Influence of Age (Body Size) on the Fontan Circulation

— Analysis by a Theoretical Model —

Hideaki Senzaki, MD; Chiharu Naito, BS; Toshiki Kobayashi, MD; Nozomu Sasaki, MD;
Shunei Kyo, MD; Yuji Yokote, MD; Akira Ishizawa, MD*

Among the original selection criteria for the Fontan operation, the recommended age at the time of surgery has been 4 years or older, but recent clinical data have indicated the feasibility of this procedure in younger patients. Because age may influence the properties of the systemic vascular bed, changes in systemic vascular resistance (Rs) and systemic vascular compliance (Cs) associated with physical development were quantified in 86 pediatric patients without known abnormalities of the systemic circulation, and the effects of age (body size) on Fontan circulation were then analyzed using an analytical model of the cardiovascular system. As the body surface area (BSA) of the patient decreased, Cs also decreased significantly ($r=0.81$, $p<0.001$). Based upon this relationship between BSA and Cs, the analytical model showed that the impedance (ventricular afterload) of the Fontan circulation significantly increased as Cs decreased with the decrease in BSA. Moreover, the increase in impedance in response to changes in heart rate or Rs was inversely proportional to the BSA. However, these findings were significant only when the BSA was below 0.3 m^2 . Small BSA, or a lower age, has minimal effects on the Fontan circulation until it comes close to the infant value, and thus the Fontan procedure may be feasible much earlier than formerly recommended when the hemodynamics are otherwise acceptable. (*Jpn Circ J* 2000; 64: 943–948)

Key Words: Blood flow; Cardiovascular surgery; Congenital defects; Hemodynamics

The Fontan operation and its modifications have been used to treat various types of congenital heart disease when repairing into the 2-ventricle system is impossible.^{1–4} Because this operation provides not anatomical but functional repair, patient selection is critical in influencing the outcome of the procedure.^{5,6} Among the original selection criteria, Fontan et al suggested that the age at the time of surgery should be 4 years or older,⁷ and many other investigators have also reported that a lower age at the time of surgery would become a risk factor.^{8–10} However, Fontan surgery on children under the age of 4 years has recently been successfully performed,^{11–14} so a lower age may not be an independent risk factor for this procedure.^{13,14}

The results from clinical studies are often confounded by the complex interplay among many variables. Theoretical model analysis has advantages in this regard, because the effects of individual parameters can be tested independently. The present study examined the effect of age on postoperative Fontan circulation. The single ventricle (anatomically or functionally) in Fontan circulation has to maintain both the systemic and pulmonary circulations, and this circulation can be represented as an electric circuit (Fig 1). The characteristics of this circuit are determined by the function of the

ventricle as a flow generator and by the following physiological properties of the vessels: systemic vascular resistance (Rs), systemic vascular compliance (Cs), pulmonary vascular resistance (Rp), and pulmonary vascular compliance (Cp). Assuming normal ventricular function, if the characteristics of this circuit are affected by age, then the physiological properties of the blood vessels should vary with age. Thus, to determine the influence of age on postoperative Fontan circulation, we first investigated the relationship between age and the properties of blood vessels. Because the properties of the pulmonary vascular bed (Rp and Cp) are constant throughout childhood, except during the neonatal and early infant periods,¹⁵ we focused on the systemic vascular bed. Based upon the relationship between age and the properties of the systemic vascular bed, we then examined the influence

Fig 1. Analogy of the Fontan circulation to an electric circuit. Rp, pulmonary vascular resistance; Cp, pulmonary vascular compliance; Rs, systemic vascular resistance; Cs, systemic vascular compliance.

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Department of Pediatrics and Pediatric Cardiology, and Cardiovascular Surgery, Saitama Medical School Hospital, Saitama and *Department of Pediatric Cardiology, National Children's Hospital, Tokyo, Japan

Mailing address: Hideaki Senzaki, MD, Department of Pediatric Cardiology, Saitama Heart Institutes, Saitama Medical School Hospital, 38 Morohongo, Moroyama, Iruma-Gun, Saitama 350-0451, Japan. E-mail: hsenzaki@saitama-med.ac.jp

Fig 2. Schema of the theory for the calculation of systemic vascular compliance. (A) RC electric circuit analogy of the systemic circulation, (B) theoretical aortic pressure pulse with mean right atrial pressure, (C) formula representing summarized equations with which to calculate systemic vascular compliance. R, resistance; C, capacitor (compliance); AOP, aortic pressure; mRAP, mean right atrial pressure.

of age on postoperative Fontan circulation using a theoretical model. As it is well known that vascular size has a significant impact on vascular properties, age effects would be closely related to changes in vascular size associated with physical development with age. Thus, effects of age were analyzed in terms of physical development.

