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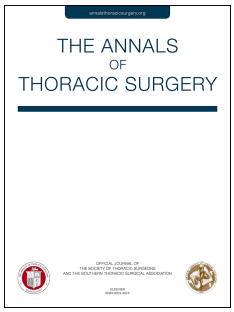

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Cardiac Autonomic Nervous System Activity and Cardiac Function in Children after Coarctation Repair

Running head: Autonomic activity in coarctation

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ABSTRACT

Background. Coarctation of the aorta (CoA) is one of the most common congenital heart defects. Due to improved surgical techniques, most patients live into adulthood. However, late complications including hypertension, recoarctation and arrhythmias are common. The autonomic nervous system (ANS) might play a role in the pathology. The aim of this study was to evaluate cardiac ANS activity and cardiac function in children after CoA repair and investigate the relationship between the two.

Methods. 31 children after CoA repair and 62 healthy controls aged between 8 and 18 years old participated in the study. By the use of ambulatory impedance cardiography, cardiac ANS activity and cardiac output were measured for 24h. Cardiac function was measured by the use of transthoracic echocardiography and cardiac magnetic resonance imaging.

***Results*.** No group differences were found in ambulatory cardiac ANS. However ambulatory cardiac output and left ventricular function were significantly decreased in patients compared to controls.

***Conclusions*.** Left ventricular function and ambulatory cardiac output are impaired in patients after CoA repair, despite unchanged cardiac ANS activity in this group. These results underscore the importance of clinical follow up, even in patients without residual stenosis.

Coarctation of the aorta (CoA) is one of the most common congenital heart defects with a reported prevalence of 4/10.000 births approximately [1]. Today, survival is good -89% survival at 60 years [2] - due to available techniques for repair and improved postoperative care. Even after successful repair, late complications are common and may include recoarctation, aortic aneurysm, coronary artery disease, cerebrovascular events, heart failure and arterial hypertension. The latter being especially common: according to a review on hypertension after CoA repair, the median prevalence is 32.5% (range 25-68%) [3]. However the timing and pathophysiology of the long term complications are still largely unknown. Previous studies showed a decreased cardiac function after coarctation repair in adults [4–6] and this cardiac impairment appears to be already present in childhood [7–9]. Altered cardiac autonomic nervous system (ANS) activity may play a role in the pathophysiology of long-term complications. The ANS nerves travel along the great arteries and may be damaged during surgery. Also, baroreceptors are highly expressed in the aortic arch and increased stiffness and aberrant flow patterns due to the stenosis or valve abnormalities may affect their function. Cardiac ANS can be measured non-invasively using impedance cardiography (ICG) in combination with electrocardiography (ECG). This technique can be used in an ambulatory setting, which arguably has the highest clinical relevance.

The aim of this study was to evaluate ambulatory ANS activity and cardiac function in children after CoA repair and to investigate the relationship between cardiac ANS activity and cardiac function.

PATIENTS AND METHODS

Participants

Patients with a repaired isolated CoA from the outpatient clinic aged 8-18 years old were asked to participate. Children with chromosomal disorders were excluded to reduce heterogeneity of the patient group. Additionally, a group of healthy control subjects was

recruited; chronic disease or medication use were exclusion criteria for inclusion in this group. These volunteers were age and sex matched to the patient group. All participants and both (one in the case of single-parent families) of their parents/guardians provided written informed consent. All study procedures were reviewed and approved by the Medical Ethics Review Committee of the LUMC medical centre (P13.198 and P14.095).

Ambulatory cardiac ANS measurement

24 hour ECG and ICG registration was done using the 5fs version of the VU Ambulatory Monitoring System (VU-AMS; VU University, The Netherlands [10]). One lead ECG was derived from 3 pregelled Ag/AgCl (Kendal H124SG) spot electrodes on the chest. Thoracic impedance (Z) was conducted by introducing a small alternating current (50kHz, 350 μA) through the thorax, also by the use of spot electrodes. The measuring electrodes were placed just above and below the sternum and current electrodes were placed on the back. Ectopic beats were removed from the data before analysis.

