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Characterization of volumetric flow rate waveforms at the carotid bifurcations of older adults

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Abstract

While it is widely appreciated that volumetric blood flow rate (VFR) dynamics change with age, there has been no detailed characterization of the typical shape of carotid bifurcation VFR waveforms of older adults. Towards this end, retrospectively gated phase contrast magnetic resonance imaging was used to measure time-resolved VFR waveforms proximal and distal to the carotid bifurcations of 94 older adults (age 68 ± 8 yrs) with little or no carotid artery disease, recruited from the BLSA cohort of the VALIDATE study of factors in vascular aging. Timings and amplitudes of well-defined feature points from these waveforms were extracted automatically, and averaged to produce representative common, internal and external carotid artery (CCA, ICA and ECA) waveform shapes. Relative to young adults, waveforms from older adults were found to exhibit a significantly augmented secondary peak during late systole, resulting in significantly higher resistance index (RI) and flow augmentation index (FAI). Cycle-averaged VFR at the CCA, ICA and ECA were 389 ± 74 , 245 ± 61 and 125 ± 49 mL min⁻¹, respectively, reflecting a significant cycle-averaged outflow deficit of 5%, which peaked at around 10% during systole. A small but significant mean delay of 13 ms between arrivals of ICA versus CCA/ECA peak VFR suggested differential compliance of these vessels. Sex and age differences in waveform shape were also noted. The characteristic waveforms presented here may serve as a convenient baseline for studies of VFR waveform dynamics or as suitable boundary conditions for models of blood flow at the carotid arteries of older adults.

Keywords

volumetric flow rate; carotid bifurcation; magnetic resonance imaging; human studies; augmentation index

1. Introduction

Papers published in this journal over the past decade have sought to characterize the nature of volumetric flow rate (VFR) waveforms at the carotid arteries of young adults. Holdsworth *et al.* (1999) characterized a now-widely-used common carotid artery waveform via Doppler ultrasound measurements of N=17 subjects, also providing extensive descriptive statistics of inter- and intra- individual variations. Marshall *et al.* (2004) used cine phase contrast magnetic resonance imaging (PCMRI) to investigate time-varying flow rates and flow divisions at the carotid bifurcations of N=9 subjects. Using a waveform analysis approach similar to Holdsworth *et al.*, Ford *et al.* (2005) derived representative VFR waveform shapes and descriptive statistics for internal carotid arteries, and also vertebral arteries, from N=17 subjects, using cine PCMRI having a higher temporal resolution than that used by Marshall *et al.* Together, these data establish the baselines against which normal and pathological changes in VFR dynamics can be assessed, and they also provide necessary inputs to computational and physiological studies (e.g., Lee *et al.*, 2008).

It is well known that VFR dynamics of older adults differ from those of young adults. For example, Scheel *et al.* (2000) have reported significant age-related changes in carotid artery resistance index (RI), a measure of fractional difference in peak systolic versus end diastolic VFR. Hirata *et al.* (2006) also presented evidence that arterial stiffening with aging increases carotid flow augmentation index (FAI), which is thought to measure the contribution of the reflected pulse wave at late systole. To date, however, there has been no attempt to characterize the shape of older adult carotid VFR waveforms with the same level of attention given to young adults. With this in mind, the aim of this study was to provide reference data for VFR waveforms at the common, internal and external carotid arteries (hereafter denoted CCA, ICA and ECA, respectively) in a cohort of older adult individuals imaged by cine PCMRI, as part of broader investigation into risk factors for vascular aging.

2. Methods

2.1. Study subjects

Data for this study were acquired from the ongoing VALIDATE (Vascular Aging – The Link That Bridges Age to Atherosclerosis) study, which aims to test the hypothesis that vascular age is an important determinant of the age-associated increase in atherosclerotic disease. Specifically, of the three VALIDATE groups, the present study focused on the community-based cohort (i.e., normal vascular aging group), recruited from Baltimore Longitudinal Study for Aging (BLSA) participants (Ferrucci, 2008), namely those scanned and reviewed by the VALIDATE reading center until September 2008. Of these 130 cases, 9 were excluded for having NASCET stenosis severities >20% in order to minimize possible confounding effects of carotid artery disease on the waveform characteristics.

