Aortic Backward Flow Indices Estimated from Phase-Contrast Cardiovascular Magnetic Resonance Data

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Abstract

Aging is a major cardiovascular risk factor and is associated with arterial stiffness. We hypothesized that quantitative parameters related to backward flow (BF) in the ascending aorta (AA) estimated from phase-contrast cardiovascular magnetic resonance (PC-CMR) data could be relevant markers of aging. We studied 100 healthy subjects (age: 40±15years). Aortic stiffness (aortic arch pulse wave velocity, AA distensibility) and geometry (AA diastolic diameter and arch length) indices and parameters of AA global flow, forward flow (FF) and BF (volumes and flow rate peaks) were semi-automatically estimated from 2D PC-CMR data. Carotid-femoral pulse wave velocity and carotid augmentation index (AIx) were assessed using applanation tonometry. AA flow parameters were highly reproducible (inter-observer variability<1.6±8.4%). Aortic BF significantly increased in terms of volume and flow rate peak with age (r>0.50, p<0.0001), while global flow and FF parameters were stable (p>0.06). Multivariate analysis showed that BF was strongly associated to aortic geometry and AIx independent of age, gender, body size, blood pressure and heart rate. Thus, aortic PC-CMR BF parameters could be early functional markers of subclinical impairment of circulatory efficiency and could help to further understand physiology of vascular aging.

1. Introduction

Aging is a major risk factor of cardiovascular disease and is associated with arterial stiffness [1]. Tonometry-derived carotid-femoral pulse wave velocity (PWV_{CF}), carotid pulse pressure (cPP) and wave reflection indices, such as augmentation index (AIx), are the most widely used parameters to describe the arterial system. Cardiovascular magnetic resonance (CMR) allows an accurate non-invasive estimation of central aortic stiffness parameters (distensibility and arch pulse wave velocity, PWV_{AO}) [2], in addition to geometry indices (diameters or arch length) [2]. Flow profiles within cross sections of the ascending aorta (AA) have been described using phase-contrast (PC) CMR in healthy volunteers, as skewed in end-systole with a backward flow (BF) in early diastole [3]. More recently, blood flow patterns in the AA have been studied using 3D [4] or 4D [5] PC-CMR data. However, comparison of quantitative AA BF and forward flow (FF) parameters against aortic stiffness, wave reflection and aortic arch geometry has never been reported. We hypothesized that such quantitative parameters derived from BF could be relevant markers of arterial stiffness and aging. Accordingly, our aims were to estimate parameters related to BF and FF in the AA in healthy subjects using 2D PC-CMR data, as well as to evaluate their relationships with age and to define major determinants of BF among aortic geometry and arterial stiffness parameters, including wave reflection indices.

2. Methods

2.1. Study population

We studied 100 healthy subjects without overt cardiovascular disease (50 men, age: 40±15 years), who had blood pressure measurement and a CMR exam.

Brachial blood pressures were measured with an oscillometric cuff (Vital Signs Monitor, Welch Allyn, US) simultaneously to CMR acquisitions. Applanation tonometry of right carotid and femoral arteries was performed immediately after CMR acquisitions (Pulse Pen, Diatecne, Italy). At least 10 consecutive waveforms at each site were used to estimate carotid AIx, central systolic (cSBP) and diastolic (cDBP) pressures, cPP and PWV_{CF}, after rescaling tonometric measurements by mean and diastolic brachial pressures. PWV_{CF} was estimated as the distance between recording sites, measured using a tape ruler over body surface, divided by pulse wave transit time, calculated as foot-to-foot delay between waveforms.

CMR was performed using a 1.5T scanner (Signa, GEMS, US) with cardiac-phased array coil (8 channels). Steady state free precession (SSFP) cine sequences were acquired during breath-holding in the axial and sagittal oblique planes to cover the whole thoracic aorta, using the following scan parameters: field-of-view=370x370mm², repetition time TR=3.7ms, echo time TE=1.5ms, flip angle=50°, rec FOV=0.8, views per segment VPS=32, slice thickness ST=8mm, acquisition matrix=224x192, pixel size=1.65x1.92mm². Temporal resolution was 15ms. An additional axial cine plane was acquired with a high temporal resolution, using a fast retrospectively gated gradient echo sequence, at the level of pulmonary bifurcation perpendicular to the aorta, using the following parameters: TR=3.3ms, TE=1.4ms, ST=8mm, VPS=6, acquisition matrix=224x190. Mean temporal resolution was 8ms. The latter slice location was used to acquire PC images, using a 2D trough-plane velocity-encoded sequence with retrospective gating during breath-holding, providing blood flow velocities in both AA and descending aorta (DA). PC acquisition parameters were: TR=4.8ms, TE=2.3ms, flip angle=50°, number of excitations=1, ST=8mm, acquisition matrix=256x128, VPS=2. Mean temporal resolution was 10 ms. Encoding velocity was Venc=150cm/s, and the acquisition was repeated with Venc=200 cm/s in case of velocity aliasing.

