



Vascular aging in adult congenital heart disease-a narrative review

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Background and Objective: Many studies about the high prevalence of cardiovascular disease in adults with congenital heart disease (CHD) have been published in response to the growing number of adult patients with CHD. The aging process leads to hypertension and cardiovascular disease, which is caused by a degenerative change in the systemic arterial system characterized by the stiffening of elastic arteries (known as arteriosclerosis) and the enlargement of aorta. In patients with CHD, aortic dilatation (so-called aortopathy) is one of the most frequent complications. It is well known the anatomical and histological changes in aortopathy are similar to those in aging process. The increase of pulse wave velocity (PWV) enhances pressure wave reflection, and it augments left ventricular afterload and impairs the coronary supply-workload balance in aging. This article reviews the aortic function in patients with CHD, aiming to provide a new direction for the management of their cardiovascular aging process.

Methods: Papers on vascular physiology in CHD were retrieved. I searched all original papers and reviews about the vascular physiology in CHD using PubMed, published from January 1, 1973 to June 30, 2022, in English.

Key Content and Findings: Enhancement of pressure wave reflection has been reported in many CHDs. Although PWV in whole aorta is not necessarily elevated, the abnormal arterial stiffness gradient is common in patients with CHD.

Conclusions: Many reports concerning functional abnormalities of the aorta have been reported. The abnormalities can result in cardiovascular disease and organ damage. The practitioners should carefully treat patients with CHD while paying attention to their aging process.

Keywords: Congenital heart disease (CHD); hypertension; cardiovascular disease; arterial stiffness; pressure wave reflection

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Introduction

Owing to advances in surgical procedures and medical treatments, patients with congenital heart disease (CHD) have a long life expectancy (1). Therefore, the influence of the aging process needs to be considered in the management of patients. Systemic blood pressure gradually elevates with age, and high blood pressure can cause potentially fatal conditions such as ischemic heart disease, cerebral vascular disease, and renal failure. High blood pressure is common in patients with CHD (2) and cardiovascular disease (e.g., ischemic heart disease, cerebrovascular disease, and renal disease) is common in adults with CHD (3-6), according to

previous research. Their hearts are vulnerable to the effects of high blood pressure because they have been overloaded in some form since birth (e.g., cyanosis, volume overload, and systemic right ventricle). High blood pressure can have a detrimental effect on their cardiovascular health. The cause of hypertension in CHD patients is unknown; however, renal factors may play a role, given that cyanosis and cardiac surgery can both impair renal function (7).

A man is said to be as old as his arteries. One of the key factors in hypertension and cardiovascular disease is vascular aging. Early vascular aging (EVA), which refers to the acceleration of the aging process of the elastic arteries, has

Table 1 The search terms used

“early vascular aging”
“vascular aging” AND “congenital heart disease”
“pulse wave velocity” AND “congenital heart disease”
“pulse wave velocity” AND “aortic coarctation”
“pulse wave velocity” AND “tetralogy of Fallot”
“pulse wave velocity” AND “hypoplastic left heart syndrome”
“pressure wave reflection” AND “congenital heart disease”
“pressure wave reflection” AND “aortic coarctation”
“pressure wave reflection” AND “tetralogy of Fallot”
“pressure wave reflection” AND “hypoplastic left heart syndrome”
“subendocardial viability ratio” AND “congenital heart disease”
“aortic stiffness gradient”

recently emerged as a promising tool for clinical guidance in the treatment of people who are at risk for cardiovascular disease (8,9). In the definition of the EVA, the stiffness of large arteries is generally evaluated and referenced. The enhancement of aortic stiffness impairs the reservoir function of large arteries.

Concerning large arteries in CHD, morphological evaluation is commonly performed. However, there is not much research targeting reservoir function of large arteries in patients with CHD. Aortopathy, a common condition in CHD, is a term used to describe structural abnormalities of the aorta in patients with CHD. The aortopathy in CHD patients is similar to that of aged aorta from a histological standpoint. In fact, we previously reported that the prevalence of EVA is high in CHD patients (10).

In this article, I will review the studies on systemic vascular physiology in patients with CHD and discuss vascular aging. I present the following article in accordance with the Narrative Review reporting checklist (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-22-218/rc>).

