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Pulse wave analysis aortic pressure: diastole should also be considered

THESE

préparée sous la direction du Professeur associé François Feihl
(avec la co-direction du Professeur Bernard Waeber)

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RESUME

La rigidité anormalement haute des artères à grande conductance est un marqueur de l'augmentation du risque cardiovasculaire et est typiquement retrouvée chez les patients diabétiques ou hypertendus. Ces vaisseaux deviennent plus rigides avec l'âge, expliquant la haute prévalence d'hypertension systolique chez les personnes âgées. Cette rigidification agit sur la pression sanguine de plusieurs façons. Notamment la fonction windkessel est gênée, menant à l'augmentation de la pression systolique et de la pression pulsée, la diminution de la pression diastolique, et ainsi à l'augmentation de la postcharge ventriculaire gauche associée à une probable diminution de la perfusion coronarienne. De plus, la propagation des ondes de pression le long de l'arbre vasculaire est accélérée, de sorte que les ondes réfléchies générées au site de décalage d'impédance atteignent l'aorte ascendante plus tôt par rapport au début de l'éjection ventriculaire, aboutissant à une augmentation de la pression systolique centrale, ce qui n'arriverait pas en présence de vaisseaux moins rigides. Dans ce cas, au contraire, les ondes de pression antérogrades et réfléchies voyages plus lentement, de sorte que les ondes de réflexion tendent à atteindre l'aorte centrale une fois l'éjection terminée, augmentant la pression diastolique et contribuant à la perfusion coronarienne.

La tonométrie d'applanation est une méthode non invasive permettant l'évaluation de la forme de l'onde de pression au niveau l'aorte ascendante, basée sur l'enregistrement du pouls périphérique, au niveau radial dans notre étude. Nous pouvons dériver à partir de cette méthode un index d'augmentation systolique (sAIX) qui révèle quel pourcentage de la pression centrale est du aux ondes réfléchies. Plusieurs études ont montré que cet index est corrélé à d'autres mesures de la rigidité artérielle comme la vitesse de l'onde de pouls, qu'il augmente avec l'âge et avec les facteurs de risques cardiovasculaires, et qu'il est capable de préciser le pronostic cardiovasculaire. En revanche, peu d'attention a été portée à l'augmentation de la pression centrale diastolique due aux ondes réfléchies (dAIX). Nous proposons donc de mesurer cet index par un procédé d'analyse développé dans notre laboratoire, et ce dans la même unité que l'index systolique. Etant donné que les modifications de la paroi artérielle modulent d'une part la vitesse de l'onde de pouls (PWV) et d'autre part le temps de voyage aller-retour des ondes de pression réfléchies aux sites de réflexion, toute augmentation de la quantité d'énergie réfléchie atteignant l'aorte pendant la systole devrait être associée à une diminution de l'énergie arrivant au même point pendant la diastole. Notre étude propose de mesurer ces deux index, ainsi que d'étudier la relation de l'index d'augmentation diastolique (dAIX) avec la vitesse de propagation de l'onde de pouls (PWV) et avec le rythme cardiaque (HR), ce dernier étant connu pour influencer l'index d'augmentation systolique (sAIX) . L'influence de la position couchée et assise est aussi étudiée. Les mesures de la PWV et des sAIX et dAIX est réalisée chez 48 hommes et 45 femmes âgées de 18 à 70 ans, classés en 3 groupes d'âges.

Les résultats montrent qu'en fonction de l'âge, le genre et la position du corps, il y a une relation inverse entre sAIX et dAIX. Lorsque PWV et HR sont ajoutés comme covariables à un modèle de prédiction comprenant l'âge, le genre et la position du corps comme facteurs principaux, sAIX est directement lié à PWV ($p<0.0001$) et inversement lié à HR ($p<0.0001$). Avec la même analyse, dAIX est inversement lié à PWV ($p<0.0001$) et indépendant du rythme cardiaque ($p=0.52$).

En conclusion, l'index d'augmentation diastolique est lié à la rigidité vasculaire au même degré que l'index d'augmentation systolique, alors qu'il est affranchi de l'effet confondant du rythme cardiaque. La quantification de l'augmentation de la pression aortique diastolique due aux ondes réfléchies pourrait être une partie utile de l'analyse de l'onde de pouls.

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Pulse wave analysis of aortic pressure: diastole should also be considered

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Original Article

Pulse wave analysis of aortic pressure: diastole should also be considered

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Background: The systolic augmentation index (sAix), calculated from the central aortic pulse wave (reconstructed from the noninvasive recording of the radial pulse with applanation tonometry), is widely used as a simple index of central arterial stiffness, but has the disadvantage of also being influenced by the timing of the reflected with respect to the forward pressure wave, as shown by its inverse dependence on heart rate (HR). During diastole, the central aortic pulse also contains reflected waves, but their relationship to arterial stiffness and HR has not been studied.

Methods: In 48 men and 45 women, all healthy, with ages ranging from 19 to 70 years, we measured pulse wave velocity (PWV, patients supine), a standard evaluator of arterial stiffness, and carried out radial applanation tonometry (patients sitting and supine). The impact of reflected waves on the diastolic part of the aortic pressure waveform was quantified in the form of a diastolic augmentation index (dAix).

Results: Across ages, sexes, and body position, there was an inverse relationship between the sAix and the dAix. When PWV and HR were added as covariates to a prediction model including age, sex and body position as main factors, the sAix was directly related to PWV ($P < 0.0001$) and inversely to HR ($P < 0.0001$). With the same analysis, the dAix was inversely related to PWV ($P < 0.0001$) and independent of HR ($P = 0.52$).

Conclusion: The dAix has the same degree of linkage to arterial stiffness as the more conventional sAix, while being immune to the confounding effect of HR. The quantification of diastolic aortic pressure augmentation by reflected waves could be a useful adjunct to pulse wave analysis.

