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Left ventricular ejection time, not heart rate, is an independent correlate of aortic pulse wave velocity

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Salvi P, Palombo C, Salvi GM, Labat C, Parati G, Benetos A. Left ventricular ejection time, not heart rate, is an independent correlate of aortic pulse wave velocity. *J Appl Physiol* 115: 1610–1617, 2013. First published September 19, 2013; doi:10.1152/japplphysiol.00475.2013.— Several studies showed a positive association between heart rate and pulse wave velocity, a sensitive marker of arterial stiffness. However, no study involving a large population has specifically addressed the dependence of pulse wave velocity on different components of the cardiac cycle. The aim of this study was to explore in subjects of different age the link between pulse wave velocity with heart period (the reciprocal of heart rate) and the temporal components of the cardiac cycle such as left ventricular ejection time and diastolic time. Carotid-femoral pulse wave velocity was assessed in 3,020 untreated subjects (1,107 men). Heart period, left ventricular ejection time, diastolic time, and early-systolic dP/dt were determined by carotid pulse wave analysis with high-fidelity applanation tonometry. An inverse association was found between pulse wave velocity and left ventricular ejection time at all ages (<25 years, $r^2 = 0.043$; 25–44 years, $r^2 = 0.103$; 45–64 years, $r^2 = 0.079$; 65–84 years, $r^2 = 0.044$; ≥85 years, $r^2 = 0.022$; $P < 0.0001$ for all). A significant ($P < 0.0001$) negative but always weaker correlation between pulse wave velocity and heart period was also found, with the exception of the youngest subjects ($P = 0.20$). A significant positive correlation was also found between pulse wave velocity and dP/dt ($P < 0.0001$). With multiple stepwise regression analysis, left ventricular ejection time and dP/dt remained the only determinant of pulse wave velocity at all ages, whereas the contribution of heart period no longer became significant. Our data demonstrate that pulse wave velocity is more closely related to left ventricular systolic function than to heart period. This may have methodological and pathophysiological implications.

arterial stiffness; heart rate; left ventricular ejection time; left ventricular function; pulse wave velocity

ARTERIAL STIFFNESS MEASURED by carotid-femoral pulse wave velocity (PWV) is an established independent predictor of cardiovascular morbidity and mortality (13, 20, 21, 24, 27). Arterial pulse waves generated from the left ventricle travel from the aortic root along the arteries at a speed that varies according to wall distensibility: the less distensible the wall, the higher the velocity of pulse wave propagation (28, 35). PWV can be affected by both arterial structural and functional changes (35). Structural changes influence arterial stiffness through a steady alteration in the elastin-collagen fibers and the organization of the extracellular matrix of the arterial wall. Although it has less importance than structural changes, the role of functional changes is also very complex. The main functional factors that determine transient and variable changes in vascular distensibility include mean arterial pressure levels (30), arterial smooth muscle tone (related mainly to adrenergic activity), left ventricular systolic ejection function, and heart rate (HR). The relationship between PWV and these functional factors could affect the reproducibility of PWV and the reliability of between-subjects comparison of PWV values. Although structural vascular alterations are likely to be the most important determinants of PWV, it is a common habit in clinical studies to adjust PWV values for functional factors such as mean arterial pressure and HR.

Several clinical studies have shown positive associations between HR and PWV (1, 43). We have previously shown in a longitudinal study in hypertensive subjects that the presence of increased HR was a predictor for accelerated PWV later in life independently of other risk factors (5). In addition several but not all studies showed that the HR increase induced by pacing yields an elevation in PWV (1, 15, 19, 25). Although the PWV-HR relationship was clearly observed in middle-aged and elderly subjects (19), no such relationship was found in children (33). On the one hand, these data corroborate a significant direct role of cardiac cycle duration in determining PWV, but on the other they show how this effect might not be constant at different ages. Surprisingly, such an extensive interest in the relationship between PWV and HR has not been accompanied by a parallel interest in the possible relationship between PWV and different components of the cardiac cycle, which have been shown by physiological studies to contribute to the genesis of pulse waves. Indeed, to the best of our knowledge, so far only one study has specifically addressed the dependence of PWV on left ventricular ejection time (LVET). Based on data collected from a little cohort of young healthy males, Nurnberger et al. described an inverse relationship between PWV and LVET, under resting conditions as well as under β-adrenergic stimulation (29).