Methods

Relevant studies published from January 1, 1973 to June 30, 2022 were identified via a PubMed search using different combinations of the following search terms: “early vascular aging”, “vascular aging”, “congenital heart disease”, “pulse wave velocity”, “aortic coarctation”,

“tetralogy of Fallot”, “hypoplastic left heart syndrome”, “pressure wave reflection”, “subendocardial viability ratio”, “arterial stiffness gradient”. Most of the search formulas I use are shown in *Table 1*. Additional papers were identified by reviewing reference lists of relevant publications. Publications with relative low credibility and non-English publications were excluded. Data were extracted based on their relevance to the topic instead of implementing a systematic approach to paper selection. More details of the method are shown in *Table 2*.

What is vascular aging?

It is well known that the aorta stiffens with age. The histological changes of aortic aging consist of elastin fracture, collagen storage, and calcium deposition (11). The elastin fracture progresses with a large strain and cyclic number (12). Moreover, metabolic factors, such as advanced glycation end products, accelerate the stiffening of the aorta (13). These histological changes of the aorta with age are similar to the so-called aortopathy in CHD (14).

The functional markers of aortic aging are elevation of pulse wave velocity (PWV) and damaged aortic reservoir function. The elevation of PWV results in an early return of reflected pressure to the heart (15). *Figure 1* shows ascending aortic pressure waveforms in young (*Figure 1A*) and old (*Figure 1B*). Because of the low PWV in adolescents, the reflected pressure wave (arrow) returns to the heart during diastole (*Figure 1A*). However, PWV elevates with age, and the reflected pressure (arrow) wave returns to the heart during systole (*Figure 1B*), increasing left ventricular afterload. Furthermore, because the reflected pressure wave returns to the heart early, the forward and reflected pressure have a small time phase difference, resulting in a large central pulse pressure (so-called isolated systolic hypertension, which is common in elderly people). Concerning aortic reservoir function, more than half of the blood ejected from the left ventricle is temporarily stored in the aorta during systole and then runs off during diastole (16). The heart is one of the most important organs that is primarily perfused during diastole (coronary circulation). The reflected pressure wave that returns to the heart during diastole can help to increase the amount of blood that is stored during systole and runs off to the heart during diastole. However, as the aorta loses elasticity with age, its role as a functional reservoir is diminished, because the reflected pressure wave returns to the heart during systole due to the increased PWV.

Table 2 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	2022/2/9–2022/6/30
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	See <i>Table 1</i> for details
Timeframe	1973–2022
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion criteria: research articles and reviews in English about themes. Exclusion criteria: some papers which I considered with low reliability
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	TM conducted the selection
Any additional considerations, if applicable	Some papers were identified by reviewing reference lists of relevant publications

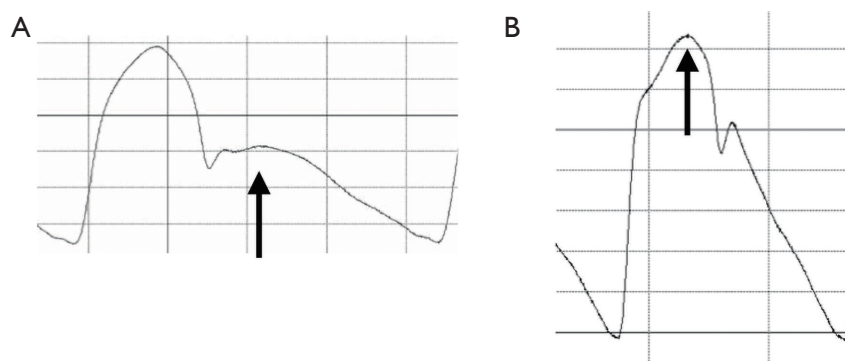


Figure 1 Ascending aortic pressure waveforms. (A) In patients with low PWV, the reflected pressure wave returns to ascending aorta during diastole. (B) In patients with high PWV, the reflected pressure wave returns to ascending aorta during systole. Arrow indicates the reflected pressure wave. PWV, pulse wave velocity.

The PWV value is used as a parameter of EVA. EVA is defined as PWV values higher than the 95th percentile for age and sex (17). One of the reasons why PWV is generally used in the evaluation of vascular aging is its convenience of measurement. As mentioned above, the increment of PWV becomes disadvantageous to systemic circulation through the increment of pressure wave reflection. Therefore, the augmentation index, which is a commonly used measurement in evaluating pressure wave reflection (18), can be important in the evaluation of vascular aging. The augmentation index is defined as the ratio of augmentation pressure to pulse pressure, and the index becomes negative when the peak systolic pressure precedes the inflection point (*Figure 2*). The augmentation index is important parameter in evaluating aortic reservoir function, however,

the measurement of the augmentation index has technical difficulties (identification of inflection point) compared to PWV measurement. It may be one of the reasons why the PWV is commonly used in clinical practice. Regarding the aortic reservoir function, subendocardial viability ratio is commonly adopted for evaluation (19,20) and can be one of the important biomarkers in evaluating vascular aging. The measurement of the subendocardial viability ratio is also more complex than the measurement of PWV (*Figure 3*).