Sympathetic nervous system (SNS) activity was measured by the pre-ejection period (PEP) as it is a measure of ventricular contractility [11,12]. PEP is defined as the time interval between the ventricular electrical depolarization (i.e. Q-wave onset in the ECG signal) and the start of left ventricular outflow (i.e. the B-point in the ICG signal). A shorter PEP reflects higher sympathetic activity. Parasympathetic nervous system (PNS) activity was measured by respiratory sinus arrhythmia (RSA) [13]. RSA was calculated using the peak valley method [14] by combining the respiration signal, extracted from the thorax impedance signal (dZ) and the inter-beat-interval time series. This method scores RSA by subtracting the shortest inter-beat-interval during inhalation from the longest inter-beat-interval during exhalation. If no shortest or longest inter-beat-interval could be detected, RSA was set to zero for that breath. A higher RSA reflects higher PNS activity. Stroke volume was estimated using an adjusted Kubicek formula [15]. Cardiac output (CO) was calculated as heart rate * stroke volume.

By the use of the activity diary filled in by the participant in combination with the inbuilt accelerometer data from the VU-AMS device, the 24 hour recording was divided into fixed periods, coded for activity. Ensemble averaged ICG and ECG over these periods were analysed. Ultimately, for each subject, the mean heart rate (HR), RSA, PEP and CO was calculated for sleeping (mean of all sleeping labels), sitting (mean of watching TV, reading, computer), active sitting (class, crafts, homework), light physical activity (walking, chores) and heavy physical activity (cycling, gymnastics, playing). Participants were queried on their physical activity by the use of a short lifestyle interview [16] as differences in ANS activity might partly be explained by physical activity level [17].

Cardiac function and structure

Supine resting transthoracic echocardiograms (TTE) were conducted by a pediatric cardiologist or an experienced technician (Vivid 9, General Electric healthcare, Norway). Images were stored and analyzed offline using EchoPac software (General Electric Healthcare, version 113). Left ventricular longitudinal global peak strain (LV GLS, %) was calculated as the average of the peak strain obtained from the apical 2- 3- and 4-chamber view using speckle tracking strain analysis [18]. Biventricular performance was characterized using pulsed wave Tissue Doppler Imaging (TDI) from an apical 4-chamber view. Myocardial velocity curves were obtained at the basal part of the left and right ventricular wall and the intraventricular septum. Peak systolic velocity (S') and peak early (E') diastolic velocities (cm/s) were assessed in three consecutive heart beats; the average was used for analysis.

Cardiac magnetic resonance imaging (MRI) was done in a 3T scanner (Ingenia, Philips Healthcare). Pulse wave velocity (PWV) and left ventricular (LV) wall mass were assessed in patients only. Analyses were done offline using in-house developed MASS software (Leiden, The Netherlands). PWV was determined from two high-temporal 1-directional velocity encoded time-resolved MRI acquisitions, planned perpendicular to the aorta, one at the ascending aorta at the level of the pulmonary trunk and one at the

abdominal aorta 3 cm below the diaphragm. Flow mapping was performed to obtain velocity-time curves. The PWV was determined over both the proximal aorta (ascending aorta plus aortic arch and thoracic descending aorta, see figure 1) as well as the distal descending aorta (see figure 1). The validated foot-to-foot transit-time method was used to define PWV [19]. LV wall mass was assessed from a cine multi-slice short-axis data set acquired with steady-state free-precession gradient echo. Epi- and endocardial contours were drawn in every slice. Subsequently, the areas were subtracted, and the resulting areas were multiplied with slice thickness, number of slices and the density of myocardium. Contours were drawn end-diastole and end-systole by one researcher and supervised by one radiologist. The average from the end-diastolic mass and end-systolic mass was used for analysis.

The TTE, cardiac MRI and 24h monitoring were all obtained within 48 hours for all but one patient who had 7 days between the cardiac MRI and the TTE and 24h monitoring.

Statistical analyses

IBM SPSS statistics software (version 23.0, Armonk, NY) was used for statistical analysis. Differences in HR, PEP, RSA and CO between the healthy control and the patient group were studied by fitting a linear mixed model. Because RSA was skewed, its natural log transformation was used for further analysis. In the mixed model, we treated activity as a within-subject factor with 5 levels (sleep, inactive sitting, active sitting, moderate physical activity, heavy physical activity) and we treated group as a between-subject factor, with 2 levels (Healthy control and CoA patient). In the model, a random intercept was allowed over persons. Weekly physical activity was included as a covariate in the analysis of ANS activity and additionally breathing frequency in the analysis of RSA and mean arterial blood pressure in the analysis of PEP. Differences in subject characteristics between groups were evaluated by means of an independent t-test. For comparison of the 7 cardiac function parameters between groups, a MANOVA was carried out. In case of significance of the omnibus group effect ($p<0.05$), post hoc testing on each separate variable used a Bonferroni correction of

the overall p-value. Lastly, a correlation matrix was computed for the cardiac function parameters, blood pressure and ambulatory cardiac ANS parameters PEP and RSA during sleep in the patient group.

