptic NE concentration in the SA node.

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Preliminary Study on the Detection of Cardiac Arrhythmias based on Multiple Simultaneous Electrograms

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Abstract— **Although implantable cardioverter-defibrillators have improved significantly in the past decades, the algorithms used in the identification of life-threatening arrhythmias are still not accurate enough. Conventional methods commonly misclassify tachycardias, sometimes initiating an unnecessary and uncomfortable treatment. In this paper, we proposed a new method for the identification of ventricular tachycardias and fibrillations based on the comparison of simultaneous electrograms. Our method could successfully separate supraventricular tachycardias and normal sinus rhythm, which do not require any treatment, from ventricular tachycardias and fibrillation, which are life-threatening arrhythmias and must be terminated, with a sensitivity of 93.0% and a specificity of 92.7% from the comparison of ventricular electrograms. In future studies, the classification using electrograms from the right heart must be improved.**

I. INTRODUCTION

Each year in the United States, about 450,000 people die of unexpected sudden cardiac death [1]. Further, it is known that the risk of a recurrence is high in survivors of sudden cardiac death. Therefore, in patients at risk for recurrent sustained ventricular tachycardia (VT) or fibrillation (VF), implantable cardioverter defibrillators (ICDs) are used to automatically deliver electrical shocks in order to restore the normal rhythm.

The ICDs have been used for more than 2 decades; in this period they have improved substantially becoming highly effective in terminating malignant arrhythmias. However the detection of life-threatening arrhythmias still lacks accuracy. Delivery of inappropriate shocks, commonly related to the misclassification of a supraventricular tachycardia (SVT) as a VT, can lead to pain, anxiety, depression, impaired quality of life, proarrhythmia, and poor tolerance of life-saving ICD therapy [2], [3], [4], [5], [6].

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On the other hand, the long ICD lifetime operating with typical batteries demands very low power consumption by the ICD microprocessor, which limits the use of complex detection algorithms [3].

Conventionally, ventricular arrhythmias are detected either based on the heart rate or based on the electrograms (EGMs) morphology. One example of criterion based on the heart rate is to use programmable thresholds to discriminate the arrhythmias since during a VF the heart rate is higher than during a VT, and during a VT the heart rate is higher than during a normal sinus rhythm (SR). The morphologic criterion is based on comparing the EGM morphology with a sample of pre-stored EGMs of each arrhythmia. However, both heart rate and EGM morphology are not stable, which makes it difficult to define a threshold or a particular morphology for each arrhythmia.

In this paper we propose a method for detection of ventricular arrhythmias based on the comparison of simultaneous EGMs from the left ventricle (EGM_{LV}), the right ventricle (EGM_{RV}) and the right atrium (EGM_{RA}). Preliminary results indicate that this algorithm permits earlier classification of the cardiac rhythm and with a lower computational cost than the conventional methods; however, further comparative studies are necessary. During the SR or during a SVT, the excitation is transmitted from the atrium to both ventricles through the His-Purkinje bundle; therefore, the EGM of both ventricles are synchronized with each other and with the EGM_{RA}. On the other hand, VTs and VFs are caused by an ectopic electrical excitation in the ventricle which is not transmitted through the His-Purkinje bundle causing the ventricular electrograms to be independent of each other and also of the EGM_{RA}.

II. METHODS

A. Data Description

In this study *in vivo* data were obtained from a dog in an acute experiment. EGMs were measured from leads in the left and right ventricles and right atrium and sampled at 250Hz. SVT was simulated by right atrial pacing. VT was simulated by right or left ventricular pacing. And VF was induced by electrical stimuli after the R-wave of the surface electrocardiogram. The distribution of the episodes and the length of the data of each rhythm are detailed in Table I.

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TABLE I

NUMBER OF EPISODES AND TOTAL DURATION OF THE DATA OF EACH RHYTHM

	Number of Episodes	Total Duration [s]
SR	14	179.2
SVT	5	41.6
VT	7	61.4
VF	4	40.6

B. Preprocessing

The data were analyzed in a moving data window with 1.0s length and 0.2s shift. Before the analysis, the signals were band-pass filtered between 0.8Hz and 35Hz to reduce noise and remove the baseline. Next, the relative distribution of each pair of EGMs was extracted from two dimensional histograms with 5x5 bins. In Fig. 1 are represented examples of histograms of EGM_{LV} versus EGM_{RV} for the SR and for some arrhythmias.

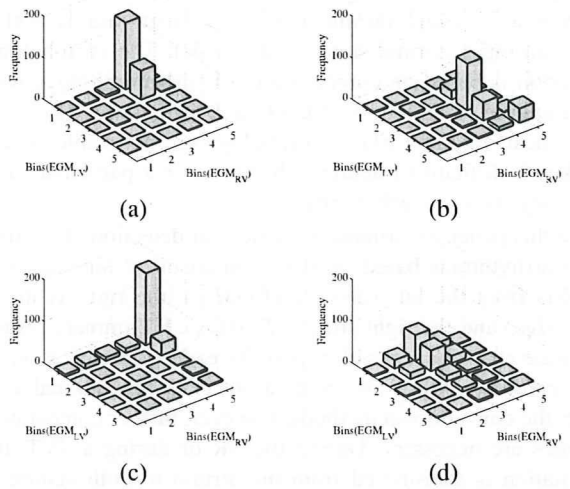

Fig. 1. Histograms representing relative distribution of EGM_{LV} and EGM_{RV} during (a) SR, (b) SVT, (c) VT and (d) VF

C. Classification

The classification was based on a decision tree using the Pearson's χ^2 statistic and the variation of the histograms. The first index was used to separate SRs and SVTs from VTs and VFs, while the second one was used to separate VTs from VFs.

The Pearson's χ^2 statistic was used to test the null hypothesis that the EGM_{LV} and the EGM_{RV}, or the EGM_{RA} and the EGM_{RV}, are independent, which is false in SRs and SVTs. The value of the test statistic χ^2 is

$$\chi^2 = \sum_{i=1}^{n_i} \sum_{j=1}^{n_j} \frac{(O_{ij} - E_{ij})^2}{E_{ij}}, \qquad (1)$$

where O_{ij} is an observed frequency, E_{ij} is the expected frequency if confirmed the null hypothesis and n is the number of possible outcomes of each event.

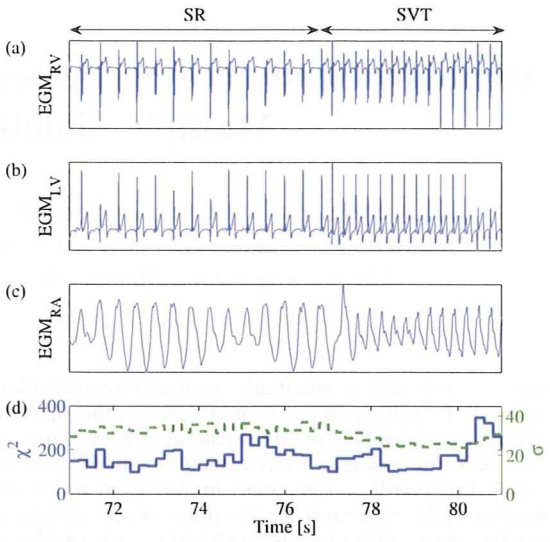

Fig. 2. Example of (a) EGM_{RV}, (b) EGM_{LV}, (c) EGM_{RA} and (d) the calculated χ^2 statistic (continuous line) and dispersion σ (dashed line) during a SVT episode.

We calculated the χ^2 using (2) approximating the joint probability distribution ($p(a_i,b_j)$) to the frequency of each bin of the histogram and the probability distribution corresponding to each EGM ($p(a_i)$ and $p(b_j)$) to the sum of the frequency of each column and each row, respectively.

$$\chi^2 = \sum_{i=1}^{5} \sum_{j=1}^{5} \frac{(p(a_i,b_j) - p(a_i) \cdot p(b_j))^2}{p(a_i) \cdot p(b_j)}. \qquad (2)$$

Next, the dispersion of the histogram of two EGMs was used to identify VFs. The dispersion of the histogram was calculated as the standard deviation (σ) of the counts in each bin of the histogram, as in (3).

$$\sigma = \frac{1}{n_a \cdot n_b} \sum_{i=1}^{n_a} \sum_{j=1}^{n_b} (p(a_i,b_j) - \mu)^2, \qquad (3)$$

where μ is the mean of $p(a_i,b_j)$.

The classification was validated using a 10-fold cross validation. The training and validation sets were separated maintaining a constant rate of 9:1 samples of each rhythm. The thresholds were interactively defined as the value that maximizes the sensitivity and the specificity of the classification of the training set.

III. RESULTS

Figs. 2, 3 and 4 show examples of EGMs and the calculated indices during the transition to a SVT, a VT and a VF episode, respectively. In the top three graphs ((a), (b) and (c)) of each figure are represented segments of EGMs acquired simultaneously from the right ventricle, left ventricle and right atrium. In the bottom graph (d) of each figure are shown the values of the indices used for the classification: χ^2-statistic and σ, extracted from the ventricular EGMs represented in the top graphs.