Keywords: adult, aging, aorta, blood pressure, diastole, sex, pulse

Abbreviations: dAix, diastolic augmentation index; dMTT, mean transit time of diastolic reflection wave; dT1r, onset time of diastolic reflected wave; ED, ejection time; PWA, pulse wave analysis; PWV, pulse wave velocity; sAix, systolic augmentation index; sAix@75, sAix corrected for the influence of heart rate; sT1r, onset time of systolic reflected wave

INTRODUCTION

An abnormally high stiffness of large conductance arteries is a marker of increased cardiovascular risk and is typically found in patients with diabetes or hypertension. These vessels also become stiffer with advancing age [1,2], explaining the high prevalence of systolic hypertension in the elderly. The stiffening of large conductance arteries acts on blood pressure (BP) in several ways (reviewed in [3]). The windkessel function is hampered, leading to elevation of systolic and pulse pressure, lowering of diastolic pressure, and thus increased left ventricular afterload possibly associated with reduced coronary perfusion pressure. In addition, the propagation of pressure waves along the arterial tree is accelerated, so that the reflections generated at sites of impedance mismatch reach the ascending aorta sooner relative to the onset of ventricular ejection, resulting in a greater augmentation of central (aortic) systolic pressure, than would occur with more compliant vessels. In this latter case by contrast, forward and reflected pressure waves travel more slowly, so that reflections tend to reach the central aorta after ejection termination, thereby augmenting aortic diastolic pressure and thus contributing to coronary perfusion pressure.

Applanation tonometry is an easily applicable noninvasive method for the assessment of the pressure waveform in the ascending aorta [4,5], based on the recording of the peripheral pulse by means of a piezoelectric high-fidelity pressure sensor applied on the skin overlaying a peripheral vessel, usually the radial artery. From the raw radial pulse, a well validated algorithm [6,7] estimates the detailed shape of the pressure wave within the ascending aorta, allowing to recognize if, and in which phase of the cardiac cycle (systole, diastole or both) aortic pressure is augmented by reflected waves. With this method, it is

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possible to derive a systolic augmentation index (sAix), which expresses the percentage of central pulse pressure caused by reflections. A string of studies have shown that the sAix correlates with other measures of arterial stiffness such as pulse wave velocity (PWV) [8], increases as does the latter with age [9] and with cardiovascular risk factors, and has an ability to predict cardiovascular outcome [10]. In contrast with this abundance of data centered on systolic events, the augmentation of diastolic central pressure by reflected waves has received very little attention.

We have recently developed an analysis of the diastolic part of central aortic pressure, as reconstructed from the radial pulse recorded with applanation tonometry [11–13]. In this analysis, the contribution of reflected waves to central diastolic pressure is quantified by a diastolic augmentation index (dAix), computed based on the deviation of the diastolic pressure profile from the monexponential decay that would be expected in absence of reflections. The dAix is expressed in the same units used for the sAix (i.e. percentage of central pulse pressure). We reasoned that, because changes in arterial stiffness modulate PWV and thus the travel times of pressure waves to the reflection sites and back to the central aorta, any increase in the amount of reflected energy reaching the aorta in systole should be associated with less reflected energy arriving at the same point in diastole. On the basis of this consideration, and if the sAix and dAix are true quantification of reflection phenomena, one would expect an inverse relationship between both indices.

The purpose of the present study was to verify this prediction in a sample of healthy controls of both sexes, with a wide range of ages. Specifically, because the sAix is known to increase with age and to be larger in women than in men of the same age [9,14], we tested whether differences in the opposite direction would be observed for the dAix. In addition, the effects on both indices of a change in body position was also examined, because the sAix has been shown to be larger when evaluated with the patient sitting rather than lying supine [14]. A further incentive for the present experimental design consisted in recent results from our laboratory, which showed major effects of body position on the dAix in young women [13], prompting us to evaluate whether this specific finding could be extended to men and too other age groups.

METHODS

Participants

Healthy men and women were enrolled by public advertisement. The recruitment was stratified by age (young: 18–39 years, middle-aged: 40–55 years, aged: 56–70 years) and sex, thus defining six experimental groups. Exclusion criteria were current smoking, any history of chronic or cardiovascular disease, office BP more than 140/90 mmHg, BMI more than 30 kg/m^2, regular intake of any drug, and intake of any drug in the week preceding the examination.

The study was approved by the local Ethics Committee. All included participants had signed a consent form after receiving detailed explanations.

The study size was chosen so as to obtain 80% power to detect a two-fold difference in mean dAix between any pair of experimental groups, keeping the overall rate of type I errors below 5%. Information on interindividual variance of the dAix was available from previous studies by our group [11,15], leading to a planned inclusion of 16 patients per group.

Measurement of blood pressure

BP was measured with an oscillometric device (Stabil-O-graph; IEM Gmbh, Stolberg, Germany), in compliance with the recommendations of the European Society of Hypertension [16]. In each of the studied positions (seated and supine), three determinations were made, and the average of the last two was recorded.

Pulse wave analysis

Pulse wave analysis (PWA) was performed in both the supine and seated position, using applanation tonometry of the radial artery carried out with the SphygmoCor device (AtCor Medical; Sydney, Australia), as previously described [11–13,15]. In short, the central element in this system is a pen-shaped piezoelectric pressure transducer, with which the radial artery is flattened against the radial bone, thus allowing recording the radial pulse. Pulse waves obtained during 10 s are then processed in order to reconstruct a central waveform using a Generalized Transfer Function, as abundantly described elsewhere [4,7].

The SphygmoCor software, provided by the manufacturer, implements a range of criteria to determine whether the quality of the recorded waveform is sufficient for subsequent analysis. These criteria include a mean pulsatile amplitude of the raw tonometric signal higher than 80 mV and a beat-to-beat variability of pulse pressure and diastolic pressure lower than 5% of average pulse pressure. We rejected any recording, which did not fulfill these criteria. All recordings were carried out in triplicate.