Vascular aging in CHD

PWV in patients with CHD

Although we previously reported that EVA is common in adults with CHD (10), it means their PWV is elevated.

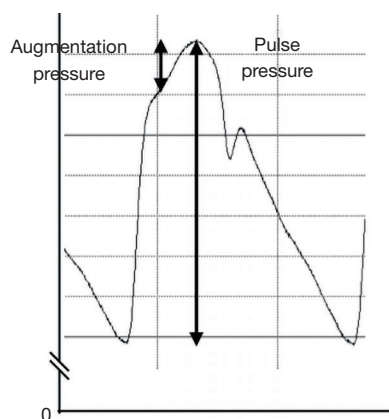


Figure 2 Evaluation of pressure wave reflection. Augmentation index (%) = $100 \times (\text{augmentation pressure} / \text{pulse pressure})$.

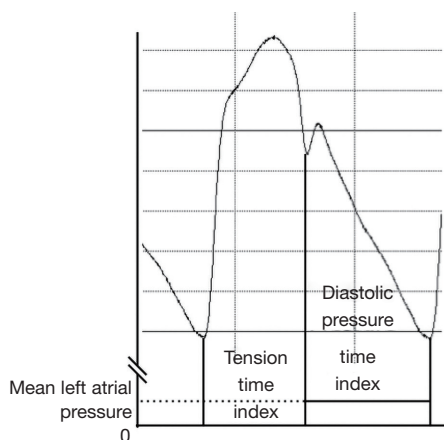


Figure 3 Evaluation of aortic reservoir function. Subendocardial viability ratio (%) = $100 \times (\text{diastolic pressure time index} / \text{tension time index})$.

Some studies reported PWV in patients with various types of CHD, especially aortic arch disease, tetralogy of Fallot (TOF), Fontan candidates, and the results of measurements were varied. Hartevelde *et al.* (21) demonstrated an increase in carotid-femoral PWV in patients following Fontan surgery. However, Sarkola's group (22) and Tomkiewicz-Pajak's group (23) reported that the carotid-femoral PWV values in patients with Fontan circulation were not significantly different from the data in control subjects. Concerning patients with repaired TOF, which is the most common cyanotic heart disease, Cheung and colleagues demonstrated that the heart-femoral PWV in the patients is higher than that in control subjects (666 ± 15 vs. $587 \pm$

81 cm/s, $P=0.021$) (24). However, there was no difference in carotid-femoral PWV between patients with repaired TOF and controls in de Groot's study (25). In addition, Currie and colleagues also reported that whole-body PWV (heart-dorsal pedal artery in the study) was not elevated in children with TOF and aortic coarctation (26). Tronjnarska and colleagues reported that carotid-femoral PWV in adult cyanotic patients with CHD was elevated (7.40 ± 2.07 vs. 6.33 ± 0.76 m/s, $P=0.003$) (27). Weismann *et al.* (28) reported that the carotid-femoral PWV was not elevated in patients with bicuspid aortic valve, one of the most common CHDs. The age of the patients could be one of the reasons for the wide variety of PWV values. In our study of adults with CHD (10), we found that the prevalence of EVA was high in elderly CHD patients. The age of the patients enrolled in each study may have an influence on the result. Another reason could be the range of the examined artery (see below).