MRI acquisitions focused on the right carotid bifurcation unless the image quality was inferior to that from the left side, for example due to metal/dental-work artifacts or surface RF coil placement. Two cases were excluded owing to inconsistent gating. Of the remaining 119 cases, 47 were male, and so to ensure an equal balance of sexes we included only 47 females, taking care to match the number of cases in each decade of age. Demographic and risk factor data for these N=94 (92 right, 2 left) cases were: 68±8 years old; 50% female; 42% African American; 35% current or former smoker; 11% diabetic; 45% hypertensive; 129±16 mmHg systolic BP; 69±10 mmHg diastolic BP; 192±39 mg/dL cholesterol; 94±24 mg/dL glucose. Written informed consent was obtained from all participants and approval was given by the institutional review boards.

2.2. Magnetic resonance imaging

Subjects were scanned, in a supine position on a 1.5 Tesla scanner (Intera, Philips Medical Systems; Eindhoven, The Netherlands) equipped with a four channel phased array carotid radiofrequency coil (Machnet; Eelde, The Netherlands). The complete MRI protocol included a variety of MR angiographic, black blood and phase contrast acquisitions. Here we focused on ECG-gated, retrospective cine phase contrast (PCMRI) images of the through-plane velocity acquired transverse to the nominal long axis of the selected common carotid artery (CCA) at a distance 1.5 cm proximal to the flow divider; and a separate acquisition 0.5 cm distal to the flow divider, through the ICA and ECA. Scan parameters were: 5 mm slice thickness; 130 mm square field of view; 256×128 acquisition matrix zero padded to 256×256 ; 25° flip angle; scanner minimum repetition times (~ 7 – 8 ms) and echo times (~ 4 – 5 ms); 70 cm s^{-1} maximum encoding velocity; and 32 uniformly-spaced time points per cardiac cycle.

2.3. Flow waveform extraction

Extraction of VFR data from the PCMRI images and subsequent characterization of the VFR waveform shapes were carried out following the methodology described by Ford *et al.* (2005). Briefly, the lumen boundaries from each PCMRI image were delineated semi-automatically, from which the instantaneous VFR was calculated as the product of the lumen area and the average velocity within the boundary. Splines were then fitted through the 32 instantaneous VFR data points to produce continuous VFR waveforms for each of the CCA, ICA and ECA of each subject. Finally, feature points characterizing systolic extrema and diastolic decay (see Figure 1) were identified from these continuous VFR waveforms in an automated manner.

2.4. Data analysis

Cycle-averaged VFR (VFR_{avg}) was calculated for each VFR waveform by integrating the spline-fitted PCMRI data. A number of popular dimensionless waveform indices were calculated from each set of feature points as follows: pulsatility index, $\text{PI} = (\text{VFR}_{\text{P1}} - \text{VFR}_{\text{D4}}) / \text{VFR}_{\text{avg}}$; resistance index, $\text{RI} = (\text{VFR}_{\text{P1}} - \text{VFR}_{\text{D4}}) / \text{VFR}_{\text{P1}}$; and flow augmentation index, $\text{FAI} = (\text{VFR}_{\text{P2}} - \text{VFR}_{\text{D4}}) / (\text{VFR}_{\text{P1}} - \text{VFR}_{\text{D4}})$. To characterize waveform *shape*, the VFR feature point amplitudes were normalized by the respective waveform's VFR_{avg} . The spline-fitted waveforms were then shifted in time so that the H0 feature point occurred at $t = 0$.

For the CCA, ICA and ECA separately, waveform feature point timings/amplitudes and derived indices were pooled across all cases to provide descriptive statistics for the older-adult waveform shape. Differences among these older adult data were tested using two-tailed paired t-tests (R Project for Statistical Computing, version 2.8.1). For the ICA, unpaired t-tests were used to determine the significance of differences between older adult versus Ford *et al.*'s (2005) young adult data, comprising $N=17$ (16M:1F) individuals with no known neurological problems, ranging in age from 20 to 39 years old. Unless otherwise indicated, differences were deemed significant for $p < 0.05$, and results are tabulated or plotted as $\text{mean} \pm \text{standard deviation}$ (SD).