Pulse wave velocity

Carotid-femoral PWV was evaluated in the supine position using simultaneous noninvasive recordings of the carotid and femoral pulse with the Complior device and version 1.3.0 of the Complior SP software (Alam Medical, 94300 Vincennes, France) [17]. All recordings were carried out in triplicate. The carotid to femoral distance was obtained with a compass, so as to avoid any influence body surface shape on the measurement.

Protocol

The study took place in the morning, in the fasting state, in a quiet room. The patients were weighed, their height measured, and they were run through a short questionnaire to evaluate whether or not they had regular physical activity [18]. After that, examinations were sequentially carried out in the seated and in the supine position, in randomized order. In each position, 15 min were allowed for stabilization. Then, brachial BP was measured, after which PWA was carried out. As carotid-femoral PWV is technically difficult to obtain in seated patients, this measurement was restricted to the supine position, where it took place in randomized order with respect to PWA.

Data analysis

To obtain a graphical overview of the influence of experimental conditions, the central arterial pulse waveforms were ensemble-averaged across patients and expressed in percentage of the corresponding pulse pressure, as previously described [11–13,15].

From the radial pressure waveform, the Sphygmocor software estimates ejection duration as the time from the foot of the pressure wave to the incisura. On the reconstructed central pressure waveforms, it then positions the systolic points P1 and P2 (Fig. 1). P1 is the inflection point marking the onset of the reflected systolic wave, the peak of which is indicated by P2, as shown in Figure 1. The time lag sT1r from the initial systolic upstroke to point P1 gives an estimate of twice the travel time of the systolic reflected wave. The relative importance of the forward and reflected pressure waves is expressed as a sAix according to the formula:

$$\text{sAix} = \frac{100 \times (\text{P2} - \text{P1})}{\text{pulse pressure}}$$

The sAix may be positive or negative, with a positive value indicating augmentation of peak systolic pressure by reflections. Because the sAix is dependent on HR, the software also corrects for this influence by estimating the value that would be observed with a beating frequency of 75 per min (sAix@75).

We complemented the above calculations by computing the amplitude of diastolic reflection waves (dAix), as previously described [11–13,15]. Briefly, the dAix corresponds to the maximal distance between the upward convexity seen on the diastolic part of the aortic or radial pressure waveform and a straight line passing through the onset of the incisura and tangent to the last diastolic part of the waveform (i.e. the vertical distance between points P3 and P4 on Figure 1). This distance is interpreted as an approximate deviation from the monoexponential decay that would be expected if there were no reflected waves in diastole. As in the case of the sAix, the dAix is expressed in percentage of aortic pulse pressure, that is

$$\text{dAix} = \frac{100 \times (\text{P3} - \text{P4})}{\text{pulse pressure}}$$

Finally, information regarding the timing of the diastolic reflected wave was captured by computing its mean transit time (dMTT), according to the formula shown in the legend to Figure 1, using the trapezoidal rule to carry out numerical integration.

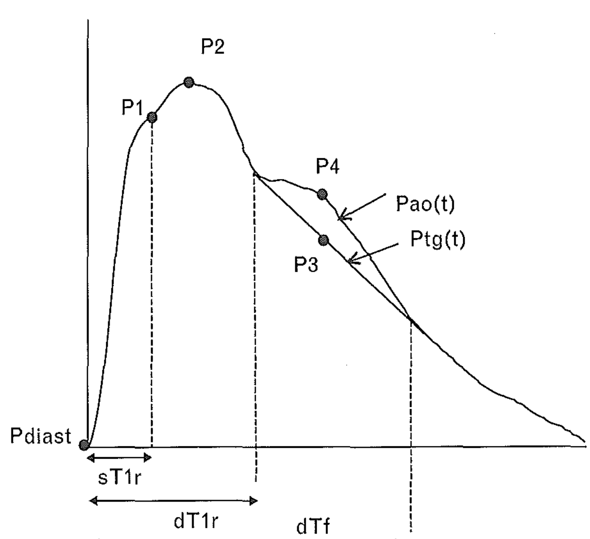

FIGURE 1 Landmarks used to characterize systolic and diastolic reflected waves on the central pressure pulse. P1 pressure at onset of reflected wave in systole. sT1r time elapsed from begin of systolic upstroke to P1. P2 peak of reflected wave in systole. dT1r time to onset of reflected wave in diastole. P3 pressure at peak of reflected wave in diastole. dT1f time at end of reflected wave in diastole. dT1r and dTf defined by the contact points of a straight line tangent to the diastolic part of the waveform as shown. Pao(t) and Ptg(t) are two functions of time describing the actual pressure waveform and the aforementioned tangent, respectively. P4 approximates the pressure that would exist at the time of P3 in absence of reflection. Indices of wave reflection are calculated according to the formulas shown in the METHODS, where PP is pulse pressure. Mean transit time of diastolic reflected wave (dMTT) calculated as $\text{dMTT} = \int_{\text{dT1r}}^{\text{dTf}} t[\text{Pao}(t) - \text{Ptg}(t)]dt$.

Statistical analysis

As subjected to statistical analysis, indices derived from PWA were mean values calculated from recordings made in triplicate. We used analysis of variance for repeated measures, with a model including age group and sex as nonrepeated fixed factors, body position as a repeated fixed factor, and patient as a random factor nested under age group and sex. In the first step, all two-way and three-way interactions between the fixed factors were included. Only significant interactions were retained in the final model. Relationships of each PWA index with HR and PWV was evaluated by simultaneously adding both variables as covariates to the final model. When omnibus F-tests were significant, further pairwise comparisons were made using Tukey's honestly significant difference (HSD, also designated as Tukey-a test), a conservative approach [19]. The alpha level of all tests was set at 0.05, except for interaction terms (in their case, F-tests yielding a P value less than 0.1 were deemed to justify separate tests of each involved factor at each level of the other factor, such tests being then carried out with HSD and alpha = 0.05). Group summary statistics are means and SD.