Thus the aim of this study was to investigate the relationship not only between PWV and HR, but also between LVET and diastolic time (DT) at different ages in a large population of untreated subjects.

METHODS

A large database of central pulse wave recordings obtained from 3,020 subjects (1,107 men) aged 15–104 years (mean 60.6 ± 25.7 years) was retrospectively assessed. Detailed main characteristics of

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the study population were previously described in the parent studies, which focused on PWV reference values, epidemiological features, pulse wave analysis validation, and PWV impact on outcome, respectively (2, 3, 6–8, 14, 17, 37–40, 44). Subjects from these cohorts who were receiving any cardiovascular drug were not included in the present analysis. Thus data analysis focused only on either normotensive subjects or untreated patients with mild to moderate hypertension with preserved functional capacity and without previous clinical cardiovascular events or heart failure. All study protocols were approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Carotid-femoral PWV (an established surrogate for aortic PWV) was determined by means of a PulsePen device (DiaTecne, Milan, Italy), a validated and easy-to-use tonometer (16, 36). All measurements were performed in the morning (between 8:00 A.M. and noon), after a 10-min rest in a quiet room at stable temperature (20 ± 2°C). The procedure has been described in detail previously (36). Briefly, the PulsePen consists of a tonometer and an integrated electrocardiographic (ECG) unit. PWV is measured by sequential recordings of the arterial pressure waveform at the common carotid and femoral artery and calculated as the distance between the sampling sites divided by the time difference between the respective delays in the onset of femoral and carotid pulses with regard to the preceding R wave of an ECG recording. The distance traveled by the pulse waveform from heart to femoral artery site is thus approximately estimated as 80% of the direct carotid-to-femoral tape measure distance, as recommended by a recent expert consensus document on the measurement of aortic stiffness in daily practice (45).

The PulsePen is implemented with an inner quality control that rejects PWV estimates when systolic blood pressure and HR measurements, separately obtained during carotid and femoral recordings, differ by more than 10%. The intra- and interobserver reproducibility of PWV estimates by PulsePen tonometer have been previously reported, with a coefficient of variation reaching 4.8% and 7.3%, respectively (31).

The heart period (HP), LVET, DT, and dP/dt were obtained from the carotid pressure waveform analysis. HP is the reciprocal of HR (HR in beats per min = 60,000/HP in ms) and is defined in pulse wave analysis as the interval between the foot of two consecutive pulse pressure waves. This measurement largely coincides with the R-R interval on an ECG (35). HP is the sum of LVET and DT, the contribution of preejection time being regarded as negligible. The point corresponding to the end of LVET and the beginning of DT is identified by the dicrotic notch in the carotid pulse waveform. This point is automatically estimated by the PulsePen software.

The dP/dt defines the entity of variation of blood pressure as a function of time in the initial upstroke. It is obtained as the time derivative of early systolic pressure raise from the foot of the carotid pressure waveform to the inflection point, corresponding to the meeting between forward and backward waves. Thus it was not computed in the youngest age group (<25 years) due to the high prevalence of waveforms with the inflection point following the peak-systolic pressure point. PulsePen tonometer is high-fidelity, and the device used in this study had a sample rate of 500 Hz (i.e., it acquired a pressure signal every 2 ms). The pressure signal was not filtered and no interpolation system was implemented in PulsePen. Thus the high sampling rate and the absence of interpolation make the dicrotic notch clearly detectable and the dP/dt was accurately estimated in almost all carotid waveforms. Moreover, the recorded waveforms were checked one by one by an expert operator (P.S.). A very strong correlation was shown at resting HR between LVET intervals derived from the central invasive aortic pressure tracings and from carotid tracings (46).

Statistical analysis. The influence of age, sex, mean arterial pressure, HR, diastolic time, LVET, and dP/dt on PWV was evaluated by dividing our population into subgroups of about equal size taking into account the age distribution of the whole population. Considering the quintiles of distribution for age of our population, we subdivided the population into five classes of 20 years each: <25, 25–44, 45–64, 65–84, and 85–104. A linear trend analysis was performed to identify decreasing or increasing trends with age in the main hemodynamic parameters. The significance of the difference between two correlation coefficients was calculated using the Fisher r-to-z transformation.

Multiple ascending stepwise regression analyses were used to determine independent predictors of carotid-femoral PWV.