RESULTS

Table 1 summarizes the subject characteristics and weekly physical activity level. Resting systolic blood pressure was significantly higher (p=0.030) in patients compared to controls. Surgical technique employed for CoA repair was end-to-end anastomosis in 28 and subclavian flap in 3 patients. Time after surgery was on average 12 years (range 3.6 - 17.6 years). None of the patients had a clinically significant residual stenosis; maximal flow velocity at the coarctation site was on average 2.3 m/s (SD=0.6). 19 (59%) had a bicuspid aortic valve. Three patients were using medication (labetalol or enalapril) at the time of the study. Adjusted group means of HR, RSA, PEP and CO in each of the five ambulatory activities are summarized in table 2.

Results of the mixed linear modelling included a main effect of ambulatory activity on all four measures. For HR, no main effect of group was found ($F(1,96)=2.10$, $p=0.15$) but there was a group*activity interaction effect ($F(4,91)=2.74$, $p=0.033$). HR was higher in healthy controls during all periods except for sleep, however univariate test results showed no significant differences. For PEP, no main effect of group ($F(1,74)=0.43$), $p=0.515$) but an interaction effect of group*activity ($F(4,81)=4.55$, $p=0.002$) was found. The adjusted mean for PEP was higher in patients during sleep and higher in healthy controls during periods of moderate or heavy physical activity. However, univariate tests did not show significant differences. RSA showed neither a group effect ($F(1,95)=1.09$, $p=0.300$) nor an interaction of group*activity ($F(4,97)=1.04$), $p=0.393$). Lastly, CO showed a main effect of group ($F(1,98)=8.06$, $p=0.006$) which was due to lower CO in the CoA patients throughout the entire ambulatory recording period.

Cardiac function was significantly different between the two groups (Pillai's Trace, V=0.340, F(7,74)=5.46, p<0.001). Univariate tests show a significantly lower peak S' and E' wave velocity in the left ventricular wall and lower peak E' velocity in the intra ventricular septum in patients compared to controls (table 3).

A significant correlation was found between basal RSA during sleep and LV GLS (r=0.51, p=0.004) and between basal RSA and PWV in the proximal aorta (r=0.47; p=0.012). Also, the correlation between basal PEP during sleep and LV GLS (r=-0.45; p=0.002), between basal PEP and LV mass (r=0.55; p=0.002) and between basal PEP and peak S' wave in the intraventricular septum (r=-0.45; p=0.010) were significant. These associations were not found in the healthy control group. The correlation matrix can be found in table 4.

Rerunning the analyses without the three patients on medication did not alter the pattern of results.

COMMENT

In adults with a repaired CoA, several studies show a decreased LV function [4–6]. Klitsie et al. [7] studied LV function in infants before, shortly after and 1 year after correction of CoA. Before surgery, LV function (measured by TDI) was significantly impaired compared to healthy age matched controls. This improved after surgery, however LV function remained significantly lower compared to controls 1 year after repair. Similarly, Lombardi et al. found a reduced diastolic myocardial velocity (E') in the septum and LV lateral wall [8] in their cohort of children aged 8±7 years. The results from our study are in line with these results. We did not replicate Van der Ende et al. [9] who showed reduced longitudinal LV strain despite normal ejection fraction in their pediatric cohort after CoA repair. In the current study longitudinal LV strain was not different between patients and controls.

Before intervention, the decreased blood pressure in the lower part of the body – including the kidneys- may activate the renin-angiotensin system to increase systemic blood pressure. Also, increased pressure proximal to the coarctation, decreased elastic wall properties [20] and secondary flow patterns [21] in the aortic arch may alter baroreceptor function. After intervention, ANS may be altered by damaging of the ANS nerves traveling along the aorta. The current study is the first study to measure cardiac ANS activity in an ambulatory setting for a prolonged period and does not find differences in cardiac ANS regulation between healthy controls and children after CoA repair. Additionally, in patients operated at >1 year of age (N=8) versus patients operated <1 year of age (N=23), no difference was found in autonomic nervous system activity, nor when patients were divided into neonatal (operated in the first month of life; N=15) or non-neonatal repair (operated after the first month of life; N=16) as suggested by Klitsie et al. [7] (data not shown). Kenny et al. studied cardiac ANS activity in CoA patients by measuring (15 minute supine) heart rate- and blood pressure variability and baroreceptor sensitivity [22,23] and they did not find a difference between patients and controls. In contrast, Beekman et al. and Millar et al. report decreased heart rate variability and baroreceptor function post-repair in their pediatric cohorts [24,25]. In adults after CoA repair, Moutafi et al. found no differences in autonomic activity between patients and controls [26].