Methods

Relationship Between Age and Systemic Vascular Properties

Based on data obtained from routine cardiac catheter examination of 86 consecutive patients without systemic circulation abnormalities, we examined whether or not Rs and Cs changed with physical development, namely, age. The study included 52 patients with a closed or small ventricular septal defect (VSD) (pulmonary to systemic blood flow ratio, 1.0–1.1), and 34 patients with paroxysmal supraventricular tachycardia (PSVT). All VSD patients had subpulmonic VSD and the catheter studies examining aortic valve deformities and regurgitation found no significant regurgitation in any of the patients. Measurements from the PSVT patients were taken during electrophysiological studies at normal sinus rhythm. For the Cs calculation to be theoretically sound, patients with patent ductus arteriosus,

Fig 3. Relationship between body surface area (BSA) and time constant (RC).

aortic regurgitation, and systemic-to-pulmonary shunt operations were excluded. None of the participating patients were taking afterload reducing medication or antiarrhythmic agents. Ages ranged from 2 months to 20 years; written informed consent was obtained from the parents of all patients, and the investigation conformed with the principles outlined in the Declaration of Helsinki.

Systemic blood flow (Qs) was determined by the Fick method and Rs was calculated according to the formula:

$$R_s = (mAP - mRAP) / Q_s$$

where mAP is mean aortic pressure and mRAP is mean right atrial pressure, which were measured using a micromanometer-tipped catheter (Millar, Houston, TX, USA). The value of Cs was obtained as shown in Fig 2 (analogy of the systemic circulation to a simple RC circuit).¹⁶ In the RC circuit, the voltage discharge from the capacitor is an exponential function of time. Accordingly, the diastolic pressure difference between the aorta and the right atrium also shows exponential decay, which is related to the time constant (RC) of this circuit. Values for Cs can be obtained by substituting Rs for R in the formula in Fig 2C. To evaluate the relevance of this analogy, the instantaneous diastolic pressure difference between the aorta and the right atrium was represented as a semilogarithmic plot, which revealed a highly linear correlation between the pressure difference and the diastolic time interval (on regression analysis, the correlation coefficient was above 0.97). Cs is generally dependent upon the pressure level at which the Cs is calculated. We chose diastolic Cs for this study because the Cs value obtained by our method is a good representation of the value at mean aortic pressure.¹⁷

The physical development of the patient was quantified by the body surface area (BSA), and the relationship between BSA and the properties of systemic vascular bed was then examined.

Influence of Age (Body Size) on Postoperative Fontan Circulation

Based on the relationship between age and the properties of the systemic vascular bed (Rs and Cs), we investigated the influence of age on the postoperative Fontan circulation.

Fig4. Relationship between body surface area (BSA) and systemic vascular resistance (Rs).

When considering the steady circulatory state, the systemic blood flow is expressed using a Fourier series:¹⁸

$$I = i_0 + i_n \sin(\omega n t + \alpha_n) \quad (1)$$

where I = systemic blood flow, i_0 = mean-steady flow, i_n = amplitude of the n th harmonic, $\omega_n = 2\pi f_n$, $f_n = n \text{ HR}/60$ (HR, heart rate; $n = 1, 2, 3, \dots$), α_n = phase angle of the n th harmonic of flow, and t = length of sequence.

The systemic blood pressure generated by the flow expressed in formula (1) is described using input impedance (Z_n , θ_n) as follows:¹⁸

$$P = p_0 + Z_n i_n \sin(\omega n t + \theta_n) \quad (2)$$

where P = systemic blood pressure, p_0 = mean pressure, Z_n = impedance modulus of the n th harmonic, and θ_n = impedance phase angle of the n th harmonic.

Impedance is a measure of opposition to the pulsatile flow, and it plays an important role not only as a decisive factor in the pressure wave form, but also as the afterload to the ventricle.^{19,20} Impedance in the Fontan circulation (Z) shown in Fig 1 is the combined impedance of the aorta (Z_s) and the pulmonary vessel (Z_p), and it becomes afterload to the single ventricle. It is expressed as:

$$\begin{aligned} 1/Z_s &= 1/R_s + j\omega C_s \\ 1/Z_p &= 1/R_p + j\omega C_p \\ j^2 &= -1 \end{aligned} \quad (3)$$

$$Z = Z_s + Z_p \quad (4)$$

Hence, the afterload to the single ventricle (Z_n) can be arranged as follows:

$$\begin{aligned} Z_n &= |Z_s + Z_p| \\ &= \left[\left\{ \frac{R_s}{1 + R_s^2 C_s^2 \omega^2} + \frac{R_p}{1 + R_p^2 C_p^2 \omega^2} \right\}^2 \right. \\ &\quad \left. + \left\{ \frac{\omega C_s R_s^2}{1 + R_s^2 C_s^2 \omega^2} + \frac{\omega C_p R_p^2}{1 + R_p^2 C_p^2 \omega^2} \right\}^2 \right]^{0.5} \end{aligned} \quad (5)$$

As indicated by Formula (5), impedance, as the afterload to the single ventricle, is a function of R_s and C_s . Therefore, together with the relationship between age (BSA) and the properties of the systemic vascular bed, Formula (5) was used to investigate how age (BSA) influences the postoperative Fontan circulation.