Values are presented as means ± SD. A value of $P < 0.05$ was considered the minimum level of statistical significance throughout the study. Statistical analysis was performed using the statistical software package NCSS 2000 (NCSS, Kaysville, UT).

RESULTS

The descriptive and hemodynamic characteristics of the entire study population and the five age groups are shown in Table 1. Significant differences were observed among the age groups for all considered parameters. Systolic blood pressure, pulse pressure, mean arterial pressure, and PWV showed the most important increases with age ($P < 0.001$ for all).

Relationship between HP, LVET, and DT. Figure 1 shows the relationship between HP and DT (Fig. 1*A*) and between HP and LVET (Fig. 1*B*). HP was very tightly related with DT ($r^2 = 0.98$, $P < 0.0001$), and more weakly with LVET ($r^2 = 0.53$, $P < 0.0001$). As expected from the above results the DT/LVET relationship (Fig. 1*C*) was very similar to that of HP/LVET ($r^2 = 0.38$, $P < 0.0001$). When these analyses were performed in the different age groups we found even weaker

Table 1. *Descriptive characteristics and hemodynamic parameters of all participants*

	All	<25 years	25–44 years	45–64 years	65–84 years	≥85 years	Trend
Subjects	3020	563	285	742	738	692	
Sex, M/F	1107/1913	280/283	102/183	275/467	312/426	138/554	
Age, years	60.6 ± 25.7	17.8 ± 1.1	39.5 ± 4.7	55.3 ± 6.0	76.3 ± 6.6	90.1 ± 3.8	
SBP, mmHg	133.0 ± 18.3	121.4 ± 11.8	124.5 ± 15.7	135.1 ± 17.9	139.7 ± 18.0	136.6 ± 19.0	†
PP, mmHg	58.9 ± 14.9	52.8 ± 11.1	48.3 ± 9.7	55.3 ± 12.8	64.9 ± 14.6	65.7 ± 16.0	†
DBP, mmHg	74.1 ± 11.0	68.6 ± 7.9	76.2 ± 10.2	79.8 ± 10.1	74.9 ± 10.8	70.9 ± 11.6	*
MAP, mmHg	97.7 ± 12.4	89.7 ± 8.0	95.5 ± 11.8	101.9 ± 12.2	100.8 ± 12.2	97.2 ± 12.8	†
LVET, ms	301 ± 30	301 ± 22	297 ± 25	300 ± 31	301 ± 33	306 ± 33	*
DT, ms	583 ± 141	586 ± 145	551 ± 147	571 ± 145	593 ± 134	594 ± 136	*
HP, ms	884 ± 161	887 ± 156	848 ± 165	871 ± 169	894 ± 158	899 ± 157	*
HR, bpm	70.4 ± 13.3	69.9 ± 12.2	73.6 ± 14.8	71.6 ± 14.8	69.4 ± 12.7	69.0 ± 12.2	*
PWV, m/s	10.7 ± 5.0	6.2 ± 1.0	7.5 ± 1.2	8.9 ± 2.2	12.7 ± 4.6	15.3 ± 5.4	†

DBP, diastolic blood pressure; DT, diastolic time; HP, heart period; HR, heart rate; LVET, left ventricular ejection time; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure. A linear trend test was applied to identify a decline or increase in trend: *$P < 0.05$; †$P < 0.001$.