RESULTS

Overall, 93 patients were recruited. Their demographic and hemodynamic characteristics are shown in Tables 1 and 2. To avoid cluttering with statistical symbols, the results of statistical analyses relevant to the data in Table 1 are displayed separately in Table 2. Within each age class, groups of women and men were well balanced for age, and only minor imbalances were noted between sexes, if at all, regarding body size, heart rate (HR) and BP. However, there was an uneven distribution of sedentary versus physically active patients between experimental groups. The impact of changing body position from seated to supine was to lower HR by approximately 10% and BP (whether peripheral or central) by a few mmHg.

PWV, which could only be measured in the supine position, was systematically higher in men than in women. The difference between age groups did not reach statistical significance (omnibus F: $P = 0.07$). However, with a model

TABLE 1. Demographic and hemodynamic data in the three age groups

		Young (18–39 years)		Middle-aged (40–55 years)		Aged (56–70 years)	
		Women	Men	Women	Men	Women	Men
Number of patients		17	16	16	16	15	13
Age (years)		25.4±5.2	24.8±3.0	44.7±3.3	45.2±3.5	61.6±4.3	62.3±4.8
Weight (kg)		57.1±5.6	74.8±6.1	61.9±9.6	75.4±9.8	60.4±7.5	76.8±11.1
Height (cm)		167±5	182±4	168±8	177±7	167±8	176±4
BMI (kg/m^2)		20.4±1.7	22.6±1.3	22.0±2.9	23.9±2.7	21.7±2.5	24.7±3.3
Number sedentary (%)		6 (35)	10 (63)	8 (50)	5 (31)	5 (33)	4 (30)
Heart rate (b/min)	seated	66±12	63±8	68±13	63±7	68±8	61±6
	supine	61±11	58±7	63±11	58±6	62±7	58±7
Peripheral BP (mmHg)							
Systolic	seated	110±10	125±9	110±11	123±10	124±10	125±9
	supine	108±4	120±9	110±7	121±9	123±9	123±9
Diastolic	seated	66±9	74±11	73±9	83±8	81±8	85±9
	supine	64±8	67±10	70±7	76±8	77±7	81±10
Mean	seated	80±9	89±10	87±10	97±8	97±8	99±9
	supine	77±7	82±10	85±7	92±9	95±7	96±10
Central BP (mmHg)							
Systolic	seated	94±11	106±8	102±12	112±9	117±9	117±10
	supine	92±7	101±9	102±7	110±11	117±10	115±9
Diastolic	seated	67±9	75±10	74±9	84±8	82±8	86±8
	supine	64±8	68±10	71±7	77±8	78±7	82±10
Mean	seated	80±9	89±10	87±10	97±8	97±8	99±9
	supine	77±7	82±10	85±7	92±9	95±7	96±10
Pulse wave velocity (m/s)		8.1±1.6	9.4±1.6	9.0±1.1	9.4±1.2	9.3±2.2	10.0±1.9

BP blood pressure. Summary of statistical analysis in Table S2. Data are means±SD.

including sex, age as a continuous variable, and their interaction, the association of PWV with age was highly significant ($P=0.006$).

The ensemble-averaged profiles of central aortic pressure, as recorded in the two body positions, are shown for the six study groups in Figure 2, allowing qualitative

TABLE 2. Complete statistical comparisons for variables presented in Table 1

		Young							Middle-aged					Aged			Interactions			
			Women			Men				Women		Men			Women	Men	2-way			3-way
		Women vs Men	*vs Middle-aged*	*vs Aged*	*vs Seated*	*vs Middle-aged*	*vs Aged*	*vs Seated*	*Women vs Men*	*vs Aged*	*vs Seated*	*vs Aged*	*vs Seated*	*Women vs Men*	*vs Seated*	*vs Seated*	*Gender * age*	*Gender * position*	*Age * position*	*Age * gender position*
Number of subjects				17			16			16		16			15	13				
Age		*ns*	–	–	–	–	–	–	*ns*	–	–	–	–	*ns*	–	–	–	–	–	–
Weight		***	*ns*	*ns*	–	*ns*	*ns*	–	***	*ns*	–	*ns*	–	***	–	–	*ns*	–	–	–
Height		***	*ns*	*ns*	–	*ns*	*ns*	–	***	*ns*	–	*ns*	–	***	–	–	*ns*	–	–	–
BMI		***	0.018	0.011	–	0.018	0.011	–	***	*ns*	–	*ns*	–	***	–	–	*ns*	–	–	–
Number sedentary		*ns*	*ns*	*ns*	–	*ns*	*ns*	–	*ns*	*ns*	–	*ns*	–	*ns*	–	–	*ns*	–	–	–
Heart rate	Seated	0.012	*ns*	*ns*	–	*ns*	*ns*	–	0.012	*ns*	–	*ns*	–	0.012	–	–				
	Supine	0.012	*ns*	*ns*	***	*ns*	*ns*	***	0.012	*ns*	***	*ns*	***	0.012	***	***	*ns*	*ns*	*ns*	*ns*
Peripheral BP																				
Systolic	Seated	***	*ns*	***	–	*ns*	*ns*	–	0.002	***	–	*ns*	–	*ns*	–	–				
	Supine	***	*ns*	***	*ns*	*ns*	*ns*	0.020	0.002	***	*ns*	*ns*	0.020	*ns*	*ns*	0.020	0.007	0.072	*ns*	*ns*
Diastolic	Seated	***	***	***	–	***	***	–	***	0.011	–	0.011	–	***	–	–				
	Supine	***	***	***	***	***	***	***	***	0.011	***	0.011	***	***	***	***	*ns*	*ns*	*ns*	*ns*
Mean	Seated	***	***	***	–	***	***	–	***	0.002	–	0.002	–	***	–	–				
	Supine	***	***	***	***	***	***	***	***	0.002	***	0.002	***	***	***	***	*ns*	*ns*	*ns*	*ns*
Central BP																				
Systolic	Seated	0.010	*ns*	***	–	*ns*	0.003	–	*ns*	***	–	*ns*	–	*ns*	–	–				
	Supine	0.010	*ns*	***	0.024	*ns*	0.003	0.024	*ns*	***	0.024	*ns*	0.024	*ns*	0.024	0.024	0.027	*ns*	*ns*	*ns*
Diastolic	Seated	***	***	***	–	***	***	–	***	0.013	–	0.013	–	***	–	–				
	Supine	***	***	***	***	***	***	***	***	0.013	***	0.013	***	***	***	***	*ns*	*ns*	*ns*	*ns*
Mean	Seated	***	***	***	–	***	***	–	***	0.002	–	0.002	–	***	–	–				
	Supine	***	***	***	***	***	***	***	***	0.002	***	0.002	***	***	***	***	*ns*	*ns*	*ns*	*ns*
Pulse wave velocity		0.018	*ns*	*ns*	–	*ns*	*ns*	–	0.018	*ns*	–	*ns*	–	0.018	–	–	*ns*	–	–	–

