Published in final edited form as:

Am J Cardiol. 2014 December 15; 114(12): 1902–1907. doi:10.1016/j.amjcard.2014.09.032.

Comparison by Magnetic Resonance Phase Contrast of Pulse Wave Velocity in Patients with Single Ventricle and Reconstructed Aortas versus Those Without

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Abstract

Pulse wave velocity (PWV), a measure of arterial stiffness, is a known independent risk factor for cardiovascular events. Single ventricle patients who undergo aortic to pulmonary anastomosis (recon) have non-compliant patch material inserted into the neo-aorta, possibly increasing vessel stiffness and afterload. The purpose of this study is to determine if PWV differed in single ventricle patients who did and did not undergo aortic reconstruction (no-recon). We retrospectively reviewed cardiac magnetic resonance anatomic, cine and phase contrast evaluations in the ascending (AAo) and descending aorta (DAo) at the level of the diaphragm data from 126 single ventricle patients (8.6±8.0 years) from January 2012 to May, 2013. Significance = $P < 0.05$. Seventy-five underwent recon and 51 did not. PWV in recon were significantly higher than in no-recon (3.9 ± 0.9 m/s vs 3.2 ± 1.0 m/s, $P = 0.008$); in recon, patients > 13 years had a higher PWV than those < 7 years (4.5 ± 0.6 vs 3.5 ± 0.7 m/s, $P = 0.004$). DAo distensibility was similar

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Conflict of Interest

Dr. Fogel receives grants from Edwards Life Sciences and the Cooley's Anemia Foundation to be cardiac magnetic resonance imaging core labs, AMAG to participate in the FACT trial and Kereos to be a medical monitor.

between both groups. There was no difference in age, body surface area or cardiac index between recon and no-recon. No correlations between various hemodynamic and ventricular function parameters with PWV were noted. In conclusion, PWV in recon is higher than in no-recon with similar DAo distensibility implicating the aortic reconstruction as a possible cause of increased afterload; older recon have stiffer aortas than younger ones possibly imposing an additional cardiovascular risk in the future. Other biomaterials may potentially moderate PWV if clinical outcome is adversely affected.

Keywords

heart defects; congenital; magnetic resonance imaging; aorta; followup studies

Introduction

The purpose of this study is to compare aortic stiffness^{1,2} utilizing pulse wave velocity (PWV) and distensibility of the descending aorta (DAo) at the level of the diaphragm in single ventricle patients with and without an aortic reconstruction of all types (eg Damus-Kaye-Stansel or Norwood stage I procedures). We utilized cardiac magnetic resonance (CMR), which has successfully been used for years to assess single ventricle function, blood flow^{3,4,5} and PWV.^{6,7} In a small study, PWV in the neo-aorta of patients undergoing the Norwood procedure were compared with normal individuals and were found not statistically different from each other.⁸ Because of the variability in the amount and placement of patch material along with the inability to non-invasively identify all areas of patch, the utility of distensibility in the ascending aorta (AAo) was limited since the cross-section of the AAo in some patients may contain all native tissue and in others may contain variable amounts of graft material; because of this PWV was utilized. To determine the effect of aortic reconstruction on native aortic tissue, this study utilized distensibility of the DAo at the level of the diaphragm. Aortic PWV has been demonstrated to be an independent risk factor for cardiovascular events in adults such as all cause cardiovascular mortality, coronary artery disease including myocardial infarction and stroke.^{9,10,11} We hypothesized that insertion of patch and suture material in the aortic wall will increase PWV.

Methods

A search of CMR database at our institution was performed for all single ventricle patients who were studied between January, 2012 and May, 2013. Studies needed to include a stack of cine short axis slices for ventricular function, a cine of the candycane view of the aorta and phase encoded velocity mapping in the AAo and DAo at the level of the diaphragm. All patients who underwent CMR were enrolled making this series consecutive. Demographics obtained included age, body surface area, blood pressure, diagnosis and stage of surgical reconstruction. Patients under 12 years of age underwent general anesthesia or sedation per hospital protocol. This study was approved by the hospital Institutional Review Board.