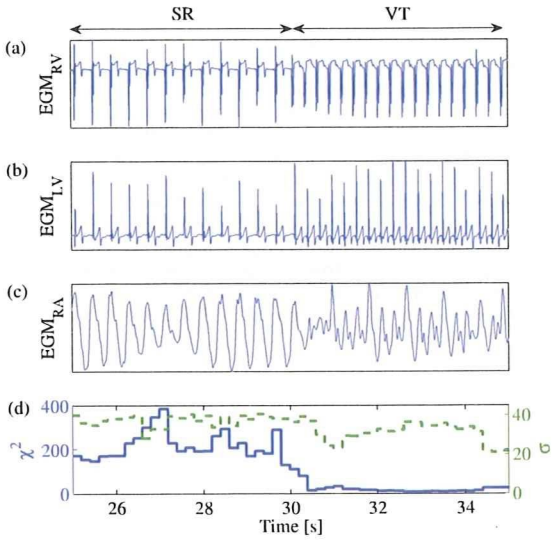

Fig. 3. Example of (a) EGM_{RV}, (b) EGM_{LV}, (c) $EGM_{RA}$and (d) the calculated χ^2 statistic (continuous line) and dispersion σ (dashed line) during a VT episode.

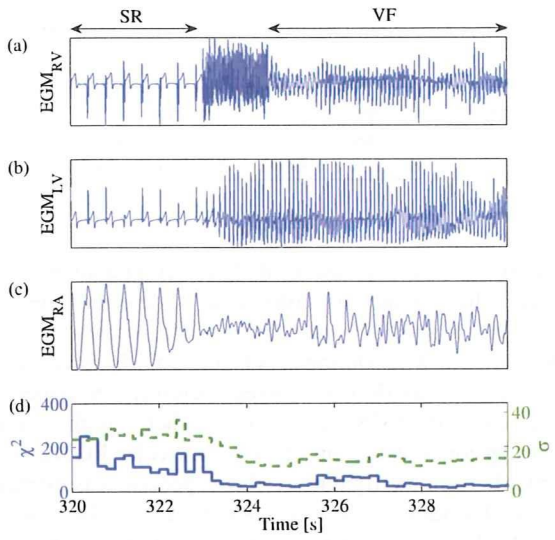

Fig. 4. Example of (a) EGM_{RV}, (b) EGM_{LV}, (c) $EGM_{RA}$and (d) the calculated χ^2 statistic (continuous line) and dispersion σ (dashed line) during a VF episode.

TABLE II

PERFORMANCE OF THE CLASSIFIER USING EGM_{LV} AND EGM_{RV} (VENTRICULAR ARRHYTHMIAS VS. OTHER RHYTHMS)

	VT or VF	SR or SVT
Shock	TP = 549	FP = 86
Ignore	FN = 41	TN = 1104
	Sensitivity = 93.0%	Specificity = 92.7%

TABLE III

PERFORMANCE OF THE CLASSIFIER USING EGM_{LV} AND EGM_{RV} (VT VS. VF)

	VF	VT
Shock	TP = 229	FP = 7
Pacing	FN = 10	TN = 303
	Sensitivity = 95.8%	Specificity = 97.7%

The results from the validation of the classifier are shown in Tables II - V. In the classification using both ventricular EGMs, EGM_{LV} and EGM_{RV}, the mean ($\pm$ standard deviation) threshold for the χ^2 was 76.4 ($\pm$ 1.9) and the mean threshold for the σ was 16.8 ($\pm$ 0.3). In the classification using ECGs from the right heart, EGM_{RA} and EGM_{RV}, the mean ($\pm$ standard deviation) threshold for the χ^2 was 61.1 ($\pm$ 0.9) and the mean threshold for the σ was 13.2 ($\pm$ 0.2).

The sensitivity and specificity of the classifier were calculated from the sum of the respective true positive (TP), false positive (FP), false negative (FN) and true negative (TN) of each interaction of the cross validation. The detailed results of the detection of life-threatening arrhythmias, by separating VTs and VFs from SVTs and SRs, are shown in Tables II and IV. The results of the decision of whether the ICD should apply a shock to recover from a VF, or start pacing to recover from a VT, are detailed in Tables III and V.

The results presented in Tables II and III correspond to the classification based on the EGM_{LV} and the EGM_{RV}, which are available only in biventricular ICDs. The results presented in Tables IV and V correspond to the classification based on the EGM_{RA} and the EGM_{RV}, which are available also in dual chamber ICDs.

IV. DISCUSSION

Conventional methods for the discrimination of the cardiac rhythms have a special limitation for the separation between SVTs and VTs. Studies using morphology-based algorithms have reported higher specificity and sensitivity in this detection, however it was still necessary to have a more accurate method that could fit the low computational cost requirements of an ICD [5].

In this paper, we proposed a new algorithm for the detection of arrhythmias for ICDs. On the basis of the comparison of EGMs, VF and VT were separated from SVT or SR by the comparison of the independence of the two simultaneous EGMs. It was observed that during the normal SR, and also during SVT, there was a high similarity especially between the EGM_{LV} and the EGM_{RV}, which decreased during ventricular arrhythmias. Dependencies are commonly measured using mutual information or χ^2 statistics; in this study, we

TABLE IV

PERFORMANCE OF THE CLASSIFIER USING EGM_{RA} AND EGM_{RV} (VENTRICULAR ARRHYTHMIAS VS. OTHER RHYTHMS)

	VT or VF	SR or SVT
Shock	TP = 439	FP = 318
Ignore	FN = 151	TN = 872
	Sensitivity = 74.4%	Specificity = 73.3%

TABLE V

PERFORMANCE OF THE CLASSIFIER USING EGM_{RA} AND EGM_{RV} (VT VS. VF)

	VF	VT
Shock	TP = 223	FP = 1
Pacing	FN = 26	TN = 189
	Sensitivity = 89.6%	Specificity = 99.5%

choose the χ^2 statistics due to its lower computational cost.

Once a life-threatening arrhythmia is detected, the ICD must apply a shock, if rhythm is a VF, or start pacing, if rhythm is a VT. During a VF, the EGMs have higher frequencies and are desynchronized; therefore, the dispersion of one ventricular EGM against the another is high. Using a two-dimensional histogram of two ventricular EGMs, or of two EGMs from the right heart, the dispersion was extracted from the deviation of the frequency in each of the bins.

A 10-fold cross-validation showed that the method has a high sensibility and specificity even in the separation of SVTs from VTs when using ventricular EGMs. However, EGMs of both ventricles are not usually acquired in dual-chamber ICDs. The results of the classification using EGMs from the right heart showed a poor separation of SVTs and VTs. These results are expected to be improved when accounting information from past windows. For instance, during a SVT if some isolated samples was classified as VT, the classification as a VT is probably wrong. The low standard deviation of the threshold during the cross validation reflects the stability of the chosen indices.

These results were obtained from a limited data set. The algorithm must be evaluated in more data from different conditions. The use of indices obtained from histograms has the advantage to be independent of the signal amplitude. Therefore, it is expected to be more robust, for example, to differences among patients and to patients activities.

V. CONCLUSIONS AND FUTURE WORKS

In a limited dataset, this preliminary study showed the possibility to detect life-threatening arrhythmias from the comparison of simultaneous electrograms by the extraction of the independence of electrograms using the χ^2 statistic and of the relative dispersion of electrograms using the standard deviation of their joint probability.

In future studies, other features should be extracted from the EGM_{RV} and EGM_{RA}, such as phase synchronization and delay or relative period, in order to improve the classification using EGMs from the right heart only, which would permit the application of this algorithm not only in biventricular ICDs but also in dual-chamber ICDs.

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Coronary Artery Volume Noninvasively Measured With Multislice Computed Tomography

— Definition, Accuracy and Implication —

Masaru Sugimachi, MD; Toru Kawada, MD

In this issue of *Circulation Journal*, Ehara et al[1] describe a new concept of measuring 'coronary artery volume' (CAV) to examine the balance between coronary vasculature and myocardial mass. They have developed a method of measuring CAV as accurately as possible using 64-slice computed tomography (64-MSCT). An adaptive threshold value was used to detect the coronary artery border to improve the accuracy of CAV. Ehara et al have exemplified the usefulness of CAV by examining the relationship between CAV and left ventricular mass (LVM) in consecutive patients undergoing MSCT without significant coronary artery stenosis or left ventricular wall motion abnormality. The authors concluded that CAV increases with LVM, but that the increase was not sufficient for the increase in LVM.

Article p 1448

What is CAV?

The authors have defined CAV as the sum of the small volumes opacified by the contrast medium. The opacified small volumes were detected by the difference of radiodensity or Hounsfield unit (an index showing the degree of transparency to X-ray) using 64-MSCT (see below for details). Because the authors have analyzed data of routine 64-MSCT for the evaluation of coronary artery disease, the image is taken when the arterial side is mainly opacified, during the diastolic cardiac phase, and under coronary vasodilatation. Therefore, CAV mainly represents the sum of volumes of epicardial coronary arteries larger than the arteries undetectable due to the limited resolution of MSCT (see below).

How Accurate and Reproducible is CAV Measurement?

In this article, the authors have established a method of measuring CAV with every attempt to improve the accuracy and reproducibility for their MSCT device. These procedures are worthy of being discussed for other researchers who are interested in and would like to reproduce CAV measurement.

Inaccuracies and variability of CAV measurement would arise from (1) an arbitrary cut-off value for border detection, (2) partial volume effect, (3) motion artifact and (4) possible variable resolution of various MSCT devices. The authors have wisely minimized the errors introduced by the first 3 factors.

It is usually difficult to determine the border of the coronary arteries with a reasonable criterion. This may be because opacification of arteries is incomplete, or the opacification is thinner near the border than the center, resulting in a gradual decrease in radiodensity at the border, rather than a clear-cut abrupt change in radiodensity. In addition, at the border of small arteries, a voxel (the smallest size identified by 64-MSCT) may contain both arterial lumen (which is opacified) and arterial wall (which is not opacified). A voxel has a radiodensity of an intermediate value between an opacified and unopacified voxel, which is known as the 'partial volume effect'.