P values indicated numerically when greater than 0.001 and less than 0.05 (specific comparisons) or less than 0.1 (F test for interaction). ns: $P>0.05$ (specific comparisons) or greater than 0.1 (interactions). *** $P<0.001$. *P* values for interactions reported for the full model containing all two-way and three-way interactions. *P* values for specific comparisons obtained with nonsignificant interactions removed (see Methods). BP blood pressure.

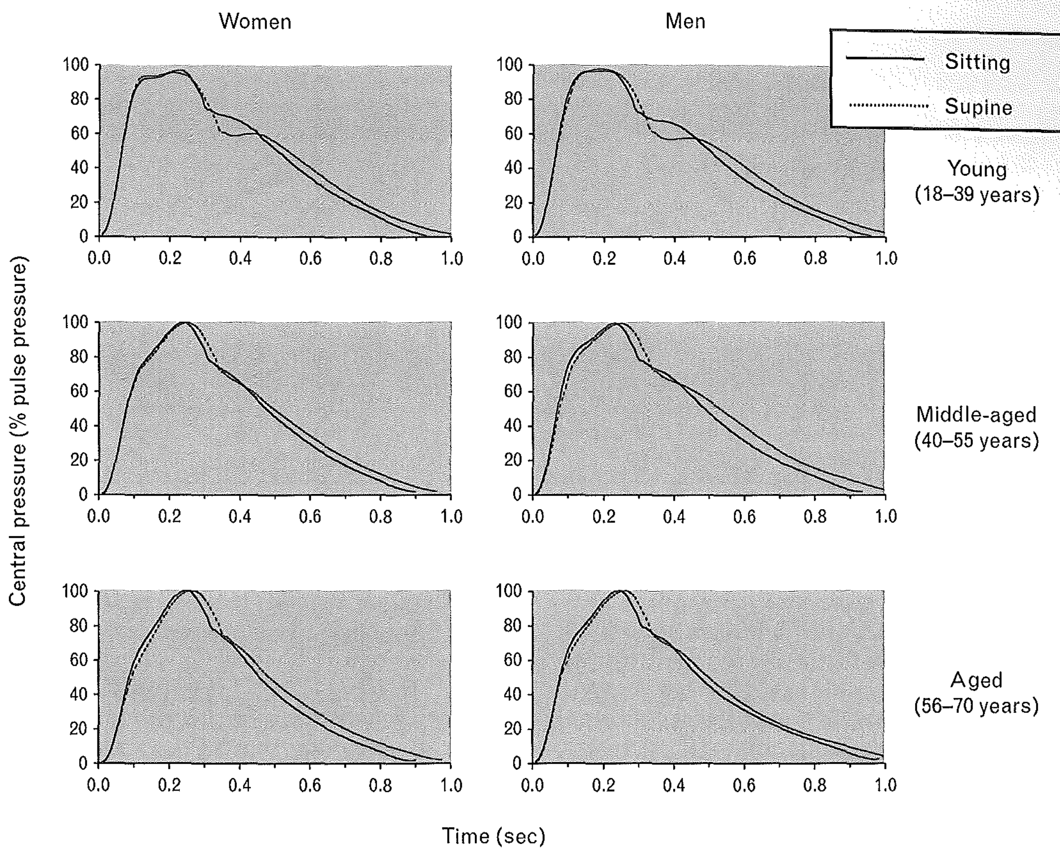

FIGURE 2 Ensemble-averaged central aortic pressure waveforms in the different age-groups. Waveforms reconstructed from the radial pulse recorded with the subject in either the sitting or the supine position.

comparisons to be made between waveform morphologies. In that respect, there were no obvious differences between men and women. In both sexes, the waveforms of the middle-aged and aged had, in comparison of the young groups, a much more prominent late systolic followed by a much smaller diastolic augmentation by reflected waves. The effect of body position on the profiles was especially noticeable in young patients, and especially on diastolic augmentation, which seemed delayed and of larger amplitude when recorded in the supine, in comparison with the sitting condition.