CMRs were performed on a Siemens 1.5 Tesla Avanto MRI system (Siemens Medical Solutions, Malvern PA) with data analyzed using the standard Siemens' analysis package (ARGUS) on a Leonardo workstation. A stack of static steady state free precession images

were obtained from the diaphragm to the neck to assess cardiovascular anatomy and to use as localizers for cine imaging and phase encoded velocity mapping. Three dimensional reformatting of this stack was utilized to obtain the “3-chamber view” of the single ventricle, ventricular short axis and candy cane view of the aorta used in cine imaging as well as slice positions and orientation for phase encoded velocity mapping. If the patient was under general anesthesia or sedation, multiple excitations were used to offset the effects of respiratory motion.

A stack of 8–12 steady state free precession cine images using contiguous slices were obtained across the ventricle from atrioventricular valve to apex to obtain end-diastolic volume and ejection fraction. Volumes were obtained by contouring the endocardial borders at enddiastole and end-systole and summing the product of the area by the slice thickness across the entire ventricle; ejection fraction was calculated in the usual fashion.

A candy cane view of the aorta was obtained by aligning a plane through the AAo and DAo on the stack of static bright blood axial images and angling this plane axially through the apex of the aortic arch; parameters were similar to cine imaging for ventricular function. Retrospective, electrocardiographic gated phase encoded velocity mapping was obtained in the AAo and DAo. Velocity encoding (VENC) was set between 150 – 200 cm/s for the aorta.

PWV was calculated by measuring the distance between the AAo and DAo phase encoded velocity map planes and the time delay between AAo and DAo flow-time curves (figure 1). The distance between the AAo and DAo phase encoded velocity map planes was obtained from the candy cane view of the aorta (x) and taken in the mid-section of the vessel throughout its length. AAo and DAo flow-time curves were superimposed on each other and midpoints of the systolic upslope of AAo and DAo determined; the time delay between these two were used as the time for the pulse wave to travel from one imaging plane to the other (t). PWV was calculated simply as x/t .^{8,12}

Distensibility was measured from 2-dimensional phase encoded velocity mapping images in the descending aorta at the level of the diaphragm to determine the effect of the AAo patch and suture material distally; this was not calculated in the AAo because the variable amount of patch and suture material along with the variable placement of these materials would make distensibility determination in the AAo highly variable and an unreliable measure of stiffness. Distensibility of the DAo was calculated as follows:⁸

$$\text{Distensibility (10}^{-3} \text{ mm Hg}^{-1}) = (A_{\max} - A_{\min}) / [A_{\min} \times (P_{\max} - P_{\min})]$$

where $A_{\max}$ and $A_{\min}$ represent the maximal and minimal cross-sectional lumen area of the DAo on phase encoded velocity mapping images, and $P_{\max}$ and $P_{\min}$ are the systolic and diastolic blood pressures (in millimeters of mercury), respectively. Blood pressure was obtained noninvasively with sphygmomanometer placed around the right arm.

Table 1 lists all abbreviations and equations.

Descriptive statistics were used, recorded as mean $\pm$ standard deviation. Comparisons were made using the unpaired Students t-test if the data was normally distributed as determined

by the Chi squared goodness of fit test; if the data failed normality, the Wilcoxon Rank Sum test was used. Both Pearson and Spearman correlation were used, depending upon if the data was normally distributed. A P-value ≤ 0.05 was considered significant.

Results

One hundred and twenty six single ventricle patients comprise the study population. Of those, 75 patients (56%) had undergone an aortic to pulmonary anastomosis (recon) such as a Norwood stage I or Damus-Kaye-Stansell procedure; 51 (44%) had not undergone aortic reconstruction (no-recon). Patient characteristics divided by reconstructed and non-reconstructed aortic groups including ventricular function are described in Table 2. The vast majority of recon patients were single right ventricles (85%), however, in the no-recon group, 39% were single right ventricles. Twenty three patients were prior to bidirectional Glenn or hemiFontan, 45 were in the bidirectional Glenn or hemiFontan stage and 58 were after Fontan. Age of the entire cohort was 8.6 ± 8.0 years with body surface area of 0.9 ± 5.6 m². No significant difference was noted between these groups within ventricular type was noted. No patients had aortic or neo-aortic valve stenosis or greater than mild regurgitation on echocardiography and no one had a blood pressure difference of > 10 mm Hg from arm to leg.