Pressure wave reflection in patients with CHD

The degree of enhancement of pressure wave reflection is typically measured using the augmentation index (18) (Figure 2). We previously reported that adults with CHD commonly have a high augmentation index (29). Many studies have shown that patients with Fontan circulation [$(17.5 \pm 9.9)\%$ vs. $(11.2 \pm 7.8)\%$, $P=0.006$] (21), [$(17.01 \pm 3.3)\%$ vs. $(6.05 \pm 11.0)\%$, $P<0.001$] (23), cyanosis [$(24.75 \pm 13.49)\%$ vs. $(3.03 \pm 13.57)\%$, $P=0.00001$] (27), bicuspid aortic valve (10.1% vs. 6.3% , $P<0.001$) and TOF [$(-14.1 \pm 17.0)\%$ vs. $(-25.2 \pm 14.6)\%$, $P=0.016$] (24) have an increased augmentation index. From the theory mentioned above, the high PWV enhances pressure wave reflection. However, some reports demonstrated a high augmentation index without a high PWV (23,28). The prevalence of enhanced augmentation index in adults with CHD in our study (44.4%) (29) is higher than that of EVA (15.6%) (10). It is possible that pressure wave reflection in CHD patients is enhanced through a mechanism other than PWV enhancement.

Aortic reservoir function in patients with CHD

The subendocardial viability ratio (Figure 3) is an important biomarker or aortic reservoir function. In Figure 1, the subendocardial viability ratio of the pressure waveform A is higher than that in the pressure waveform B. We previously

Table 3 PWV: proximal and distal aorta

Study	Objects	PWV	
		Proximal	Distal
Schäfer <i>et al.</i> (38)	HLHS	5.1 m/s*	3.1 m/s
	Control	2.6 m/s	2.7 m/s
Voges <i>et al.</i> (40)	HLHS	3.7±1.4 m/s	3.7±1.3 m/s
	Control	3.2±0.4 m/s	4.0±1.0 m/s
Voges <i>et al.</i> (34)	CoA	4.6±1.7 m/s*	4.3±1.6 m/s
	Control	3.5±0.8 m/s	3.9±0.8 m/s
Cheung <i>et al.</i> (24)	TOF	666±151 cm/s*	Right: 888±202 cm/s, left: 918±207 cm/s
	Control	587±81 cm/s	Right: 845±207 cm/s, left: 851±215 cm/s
Saiki <i>et al.</i> (37)	Repaired TOF	588±205 cm/s*	441±189 cm/s
	Unrepaired TOF	680±288 cm/s*	430±114 cm/s
	Control	439±101 cm/s	461±164 cm/s

Values are presented as mean ± standard deviation. *, P<0.05 vs. control. PWV, pulse wave velocity; HLHS, hypoplastic left heart syndrome; CoA, coarctation of the aorta; TOF, tetralogy of Fallot.

measured the subendocardial viability ratio in pediatric patients with repaired aortic coarctation (30), repaired TOF (31) and transposition of great arteries after arterial switch operation (32). In comparison with age-matched controls, the subendocardial viability ratio was preserved in each study. The ratio can be preferentially maintained because it represents the balance of cardiac workload and blood supply to the heart. The patients in each study did not have heart failure, so the subendocardial viability ratio could be maintained. Saiki and colleagues reported a low subendocardial viability ratio in Norwood procedure patients, and the low value was associated with poor outcomes (33).

Regional PWV in patients with CHD

Recently, studies concerning regional PWV have been increasing. One of the reasons increasing the studies may be progress of magnetic resonance imaging. Those papers reported that the PWV in the proximal aorta in patients with aortic coarctation (34,35) and TOF (36,37) was higher than that in control subjects, although there were variations in the measurement position. Some papers reported an increase in PWV in the proximal aorta (38,39) in patients with Fontan circulation (mostly hypoplastic left heart syndrome patients), while others reported no increase

(40,41).

In some studies, researchers measured the PWV at the proximal and distal aorta, although there were variations in the measurement sites (*Table 3*). The PWV in the whole aorta was not necessarily elevated (see above). However, these data concerning the regional PWV suggest that the PWV in the proximal aorta elevated in patients with CHD. Another notable thing is the arterial stiffness gradient (42). In control subjects with a normal arterial tree, the PWV in the proximal aorta was smaller than that in the distal aorta. However, in CHD patients (*Table 3*), the enhancement of the PWV in the proximal aorta results in the discontinuity of the stiffness gradient. In normal vascular tree, stiffness gradient, which means a constant increase in stiffness from the aorta to the periphery, is formed by the loss of elastin content and the decrease in vessel diameter (*Figure 4A*) (42). By the study in aortic aging, the importance of “normal” stiffness gradient has been recently come to light. Age-related increase in aortic stiffness causes the loss of stiffness gradient and results in increasing forward wave amplitude and pulse pressure (*Figure 4B*) (43). The loss of stiffness gradient leads to the transmission of a highly pulsatile pressure wave into the microcirculation (44). It can lead to endothelial dysfunction, reducing organ perfusion, and ultimately organ dysfunction (45). A recent study in a dialysis cohort has shown that the aortic-brachial arterial