The current study finds a positive relationship between PWV (a measure of artery stiffness) in the proximal aorta and basal RSA during sleep (a heart rate variability measure of cardiac PNS activity). The only study investigating the relationship between PWV and cardiac PNS regulation in CoA patients found a negative relationship between baroreceptor sensitivity and aortic PWV [23]. The authors argue that hypertension becomes manifest once the ANS fails to compensate adequately in these patients. Although plausible, more research is necessary on this topic.

The current study also finds a positive relationship between basal RSA during sleep and LV longitudinal strain. The positive relationship between longitudinal strain and basal

cardiac PNS regulation is in line with the suspected protective effect of vagal activity on the heart [27]. The protective effect of vagal activity has especially been investigated in its role in sudden cardiac death [28], but it may also improve LV function [29,30].

A negative relationship was found between basal PEP during sleep and septal peak systolic velocity (S') and between basal PEP and longitudinal LV strain. This validates the PEP as an index of cardiac sympathetic activity, with shortened PEP reflecting the increased contractility also indicated by higher S' and strain. However, PEP is known to be sensitive to the effect of aortic pressure (afterload) which is in turn a function of mean arterial blood pressure. When the heart has to pump against a high afterload, it will also take more time to build up enough force to open the aortic valve. Hence, afterload may prolong PEP independent of cardiac inotropic drive [31,32]. In keeping with these afterload effects we find a positive relationship between basal PEP and LV mass. Increased afterload on the heart may, over time, cause LV hypertrophy and deterioration of LV function.

Hypertension is a well-known and common complication in CoA patients [3]. We reconfirm this, with resting blood pressure being higher in patients compared to controls (see table 1). Therefore, the use of PEP as a measure of SNS activity in this patient group is a limitation of the current study. A difference in PEP between two groups could be the result of a difference in contractility due to SNS activity, but may also be the result of a difference in afterload. We attempted to correct for afterload effects by including resting mean arterial blood pressure as a covariate in the model. However we did not measure blood pressure 24 hours and therefore we were unable to correct for the blood pressure during different activities during the day.

In conclusion, despite no differences in cardiac ANS activity between children after successful CoA repair and healthy peers, ambulatory cardiac output and left ventricular function were significantly decreased in these young patients. These results underline the importance of life long follow up in CoA patients, even after successful repair as none of the

patients included in this study had a residual stenosis. Also, altered cardiac ANS function might still play a role in the long term complications at older age and this should be addressed in future studies.

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Table 1. subject characteristics, exercise parameters and physical activity level

	CoA patients	Heathy controls
N	31	62
Male (%)	59	59
Age (y)	13.2 (2.9)	13.2 (3.1)
Age at repair		
Range	3d – 5.8y	-
Median, IQR (y)	0.4,0.0-1.3	-
Time after surgery (y)	12.3 (3.6)	-
Length (cm)	158.8 (15.1)	160.9 (17.1)
Weight (kg)	52.0 (17.0)	51.0 (16.9)
SBP (mmHg)*	120 (13)	114 (12)
DBP (mmHg)	66 (7)	66 (9)
Physical activity (METs/week)*	38.9 (21.6)	50.2 (23.8)

Mean (SD). IQR=Inter Quartile Range. CoA= Coarctation of the Aorta. D=days. Y=years. SBP=systolic blood pressure. DBP=diastolic blood pressure. MET=metabolic equivalent task. *significant difference between patients and healthy control group ($p<0.05$).