Figure 2 is a graph of PWV of patients with recon and no-recon; as can be seen, PWV of recon patients had a significantly higher PWV than no-recon. Because of the notion that PWV increases with increasing age, the patient population was subdivided into those < 7 years old and those > 13 years old (figure 3). Whether young or old, patients with recon demonstrated higher PWV than no-recon (ie within the < 7 year old or > 13 year old groups, PWV of recon were higher than PWV of no-recon, figure 3A). The comparison PWV of patients within < 7 year old or > 13 year old groups took into account the variable of sedation and general anesthesia; since all subjects < 7 years old underwent sedation and those > 13 years old did not, PWV comparison between recon and no-recon within the age group were made under the same conditions. Of those patients with recon, older ones had a significantly higher PWV than younger ones; this pattern did not hold in no-recon patients (ie they had similar PWV) (figure 3B). Ventricular morphology, stage of aortic reconstruction, whether aortic atresia or stenosis or aortic to pulmonary collateral flow did not make a difference in these findings.

Figure 4 is a graph of distensibility from the DAo; no significant difference was noted between reconstructed aortas and those without reconstruction. No significant correlations were noted between PWV and blood pressure, heart rate, ventricular volumes, ventricular mass, ejection fraction or cardiac index.

Discussion

This study demonstrated that PWV in single ventricle patients is increased in recon compared with no-recon; this held true whether patients were older or younger. In patients with recon, PWV of older patients were higher when compared with younger patients, however, this did not hold true for those patients without recon. The increased aortic

stiffness implied by increased PWV was limited to the AAO where patch material was placed and did not extend to the DAO (native aortic tissue) as demonstrated by similar distensibility between the 2 groups; this implicated the aortic reconstruction conferring increased aortic stiffness which did not change the native aortic tissue properties.

PWV is a function of the properties of the aortic wall, directly proportional to Young's modulus and wall thickness and inversely proportional to the radius and the density of blood using the Moens-Korteweg equation.¹³ The higher the PWV, the higher the aortic wall stiffness; PWV is an independent risk factor for cardiovascular events in the adult population.^{9,10,11} This is presumably because of the increased afterload this poor aortic compliance imposes on the ventricle. Our study suggests that single ventricle patients with recon may have an additional cardiovascular risk factor as they enter their teen and adult years over and above no-recon; a prospective large scale outcomes trial would be needed to determine whether this indeed is true.

The radius of the AAO and transverse aortic arch in patients with recon is generally always large⁸ which should make PWV smaller by the Moens-Korteweg equation; the finding that PWV in recon is actually higher leads to the conclusion that Young's modulus and/or the aortic wall thickness are exceptionally high to compensate for this increased diameter. Similarly, PVW was higher in the older recon patients despite the patch and suture materials accounting for proportionally less aorta as growth occurs. This may be due to slowly developing fibrosis within the aortic wall due to surgery, abnormal vascular mechanics secondary to the patch or aortic geometry or the increased wall thickness and Young's modulus as the patient ages.

There have been a few studies in children and single ventricles on PWV. In a study of over 1,000 healthy children, Reusz et al created normal table and percentiles for PWV using applanation tonometry,¹⁴ a different technique than our study. Our values for all single ventricle patients fall into the ranges of Voges I et al.¹² who studied 71 normal volunteers using CMR on a 3T scanner. Voges I et al.⁸ went on to study 40 patients with HLHS and normal with an average age of 6 years old and found no difference in PWV between the 2 groups although their values almost reached statistical significance. The values in our study fall in the range of their study, however, our study compared recon to no-recon within the single ventricle population, controlling for surgery and fibrosis surrounding the aorta. Our study also compared all types of aortic to pulmonary anastomosis patients (as opposed to solely Norwood operations), all types of ventricular morphology and contained more patients which may have accounted for the statistical significance shown in our study relative to theirs.