To minimize the errors introduced by an arbitrary cut-off value and the partial volume effect, the authors have developed a way of reasonably determining the cut-off value for border detection, based on preliminary phantom experiments with moving cylinders containing various concentrations of contrast medium. The results of these preliminary experiments are summarized in Figures 1–3 in Ehara et al! Figure 2 clearly shows that a cut-off value that exactly reproduces the phantom cylinder volume can be determined. The cut-off value is, however, not fixed, but changes with the true radiodensity of the contrast medium in the cylinder. Based on this, the authors determined the cut-off value for CAV measurement, adaptively in each subject, in reference to the radiodensity of the proximal region of the left and right coronary arteries. The cut-off value was not relatively influenced by different heart rates, which also decreased the degree of error by motion artifacts. Similar procedures may be applicable to quantitative coronary angiography.

The determined threshold is, however, only valid for the specific MSCT device used in the study by Ehara et al! If other researchers are to reproduce their CAV measurement, another attempt to determine the threshold for their device is necessary.

The limited resolution of MSCT would determine the definition of CAV. The authors used MSCT with an isotropic resolution of 400μm. This indicates that CAV in the paper by Ehara et al would be the sum of volume of the arteries >400μm. If MSCT is used with a different resolution, the definition of CAV would be different and CAV would be systematically different.

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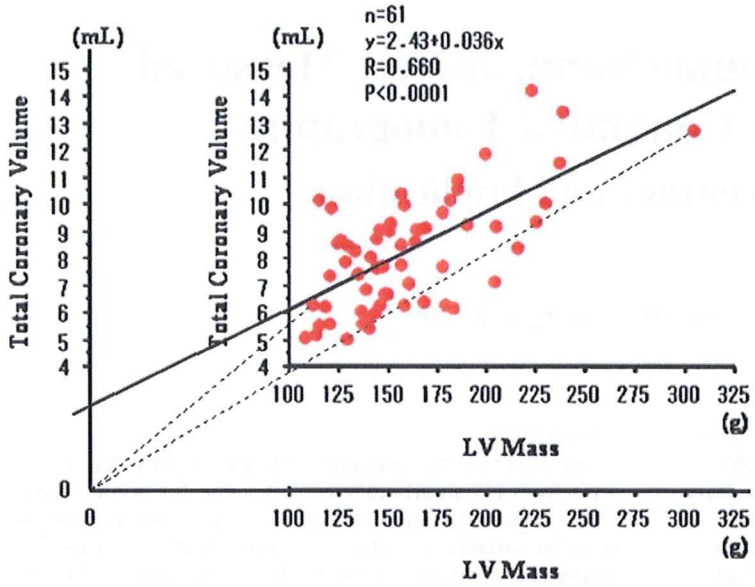

Figure. Linear regression between coronary artery volume (total coronary volume) and left ventricular (LV) mass (reproduced and modified from Ehara et al[1]). The axes are extended and the regression line is extrapolated to show a positive offset of coronary artery volume. Schematically, the authors have compared the slopes of dashed lines.

Is CAV a Proxy for Capillary Density or Coronary Flow Reserve?

The relation between coronary vasculature and myocardial mass, or more specifically inappropriate perfusion of the myocardium, has been traditionally examined histologically[2] by capillary density. Later, similar information was obtained in vivo by the measurement of coronary flow reserve. In fact, some have described the relationship between coronary capillary density and coronary flow reserve in patients with hypertrophic cardiomyopathy[3] in patients with idiopathic dilated cardiomyopathy[4] or in mini pigs with hypercholesterolemia[5]

In contrast, the way in which CAV correlates with coronary capillary density or coronary flow reserve is yet to be determined. As CAV measures the volume of arteries far larger than capillaries, these problems need to be resolved (eg, by animal experiments) before we can measure CAV in patients with a wide variety of cardiovascular diseases.

It is also reasonable to assume CAV may provide information other than coronary capillary density or coronary flow reserve. In Ehara et al, CAV is only measured under nitroglycerine. The response of CAV to increased coronary flow or to endothelium-dependent vasodilatation may be of clinical value. If better accuracy and reproducibility is established, CAV may potentially replace quantitative coronary angiography for this purpose because of its noninvasive nature.

Is CAV Really Unmatched With LVM?

The authors' conclusion of unmatched CAV with LVM should be discussed. **Figure** shows the linear regression between CAV and LVM reproduced and modified from Figure 6 of Ehara et al. The modified figure has extended axes and the extrapolated regression line has been added.

Even though there is only a single data set for each patient, the authors assumed that the line started at the origin and calculated the slope. Schematically, they have compared the slopes of dashed lines.

Figure, however, indicates that the CAV–LVM relationship obtained from pooled data has a positive CAV offset, but does note indicate that the slope is shallow. Because there is no reason to deny the presence of a positive CAV offset, and because the slope was not compared with a standard slope, the conclusion of unmatched CAV with LVM is not solid.

This question may be resolved by comparing the CAV–LVM relationship obtained by sequential CAV measurement during physiological growth and that obtained during the progression of pathological hypertrophy of the heart in animal experiments.

Advantage of CAV Measurement

The noninvasive nature of CAV measurement enhances its clinical usefulness because it enables sequential evaluation and may help to bring evaluations still in the investigational stage into routine bedside practice. Similar technological developments (eg, coronary flow reserve by cine magnetic resonance[6]) may be combined and eventually enable the detailed pathophysiology of cardiovascular disease to be described.

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Feedback Control of Multiple Hemodynamic Variables with Multiple Cardiovascular Drugs

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Abstract— **The ultimate goal of disease treatment is to control the biological system beyond the native regulation to combat pathological process. To maximize the advantage of drugs, we attempted to pharmacologically control the biological system at will, e.g., control multiple hemodynamic variables with multiple cardiovascular drugs. A comprehensive physiological cardiovascular model enabled us to evaluate cardiovascular properties (pump function, vascular resistance, and blood volume) and the feedback control of these properties. In 12 dogs, with dobutamine (5±3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), nitroprusside (4±2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dextran (2±2 $ml \cdot kg^{-1}$), and furosemide (10 mg in one, 20 mg in one), rapid, sufficient and stable control of pump function, vascular resistance and blood volume resulted in similarly quick and stable control of blood pressure, cardiac output and left atrial pressure in 5±7, 7±5, and 12±10 minutes, respectively. These variables remained stable for 60 minutes (RMS 4±3 mmHg, 5±2 $ml \cdot min^{-1} \cdot kg^{-1}$, 0.8±0.6 mmHg, respectively).**

I. Introduction

THE ultimate goal of disease treatment is to control the biological system beyond the native regulation to combat pathological process. This control may be partly achieved by native regulatory systems, but these frequently fail when disease progresses.

Many pharmacological treatments have provided us with control measures that may act in ways not possible by native regulators. To fully take advantage of these medicines, we must establish ways of using these agents to control the biological system at our will. As an example, we tried to control multiple hemodynamic variables with multiple cardiovascular drugs.

Several closed-loop systems have succeeded in directly controlling a single hemodynamic variable [1,2]. Multiple-variable control, however, has been unsuccessful [3-5].

Multiple-input multiple-output feedback control remains a challenge if the input-output relationships for all combinations are of equal significance. We therefore tried to decouple the input-output relationships by using a comprehensive physiological cardiovascular model. The model enabled us to define a set of parallel independent relationships between cardiovascular properties and drugs: pump function / inotrope, vascular resistance / vasodilator, and blood volume / volume expander. The model also provided us with a method to quantitatively calculate cardiovascular properties.

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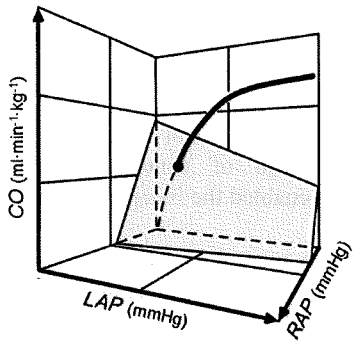

Fig. 1. Extended Guyton's model.
Thick curve, pump function of left and right heart; shaded surface, capacitive function of total vascular beds; CO, cardiac output; LAP, left atrial pressure; RAP, right atrial pressure.

II. Model and Methods

A. Cardiovascular property identification

Abnormalities of hemodynamic variables arise from abnormalities of cardiovascular properties, including pump function, vascular resistance, and blood volume. We identified these properties using an extended version of Guyton's circulatory equilibrium framework (Fig. 1) [6,7].

Pump function of the left heart (S_L) can be quantified as the ratio of cardiac output (CO) to the logarithm of left atrial pressure (LAP) ($S_L = CO / [\ln (LAP - 2.03) + 0.80]$). Systemic vascular resistance (R) can be calculated as blood pressure (BP) minus right atrial pressure (RAP) divided by CO. Stressed total blood volume (V) is obtained by $V = (CO + 19.61\ RAP + 3.49\ LAP) \times 0.129$.