Table 2. Ambulatory measurement of HR, PEP, RSA and CO

	Activity	CoA patients	Healthy controls
Heart rate (bpm)	Sleep	66 (8)	66 (9)
	Quiet sitting	78 (10)	80 (13)
	Active sitting	83 (9)	86 (11)
	Moderate PA	105 (12)	111 (15)
	Heavy PA	123 (16)	128 (16)
RSA (ms)	Sleep	114 (52)	118 (55)
	Quiet sitting	95 (36)	94 (45)
	Active sitting	87 (30)	81 (36)
	Moderate PA	42 (21)	36 (15)
	Heavy PA	28 (14)	24 (11)
PEP (ms)	Sleep	93 (17)	97 (17)
	Quiet sitting	91 (15)	91 (14)
	Active sitting	93 (16)	93 (15)
	Moderate PA	81 (16)	75 (16)
	Heavy PA	74 (17)	66 (16)
CO (L/min)	Sleep	3.2 (1.0)	3.7 (1.0)
	Quiet sitting	3.5 (1.1)	4.1 (1.2)
	Active sitting	3.5 (1.0)	4.3 (1.3)
	Moderate PA	4.0 (1.3)	4.9 (1.6)
	Heavy PA	4.0 (1.2)	5.0 (1.7)

Estimated marginal means (SD). PA=physical activity. HR=heart rate. RSA=respiratory sinus arrhythmia. PEP=pre ejection period. CO=cardiac output.

Table 3. Cardiac structure and function parameters

	Measure of / related to	CoA patients	Heathy controls
LV GLS (%)	LV global function / contractility	17.9 (2.4)	18.2 (2.2)
LV TDI S' (cm/s)	Systolic function / contractility	8.7 (3.1) *****	10.8 (3.0)
LV TDI E' (cm/s)	Diastolic function / contractility	15.0 (4.6) *****	19.4 (3.7)
Septum TDI S' (cm/s)	Systolic function / contractility	6.9 (1.0)	7.2 (1.0)
Septum TDI E' (cm/s)	Diastolic function / contractility	12.6 (2.3) *****	14.0 (2.1)
RV TDI S' (cm/s)	Systolic function / contractility	13.0 (2.2)	12.3 (1.8)
RV TDI E' (cm/s)	Diastolic function / contractility	16.0 (3.4)	14.8 (3.3)
PWV proximal aorta (m/s)	Aortic stiffness / blood pressure	4.9 (1.3)	-
PWV distal aorta (m/s)	Aortic stiffness / blood pressure	3.9 (0.8)	-
LV mass (g)	Hypertrophy / afterload	85 (27)	-

Mean (SD). LV=left ventricle. GLS=global longitudinal strain. S=systolic motion. E=early filling. TDI=Tissue Doppler Imaging. RV=right ventricle. PWV=Pulse wave velocity *****significant difference between groups after Bonferroni correction for multiple comparisons ($p<0.007$).

Table 4. Correlation between cardiac ANS and cardiac function and structure in the CoA group

	PEP (sleep)	RSA (sleep)
LV GLS	-0.54 (95%CI: -.34;-.09) *****	0.51 (95%CI:.08;.36) *****
LV TDI S'	-0.31 (95%CI: -.67;.05)	0.04 (95%CI: -.33;.42)
LV TDI E'	-0.25 (95%CI: -.62;.12)	0.10 (95%CI: -.29;.48)
Septum TDI S'	-0.45 (95%CI: -.78;-.11) *****	0.23 (95%CI: -.13;.59)
Septum TDI E'	-0.23 (95%CI: -.60;.15)	0.06 (95%CI: -.32;.44)
RV TDI S'	-0.04 (95%CI: -.42;.34)	-0.14 (95%CI: -.52;.24)
RV TDI E'	-0.01 (95%CI: -.38;.37)	0.04 (95%CI: -.34;.41)
CO (sleep)	-0.09 (95%CI: -.47;.29)	-0.03 (95%CI: -.41;.35)
SBP	0.20 (95%CI:- 17.;.53)	0.08 (95%CI: -.29;.43)
DBP	0.10 (95%CI: -.26;.45)	0.13 (95%CI:- 23.;.48)
LV mass	0.55 (95%CI: .23;.86) *****	0.13 (95%CI: -.24;.50)
PWV PA	-0.04 (95%CI: -.45;.37)	0.47 (95%CI: .11;.83) *****
PWV DA	-0.01 (95%CI: -.41;.40)	-0.02 (95%CI: -.42;.38)