Using wave intensity analysis, Biglino et al.¹⁵ compared 12 patients with HLHS to 11 single ventricle no- recon patients, all after bidirectional superior cavopulmonary surgery and demonstrated significantly increased wave speed and AAO stiffness of recon relative to non-recon, similar to our findings. Interestingly, they also described a lower peak wave intensity and reduced energy carried by these waves HLHS than no-recon; this is consistent with the study of Sundareswaran et al who found impaired power output in HLHS relative to those with single left ventricle in whom most did not undergo recon.¹⁶

No correlations were noted between PWV and hemodynamics or ventricular function parameters. This may be due to the variability in sedation and general anesthesia as well as variability in physiology at the time of scanning. It is also interesting that ventricular mass did not correlate with PWV; this may be due to either an abnormality of ventricular response to afterload in single ventricles or it may simply take longer to for ventricular mass to increase. Ideally, PV-loops would've been obtained to determine ventricular elastance, which can be directly compared with arterial elastance to assess "ventricular-arterial mismatch."

Distensibility is inversely proportional to PWV using the Bramwell and Hill equation.² The range of distensibility of the DAo in our study falls within the range found in the DAo by Voges I et al.⁸ in their study of HLHS; they too found no difference between HLHS and normals at that level. Once again, this implies the aortic reconstruction at the heart of increased aortic stiffness. We did not attempt to compare the AAo of reconstructed aortas to those without because of the highly variable placement and amount of patch material and sutures.

This study is retrospective and is subject to all of the inherent biases that come with this type of investigation. For example, phase encoded velocity mapping only utilized 20–30 phases of the cardiac cycle limiting our temporal resolution which in turn, limited our ability to measure the delay time between AAo and DAo; acquiring these data with a higher temporal resolution in a prospective study may have demonstrated even more significant results. Our study only investigated patients referred for CMR which may involve referral bias.

No follow-up data was obtained during this study and indeed, as mentioned above, may be a reason why there was no correlation between PWV and ventricular function or hemodynamic parameters. To fully discern the clinical impact of increased PWV, this data would be needed. A future trial would need to have large numbers of patients to determine how aortic stiffness affects long term outcome independent of ventricular morphology for example. Nevertheless, our data may be used as a starting point.

Finally, our study did not tease out the etiology for increased aortic stiffness in recon; whether it is due to the inserted patch material, sutures, post-operative fibrosis, intrinsic aortic wall abnormalities or a combination of either or all remains a question.

Acknowledgments

Funding Sources

This work was supported in part by the United States National Institute of Health grants – NIH R01HL098252-01, NIH HL67622 and NIH HL098252.

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Highlights

- Pulse wave velocity (PWV) is a measure of aortic stiffness.
- PWV is higher in patients with reconstructed aortas than those without.
- Within reconstructed aortas, those > 13 years had a higher PWV than those < 7 years.
- DAo distensibility was similar between both groups.

Figure 1. Determination of pulse wave velocity (PWV) by cardiac magnetic resonance

The candy cane view of the aorta is on the left; rectangles demonstrate where phase encoded velocity maps were acquired. The distance between ascending (AAo) and descending aortic (DAAo) velocity maps were traced (red line). On the right are the AAo and DAAo flow-time curves superimposed on each other; the delay time utilized for PWV calculations is determined by the time between the midpoints of the upstroke of the flow-time curve in systole.

Figure 2. Pulse wave velocity (PWV) between reconstructed (recon) and non-reconstructed aortas (no-recon)

Box and whisker plot represent first, second and third quartiles along with the ends of the plots representing the minimum and maximum values.