B. Autopilot System

Autopilot controller of multiple hemodynamic variables consisted of multiple feedback loops. We designed these

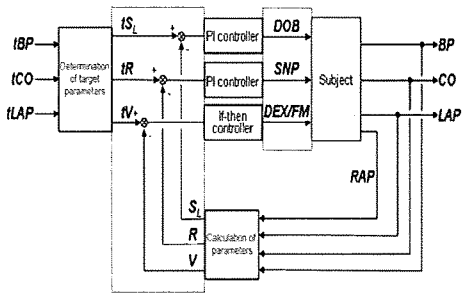

Fig. 2. Autopilot controller.
Calculated cardiovascular properties, rather than hemodynamic variables, were feedback-controlled to achieve multiple independent control of variables.

feedbacks as being independent of each other. The selection and the combination of controlled property and the controlling drugs enabled the independent operation (Fig. 2) [8].

S_L and R were controlled by proportional-integral (PI) feedback, with infusion of dobutamine (DOB) and sodium nitroprusside (SNP), respectively. Proportional and integral gain values were calculated using Chien-Hrones-Reswick's method [9] from gain, time constant, and dead-time delay of the approximated first-order step responses of S_L to DOB and R to SNP. We infused 10% dextran 40 solution (DEX, 10 $ml \cdot min^{-1}$) as long as V was <1 $ml \cdot kg^{-1}$ than the target, and injected furosemide (FM, 10 mg) every 20 minutes while V was >2 $ml \cdot kg^{-1}$ than the target.

C. *Animal Experiments*

We evaluated the performance of the autopilot controller in 12 adult anesthetized mongrel dogs (both sexes, 25±4 kg). We measured BP, CO, LAP and RAP. DOB, SNP, and DEX were automatically administered into the femoral vein through independent infusion routes, using either a computer-controlled roller pump or an infusion pump. FM was given through the jugular vein manually according to computer instructions.

These dogs underwent coronary microembolization, resulting in left ventricular failure. After hemodynamic stabilization, we began implementing control using the autopilot system.

III. Results

	Proportional gain (K_p) $\mu g \cdot ml^{-1}$	Integral gain (K_i) sec^{-1}
S_L control	0.06	0.01
R control	-1.37	0.007

Table 1. Selected gain parameters for designed controller.
Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) of drugs for the control of S_L (DOB) or R (SNP) is determined as (Dose) = $K_p (1 + K_i / s) \Delta$(Controlled variable)

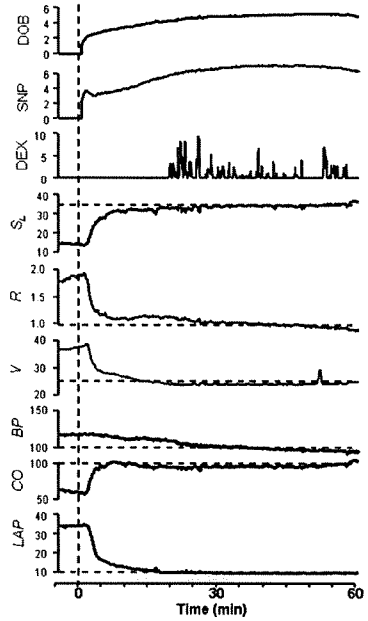

Fig. 3. An example of the automatic control of hemodynamics.
Feedback control was rapid, sufficient, and stable. DOB, dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$); SNP, sodium nitroprusside ($\mu g \cdot kg^{-1} \cdot min^{-1}$); DEX, dextran 40 solution ($ml \cdot min^{-1}$); S_L, pump function ($ml \cdot kg^{-1} \cdot min^{-1}$); R, resistance ($mmHg \cdot ml^{-1} \cdot kg \cdot min$); V, blood volume ($ml \cdot kg^{-1}$); BP, blood pressure (mmHg); CO, cardiac output ($ml \cdot kg^{-1} \cdot min^{-1}$); LAP, left atrial pressure (mmHg)

Based on the step response from coronary microembolized dogs, we determined the proportional and integral gain as shown in Table 1.

Similar to the example shown in Figure 3, in 12 dogs, by administering DOB (5±3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), SNP (4±2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), DEX (2±2 $ml \cdot kg^{-1}$), and FM (10 mg in one, 20 mg in one), rapid, sufficient and stable control of S_L, R and V. This resulted in corresponding appropriate control of BP, CO and LAP in 5±7, 7±5, and 12±10 minutes, respectively. These remained stable for 60 minutes (RMS BP=4±3 mmHg, CO=5±2 $ml \cdot min^{-1} \cdot kg^{-1}$, LAP=0.8±0.6 mmHg).

IV. Discussion

We have shown that by evaluating cardiovascular properties (pump function, vascular resistance, and blood volume), and then controlling these properties with individually selected drugs, we were able to automatically control multiple hemodynamic abnormalities rapidly, stably, and simultaneously.

Direct control of multiple hemodynamic variables, however, likely fails because each drug affects more than one variable. Direct control remains unfeasible even with more complicated methods developed in control engineering; appropriate physiological modeling and precise evaluation of cardiovascular properties are essential to achieving adequate control.

V. CONCLUSION

Calculating cardiovascular properties (pump function, vascular resistance, and blood volume) based on a comprehensive cardiovascular model and feedback control of these properties are required for the accurate control of multiple hemodynamic variables (BP, CO, LAP).

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Macroscopic Two-Pump Two-Vasculature Cardiovascular Model to Support Treatment of Acute Heart Failure

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Abstract— **Comprehensive understanding of hemodynamics remains a challenge even for expert cardiologists, partially due to a lack of an appropriate macroscopic model. We attempted to amend three major problems of Guyton's conceptual model (unknown left atrial pressure, unilateral heart damage, blood redistribution) and developed a comprehensive macroscopic model of hemodynamics that provides quantitative information. We incorporated a third axis of left atrial pressure, resulting in a 3D coordinate system. Pump functions of left and right heart are expressed by an integrated cardiac output curve, and the capacitive function of total vasculature by a venous return surface. The equations for both the cardiac output curve and venous return surface would facilitate precise diagnosis (especially evaluation of blood volume) and choice of appropriate treatments, including application to autopilot systems.**

I. Introduction

Comprehsnsive understanding of hemodynamics remains a challenge even for specialist clinicians including cardiologists. This is in part attributed to a lack of an appropriate macroscopic model of hemodynamics that would facilitate reasoning. Most cardiologists relied only on, if at all, the classical Guyton's circulatory equilibrium framework [1].

Guyton's model consists of only two subdivisions of the whole circulation: the cardiopulmonary component (in which both hearts and pulmonary vasculature are lumped) and the systemic vascular bed. These two subdivisions are characterized by the 'cardiac output curve' and 'venous return curve', respectively. The 'cardiac output curve' approximated the (total) pump function, and the 'venous return curve' approximated the capacitive function of systemic vasculature. The intersection of these curves coincides with the operating point of the circulation.

Guyton's model is, however, inappropriate (see Model and Methods) for the understanding of hemodynamics in patients with, for example, acute myocardial infarction, where only one ventricle is preferentially damaged. That is why many cardiologists gradually abandoned using Guyton's model for their reasoning.

If we can amend the shortcomings of Guyton's model and develop a more appropriate model, the new model would obviously help diagnosis procedures and treatment selection. Furthermore, the model may be able to quantify the hemodynamic abnormalities rather than just to identify them.

Therefore, the aim of this study was to develop a comprehensive macroscopic model of hemodynamics that would provide quantitative information and aid diagnosis and treatments.

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II. Model and Methods

A. Shortcomings of Guyton's Model

Guyton's model has a number of problems when used in patients with unilateral heart failure.

First, the model does not provide left atrial pressure (LAP) values directly. LAP indicates the degree of pulmonary congestion and blood desaturation, and is as important as cardiac output (CO) and blood pressure.

Second, it is impossible to precisely model unilateral heart failure, which is frequently seen in patients with ischemic heart disease.

Third, in unilateral heart failure, the relative blood volumes in pulmonary and systemic vascular beds vary. As Guyton's model assumes only blood volume within the systemic vascular bed, such redistribution would shift the venous return curve even though the total blood volume remains the same.

B. Development of Comprehensive Cardiovascular Model

To solve the above problems, we extended Guyton's model.

First, a third axis of LAP was introduced in our new model (Fig. 1) [2], [3], so that LAP can be obtained directly. The pumping ability of the heart and the capacitive function of the vasculature are expressed simultaneously in the 3D space (RAP-LAP-CO coordinate system).

Second, the pumping abilities of the left and right heart are expressed separately by the respective cardiac output surfaces that are independent of each other. In an equilibrium state, by matching the cardiac output of both sides, the pumping ability of the whole heart can be integrated and expressed by a curve

expressing the intersection of the two surfaces (integrated cardiac output curve, Fig. 1, thick curve).

Third, the capacitive function of total vasculature (including both systemic and pulmonary vasculatures) is expressed by the venous return surface (Fig. 1, shaded surface), which is an extension of the venous return curve. This surface expresses the changes in LAP and right atrial pressure (RAP) in response to CO change, while the total intravascular blood volume remains constant. In addition, blood redistribution between systemic and pulmonary vasculatures (without change in total blood volume) will be expressed by movement within the surface rather than by deviation from the surface.

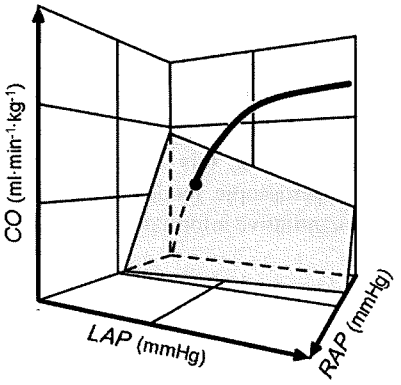

Fig. 1. An original macroscopic model of hemodynamics (an extended Guyton's model). The curve expresses the integrated pumping ability of left and right heart. The shaded surface characterizes the capacitive function of the total (systemic + pulmonary) vasculatures. The surface remains constant as long as the total intravascular blood volume remains the same. CO, cardiac output; LAP, left atrial pressure; RAP, right atrial pressure.