3. Results

3.1. Cycle-averaged VFR and derived waveform indices

As summarized in Table 1, the majority of flow from the CCA exited through the ICA. Relative to the CCA, the cycle-averaged ICA:ECA flow division was $63:32 \pm 11$, indicating a roughly 5% deficit in ICA+ECA outflow relative to CCA inflow, a difference which was statistically significant (370 ± 72 versus 389 ± 74 ; $p < 0.0001$). For all quantities reported in Table 1, there were significant differences ($p < 0.0001$) among the respective CCA, ICA and ECA values.

Relative to Ford *et al.*'s VFR data from the young adult ICA, VFR_{avg} in the older adult was not significantly lower (245 ± 61 versus 274 ± 57). There was also no significant difference between older and young adult peak:average VFR (1.67 ± 0.26 versus 1.58 ± 0.14) and pulsatility indices (1.12 ± 0.32 versus 0.92 ± 0.17). On the other hand, there were significant differences between older and young adult resistance indices (0.66 ± 0.08 versus 0.58 ± 0.06 ; $p < 0.001$) and, especially, flow augmentation indices (0.97 ± 0.19 versus 0.56 ± 0.16 ; $p < 0.0001$).

3.2. Time-varying VFR and flow divisions

VFR waveforms averaged across the 94 cases (Figure 1) reflected the differences among the CCA, ICA and ECA flows suggested by the derived indices noted above. In particular, the ICA waveform exhibited less dynamic range (lower PI and RI) and a flatter systolic peak (higher FAI) relative to the ECA and CCA waveforms. Also evident was a slight but significant difference in the time to peak VFR for the ICA relative to the CCA (124 ± 20 ms versus 136 ± 22 ms; $p < 0.0001$), corresponding to a delay of 12 ± 20 ms. There was, however, no significant delay (-0.1 ± 13 ms) between the ECA and CCA peak VFR.

The older adult heart rate was 65 ± 10 bpm (range: 43–92), not significantly different from the 68 ± 8 bpm (range: 56–83) reported by Ford *et al.* for young adults. However, being derived from different PCMRI acquisitions during the same exam, the periods of the CCA versus ICA/ECA waveforms were slightly, but not significantly, different (951 ± 148 ms versus 949 ± 149 ms). In fact, the average difference in heart rate between the two acquisitions was less than 1 bpm, with a maximum difference of 6 bpm occurring for only one case.

The division of flow to the ICA and ECA varied appreciably throughout the cardiac cycle for these older adults (Figure 2). Prior to peak systole (~ 100 ms after the ECG trigger) the fraction of CCA flow to the ICA reached a minimum of 0.48 ± 0.11 , around which time the fraction of CCA flow to the ECA reached a maximum of 0.40 ± 0.12 . In early diastole (~ 400 ms) these fractions reached their respective opposite extrema of 0.74 ± 0.19 and 0.26 ± 0.14 . These values and trends were broadly similar to those reported by Marshall *et al.* (2004) for the carotid bifurcations of young adults.

Evident from the above-reported flow divisions, and from the top curve in Figure 2, is the time-varying nature of the difference between CCA inflow and ICA+ECA outflow. At 100 ms after the ECG trigger the outflow:inflow ratio was 0.88 ± 0.12 , a minimum significantly different from unity. Throughout much of late diastole, however, this ratio was not significantly different from unity. Averaged over the cardiac cycle, the outflow:inflow ratio was 0.97 ± 0.04 , reflecting the $\sim 5\%$ cycle-averaged outflow deficit noted in Section 3.1. Implications of similarities and differences relative to Marshall *et al.* are discussed in Section 4.1.

3.3. Characteristic VFR waveform shapes

Summarized in Table 2 are the feature point timings and amplitudes for the characteristic CCA, ICA and ECA waveform shapes (i.e., after aligning in time to individual H0 and normalizing to individual VFR_{avg}). In Figure 3 the spline-fitted feature points for the older adult ICA are compared against those from the young adult ICA as reported by Ford *et al.* (2005). Broadly, the significant differences for older- versus young-adult waveform indices noted in Section 3.1 can be inferred from the much stronger late systolic peak (hence the higher FAI), and a slightly reduced diastolic minimum (hence the slightly higher RI). As indicated by the error bars in Figure 3, there was generally more interindividual variability in the timings and amplitudes of the waveform shape from older adults compared to those from young adults.