The changes noted in the amplitudes of sAix and dAix as a function of age, sex, and body position are shown in Figure 3 (with numerical counterpart in Table 3). So as not to clutter this figure with symbols, complete results of the relevant statistical comparisons are displayed in Table 4. In comparison with values in men of the same age, the sAix of women was larger, and their dAix smaller, although this latter difference did not reach statistical significance. With advancing age, the sAix increased and the dAix decreased, an effect especially marked in the transition from the young to the middle-aged groups. The impact of changing body position was age-dependent but not sex-dependent (age-position interaction: $P < 0.0001$; sex-position interaction $P > 0.3$ for both the sAix and the dAix). In young patients, switching from sitting to supine markedly enhanced the dAix, with no statistically significant effect noted on the sAix. In the middle-aged groups, position had no statistically significant effect. In aged patients, taking on the supine position increased the sAix, but did not affect the dAix.

These observations suggest the general pattern of an inverse relationship between the sAix and the dAix, which also becomes apparent when plotting these indices against each other, as done in Figure 4a. In further corroboration of this pattern, there was a highly significant negative

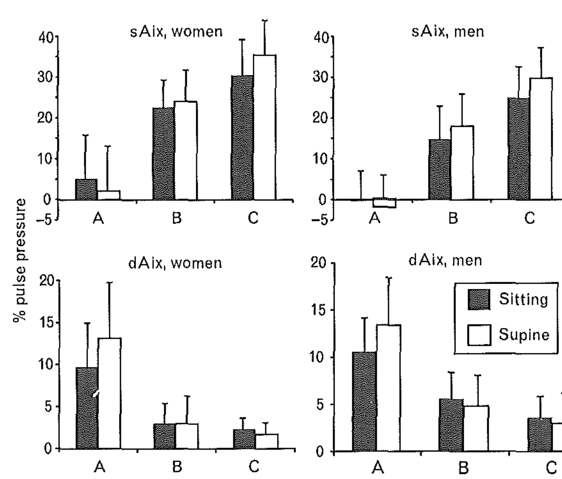

FIGURE 3 Augmentation of central aortic pressure by reflected waves. Central aortic pressure reconstructed from the radial pressure pulse recorded in two body positions, in healthy volunteers of three age groups. (a) 18–39 years, (b) 40–55 years, and (c) 56–70 years. sAix, systolic augmentation index; dAix, diastolic augmentation index. For statistical comparisons and number of patients in each subcategory, see Table 4. Data are means and SD.

TABLE 3. Indices of wave reflection in systole and diastole

		Young (18–39 years)		Middle-aged (40–55 years)		Aged (56–70 years)	
		Women	Men	Women	Men	Women	Men
Number of subjects		17 (17)	16 (16)	16 (9)	16 (14)	15 (12)	13 (10)
Systole							
sAix (%PP)	Seated	5.0 ± 10.7	−0.4 ± 7.3	22.5 ± 6.6	14.7 ± 8.1	30.2 ± 8.8	25.0 ± 7.3
	Supine	1.8 ± 11.1	−1.3 ± 7.1	23.9 ± 7.6	17.7 ± 8.1	35.2 ± 8.6	29.5 ± 7.4
sAix@75 (%PP)	Seated	0.9 ± 9.8	−6.1 ± 7.6	19.2 ± 9.0	9.0 ± 7.2	26.8 ± 6.8	18.2 ± 7.4
	Supine	−5.4 ± 11.8	−9.5 ± 8.2	18.4 ± 9.9	9.4 ± 8.0	28.8 ± 7.6	21.4 ± 7.7
sTlr (ms)	Seated	157 ± 10	171 ± 13	147 ± 13	157 ± 7	141 ± 6	150 ± 7
	Supine	161 ± 22	181 ± 18	149 ± 10	163 ± 11	140 ± 8	145 ± 13
Diastole							
dAix (%PP)	Seated	9.7 ± 5.2	10.5 ± 3.7	2.9 ± 2.5	5.5 ± 2.9	2.2 ± 1.3	3.5 ± 2.2
	Supine	13.1 ± 6.5	13.4 ± 5.0	2.8 ± 3.3	4.7 ± 3.4	1.6 ± 1.3	2.9 ± 3.2
dMTT (ms)	Seated	435 ± 41	446 ± 23	399 ± 41	413 ± 30	377 ± 21	387 ± 20
	Supine	497 ± 39	528 ± 32	476 ± 58	496 ± 40	419 ± 24	426 ± 30

sAix, systolic augmentation index; sAix adjusted, systolic augmentation index adjusted for heart rate with covariance analysis; sT1r, time to begin of systolic reflected wave; dAix, diastolic augmentation index; dMTT, mean transit time of diastolic reflected wave; dSD, dispersion of diastolic wave. Summary of statistical analysis in Table S4. Data are means ± SD. On the right of figures indicating the size of each subgroup, data shown in parentheses are counts of patients in whom two independent observers agreed on the presence of a diastolic wave on at least two recordings in each position.

correlation between the respective changes induced in the dAix and in the sAix by changes in body position (Fig. 4b).

Timing of reflected waves

Detailed data on the timing of reflected waves appear in Table 3, with statistical analysis in Table 4. In short, the transit times of reflected waves reaching the aorta in both systole and diastole were larger in men than in women, decreased with age, and lengthened upon shifting from the sitting to the supine position.

Relationships to heart rate and pulse wave velocity

Standard analysis of covariance was used to evaluate the independent relationship of the sAix and the dAix with HR and PWV, after adjustment for age, sex, and position. Table 5 shows the regression coefficients thus obtained (β), which represent estimated changes of the corresponding index (expressed in % of pulse pressure) for each increase of 10 b/min for HR, or 1 m/s for PWV.

As expected, the sAix increased with PWV (positive β). In contrast, a higher PWV was associated with a lower dAix (negative β). Although both indices were related to PWV, and thus to arterial stiffness, only the dAix was clearly independent of HR. Analyses carried out separately on each age group gave entirely similar results, indicating that the lack of relationship between dAix and HR was not driven by the clustering of low dAix values in aged volunteers (Table S1 in Supplemental Digital Content 1, http://links.lww.com/HJH/A208).