C. Animal Experiments to Characterize Venous Return Surface

Figure 2 depicts the scheme of an experiment to characterize the venous return surface. We replaced the left and right heart with roller pumps, which allows us to change CO of the right heart or left heart independently.

By adjusting the flow (i.e., CO) of the two pumps to the same level, the changes in RAP and LAP in response to a change in CO can be observed. Blood redistribution between systemic and pulmonary vasculatures can be reproduced by transiently unbalancing the flow of the two pumps.

From each dog (n = 6), we obtained 6 different sets of data (CO, RAP, LAP). These data were subjected to bivariate linear regression using RAP and LAP as independent variables and CO as the dependent variable.

III. Results

Figure 3 illustrates the venous return surfaces obtained from 6 dogs. Bivariate linear regression in each animal yielded a flat surface in 3D space. The surface is shown as a line in Fig. 3, because we have projected the surface in a

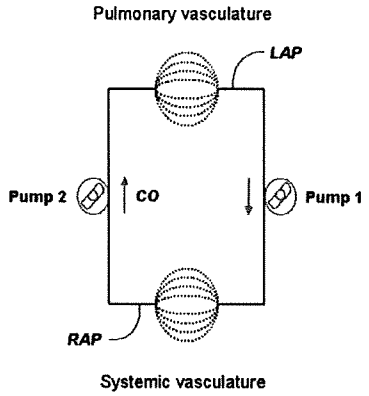

Fig. 2. An experimental scheme to characterize venous return surface. By replacing the left and right heart with roller pumps, one can change cardiac output of the right heart or left heart independently.

direction parallel to the surface. The experimental data obtained from each of the 6 animals showed good fit with the surface. In addition, the surfaces obtained from 6 animals were almost parallel, as shown by the nearly parallel 3D coordinate axes. These experimental results indicated that the venous return surface is linear and can be expressed by a common equation for all animals.

Further, by infusing or withdrawing known amounts of blood, we were able to derive an equation for the venous return surface as follows:

$$CO = V / 0.129 - 19.61\ RAP - 3.49\ LAP$$

where V is total intravascular stressed blood volume. This formula [$V = (CO + 19.61\ RAP + 3.49\ LAP) \times 0.129$] can be used to quantify V from CO, RAP and LAP.

We also succeeded to quantify the integrated cardiac output curve by logarithmic functions as follows:

$$CO = S_L\ [\ln(LAP-2.03)+0.80]$$

$$CO = S_R\ [\ln(RAP-2.13)+1.90]$$

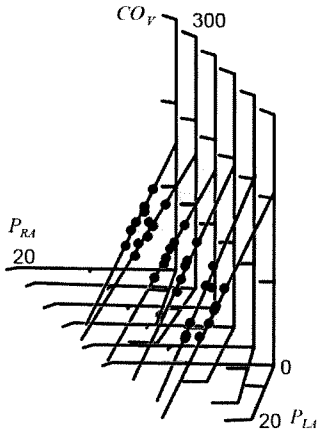

Fig. 3. Superimposed venous return surfaces obtained from 6 dogs. For each dog, the venous return surface (RAP-LAP-CO relationship) in 3D coordinate system was projected in a direction parallel to the surface, and was superimposed with each other.

where S_L and S_R are parameters expressing the pumping ability of the left and right heart, respectively. These equations are also useful for quantifying the pumping ability of right and left heart (S_L = CO / [ln(LAP - 2.03) + 0.80], S_R = CO / [ln(RAP - 2.13) + 1.90]).

Using this model, we are able to predict with acceptable precision the hemodynamics after infusion or withdrawal of known amounts of blood (CO: y = 0.93x + 6.5, r^2 = 0.96, SEE = 7.5 ml·min^{-1}·kg^{-1}; LAP: y = 0.90x + 0.5, r^2= 0.93, SEE = 1.4 mmHg; RAP: y = 0.87x + 0.4, r^2= 0.91, SEE = 0.4 mmHg) (Fig. 4) [3].

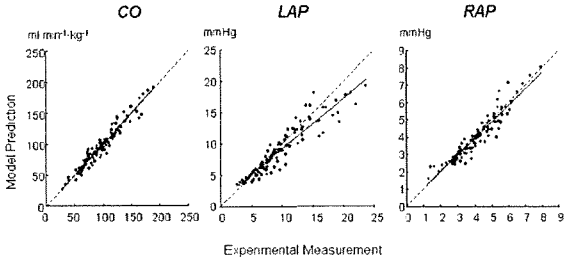

Fig. 4. Prediction of CO, LAP, and RAP based on our comprehensive macroscopic model of hemodynamics.

IV. Discussion

A. Difficulty in Decision Making of Heart Failure Treatment

Three hemodynamic variables: blood pressure, CO and LAP, appear to be the most essential factors influencing the survival of patients with heart failure. Our model clearly indicates that pump functions of left and right heart and total intravascular blood volume are determinants of CO and LAP. Systemic vascular resistance is an additional determinant of blood pressure.

For clinicians, the evaluation of blood volume is relatively difficult compared to pump functions and vascular resistance. In practice, clinicians have been using RAP as a proxy for blood volume. It is clear from our results [V = (CO + 19.61 RAP + 3.49 LAP) × 0.129] that blood volume (V) is not solely determined by RAP. Rather, all three parameters of CO, RAP and LAP are necessary to evaluate blood volume. The equation indicates that an increase of RAP by 1 mmHg is equivalent to an LAP increase of 5.6 mmHg, and a CO increase of 19.61 mL/min/kg (ca. 0.98 L/min for a 50-kg patient).

B. Application of the Model: Autopilot System

The biggest benefit of our comprehensive visual model of hemodynamics is that it enables us to diagnose the abnormality of cardiovascular system in a quantitative manner. This would lead to appropriate selection of drugs and their doses.

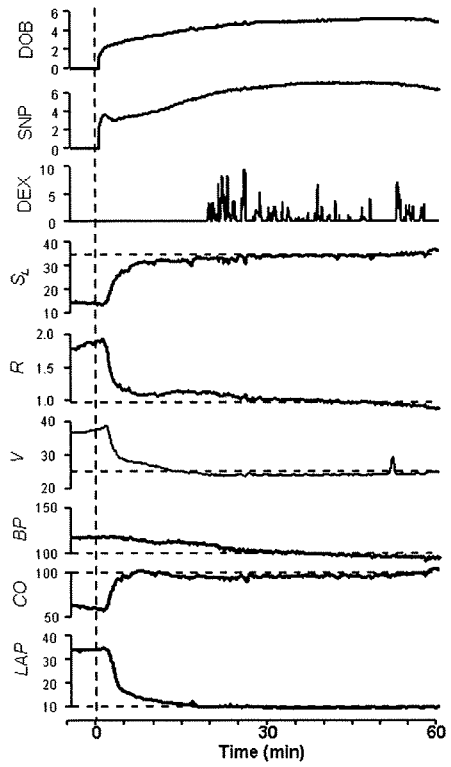

Fig. 5. An example of correction of hemodynamics with an autopilot system. By normalizing cardiovascular properties [pump function (S_L), resistance (R), blood volume (V)] with the administration of dobutamine (DOB), sodium nitroprusside (SNP), and dextran 40 solution (DEX), all the abnormal hemodynamic variables (increased blood pressure [BP], decreased cardiac output [CO], and elevated left atrial pressure [LAP]) were resolved rapidly, sufficiently, and stably.

As shown in Fig. 5, by translating hemodynamic variables into cardiovascular properties (pump function, vascular resistance, and blood volume), and by controlling each of these parameters with individual drug with preferential effect on the parameter, we are able to correct automatically all the parameters of blood pressure, CO and LAP rapidly, stably, and simultaneously.

Using an autopilot system to administer dobutamine (DOB at 5 ± 3 mg·kg^{-1}·min^{-1}), nitroprusside (SNP at 4 ± 2 mg·kg^{-1}·min^{-1}), dextran infusion (DEX at 2 ± 2 ml·kg^{-1}), and furosemide (10 mg in one, 20 mg in one) in 12 dogs with acute heart failure rapidly normalized blood pressure, CO, and LAP in 5 ± 7, 7 ± 5, and 12 ± 10 minutes, respectively. The normalized values remained stable thereafter (RMS values, blood pressure = 4 ± 3 mmHg, CO = 5 ± 2 ml·min^{-1}·kg^{-1}, LAP = 0.8 ± 0.6 mmHg).

V. Conclusion

We have successfully developed a comprehensive macroscopic model of hemodynamics that provides quantitative information. Using a 3D coordinate system, the pump functions of left and right heart are expressed by an

integrated cardiac output curve, and the capacitive function of total vasculature by a venous return surface. The equations of both the cardiac output curve and venous return surface would facilitate accurate diagnosis (especially evaluation of blood volume) and choice of appropriate treatments, including application to autopilot systems.