Taking a closer look at these characteristic ICA waveform shapes, older subjects in our cohort had slightly lower heart rates on average, leading to a longer (but not significantly so) cycle

period relative to young adults (949 ± 149 ms versus 883 ± 99 ms). The time-to-peak VFR (i.e. from H0 to P1) for the older-adult waveform was slightly but significantly longer (55 ± 13 versus 45 ± 4 ; $p < 0.01$), although the peak amplitudes (i.e., P1) were not significantly different, as noted in Section 3.1. During late systolic deceleration, amplitudes at H1, M1, P2 and H2 were significantly higher for older versus young adults ($p < 0.0001$), whereas the timings of M1 and P2 were significantly earlier ($p < 0.0001$). On the other hand, early diastole feature points M2, H3 and P3 for older adults were significantly later (for M2 and H3, $p < 0.0001$; for P3, $p = 0.006$), with the amplitude of P3 being marginally but significantly lower ($p = 0.04$). Finally, despite the older subjects having a longer diastole and significantly lower late diastolic amplitudes D1-D4 ($p < 0.0001$), the characteristics of the decay were broadly similar to those seen in the young adults.

4. Discussion

4.1. Summary, interpretation and implications of key findings

The present study characterizes VFR waveform shapes in older adults confirms, in a robust and statistically meaningful way, that older adults possess significantly different carotid bifurcation VFR waveform shapes compared to young adults. These data therefore fill an important gap left by previous studies, which have focused on young adults. Important secondary findings are of small but significant delays between ICA and ECA peak systolic flow, and a net 5% ICA+ECA outflow deficit relative to the CCA inflow.

Considering these secondary findings first, we note that Marshall *et al.* (2004) similarly reported a net 5% outflow deficit in their PCMRI-based study of young adult carotid VFR waveforms. They suggested that it might reflect the systolic distension of the nominally more compliant ICA; however, they noted that there was no diastolic outflow surplus to balance this, an observation consistent with our Figure 2. We concur with those authors that this deficit is unlikely to be due to residual phase in the PCMRI images. It is also unlikely to be due to displacement artifacts that might arise from complex flow patterns at the ICA, as our echo times were relatively short. Repetition times were sufficient to resolve 32 images without introducing low-pass-filtering effects that can be encountered by retrospectively-gated cine PCMRI (Frayne and Rutt, 1993). Even for the smaller ECA spatial resolutions were adequate to minimize partial volume effects (Tang *et al.*, 1993), which anyway would have served to overestimate VFR. Instead, we suggest that at least some of this flow deficit may be attributed to the superior thyroid or other small branch arteries that arise off the ECA, and sometimes the CCA, near the bifurcation.

In the present study we made no attempt to exclude cases with such branch vessels, or to account for their VFR. In a study on the effect of small side branches on carotid bifurcation hemodynamics, Zhao *et al.* (1999) proposed that flow to the superior thyroid artery should be at most 20% of the ECA flow, based on their clinical experience. Given our cycle-averaged ECA flow rate of 125 mL min^{-1} , this amounts to 25 mL min^{-1} or 6% of the cycle-averaged CCA flow, consistent with the 5% cycle-averaged outflow:inflow deficit found in the present study. This is not to imply that storage/release of flow by the ICA does not take place. On the contrary, we observed a small but significant delay in peak systolic flow at the ICA relative to the ECA, which, since the ICA and ECA were imaged at the same slice, can best be explained by a compliance-induced storage of flow. Since, like that of the ECA itself, the bulk of small branch flow occurs during systole, it is probable that the ~10% outflow deficit at peak systole seen in Figure 2 includes both ICA flow storage and ECA branch outflow influences. During diastole, the “missing” surplus ICA flow release may be balanced by the small diastolic component of the ECA branch outflow. With this in mind, it is interesting to note that Marshall *et al.* observed a mean outflow deficit of close to 20% at peak systole, double that observed in the present study. Those authors also showed what appears to be a roughly 50 ms delay between

ICA and ECA peaks, compared to the 13 ms delay reported here. Notwithstanding differences in PCMRI acquisition parameters and waveform averaging methods, such differences in flow deficit and peak delay would be consistent with the presumably more compliant ICA of young versus older adults.