Further-adjusted analyses

Several differences noted between women and men regarding systolic and diastolic indices (Table 3) were statistically

TABLE 4. Complete statistical comparisons for indices of wave reflexion

		Young							Middle-aged					Aged			Interactions			
Number of subjects			Women 17 (17)			Men 16 (16)				Women 16 (9)		Men 16 (14)			Women 15 (12)	Men 13 (10)	2-way			3-way
		Women vs Men	*vs Middle-aged*	*vs Aged*	*vs Seated*	*vs Middle-aged*	*vs Aged*	*vs Seated*	*Women vs Men*	*vs Aged*	*vs Seated*	*vs Aged*	*vs Seated*	*Women vs Men*	*vs Seated*	*vs Seated*	*Gender * age*	*Gender * position*	*Age * position*	*Age * gender position*
Systole																				
sAix	Seated	***	***	***	–	***	***	–	***	0.001	–	0.001	–	***	–	–				
	Supine	***	***	***	*ns*	***	***	*ns*	***	***	*ns*	***	*ns*	***	***	***	*ns*	*ns*	***	*ns*
sAix@75	Seated	***	***	***	–	***	***	–	***	0.004	–	0.004	–	***	–	–				
	Supine	***	***	***	***	***	***	***	***	***	*ns*	***	*ns*	***	*ns*	*ns*	*ns*	*ns*	***	*ns*
sT1r	Seated	***	0.006	***	–	0.006	***	–	***	*ns*	–	ns	–	***	–	–				
	Supine	***	***	***	0.040	***	***	0.040	***	0.002	*ns*	0.002	*ns*	***	*ns*	*ns*	*ns*	*ns*	0.016	*ns*
Diastole																				
dAix	Seated	*ns*	***	***	–	***	***	–	*ns*	*ns*	–	*ns*	–	*ns*	–	–				
	Supine	*ns*	***	***	***	***	***	***	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	***	*ns*
dMTT	Seated	0.024	0.002	***	–	0.002	***	–	0.024	*ns*	–	*ns*	–	0.024	–	–				
	Supine	0.024	0.044	***	0.004	0.044	***	0.004	0.024	*ns*	***	*ns*	***	0.024	***	***	*ns*	*ns*	0.045	*ns*

P values indicated numerically when more than 0.001 and less than 0.05 (specific comparisons) or less than 0.1 (F test for interaction). ns: $P > 0.05$ (specific comparisons) or more than 0.1 (interactions). ***$P < 0.001$. *P* values for interactions reported for the full model containing all two-way and three-way interactions. *P* values for specific comparisons obtained with nonsignificant interactions removed (see Methods). sAix systolic augmentation index; sAix adjusted, systolic augmentation index adjusted for a heart rate of 75 b/min; sT1r, time to begin of systolic reflected wave; dAix diastolic augmentation index; dMTT, mean transit time of diastolic reflected wave. Sizes of subgroups indicated as in Table 3.

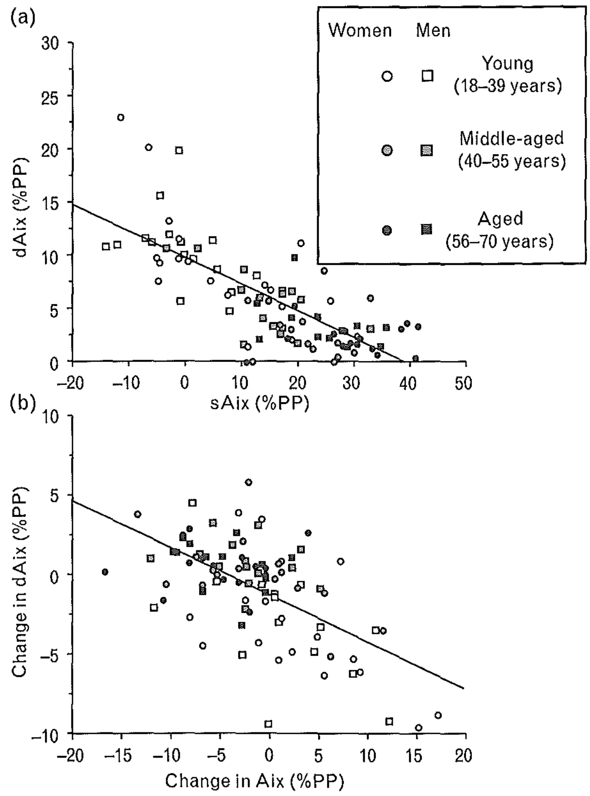

FIGURE 4 Reciprocal relationship between the systolic and diastolic augmentation of the central aortic pressure pulse. dAix, diastolic augmentation index; PP, pulse pressure; sAix, systolic augmentation index. Data from central aortic pressure waveform reconstructed from the radial pulse recorded in the sitting position. A very similar plot was obtained with values corresponding to the supine position (not shown).

significant (Table 4). Therefore, the analysis of covariance mentioned in the previous paragraph was repeated with additional adjustment for the main covariates, which differed between sexes, namely height, weight, HR, mean central BP and PWV (Table S2 in Supplemental Digital Content 1, http://links.lww.com/HJH/A208). In these adjusted analyses, sex remained a significant predictor of sAIx, sAIx@75, sT1r, and dAix, although not of dMTT. This apparent independent effect of sex on the central pulse waveform might be explained by unmeasured factors possibly differing between men and women, such as spatial distribution of reflexion sites or regional PWV, for example in arteries of the lower limbs.

TABLE 5. Relationship of augmentation indices with heart rate and pulse wave velocity

		Unit for β	sAix	dAix
HR	β	% PP beat^{-1}.min	−0.34	−0.02
	SE		0.07	0.03
	P		<0.0001	0.52
PWV	β	% PP.m^{-1}.s	2.00	−1.05
	SE		0.51	0.23
	P		<0.0001	0.0009

sAix, systolic augmentation index; dAix, diastolic augmentation index; HR, heart rate; PWV, carotid-femoral pulse-wave velocity; β, regression coefficient with units as indicated and explained in the text; PP, pulse pressure; SE, standard error of the estimate of β.