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ORIGINAL PAPER

Right ventricular stiffness constant as a predictor of postoperative hemodynamics in patients with hypoplastic right ventricle: a theoretical analysis

Shuji Shimizu · Toshiaki Shishido · Dai Une · Atsunori Kamiya · Toru Kawada · Shunji Sano · Masaru Sugimachi

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Abstract One and a half ventricle repair (1.5VR) is a surgical option for hypoplastic right ventricle (RV). The benefits of this procedure compared to biventricular repair (2VR) or Fontan operation remain unsettled. To compare postoperative hemodynamics, we performed a theoretical analysis using a computational model based on lumped-parameter state-variable equations. We varied the RV stiffness constant (B_{RV}) to simulate the various RV hypoplasia, and estimated hemodynamics for a given B_{RV}. With $B_{RV} < 150\%$ of normal, cardiac output was the largest in 2VR. With $B_{RV} > 150\%$, cardiac output became larger in 1.5VR than in 2VR. With $B_{RV} > 250\%$, RV end-diastolic volume was almost the same between 1.5VR and 2VR, and a rapid increase in atrial pressure precluded the use of 1.5VR. These results indicate that the beneficial effect of 1.5VR depends on the RV stiffness constant. Determination of management strategy should not only be based on the morphologic parameters but also on the physiological properties of RV.

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Keywords One and a half ventricle repair · Right ventricular stiffness · Hypoplastic right ventricle · Computational model

Introduction

One and a half ventricle repair (1.5VR) is a surgical option for hypoplastic right ventricle (RV) caused by various congenital heart diseases including pulmonary atresia with intact ventricular septum (PA/IVS), Ebstein's anomaly or their relatives. In this procedure, the superior vena cava (SVC) is directly connected to the pulmonary artery (PA). Therefore, the blood from SVC directly enters PA, whereas the blood from the inferior vena cava (IVC) is pumped by RV to PA. This procedure is clinically acceptable because of its low surgical risk [1, 2]. However, the benefits of this procedure on postoperative hemodynamics in patients with a wide spectrum of RV hypoplasia compared to other procedures such as biventricular repair (2VR) and Fontan operation remain unsettled [3]. Furthermore, conversion to Fontan circulation was required late after 1.5VR in a possibly inappropriate candidate [4].

Although various authors reported an arbitrary selection scheme for the procedures based on RV morphology such as RV end-diastolic volume (RVEDV) [1, 2, 5], the long-term outcomes of 1.5VR have remained insufficiently known [5]. The previous criteria do not likely predict postoperative hemodynamics of these complex circulations accurately because morphological values measured preoperatively largely depend on the RV preload and afterload conditions, which change remarkably between subjects and between before and after the operation.

Hypoplastic RV is physiologically characterized by increased RV stiffness, caused by hypertrophy and

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fibroelastosis of RV muscles [6]. However, how RV stiffness influences the postoperative hemodynamics has not been reported. Given the small number of patients with each of the wide variety of preoperative RV conditions [7, 8], the influence of RV stiffness on 1.5VR, 2VR, and Fontan operation cannot be examined by clinical study. It is also difficult to experimentally reproduce hemodynamics before and after 1.5VR for hypoplastic RV with various stiffness. In view of the above, we attempted to clarify postoperative hemodynamics by a theoretical analysis using a computational model based on lumped-parameter state-variable equations. The present results indicate that the RV stiffness constant may provide selection criteria for 1.5VR.

Materials and methods

The electrical analogs of the model used to simulate the cardiovascular system are shown in Fig. 1. We modeled the postoperative cardiovascular system mathematically by a combination of the time-varying elastance cardiac chamber model and the three-element Windkessel vascular model. We set the normal values of parameters to be appropriate for a 75-kg man. These values were obtained from the literature [9–13] and are listed in Table 1. Since the data of the pressure–volume relationship of the atrium were scarcely available, parameters of the atrium were surmised from the literature [10–12].

Heart

The right and left ventricular chambers as well as the atrial chambers are represented by the time-varying elastance model [9, 10, 13]. The end-systolic pressure–volume relationship is described by a linear formula:

$$P_{es,cc} = E_{es,cc}\left[V_{es,cc} - V_{0,cc}\right] \quad (1)$$

where $P_{es,cc}$ and $V_{es,cc}$ are end-systolic pressure and volume, respectively; $E_{es,cc}$ is the maximal volume elastance; $V_{0,cc}$ is the volume at which $P_{es,cc}$ is equal to 0 mmHg. cc denotes each chamber, i.e., RA for the right atrium, LA for the left atrium, RV for the right ventricle, or LV for the left ventricle. The end-diastolic pressure–volume relationship is represented by a non-linear formula:

$$P_{ed,cc} = A_{cc}\left[e^{B_{cc}(V_{ed,cc}-V_{0,cc})} - 1\right] \quad (2)$$

where $P_{ed,cc}$ and $V_{ed,cc}$ are end-diastolic pressure and volume, respectively; A_{cc} and B_{cc} are constants [9, 10, 13]. We assumed the time course of the time-varying elastance by defining normalized elastance curve $e_{cc}(t)$ as:

Table 1 Parameters used in modeling

Heart rate (HR), beats/min	75			
Duration of cardiac cycle (T_c), ms	800			
Time advance of atrial systole (DT), ms	16			
Total stressed blood volume (V_s), ml	750	(control only)		
	LV	RV	LA	RA
Time to end systole (T_{es}), ms	200	200	120	120
End-systolic elastance (E_{es}), mmHg/ml	3.0	0.7	0.5	0.5
Scaling factor of EDPVR (A), mmHg	0.35	0.35	0.06	0.06
Exponent scaling factor for EDPVR (B), ml^{-1}	0.033	0.023	0.264	0.264
Unstressed volume (V_0), ml	0	0	5	5
	Aortic	Pulmonary	Mitral	Tricuspid
Valvular resistance (forward), (mmHg s)/ml	0.001	0.001	0.001	0.001
	Systemic		Pulmonary (p)	
	Superior (ss)	Inferior (si)		
Arterial resistance (R_a), (mmHg s)/ml	2.25	1.5	0.03	
Characteristic impedance (R_c), (mmHg s)/ml	0.075	0.05	0.02	
Venous resistance (R_v), (mmHg s)/ml	0.0375	0.025	0.015	
Arterial capacitance (C_a), ml/mmHg	0.528	0.792	13	
Venous capacitance (C_v), ml/mmHg	28	42	8	

LV Left ventricle, *RV* right ventricle, *LA* left atrium, *RA* right atrium, *EDPVR* end-diastolic pressure–volume relationship

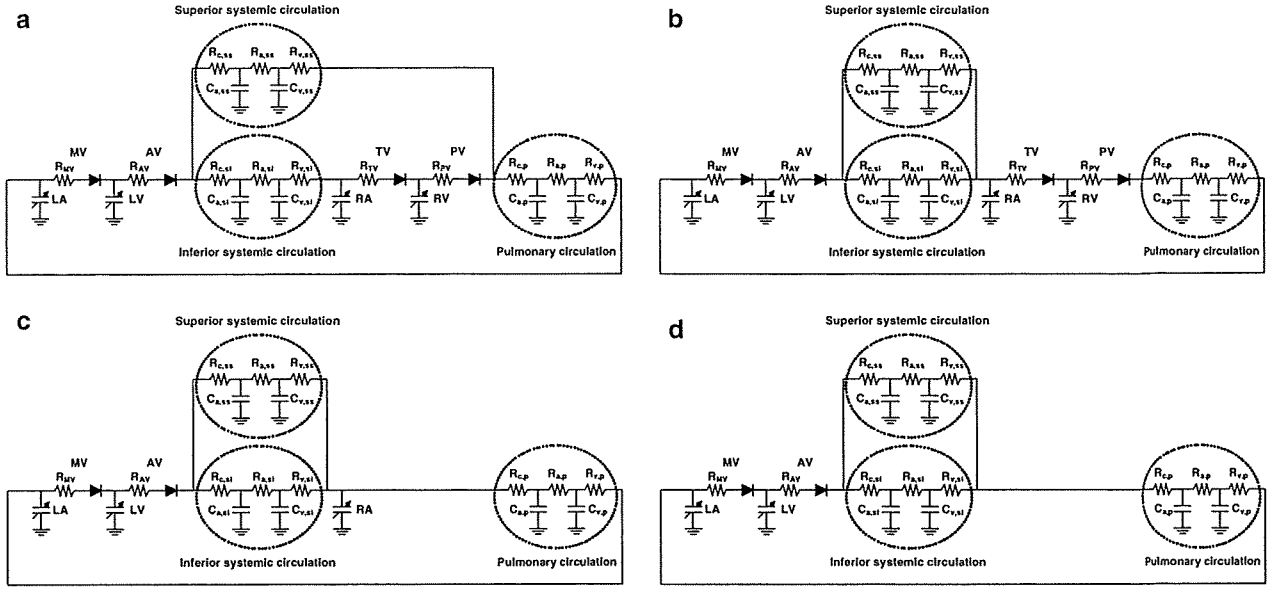

Fig. 1 **a** The electric equivalent circuit of one and a half ventricle repair. **b** Biventricular repair (normal circulation). **c,d** Variations of Fontan operation [**c** atriopulmonary connection (APC); **d** total cavopulmonary connection (TCPC)]. *LV* and *RV* left and right ventricles, *LA* and *RA* left and right atria, *AV* and *MV* aortic and mitral valves, *PV* and *TV* pulmonary and tricuspid valves, C_a and C_v lumped arterial and venous capacitances, R_c characteristic impedances, R_a lumped arterial resistances, R_v venous resistances, *ss* superior systemic circulation, *si* inferior systemic circulation, *p* pulmonary circulation

$$e_{cc}(t) = 0.5[1 - \cos(\pi t/T_{es,cc})]\ (0 \le t < 2T_{es,cc})$$
$$e_{cc}(t) = 0\ (2T_{es,cc} \le t < T_c) \quad (3)$$

where t is the time from the start of systole, $T_{es,cc}$ is the duration of systole, and T_c is the duration of cardiac cycle. Using $e_{cc}(t)$, the instantaneous pressure, $P_{cc}(t)$, is described by:

$$P_{cc}(t) = [P_{es,cc}(V_{cc}) - P_{ed,cc}(V_{cc})]e_{cc}(t) + P_{ed,cc}(V_{cc}) \quad (4)$$

Ventricular systole is preceded by atrial systole. The time advance of atrial systole (DT) is calculated as the fixed fraction of T_c (DT = $0.02T_c$). Function of each chamber is characterized by the parameters $E_{es,cc}$, $T_{es,cc}$, $V_{0,cc}$, A_{cc}, B_{cc}, and $e_{cc}(t)$. The same $e_{cc}(t)$ was used for all chambers, but the other parameters were different between chambers, as shown in Table 1.