Returning to the main finding of our study, the most prominent difference between older and young adult VFR waveforms was the presence of a strong secondary peak during late systole (feature point P2), which is thought to arise from the early return of wave reflection from local upper-body sites and its interaction with later wave reflection returning from the opposite direction from sites in the lower part of the body (Hirata *et al.*, 2006). For the ICA we did observe a significantly earlier arrival of feature point P2 for older versus young adults. Age-associated increases in arterial wall stiffness may contribute to such earlier return of reflected waves during systole, which leads to an increase in central pressure augmentation (Najjar *et al.*, 2005; Nichols, 2005), leading to flow augmentation which potentially increases cerebral microvascular damage (Hirata *et al.*, 2006). In fact, when the normalized VFR waveforms were constructed according to age in decades (Figure 4), the amplitude of this augmented second peak was found to increase monotonically with age, with a concomitant decrease of the diastolic amplitude arising from the normalization by VFR_{avg} . As a result PI increased monotonically with age, while RI and FAI decreased (data not shown), although the trends were not statistically significant.

Also evident in Figure 4 are sex differences in waveform shape, notably a stronger systolic peak at the CCA. As summarized in Table 3, males had significantly higher peak VFR at the CCA and ECA, and, consequently, significantly higher amplitudes at feature points H0, P1 and H1. Peak VFR at the ICA was not significantly different between the sexes, however, the amplitudes of feature points H0, P1 and H1 were. There were no sex differences for any other CCA, ICA or ECA waveform feature point. These findings, as well as the strong sex differences in PI, RI and FAI at the CCA, but not the ICA, suggest that body size (i.e., external circulation), but not brain size, was larger for males vs. females in our cohort, as might be expected.

The significance of such age- and sex-dependent VFR dynamics on blood flow patterns at the atherosclerosis-prone carotid bifurcation is unclear, especially in light of potentially confounding systemic factors. It is now well-appreciated that such patterns are determined primarily by the vessel geometry (Lee *et al.*, 2008); however, the harmonic content of older-versus young-adult VFR waveforms could, for example, serve to amplify or suppress specific wall shear stress frequencies that are associated with inflammatory responses in the endothelium (Himburg *et al.*, 2007). The use of convenient young adult VFR waveforms as boundary conditions for model studies of flow patterns at the older adult carotid bifurcation may therefore be questioned.

In this context the present data have obvious applications as inlet and outlet conditions for experimental or computational fluid dynamic (CFD) models of carotid bifurcation flow dynamics. Absent individual VFR waveform measurements, for example, the normalized waveform shapes presented here may be scaled to individual or assumed cycle-averaged VFR. As many such models assume rigid walls, care must be taken to “correct” for misalignment of peak flows and/or instantaneous outflow:inflow mismatches. This may be accomplished, for example, by scaling each CCA feature point in Figure 1 by its corresponding ICA:ECA flow division *relative to the total outflow* (Steinman *et al.*, 2002). Alternatively, following temporal alignment of CCA and ICA feature points, the latter can be subtracted from the former, an approach recommended under the assumption that flow deficits arise mainly due to small branches off the ECA (Zhao *et al.*, 1999).

4.2. Relationship to previous work

In the section above we compared and contrasted our PCMRI-derived older-adult VFR dynamics against PCMRI-derived data from other studies of young adults. As there is little in the way of other PCMRI studies of carotid VFR waveform dynamics for older adults, in Figure 5 we compare our findings to Doppler-ultrasound-derived cycle-averaged VFR and waveform indices of Scheel *et al.* (2000) and Hirata *et al.* (2006). Following those authors, we subdivided subjects into three age groups (<40, 40–59, >60 years old), using the PCMRI-derived young adult data from Ford *et al.* (2005) to complement our older adult data at the ICA.