DISCUSSION

Reconstruction of the central aortic pressure wave from the tonometric recording of the radial pulse is a widely used noninvasive tool for the evaluation of arterial stiffness, the main relevant information having been so far extracted from systolic augmentation of pressure by reflected waves, via computation of the sAix or an analogous index. The present study supports that, at least in healthy adults, a similar information can be retrieved by analyzing the diastolic part of the reconstructed waveform (done here by calculating the dAix). This statement is based on two lines of evidence: the reciprocal relationship found between the systolic and the diastolic indices, both at the interindividual (i.e. age and sex impacting on the dAix in a direction opposite to that observed for the sAix) and intraindividual level (impact in opposite directions of changes in body position); the statistically strongly significant relationship of both indices with PWV, a standard measure of arterial stiffness made independently from radial tonometry. In contrast to the sAix, the dAix seems immune to the confounding influence of HR, suggesting that it might have some advantage over the former for the evaluation of arterial stiffness.

Effects of age and sex on standard indices of aortic stiffness

The variation of PWV and sAix with age and sex were as expected (see Supplemental Digital Content 1, http://links.lww.com/HJH/A208).

Reciprocal relationship of diastolic and systolic augmentation

The overall shape of the aortic pressure pulse depends on many factors, including the pattern of ventricular ejection, the elastic behaviour of the great vessels [20], hydrodynamic phenomena related to flow deceleration [21], waveform dispersion [22] and wave reflections. The present study has no ambition to discriminate between these. Nevertheless, it remains a prevalent concept that wave reflections play a fundamental role [23], and that, depending on their time of arrival, the reflected pressure waves may augment aortic pressure predominantly in systole, predominantly in diastole, or in both phases of the cardiac cycle [24–27]. The present study extends the available knowledge in two ways. First, the simple calculation of the dAix allows the relationship between systolic and diastolic augmentation to be expressed quantitatively. Second, at least in this healthy population, the reciprocal relationship between the sAix and the dAix appears quite general, both at the interindividual, (impact of advancing age and sex, Figure 4a, Figure 3, Tables 3 and 4), and intraindividiual levels (impact of changing the body position, Figure 4b, Figure 3, Tables 3 and 4). With respect to the effects of age, it is particularly noteworthy that the largest changes in the dAix occurred in the transition from the young to the middle-aged groups, in a mirror image of those observed for the sAix in this study as in previous ones cited above [1,14]. The impact of body position was age-dependent. Indeed, in young patients, shifting from sitting to supine had the effects of increasing the dAix without affecting the sAix, while changes opposite to these were noted in the aged, and none reached statistical significance in the middle-aged groups (Figure 3, Tables 3 and 4). This result agrees with findings of our recent study in young women [13]; it extends them to young men and shows how the picture becomes modified with advancing age in both sexes. This picture is consistent with data reported by McEniery *et al.* in elderly normotensive patients [14].

Timing of reflected waves

The values found in the present study for the transit time of systolic reflected waves (Table 3, sT1r) are in agreement with those in the literature [1,8,14,28–30]. Regarding the transit time of diastolic reflected waves, the data presented here are entirely new. The overall very similar behavior of dMTT and sT1r with respect to changes in age, sex, and body position suggests that the same factors affect the timing of both systolic and diastolic reflected waves. A simplified view would hold that these factors comprise travelling velocity and distance between proximal aorta and sites of reflection. The lower transit times in women compared with men could thus be seen as the resultant of lower velocity (as suggested by the measurement of aortic-femoral PWV, Tables 1 and 2) – and shorter travelling distance, as documented for systolic reflected waves by Mitchell *et al.* [1]. The association of advancing age with reduced transit times is likely to be driven by increases in travelling velocity due to arterial stiffening, keeping in mind that this effect might be mitigated by the distal migration of reflection sites in older people [1].

One might be surprised by the value of dMTT (about 350 ms), which together with the measured values of PWV (8–10 m/s, Table 1) would suggest a distance of reflection sites hardly compatible with body size. However, as discussed by Westerhof *et al.* [31], reflection sites in the arterial tree are not closed ends, but loci of impedance mismatch, introducing a phase delay between the Fourier components of the reflected and the incident waves. This state of affairs translates into bidirectional transit times larger than would be expected on the mere basis of PWV and vessel length.

Regardless of sex, the transition from the sitting to the supine position resulted in a striking increase of dMTT in the young and middle-aged groups. We have already observed this striking effect of posture in young women, and refer the reader to our previous publication for a discussion of its possible mechanisms [13].

Of interest, whenever diastolic reflections reach the aorta sooner, as indicated by a shorter dMTT (i.e. old vs. young age, female versus male sex, sitting vs. supine position), the sAix tends to increase and the dAix to decrease. This observation suggests that the reciprocal relationship between systolic and diastolic augmentation (Fig. 4) is largely driven by shifts in the timing of reflected waves, with shorter transit times resulting in more of the reflected energy reaching the aorta in systole.

Perspectives

The inverse relationship between sAix and dAix points to a common dependence on fundamental characteristics of arterial hemodynamics. Nevertheless, the interpretation of the former may be confounded by the influence of HR, which is not the case for the latter. Another potential difference between these indices, the calculated sAix is very sensitive to the location of the inflection point, which is not always well recognizable. In contrast, the dAix can be determined unambiguously whenever the diastolic augmentation is evident, and otherwise may be assumed to be zero. For these reasons, the quantification of diastolic aortic pressure augmentation by reflected waves could be a useful adjunct to PWA.

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Conflicts of interest

None of the authors has any conflict of interest in relation to the present work.

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