Vascular system

Basically, the pulmonary and systemic circulations are modeled as modified Windkessel impedances. Each vascular system is modeled by lumped venous (C_v) and arterial (C_a) capacitances, a characteristic impedance (R_c) that is related to the stiffness of the proximal aorta or pulmonary artery, a lumped arterial resistance (R_a), and a resistance proximal to C_v (R_v). This framework is similar to that used in deriving Guyton's resistance to venous return [14].

To simulate the postoperative hemodynamics of 1.5VR, the systemic circulation is divided into two parts, the superior and the inferior circulation. Therefore, the parameters of the systemic circulation are also divided into the superior and inferior ones, as shown in Fig. 1. Blood flow in the descending aorta is reported to be 63.8% of the left ventricular output [15]. The compliance of the IVC is considered to be 66.6% of the total venous compliance [16]. Thus, in our model, arterial and venous compliances of the inferior systemic circulation are adjusted to 0.6 times those of the compliance of the total circulation, and the blood flow of the inferior systemic circulation is controlled to be 60% of the left ventricular output by adjusting the resistances of R_c, R_a, and R_v.

The capacitance of the superior systemic circulation is also divided into arterial ($C_{a,ss}$) and venous ($C_{v,ss}$). Similarly, arterial and venous capacitances are defined for the inferior systemic circulation ($C_{a,si}$ and $C_{v,si}$) and for the pulmonary circulation ($C_{a,p}$ and $C_{v,p}$). The ratio of C_a to C_v was obtained from the literature [9, 10, 13]. The relationship between pressure (P_c) and volume (V_c) in each capacitance is described by the following linear formula.

$$P_c = \frac{V_c}{C} \quad (5)$$

The changes in volume in each capacitance ($dV(t)/dt$) are described by the differential equations below

$$\frac{dV(t)}{dt} = \sum Q_{\text{in-flow}}(t) - \sum Q_{\text{out-flow}}(t) \quad (6)$$

where $\Sigma Q_{\text{in-flow}}(t)$ and $\Sigma Q_{\text{out-flow}}(t)$ indicate the sum of instantaneous volumetric flow rates at the inlet and outlet of each compartment, respectively. Each of the aortic, mitral, pulmonary, and tricuspid valves is described as an ideal diode with a serially connected small resistor.

In the 1.5VR model, the superior circulation flows from SVC to PA, while the inferior blood flow returns to RA through IVC as shown in Fig. 1a. The models of 2VR (Fig. 1b) and variations of Fontan operation [Fig. 1c, atriopulmonary connection (APC); Fig. 1d, total cavopulmonary connection (TCPC)] are constructed for comparisons. Although the superior and inferior systemic circulations return to RA in both 2VR and APC models, RA is directly connected to PA in the APC model. In the TCPC model, SVC and IVC are directly connected to PA. All parameter values were the same for all of these models except total stressed blood volume (see below) (Table 1).

Hypoplastic RV

Hypoplastic RV is physiologically characterized by an increase in RV stiffness caused by hypertrophy and fibroelastosis of RV muscles [6]. Recalling Eq. 2 for RV, we have:

$$P_{\text{ed,RV}} = A_{\text{RV}}\left[e^{B_{\text{RV}}\left(V_{\text{ed,RV}} - V_{0,\text{RV}}\right)} - 1\right] \quad (7)$$

where B_{RV} is stiffness constant of RV. The value of B_{RV} was changed stepwise from 0.023/ml (normal RV) to 0.143/ml (extremely stiff RV) in increments of 0.01/ml to simulate the various degrees of RV stiffness associated with hypoplasia (Fig. 2).

Protocols

First, the control state was simulated by the 2VR model with normal RV stiffness constant ($B_{\text{RV}} = 0.023$). The total stressed blood volume (V_s), equal to the sum of the stressed volumes in each capacitance and the volume of each chamber, was set as 750 ml to reproduce normal hemodynamics.

$$V_s = V_{\text{LV}} + V_{\text{RV}} + V_{\text{LA}} + V_{\text{RA}} + V_{\text{Ca,ss}} + V_{\text{Cv,ss}} + V_{\text{Ca,si}} + V_{\text{Cv,si}} + V_{\text{Ca,p}} + V_{\text{Cv,p}} \quad (8)$$

We solved these simultaneous equations (Eqs. 1–8) using the component ODE45 of MATLAB, based on the Runge–Kutta method (MathWorks). The hemodynamic parameters of 2VR with normal RV stiffness constant are listed in Table 2.

Next, systemic cardiac output, pulmonary arterial pressure (PAP), right atrial pressure (RAP), and RVEDV after each procedure were calculated for each RV stiffness constant. Heart rate was kept constant and mean systemic arterial pressure (MAP) was controlled at the same value as that of the control state, by adjusting the total stressed blood volume.

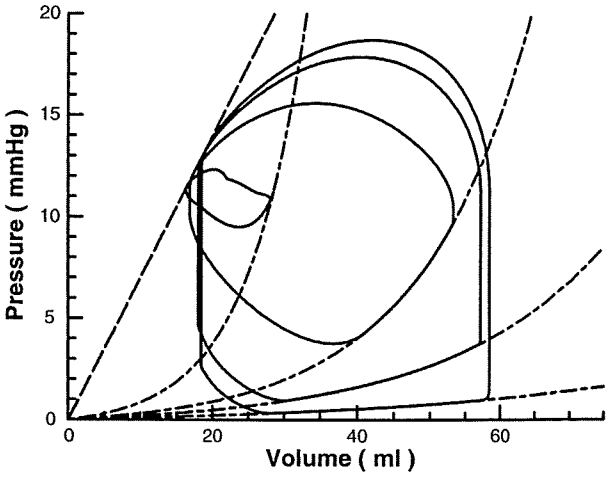

Fig. 2 Right ventricular pressure–volume loops (PV loop) after one and a half ventricle repair. With the increase in the right ventricular stiffness constant, the PV loop became smaller. The *horizontal axis* is the instantaneous right ventricular volume (ml) and the *longitudinal axis* is the instantaneous right ventricular pressure (mmHg)

Table 2 Control hemodynamic parameters (2VR with normal RV stiffness constant)

Parameter	Value
Heart rate (HR), beats/min	75
Mean systemic arterial pressure (MAP), mmHg	80.3
Mean pulmonary arterial pressure (PAP), mmHg	13.6
Mean right atrial pressure (RAP), mmHg	2.34
Mean left atrial pressure (LAP), mmHg	8.26
Left ventricular cardiac output (CO), l/min	4.95

Results

Figure 3a shows the impact of the RV stiffness constant on systemic cardiac output after each procedure. In the Fontan circulation (APC and TCPC), systemic cardiac output was independent of the RV stiffness constant and remained at 4.40 l/min. Under the condition of normal RV stiffness constant, systemic cardiac output was 4.95 l/min in 2VR and 4.73 l/min in 1.5VR, being 13 and 8% greater than that of Fontan circulation, respectively. As the RV stiffness constant was increased from the control value to mimic increased severity of RV

hypoplasia, systemic cardiac output decreased in both 2VR and 1.5VR circulations. Within the range between 100 and 150% of the control RV stiffness constant, systemic cardiac output of 2VR circulation was obviously greater than those of other two circulations. With the RV stiffness constant >150%, systemic cardiac output became greater in 1.5VR than in 2VR. In this situation, 2VR needed larger stressed blood volume than 1.5VR to maintain MAP (Fig. 3d).

The results for PAP and RAP are shown in Fig. 3b. As the RV stiffness constant increased, PAP decreased and RAP increased in both 2VR and 1.5VR circulations. In 2VR circulation, RAP increased steeply as the RV stiffness constant increased up to 150% of normal, and exceeded the atrial pressure of TCPC when the RV stiffness constant increased above 150% of normal. In 1.5VR circulation, RAP also increased but more slowly and exceeded the atrial pressure of TCPC only when the RV stiffness constant increased above 250% of normal. PAP in 1.5VR circulation, which was equal to SVC pressure, became higher than PAP in 2VR circulation in the range of RV stiffness constant >150% of normal.