Compared to Scheel *et al.*, the present study showed remarkably similar VFR_{avg} values and downward trends with age at the CCA and ICA, with corresponding means agreeing to within less than 10%. On the other hand, at the ECA our mean VFR_{avg} values were significantly lower, by about 30%. For the CCA Hirata *et al.* reported significantly higher VFR_{avg} values and an opposite trend with age compared to the present study and that of Scheel *et al.* Both Hirata *et al.* and Scheel *et al.* specifically excluded hypertensives from their studies, whereas the present study focused on a community-based cohort, of which roughly half were on hypertensive medications. In light of the excellent concordance between our VFR_{avg} values and those of Scheel *et al.*, this is unlikely to be the source of the differences with Hirata *et al.*'s values. Instead, those differences may be attributed to well-known errors in VFR measurement associated with their use of a continuous wave Doppler ultrasound approach (Lunt, 1975), demographic differences (Asian vs. North American) or sex differences (31% female vs. 50% female).

Pulsatility and resistance indices from the present study were not significantly different from those of Scheel *et al.* at the CCA and ICA, but were significantly higher, by up to 25%, at the ECA. At the CCA, our PI and RI values were slightly higher than those from Hirata *et al.*, significantly so for the >60 age group; however, our FAI values at the CCA were markedly higher compared to Hirata *et al.*'s. To place these differences in context, it is worth remembering that waveform indices from those studies were derived from Doppler-ultrasound-measured spectral peak *velocities*, whereas the present study used PCMRI-measured *VFR*.

4.3. Limitations

Although the current analysis suggests that waveform dynamics are sex- and age-dependent, complicated systemic factors (e.g. smoking, hypertension, diabetes, etc.) in older subjects, might have affected the waveform shapes and indices derived from this study cohort. In addition, as a consequence of aging, it is reasonable to expect that the number of older subjects exposed to chronic diseases increases with age, potentially generating bias in the age-dependent effects seen here. A more comprehensive study, involving not only the normal older individuals considered here but also the successful and unsuccessful vascular aging groups that are part of the VALIDATE study, is planned to better separate the role of vascular versus chronological aging. For the time being, however, the relatively large sample size of the present study lends confidence that the VFR waveforms characterized here are representative of a typical older adult population.

A potential limitation of using the presented characteristics waveforms in model studies is their fixed heart rate of 65 bpm in the CCA. Younis *et al.* (2004) reported “minimal” changes in oscillatory shear index for a carotid bifurcation model exposed to resting (72 bpm) versus exercise (104 bpm) conditions, suggesting that the effect of more modest normal variations in heart rate can be considered negligible. Nevertheless, when it is desired to scale the characteristic waveforms to accommodate a different heart rate, it is recommended to extend or reduce the timing of the diastolic tail (D1–D4) in order to preserve the timings of systole,

rather than stretch or compress the entire waveforms. Note, however, that peak:average VFR ratio may change as a result of the longer/shorter period.

5. Conclusion

VFR waveform shapes for older adults are significantly different from those of young adults. Data presented here may therefore serve as a convenient baseline for studies of older adult VFR waveform dynamics, or as boundary conditions for models of blood flow at the carotid arteries. The presence of minor compliance-induced misalignments between ICA and CCA/ECA flows, and possible outflow deficits due to small side branches, should not be overlooked when applying these or other VFR waveform measurements, especially to models assuming rigid walls. Their impact on the prediction of flow disturbances at the carotid bifurcation, and indeed the impact of the distinct older-adult versus young-adult VFR waveform dynamics, remains to be tested.

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Figure 1.

Mean carotid bifurcation VFR waveforms of older adults (N=94). CCA, ICA and ECA feature points are shown at their respective mean times relative to the ECG trigger and respective mean VFR values, fitted by splines. Note feature point labels, and error bars indicating feature point standard deviations.

Figure 2.
Time-varying ratios of ICA and ECA outflow to CCA inflow.

Figure 3.

Feature points and spline fits for characteristic normalized VFR waveforms at the ICA of older adults (solid line) and young adults (dotted line, from Ford *et al.* (2005)). Note feature point labels and standard deviation error bars.

Figure 4.

Effect of age and sex on the shape of the characteristic VFR waveform at the CCA and ICA of older adults. Note the increasing late systolic peak and decreasing diastolic amplitude with age, and the different VFR scales for CCA and ICA waveform shapes. The number of cases per decade is indicated in the legend of the top left panel.

Figure 5.

Comparison of (a) cycle-averaged VFR, (b) pulsatility index, (c) resistance index, and (d) flow augmentation index for the three different age groups indicated by the legend of panel (a). Labels “Hir” and “Sch” identify data from Hirata et al (2006) and Scheel et al. (2000), respectively. “Hoi” refers to the present study, with “Hoi*” including young-adult ICA data from Ford et al (2005). Sample sizes for the three age groups from Hir, Sch and Hoi* were 14/30/12, 24/24/30, and 17/14/80, respectively.