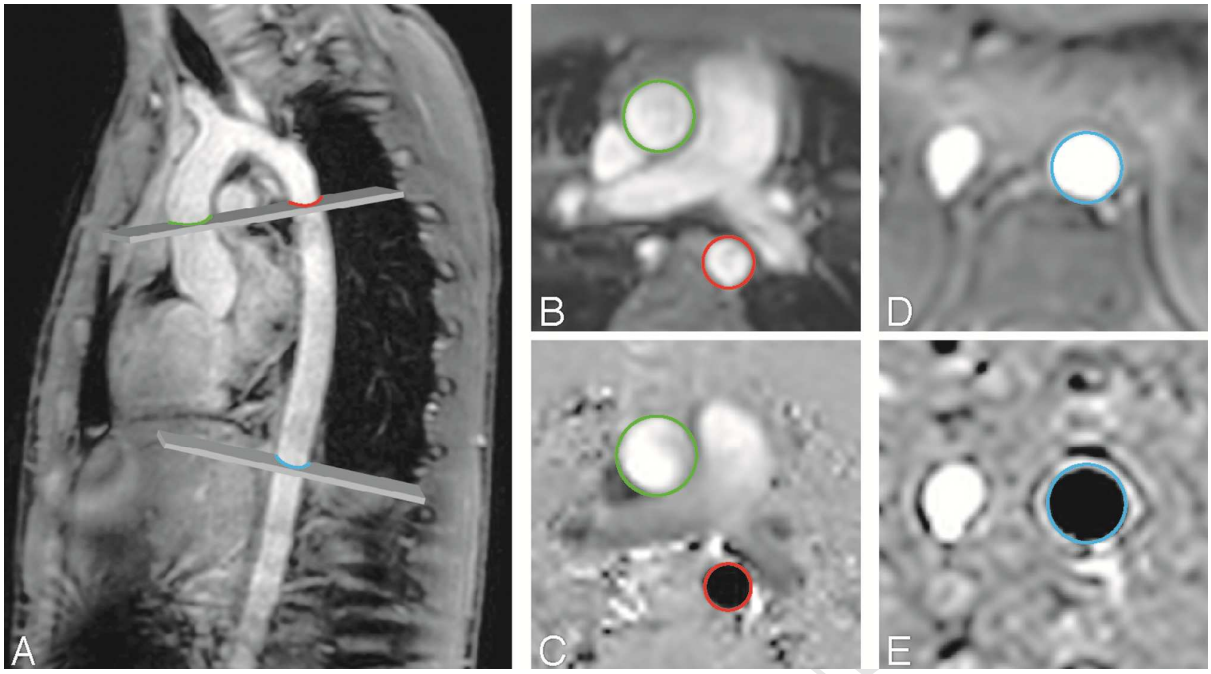
TV=tricuspid valve. S=systolic motion. E=early filling. TDI=Tissue Doppler Imaging. LV=left ventricle. RV=right ventricle. SBP=systolic blood pressure. DBP=diastolic blood pressure. PWV=pulse wave velocity. PA=Proximal aorta. DA=Distal aorta. *****significant correlation ($p<0.05$).

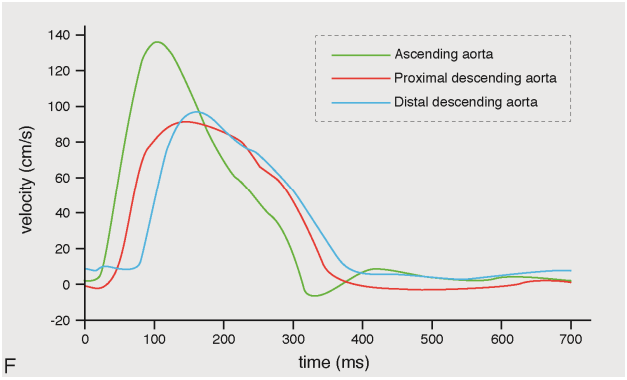
FIGURE LEGEND

Figure 1. Pulse wave velocity assessment. Sagittal scout of the aorta, indicating the three sites (green, red and blue) for through-plane velocity encoded MRI acquisitions (A). Transverse image of the upper (B) and lower (C) acquisition plane and associated velocity images (D&E), used to create the velocity-time curves (F). PWV is assessed by dividing the segment length (for the proximal aorta from the green to the red site and for the distal aorta from the red to the blue site) by the transit time needed for the pulse wave to propagate between sites, automatically determined by the foot-to-foot method.

ABBREVIATIONS

ANS	Autonomic nervous system
CoA	Coarctation
E'	Peak early velocity
ECG	Electrocardiogram
ICG	Impedance cardiogram
LV	Left ventricle
PEP	Pre ejection period
PNS	Parasympathetic nervous system
PWV	Pulse wave velocity
RSA	Respiration sinus arrhythmia
S'	Peak systolic velocity
SNS	Sympathetic nervous system
TDI	Tissue doppler imaging
TTE	Transthoracic echocardiogram





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