In the control state, RVEDV in 2VR was 87.7 ml, which was treated as the value of 100% of RVEDV. The influence of the RV stiffness constant on RVEDV is shown in Fig. 3c. In 2VR circulation, RVEDV decreased as the RV stiffness constant increased. In 1.5VR circulation, RVEDV reduced only slightly with an increase in the RV stiffness constant until 250% of normal. In the range of RV stiffness constant >250% of normal, RVEDV showed a relatively linear decay in both 2VR and 1.5VR circulations, and there was no difference in RVEDV between 2VR and 1.5VR. In this situation, both 1.5VR and 2VR needed larger stressed blood volume than Fontan circulation (Fig. 3d).

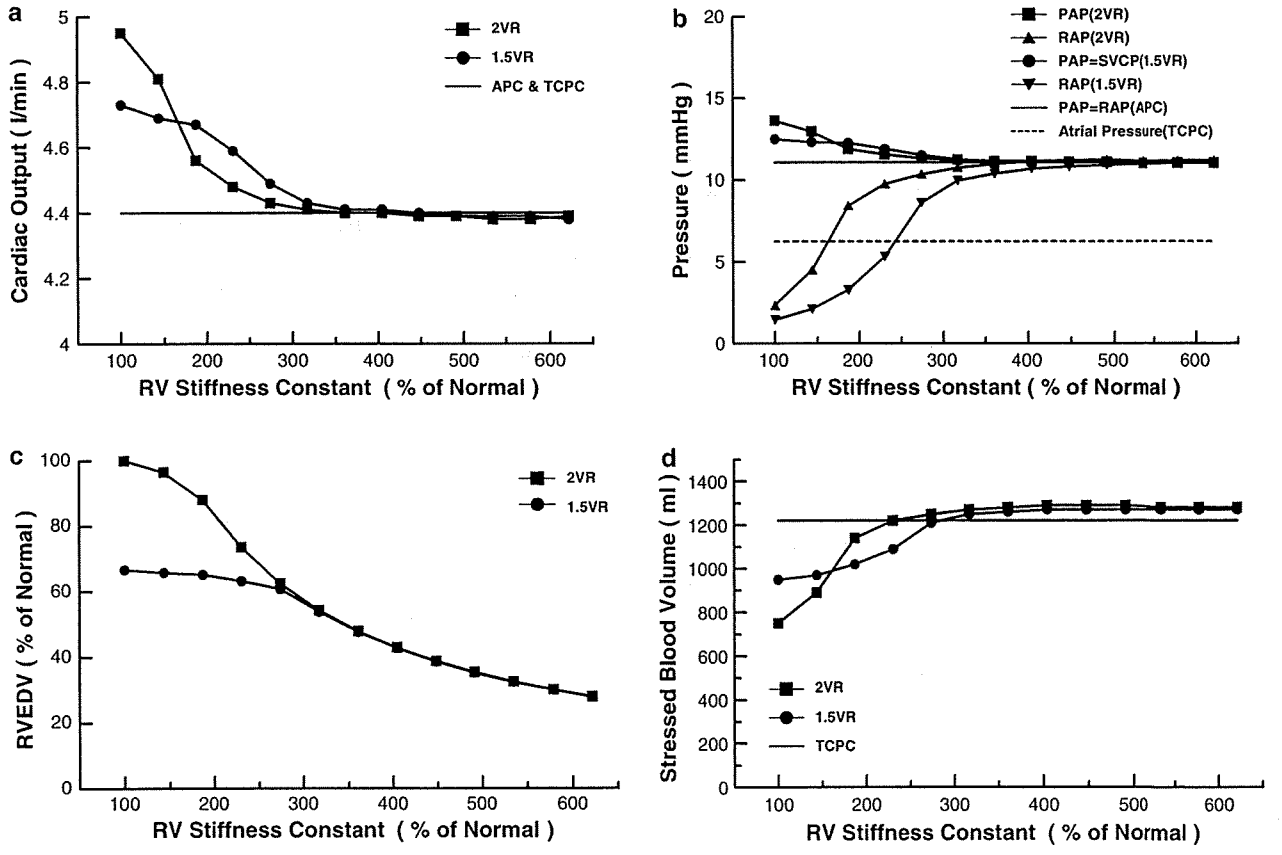

Fig. 3 **a** The relationship between systemic cardiac output (l/min) and % stiffness constant of hypoplastic right ventricle. The *horizontal axis* is the ratio of RV stiffness constant (% stiffness constant) to the normal value. **b** The relationship between pulmonary arterial pressure or right atrial pressure (mmHg) and % stiffness constant of hypoplastic RV. Pulmonary arterial pressure is the same as right atrial pressure in APC. **c** The relationship between % RVEDV and % stiffness constant of hypoplastic RV. **d** The relationship between stressed blood volume (ml) and % stiffness constant. *2VR* biventricular repair, *1.5VR* one and a half ventricle repair, *APC* and *TCPC* variations of Fontan operation (*APC* atriopulmonary connection, *TCPC* total cavopulmonary connection); *PAP* pulmonary arterial pressure, *RAP* right atrial pressure, *SVCP* superior vena caval pressure, *RVEDV* right ventricular end-diastolic volume

Discussion

The results of this theoretical analysis suggest that, in patients with hypoplastic RV, postoperative hemodynamics depends largely on the RV stiffness constant. PA/IVS, Ebstein's anomaly or their relatives are characterized by varying degrees of underdevelopment of RV. For a severely hypoplastic RV, the definitive treatment is single ventricular circulation. For a mildly hypoplastic RV, biventricular circulation is expected to have merit. Recently, 1.5VR has been proposed to reduce the surgical risk of 2VR. The use of 1.5VR has lowered the early or midterm mortality, and adequate growth of RV and the tricuspid valve has been documented in some patients [2]. However, the postoperative RV dysfunction or arrhythmic event has also been reported, in particular, when the patients are on the borderline of criteria between 1.5VR and Fontan operation [4, 5].

For the choice of surgical options among Fontan operation, 1.5VR, and 2VR, the previously used criteria were based on morphologic characteristics of the hypoplastic RV, such as RVEDV. However, simple anatomic indices may be inaccurate, since these values are dependent on the afterload and preload conditions. For that reason, the treatment strategy for hypoplastic RV based on the anatomic indices remains controversial. We focused on the intrinsic property of hypoplastic RV, i.e., RV stiffness constant. The fact that the RV stiffness constant, an index of chamber property, is relatively independent of the loading condition is important for the accurate prediction of postoperative hemodynamics. Based on the results of the present study, we propose that patients with hypoplastic RV can be classified into three groups according to the RV stiffness constant. The first group consists of patients with mild RV hypoplasia (RV stiffness constant <150% of normal), in whom enlargement of RV is expected after the operation. At the other extreme, the second group consists of patients with severe RV hypoplasia (RV stiffness constant >250%), in whom no RV reconstruction is expected to have merit. In addition, we have shown that there certainly exists a third group consisting of patients with intermediate RV hypoplasia (RV stiffness constant between 150 and 250%), who would benefit more from 1.5VR than from 2VR or Fontan operation.

Mild RV hypoplasia

When RV hypoplasia is mild (RV stiffness constant <150% of normal), systemic cardiac output is greater in 2VR than in 1.5VR or Fontan operation (APC or TAPC). Therefore, we recommend that 2VR should be chosen in the mild RV hypoplasia group. Although systemic cardiac output in 1.5VR is also greater than that in Fontan operation, SVC pressure (which is equal to PAP) is higher than that of APC. Accordingly, the upper part of the body is exposed to higher SVC pressure in 1.5VR, which may cause postoperative pleural effusion [2]. A large pressure gradient between SVC and IVC also results in abnormal venous collaterals from SVC to IVC [17–20], and they could effectively increase the venous return to RA in 1.5VR.

Intermediate RV hypoplasia

When RV hypoplasia is intermediate (RV stiffness constant between 150 and 250% of normal), systemic cardiac output in 1.5VR exceeds that in 2VR. Although SVC pressure is still higher in 1.5VR than in APC, RAP is lower in 1.5VR than in the other procedures. This condition is favorable to reduce supraventricular arrhythmias related to high RAP during the perioperative periods. This beneficial effect is not expected for 2VR since RAP in 2VR is higher than the atrial pressure of TCPC. Furthermore, 1.5VR is advantageous from the viewpoint of stressed blood volume because 1.5VR needs smaller stressed blood volume than does 2VR to maintain MAP (Fig. 3d).

In these patients, RVEDV in 1.5VR is relatively independent of the RV stiffness constant. However, abnormal systemic venous collateral channels might open after 1.5VR. These collateral channels would increase RV preload wastefully and decrease systemic cardiac output in the late postoperative phase. In such conditions, conversion to the Fontan circulation may be required in the late phase [4, 5]. Nevertheless, 1.5VR should be recommended for the intermediate RV hypoplasia group because high cardiac output and low RAP are anticipated.

Severe RV hypoplasia

When RV hypoplasia is severe (RV stiffness constant >250% of normal), neither 1.5VR and 2VR are expected to improve systemic cardiac output. In this condition, RVEDV is almost the same between 1.5VR and 2VR, and linearly decreases with an increase in the RV stiffness constant in spite of a rapid elevation in RAP. This indicates that RVEDV might be independent of the venous return to RA. Since RAP becomes higher than the atrial pressure of TCPC even in 1.5VR, supraventricular arrhythmias caused by high RAP are liable to occur [2, 5]. In this condition, 1.5VR is considered to have hemodynamics equivalent to APC and needs larger stressed blood volume than does TCPC to maintain systemic arterial pressure (Fig. 3d).

Therefore, TCPC should be chosen for patients with severe RV hypoplasia. In these patients, the arrhythmic events after TCPC are less than that after APC [21, 22]. Although a small pressure gradient between SVC and IVC