2.2. CMR Image analysis

AA contours were automatically detected on SSFP images for all phases of the cardiac cycle using the previously described custom ArtFun software [6], providing area and diameter variations. It was also used for the automated detection of AA and DA contours on modulus PC images. These contours were then superimposed on velocity PC images for flow analysis.

Segmentation of aortic images combined with carotid pressure tonometric measurements enabled the estimation for each subject of the following stiffness and geometry parameters: 1) AA distensibility = (As – Ad) / (Ad · cPP), where As and Ad are respectively the systolic and diastolic AA lumen areas (mm²) estimated from SSFP images. 2) PWV_{AO} was estimated using the ArtFun software. 3) Aortic arch length was estimated from SSFP acquisitions as the distance between AA and proximal DA locations used for PC-CMR acquisition. 4) AA diastolic diameter was calculated from Ad.

The analysis of velocity sign on PC images enabled to separate AA global flow in its FF and BF components. Global, FF and BF flow rate curves throughout the cardiac cycle were then calculated, and semi-automated peak detection and area under curve calculation were used to estimate the following AA flow parameters (Figure): 1) global flow volume (V_{GF}), from global flow rate curve; 2) FF peak (Q_{FFmax}) and volume throughout the cardiac cycle (V_{FF}), from FF flow rate curve; 3) BF peak (Q_{BFmax}) and volume throughout the cardiac cycle (V_{BF}), from BF flow rate curve. We also studied the systolic and diastolic components of V_{BF}. Q_{BFmax}/Q_{FFmax} ratio was also calculated.

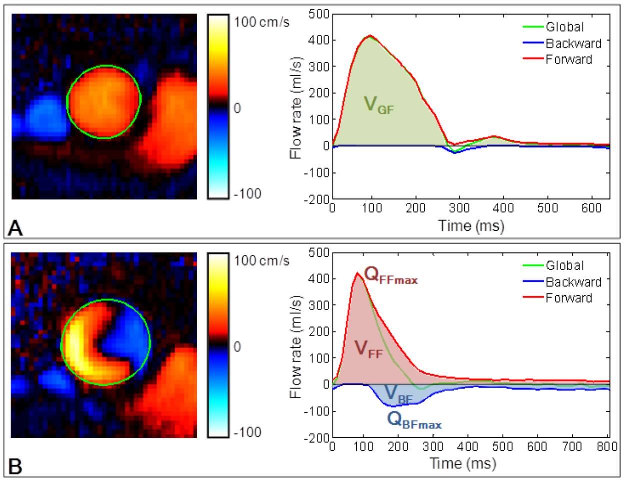

Figure: Results of the automated AA contours detection on a systolic PC-CMR cross-sectional velocity image (left) and the calculated parameters from flow rate curves (right) on a 20-year (A) and a 70 year-old (B) subject.

2.3. Variability measurements

Data of 30 subjects were analyzed by 2 independent operators to assess inter-operator variability, in terms of aortic flow parameters measurement.

2.4. Statistical analysis

Baseline characteristics are provided as mean±standard deviation. For analysis of characteristics variations over age, we divided the subjects into 2 groups: <40years (n=52) and ≥40years (n=48), according to median age. Statistical inferences for general trends of indices were evaluated by testing the equality of the conditional means using ANOVA between the two groups. Univariate Pearson correlation coefficients relating aortic stiffness, geometry and flow parameters to age were reported. Associations of V_{BF} with age, gender, weight, height, cSBP, heart rate (HR), AA diameter and distensibility, arch length, AIx, PWV_{CF} and PWV_{AO} was further studied using multivariate regression models. All reported p values are two-sided and a p value of less than 0.05 indicated statistical significance. Inter-operator variability was calculated for each subject as the absolute difference of repeated measurements in percentage of their mean.

3. Results

Subject characteristics are summarized in Table 1.

None of the subject had significant aortic regurgitation.

Table 1. Subjects characteristics according to age group.

	< 40 years	≥ 40 years	p value
Age, years	27±5.7	54±9.2	<0.0001
Gender, M/F	26/26	24/24	0.56
Weight, kg	67±13	71±12	0.11
Height, cm	171±8.9	170±8.8	0.71
Body surface area, m²	1.78±0.19	1.82±0.18	0.29
Body mass index, kg/m²	22.8±3.13	24.5±3.63	0.02
HR, bpm	66±11	65±11	0.63
cSBP, mmHg	98±8.6	106±15	0.001
cDBP, mmHg	63±8.0	73±11	<0.0001
cPP, mmHg	35±7.7	34±9.6	0.51

Inter-observer variability of aortic flow parameters was: 0.9±4.5% for V_{GF}, 0.1±0.2% for Q_{FFmax}, 0.9±4.9% for V_{FF}, 1.0±2.1 % for Q_{BFmax} and 1.6±8.4% for V_{BF}.