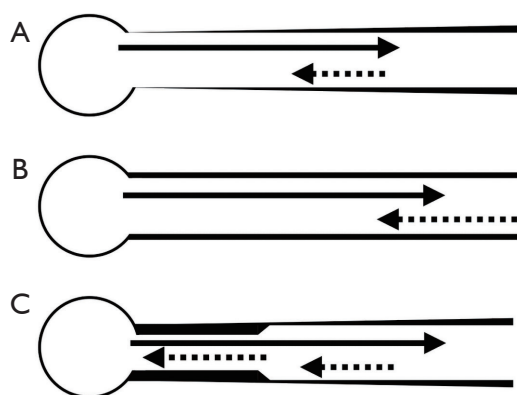


Figure 4 Forward and reflection pressure waves in arterial system. (A) Normal aorta. (B) Aged aorta. (C) Aorta with regional stiffness. Arrow indicates the forward pressure wave. Arrow with dashed line indicates the reflected pressure wave.

stiffness mismatch was strongly associated with increased mortality (46). The elevated proximal aortic stiffness causes a distal shift in major reflection sites and a paradoxical increase in reflected wave amplitude, resulting in a dissociation between aortic stiffness and augmentation index (47). The discontinuity of stiffness gradient in the CHD patients is different from the loss of stiffness gradient in elderly people in that the aorta is stiff partially (*Figure 4C*). Moreover, the degree of the impedance mismatch in CHD patients (*Table 3*) is larger than that in aging process (42). Therefore, the impedance mismatch in CHD patients can elevate augmentation index and cause disadvantage for microcirculation. The influence of the discontinuity of stiffness gradient on hemodynamics in CHD patients is more complicated than that of the loss stiffness gradient in the aged individuals.

One of the possible mechanisms of EVA in CHD—the enhancement of pressure wave reflection

In patients with CHD, surgical management and hemodynamics can influence the aortic aging process and induce EVA. Judging from the study concerning pressure wave reflection (29).

Despite apparently successful surgical repair of aortic coarctations, the early onset of cardiovascular diseases (hypertension, myocardial infarction, cardiac failure, and sudden death) has been frequently encountered (48-50). One of the possible mechanisms of it is the enhancement

of pressure wave reflection (51). It is well known that the distensibility of the reconstructed site in patients after a repair of coarctation is decreased (52,53). Wave reflections arise from any discontinuity in which there is a change in impedance (18). Therefore, the reconstructed aortic site could generate a reflection wave that traveled backward to the ascending aorta. Because the repaired site is nearer to the heart than the original reflection site (region of the main aortic bifurcation) (*Figure 5*) (54), the influence of pressure wave reflection becomes strong. As a result, central blood pressure can elevate and cardiovascular disease increases (*Figure 6*).

A systemic-pulmonary shunt operation is commonly performed in patients with cyanotic CHD to improve pulmonary blood flow and reduce cyanosis. This procedure increases ascending aortic blood flow without affecting descending aortic blood flow. The elastin fracture progresses with a large strain and cyclic number (12). Therefore, the regional increment of blood flow (which means an increment of strain) induces a regional increment of elastin fracture and results in a regional increment of PWV. As a result, the aorta can have a discontinuity in stiffness gradient, and the condition can make a new reflected pressure wave (*Figure 5*). Collateral vessels from the systemic arterial tree to the pulmonary arterial system frequently develop in patients with cyanotic CHD who do not have a systemic-pulmonary shunt. These vessels can function similarly to a systemic-pulmonary shunt in patients with cyanotic heart disease, causing discontinuity of the arterial stiffness gradient.

Studies concerning vascular physiology in patients with CHD are still few. Further research is needed to improve long-term prognosis in CHD patients.