Fig5. Relationship between body surface area (BSA) and systemic vascular compliance (C_s).

Statistical Analysis

The association between the variables was determined by linear regression analysis, and the correlation coefficient was calculated between these variables. $P < 0.05$ was considered statistically significant.

Results

Relationship Between Age (Body Size) and Systemic Vascular Properties

The relationship between the time constant (RC) and BSA is shown in Fig 3. The RC value denotes how long the blood entering the aorta in systole takes to reach the right atrium by diastolic recoil of the aorta and is, therefore, an appropriate index of the hemodynamic evaluation.²¹⁻²⁴ Fig 3 shows that the RC significantly and positively correlated with BSA ($r = 0.91$, $p = 0.001$), which is notable, because the characteristics of the systemic circulation in humans remain constant in association with physical development. The changes in R_s and C_s associated with physical development are shown in Figs 4 and 5. Fig 4 shows that there is not a statistically significant correlation between R_s and BSA, although there was a trend toward high R_s in patients with larger BSA. On the other hand, the correlation between C_s and BSA was significant ($r = 0.81$, $p = 0.001$) as shown in Fig 5; the value of C_s increased as the BSA increased.

Influence of Age (Body Size) on Postoperative Fontan Circulation

Because C_s increases with the increased body size with age, the postoperative Fontan circulation should be affected by age associated with changes in C_s . As noted in Formula (5), Z_n is inversely correlated with C_s and as a result, ventricular afterload increases when C_s decreases. Fig 6 shows how Z_n , from the first to the 10th harmonic, changes as C_s varies when HR is maintained at 120 beats/min. Because the actual pressure wave form is mostly determined by the first several harmonics at a lower frequency domain, analysis through the 10th harmonic should be sufficiently accurate.¹⁸ Normal values of $0.12 \text{ mmHg} \cdot \text{s} \cdot \text{m}^2 \cdot \text{ml}^{-1}$ (2 RUm^2), $1.5 \text{ ml} \cdot \text{m}^{-2} \cdot \text{mmHg}$, and $1.2 \text{ mmHg} \cdot \text{s} \cdot \text{m}^2 \cdot \text{ml}^{-1}$ (2 RUm^2) were assigned to R_p , C_p and R_s , respectively. Fig 6 indicates that

Fig6. Change in impedance modulus (Zn) from the first to the 10th harmonic according to alterations in systemic vascular compliance (Cs).

Fig7. Change in impedance modulus (Zn) from the first to the 10th harmonic according to alterations in heart rate (HR), by RC difference. Y axis represents a ratio of the change in Zn when HR varies from 80 to 180 beats/min.

Fig8. Change in impedance modulus (Zn) from the first to the 10th harmonic according to alterations in systemic vascular resistance (Rs), by RC difference. Y axis represents a ratio of Zn when Rs varies from 15 to 35 RUm^2 .

the impedance (ventricular afterload) begins to rise rapidly when Cs is less than 0.3 or 0.4 $\text{ml} \cdot \text{m}^{-2} \cdot \text{mmHg}$, but is quite stable and constant when the Cs is greater than 0.3 or 0.4 $\text{ml} \cdot \text{m}^{-2} \cdot \text{mmHg}$. Therefore, the postoperative Fontan circulation should theoretically be quite unstable up to a certain age. However, 0.3 or 0.4 $\text{ml} \cdot \text{m}^{-2} \cdot \text{mmHg}$ of Cs gives approximately 0 mm^2 of BSA value according to Fig 5, and thus, postoperative Fontan circulation is essentially not influenced by body size.