Results of the univariate analysis for comparison of aortic stiffness, geometry and flow parameters against age are summarized in Table 2. The relationship between Q_{BFmax} and age was significantly stronger for subjects over 40 years compared to younger subjects. Moreover, both systolic and diastolic components of BF volume increased progressively with age, and the proportion of BF volume occurring during systole increased with age (r=0.40, p<0.0001). Global V_{BF} increased by a mean factor of 3.5 between 30 and 60 years.

Table 2. Relationships between aortic parameters and age.

	Correlation coefficient (r)	p value
PWV_{CF}	0.77	<0.0001
PWV_{AO}	0.75	<0.0001
AA distensibility	-0.74	<0.0001
AA diameter	0.74	<0.0001
Arch length	0.69	<0.0001
AIx	0.65	<0.0001
V_{GF}	-0.13	0.2
Q_{FFmax}	-0.19	0.06
V_{FF}	0.18	0.07
Q_{BFmax}	0.50	<0.0001
V_{BF}	0.63	<0.0001
Q_{BFmax}/Q_{FFmax}	0.64	<0.0001

Table 3 summarizes results of the multivariate analysis for comparison between V_{BF} and aortic stiffness and geometry parameters. Overall, age alone explained 40% of the variation in V_{BF} (Model A). Addition of gender, body size, cSBP and HR moderately increased descriptive value of the model (Model B). We then evaluated a model adding individually to model B: AA diameter, arch length, AIx, PWV_{CF}, PWV_{AO} and AA distensibility as predictors of V_{BF} (Model C). Aortic geometry indices and AIx were important predictors of V_{BF} when tested individually independent of age, gender, body size, cSBP and HR. The strength of association with V_{BF} was the highest for aortic geometry parameters and slightly lower for AIx. In addition, while in univariate analysis we found significant relationships for comparison of V_{BF} against PWV_{CF}, PWV_{AO} and AA distensibility (r=0.50, r=0.50 and r=-0.47, respectively p<0.0001), these relationships did not remain significant after full adjustment.

Table 3. Relationships between V_{BF} and measures of aortic geometry and stiffness adjusted for age, gender, weight, height, cSBP and HR (adjustment models: 1) Model A: age; 2) Model B: age, gender, weight, height, cSBP and HR; 3) Model C: individual models corresponding to Model B with the separate addition of AA diameter, arch length, AIx, PWV_{CF}, PWV_{AO} and AA distensibility. Regression coefficients β are provided).

	β	Individual p	Overall R² (p)
Model A			
Age	0.03±0.003	<0.0001	0.40 (<0.0001)
Model B			
Age	0.02±0.003	<0.0001	0.44 (<0.0001)
Gender	0.01±0.137	0.92	
Weight	0.01±0.005	0.07	
Height	-0.01±0.008	0.46	
cSBP	0.002±0.004	0.57	
HR	-0.01±0.005	0.21	
Model C			
AA diameter	0.11±0.012	<0.0001	0.68 (<0.0001)
Arch length	0.01±0.003	<0.0001	0.48 (<0.0001)
AIx	0.01±0.003	0.002	0.50 (<0.0001)
PWV_{CF}	0.34±0.288	0.25	0.45 (<0.0001)
PWV_{AO}	0.19±0.196	0.33	0.45 (<0.0001)
AA distensibility	17.3±25.19	0.49	0.45 (<0.0001)

4. Discussion

We estimated reproducible parameters related to the BF in the AA of 100 healthy subjects using a semi-automated analysis of 2D PC-CMR data. The main findings of our study were that BF volume and flow rate peak increased with age, while global and FF parameters remained unchanged, and increased BF volume was independently related to increased aortic diameter and arch length and, to a lesser extent, to increased AIx.