Conclusions

Various hemodynamics unique to CHD can cause the discontinuity of the stiffness gradient in the systemic arterial tree. Although it has been reported that cardiovascular disease is common in not only complex but also simple CHD (6), the discontinuity of the stiffness gradient must be one of the causes of hypertension and cardiovascular disease. It can cause cardiovascular disease and organ damage. Magnetic resonance imaging is one of the non-invasive methods evaluating the stiffness gradient of the aorta. The PWV is most used tool evaluating the vascular

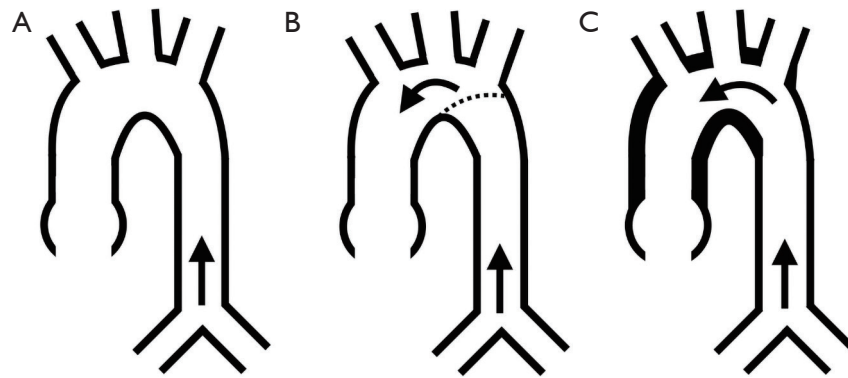


Figure 5 Possible origins of the reflected pressure wave. (A) Normal aorta. (B) Repaired aortic coarctation. (C) Cyanotic heart disease. Arrow indicates the reflected pressure wave.

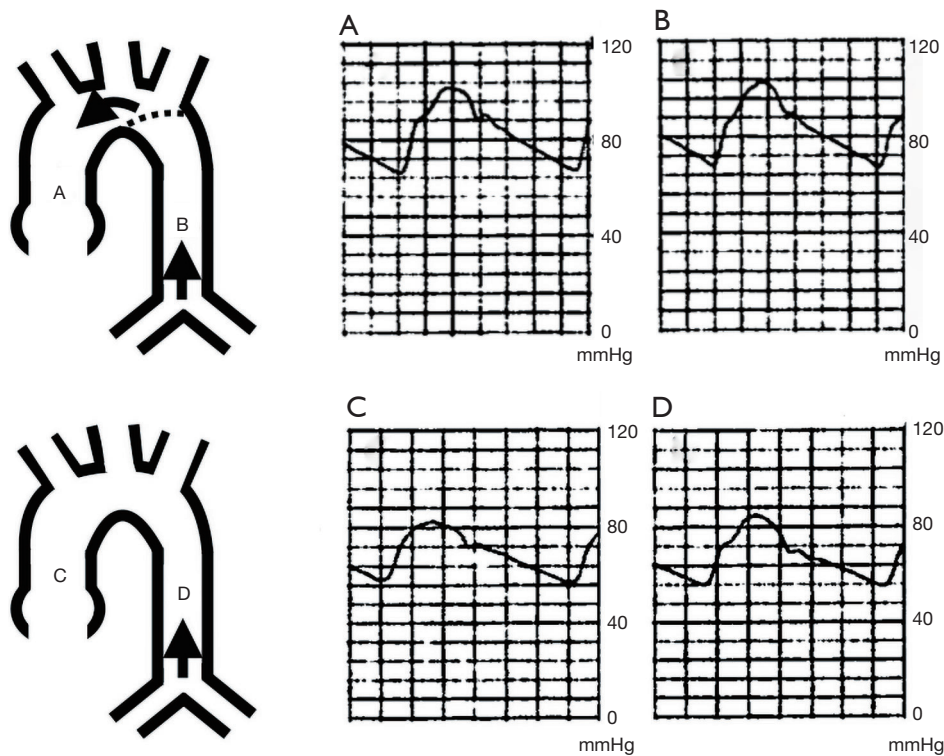


Figure 6 Aortic pressure wave forms in patients after aortic arch repair. (A) Ascending aortic pressure waveform in patients after aortic arch repair. (B) Descending aortic pressure waveform in patients after aortic arch repair. (C) Ascending aortic pressure waveform in normal aorta. (D) Descending aortic pressure waveform in normal aorta. In comparison with normal aorta, the pressure waveforms between ascending and descending aorta are almost same in patients after aortic arch repair. Arrow indicates the reflected pressure wave.

aging, however, it is insufficient in evaluation of systemic arterial system in CHD patients. The evaluation of pressure wave reflection may be superior to that of PWV in evaluating arterial system of them. However, it is more

complex and also incomplete. Further research concerning the arterial system in patients with CHD is needed to find a valid evaluation method for their arterial system and improve the prognosis of patients with CHD.

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Footnote

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