Figure 3. Pulse wave velocity (PWV) between reconstructed (recon) and non-reconstructed aortas (no-recon) as a function of age

(A) Recon versus non-recon grouped by age. There is a significantly higher PWV in recon as compared with non-recon regardless of age. (B) Less than 7 year olds versus > 13 year olds grouped by aortic reconstruction status. Recon demonstrates increased PWV in the > 13 year olds as compared with the younger age group while no difference was noted in age in the non-recon patients. Box and whisker plot similar to figure 2.

Figure 4. Distensibility between reconstructed (recon) and non-reconstructed aortas (no-recon)
Box and whisker plot similar to figure 2

Table 1

Abbreviations and Equations Used In This Study

Abbreviation	Meaning	Equations	
AAo	ascending aorta	Bramwell and Hill	$PWV = \sqrt{\frac{\Delta PV}{\Delta V \rho}} = \sqrt{\frac{1}{\rho D}}$ P is pressure, V is blood volume, ρ is density of blood and D is distensibility
CMR	cardiac magnetic resonance	Distensibility ($10^{-3} \text{ mm Hg}^{-1}$)	$(A_{\max} - A_{\min}) / [A_{\min} \times (P_{\max} - P_{\min})]$ $A_{\max}$ and $A_{\min}$ are maximal and minimal cross-sectional lumen area of the DAo and $P_{\max}$ and $P_{\min}$ are the systolic and diastolic blood pressures respectively.
DAo	descending aorta	Moens Korteweg equation	$PWV = \sqrt{\frac{Eh}{2r\rho}}$ E is Young's modulus, h is the wall thickness, r is the inside radius and ρ is blood density
HLHS	HLHS hypoplastic left heart syndrome	Pulse Wave Velocity	x / t x is distance the pulse travels and t is time
no-recon	patients who have not undergone aortic reconstruction		
PWV	pulse wave velocity		
TE	echo time		
TR	Line repetition time		
VENC	velocity encoding		

Table 2

Study Population Characteristics

Demographic	Reconstructed Aorta		P value
	No	Yes	
Age (years)	10.06 ± 9.14	7.11 ± 7.55	0.052
Gender (male/female)	41/34	27/24	0.57
Body Surface Area (m ²)	1.02 ± 0.62	0.82 ± 0.54	0.069
Systolic Blood Pressure (mm Hg)	99.90 ± 15.29	101.69 ± 16.07	0.59
Diastolic Blood Pressure (mm Hg)	60.22 ± 14.9	55.55 ± 11.09	0.08
Mean Blood Pressure (mm Hg)	73.45 ± 14.31	70.93 ± 12.02	0.36
Heart Rate (beats/minute)	98.4 ± 6.8	94.6 ± 8.7	0.22
Superior Vena Cava flow (l/min/m ²)	1.65 ± 0.94	1.60 ± 0.71	0.77
Inferior Vena Cava flow (l/min/m ²)	1.47 ± 0.46	1.64 ± 0.70	0.21
Aortic Cardiac Index (l/min/m ²)	4.47 ± 1.67	4.44 ± 1.58	0.92
Ejection Fraction (%) (RV/LV)	60 ± 10/66 ± 9	57 ± 10/66 ± 11	0.27/0.95
End-diastolic volume (cc/m ²) (RV/LV)	104.8 ± 50.9/81.4 ± 24.5	103.2 ± 44.2/81.2 ± 18.1	0.92/0.98
Stroke Volume (cc/m ²) (RV/LV)	60.3 ± 23.8/52.2 ± 15.4	58.2 ± 28.7/55.1 ± 15.9	0.81/0.73
Mass (g/m ²) (RV/LV)	102.3 ± 36.3/72.1 ± 17.3	96.3 ± 25.4/66.1 ± 28.3	0.56/0.57
RV morphology	20	64	
LV morphology	23	9	
Mixed ventricular morphology	8	2	

cc=cubic centimeters, cm=centimeters, g=grams, l/min/m²=liters per minute per meter squared, LV=left ventricle, mm Hg=millimeters of mercury, m²=meters squared, RV=right ventricle.