We found BF to be present in all subjects, occurring in mid- or end-systole and during diastole, as previously reported [3-5,7]. The age-related alteration of AA geometry, including cross sectional dilatation and elongation, which resulted in unfolding of the aortic arch and was associated to functional impairment of the proximal aorta, was previously demonstrated [2]. Hope et al. found, using PC-CMR, that BF was increased in patients with AA aneurysm compared to controls [5]. In the present study, we showed that an increase in BF was strongly associated with age-related AA dilatation and arch elongation. Overall, a 1.1mm increase in diameter and a 0.1mm increase in length were related to a 10ml increase in V_{BF} after adjustment. This finding favors the hypothesis that local changes in AA geometry play a key role in BF augmentation, possibly by leading to increased secondary helical and irregular counter rotating flows that were previously observed [4]. Beyond increased aortic diameter and length, arch curvature may play a role in BF generation, as suggested by 3D PC-CMR studies, reporting BF to occur along the inner curvature of the aortic arch [4]. It was also shown after coarctation surgery in young subjects that BF was increased in angulated (gothic) arches compared to round (roman) arches [8]. Consistently, we found BF to begin in systole along the left lateral aortic wall. Since flow is driven by spatial pressure gradients, with blood flowing from high to low pressure areas, the presence of BF within AA suggests a local and temporal reversal in pressure gradients due to effective mass of blood acceleration and deceleration (inertance) and to pressure reflection waves. Such aortic pressure gradients were previously observed, with a diastolic gradient reversal in the AA, using 4D PC-CMR data [9], and could participate in BF generation.

Bogren et al. also hypothesized using CMR and angiography in older subjects and in patients with coronary artery disease that irregular blood flow patterns could be related to decreased aortic compliance [7]. Age-related processes, including mechanical stress, lead to increased arterial stiffness and dilation. When aortic distensibility is markedly decreased such as in older subjects, increased diameter becomes a surrogate measure of local vascular structural and functional alteration, while in young subjects with preserved aortic elasticity, it is primarily a measure of constitutional anatomy.

It was speculated that aortic BF can also be related to wave reflection [7]. In our study, we obtained an independent association between V_{BF} and AIx, which suggests that wave reflection could participate in BF generation. However, AIx is not its prime determinant compared to geometric parameters. Thus, blood flow patterns across AA may result essentially from factors related to local and regional fluid hemodynamics and flow-structure interactions in the proximal aorta more than global wave reflection.

A limitation of our study is the potential velocity measurement errors of 2D PC-CMR sequences, due to a possible mismatch between acquisition plane positioning and local flow direction and to an inappropriate Venc setting. In our study, special care was taken to adequately position PC-CMR acquisition plane perpendicular to AA axis. Besides, Venc was chosen to maximize velocity to noise ratio and was corrected in case of aliasing. In the future, 3D or 4D PC-CMR sequences could be used to study blood flow patterns in the entire aorta, although temporal and spatial resolutions of such techniques remain limited and acquisition as well as post processing of such data are still time consuming and operator-dependent. Our study provides quantitative analysis of blood flow patterns in the AA over age. Our reproducible BF parameters estimated in healthy humans using semi-automated analysis of PC-CMR data are highly related to age and are relevant indices of age-related changes in aortic geometry. Indeed, BF increases in terms of volume and flow rate peak with aging, and seems to be related to local and regional aortic arch remodeling. Thus, BF indices may be early functional markers of subclinical impairment of circulatory efficiency and could help to further understand physiology of vascular aging and its complications.

References

[1] Adji A, O'Rourke MF, et al. Arterial stiffness, its assessment, prognostic value, and implications for treatment. Am J Hypertens 2011;24:5 – 17.

[2] Redheuil A, Yu WC, et al. Age-related changes in aortic arch geometry: relationship with proximal aortic function and left ventricular mass and remodeling. J Am Coll Cardiol 2011;58:1262 - 70.

[3] Klipstein RH, Firmin DN, et al. Blood flow patterns in the human aorta studied by magnetic resonance. Br Heart J 1987;58:316 – 23.

[4] Kilner PJ, Yang GZ, et al. Helical and retrograde secondary flow patterns in the aortic arch studied by three-directional magnetic resonance velocity mapping. Circ 1993;88:2235 - 47.

[5] Hope TA, Markl M, et al. Comparison of flow patterns in ascending aortic aneurysms and volunteers using four-dimensional magnetic resonance velocity mapping. J Magn Reson Imaging 2007;26:1471 – 9.

[6] Herment A, Kachenoura N, et al. Automated segmentation of the aorta from phase contrast MR images: validation against expert tracing in healthy volunteers and in patients with a dilated aorta. J Magn Reson Imaging 2010;31:881 – 8.

[7] Bogren HG, Mohiaddin RH, et al. The function of the aorta in ischemic heart disease: a magnetic resonance and angiographic study of aortic compliance and blood flow patterns. Am Heart J 1989;118:234 – 47.

[8] Ou P, Celermajer DS, et al. Angular (Gothic) aortic arch leads to enhanced systolic wave reflection, central aortic stiffness, and increased left ventricular mass late after aortic coarctation repair: evaluation with magnetic resonance flow mapping. J Thorac Cardiovasc Surg 2008;135:62 – 8.

[9] Meier S, Hennemuth A, et al. Non-invasive 4D Blood Flow and Pressure Quantification in Central Blood Vessels via PC-MRI. Computing in Cardiology 2010;37:903 – 6.

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