Table 1

Descriptive statistics for various quantities derived from individual CCA, ICA and ECA VFR waveforms.

	CCA	ICA	ECA
VFR _{avg} [mL min ⁻¹]	389 ± 74	245 ± 61	125 ± 49
VFR _{peak} [mL min ⁻¹]	839 ± 197	402 ± 89	353 ± 138
Peak:average VFR	2.16 ± 0.35	1.67 ± 0.26	2.89 ± 0.63
Pulsatility Index (PI)	1.72 ± 0.40	1.12 ± 0.32	2.60 ± 0.73
Resistance Index (RI)	0.79 ± 0.06	0.66 ± 0.08	0.89 ± 0.07
Flow Augmentation Index (FAI)	0.78 ± 0.16	0.97 ± 0.19	0.67 ± 0.18

Table 2

Descriptive statistics for feature point timings (in ms) and amplitudes for the CCA, ICA and ECA characteristic (normalized) VFR waveform shapes.

Feature Point	CCA						ICA						ECA					
	Timing			Amplitude			Timing			Amplitude			Timing			Amplitude		
	Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD	
M0	-57	13		0.45	0.07		-61	17		0.55	0.08		-56	13		0.29	0.14	
H0	0	0		1.30	0.15		0	0		1.11	0.11		0	0		1.60	0.27	
P1	50	9		2.16	0.35		55	13		1.67	0.26		47	9		2.90	0.62	
H1	78	16		1.93	0.23		78	15		1.59	0.19		80	17		2.38	0.40	
M1	114	29		1.69	0.18		104	19		1.51	0.14		124	27		1.87	0.35	
P2	151	33		1.75	0.18		158	28		1.60	0.13		157	31		1.96	0.32	
H2	263	37		1.28	0.14		259	26		1.28	0.10		263	38		1.25	0.21	
M2	324	46		0.81	0.18		327	51		0.96	0.14		320	46		0.55	0.29	
H3	349	47		0.91	0.12		350	51		1.01	0.10		346	47		0.77	0.18	
P3	379	48		1.02	0.09		376	52		1.06	0.09		381	49		0.99	0.17	
D1	508	64		0.74	0.08		504	67		0.84	0.08		509	66		0.60	0.12	
D2	637	89		0.62	0.08		632	92		0.73	0.08		637	92		0.49	0.13	
D3	765	118		0.57	0.07		761	120		0.66	0.07		765	122		0.47	0.12	
D4	894	148		0.45	0.07		889	149		0.55	0.08		893	153		0.29	0.14	

Table 3
Summary of sex differences for various quantities derived from individual CCA, ICA and ECA VFR waveforms.

	CCA		ICA		ECA	
	Female	Male	Female	Male	Female	Male
VFR _{avg} [mL min ⁻¹]	377 ± 68	402 ± 78	254 ± 60	238 ± 62	113 ± 45	135 ± 50 [*]
VFR _{peak} [mL min ⁻¹]	762 ± 159	917 ± 202 ^{***}	404 ± 90	402 ± 89	298 ± 93	408 ± 153 ^{***}
Peak:average VFR	2.03 ± 0.29	2.30 ± 0.36 ^{***}	1.61 ± 0.19	1.73 ± 0.30 [*]	2.73 ± 0.49	3.08 ± 0.69 [*]
PI	1.57 ± 0.34	1.87 ± 0.41 ^{***}	1.05 ± 0.24	1.18 ± 0.37 [*]	2.43 ± 0.57	2.79 ± 0.81 [*]
RI	0.77 ± 0.06	0.80 ± 0.05 ^{**}	0.65 ± 0.07	0.67 ± 0.09	0.88 ± 0.06	0.89 ± 0.08
FAI	0.85 ± 0.12	0.72 ± 0.16 ^{***}	1.01 ± 0.15	0.94 ± 0.22	0.73 ± 0.15	0.60 ± 0.18 [*]

Male versus female: ^{*} P<0.05; ^{**} P<0.01; ^{***} P<0.001