Furthermore, we used Formula (5) to investigate theoretical changes in the Zn associated with changes in HR or Rs. Fig 7 shows the values of the ratio of Zn when HR is either 80 or 180 beats/min, with RC as a variable. The change in the Zn was inversely related to RC as HR varied from 80 to 180 beats/min. The slope of the curve increased rapidly when the RC dropped below 0.3 or 0.4 s, whereas it was almost flat when RC was greater than 0.5 s. This indicates that impedance as the ventricular afterload fluctuates easily in

response to HR change when RC is less than 0.3 or 0.4 s. Therefore, the postoperative Fontan circulation will be very unstable under such conditions. Fig 3 depicts a patient with an RC of 0.4 s with a BSA of 0.1 m^2 . The postoperative Fontan circulation responds to the change in HR in an unstable manner only when the BSA of the patient is less than 0.1 m^2 , but as the BSA value of 0.1 m^2 is apparently less than that of a newborn, the age-associated effect of a change in HR on Fontan circulation was also considered negligible. The ratio of Zn when Rs is 15 and 35 RUm^2 is shown in Fig 8. The response of Zn to the change in Rs is unstable at ranges of RC less than 0.4–0.5 s, where BSA is less than 0.3 m^2 (Fig 3). For example, in a patient with a BSA of 0.3 m^2 , if Rs is increased from 15 to 35 RUm^2 , as often happens with sympathetic nerve activation, Zn is increased by a factor of 1.5. Therefore, in terms of Zn change in response to Rs alteration, only very small children with a BSA value less than 0.3 m^2 may have an unstable Fontan circulation.

Discussion

The postoperative circulation following the Fontan procedure is determined by ventricular function, which must supply both the systemic and pulmonary circulations, and by the physiological properties of the systemic and pulmonary vascular bed (Fig 1). In Fontan circulation where the ventricle does not directly supply the pulmonary circulation, the properties of the pulmonary vascular bed are especially important. To maintain adequate pulmonary circulation, an adequately low Rp is an absolute prerequisite. Additionally, we have demonstrated that low Cp is disadvantageous to the postoperative Fontan hemodynamics because of increased impedance.²⁵ As these 2 properties of the pulmonary vascular bed are minimally affected by age, except during the neonatal and early infant periods,⁵ the influence of age on the postoperative Fontan circulation should appear through changes in the systemic circulation.

The present study found that Cs increases with age (BSA) during childhood (Fig 5). This is the first quantification of age-associated changes in Cs in children. On the other hand, aging in adults is related to stiffening of the arterial wall and a decrease in vascular compliance.²⁶ Because the compliance of blood vessels is determined by the size of the vessel and the properties of the vascular wall,²⁷ the growth of vessels associated with physical development must be closely related to increased vascular compliance during childhood, whereas vascular size does not change significantly in adults when they age. Additionally, the changes in vascular wall properties often observed in adults, such as arteriosclerosis, may be negligible in childhood.

Because of this change in Cs with age, the postoperative Fontan circulation is theoretically affected by the physical development of patients. The lower the age, the smaller the Cs and the more unstable Fontan circulation became as afterload to the single ventricle increased. In addition, augmentation of ventricular afterload in response to changes in HR or Rs was more remarkable at lower ages. Considering the energy dissipation within the Fontan circuit, increased impedance associated with a smaller BSA would be also disadvantageous. Because kinetic energy is negligible, energy dissipation in the Fontan circuit is approximated as:

$$RQm^2 + 1/2\sum(Qn)^2 Z_n \cos\Phi_n$$

where R is total vascular resistance, Qm is the mean flow (cardiac index), Qn and Φn are the modulus and phase angle, respectively, of the nth harmonic of Fourier series for flow wave, and Zn is the impedance modulus of the Fontan circuit. Because Rs is kept almost constant, independent of body size as shown in Fig 4, energy dissipation is mainly determined by Zn when cardiac output matched to body size (cardiac index) is maintained. Thus, smaller body size is also disadvantageous in terms of energy dissipation within the circuit, because small BSA is associated with increased Zn.

However, these effects of age on the Fontan circulation appeared insignificant in actual practice unless the BSA was less than 0.3 m². Although Fontan candidates may have a smaller BSA compared with normal children at the same age, a BSA <0.3 m² is clearly that of small infants. Therefore, the appropriate time to perform the Fontan operation does not have to be as formerly recommended and there is no justifiable reason for postponing the operation until the age of 4 years. Rather, as Kirklin et al¹³ have suggested, earlier surgery is recommended to avoid the ventricular

hypertrophy caused by volume overload and myocardial damage caused by hypoxia.^{28,29}

However, as the present analysis was based on the assumption that both Rp and Cp are normal, patients should still be selected more strictly and carefully during early infancy when the effect of the pulmonary vascular properties, in addition to the effect of Rs change (Fig 8), may not be negligible. Patients in this age group have high Rp, and an unexpected increase in the Rp after the cardiopulmonary bypass is more likely to occur.^{30,31} In addition, the neonatal cardiac functional reserve is very poor.³² Therefore, the Fontan operation should be performed as early as possible if patients are 1 year of age or older and meet the criteria other than age. Patients under the age of 4 years should not necessarily be excluded from consideration for the Fontan operation.

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