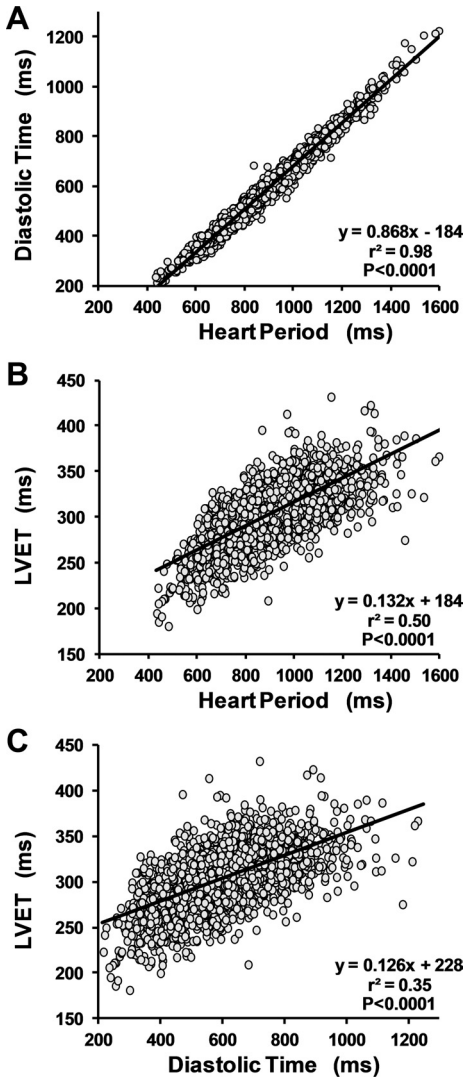

Fig. 1. Relationship between heart period and diastolic time (*A*), heart period and left ventricular ejection time (LVET) (*B*), diastolic time and LVET (*C*) in the population.

DT/LVET and HP/LVET correlations in subjects younger than 25 years (HP/LVET, $r^2 = 0.29$, $P < 0.0001$; DT/LVET, $r^2 = 0.19$, $P < 0.0001$).

Pulse wave velocity. The relationships between PWV and LVET, DT, HP, and dP/dt in the different age-groups are shown in Table 2. A significant negative association was found between PWV and LVET in all age groups ($P < 0.0001$). The correlations between PWV and HP, and between PWV and dP/dt were also significant ($P < 0.0001$) at all ages with the exception of the youngest subjects (<25 years; $r^2 = 0.003$, $P = 0.20$). An inverse relationship between LVET and dP/dt was also found ($r = -0.16$, $P < 0.001$). This relationship weakened progressively with age ($r = -0.45$ for 25–44 years, $r = -0.37$ for 45–64 years, and $r = -0.20$ for 65–84 years; $P < 0.001$) and was not significant in subjects aged >85 years ($r = -0.02$; $P = 0.74$). An analogous inverse relationship was observed between dP/dT and HP ($r = -0.17$, $P < 0.001$) and between dP/dt and DT ($r = -0.16$, $P < 0.001$). The relationship between PWV and HP in youth was significantly weaker than in adults aged 45–64 years (z = 2.91, $P < 0.002$), 65–84 years (z = 2.54, $P = 0.005$) or in the elderly (z = 1.96, $P = 0.025$). On the contrary, the relationships between PWV and LVET were constant, without significant differences among the different age groups (P = not significant). The relationship between PWV and LVET was stronger than that between PWV and HP in the youngest subjects (z = −2.73, $P = 0.0063$), with this difference waning with advancing age (z = −1.4, $P = 0.15$ in subjects aged 45 to 64 years; z = −0.40, $P = 0.69$ in subjects aged 65 to 84 years; and z = 0.19, $P = 0.85$ in subjects aged >85 years).

Table 3 shows the results of stepwise regression analysis for all 3,020 participants, with PWV as a dependent variable, making use of different models. The first model (*Model 1*) is the one usually employed in clinical research, where age, sex, mean arterial pressure, and HP (the reciprocal of HR) are included as independent variables (Table 3, *top left*). All four variables were independent determinants of PWV. Age was by far the most important determinant (accounting for 43.2% of PWV variability). In a second model (*Model 2*) LVET was added as an independent variable, thus allowing both LVET and HP to be considered (Table 3, lower left). A study of multicollinearity seems to rule out any hypothesis of collinearity between LVET and HP (variation inflation factor = 2.0; tolerance = 0.5). In the latter model, LVET explained 1.4% ($P < 0.001$) of PWV variance, whereas HP was no longer a significant determinant ($P = 0.30$). The same occurred when HP was replaced with DT. When LVET was included in *Model 1* instead of HP, similar results were obtained as in *Model 2*. In all cases when DT replaced HP identical results were obtained (Table 3, *Model 3* and *Model 4*).

Table 4 illustrates the same analyses in the different age groups. These data show that the results observed in univariate analyses (Table 2) are confirmed after adjustments for age and other covariates. With the exception of the youngest group, HP was a significant determinant of PWV (Table 4, *Model 1*);

Table 2. *Relationship between PWV and LVET, DT, HP, and dP/dt in different age classes*

	PWV vs. LVET		PWV vs. DT		PWV vs. HP		PWV vs. dP/dt	
Age, years	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
<25	−0.21	<0.0001	−0.03	0.52	−0.05	0.20		
25–44	−0.32	<0.0001	−0.21	0.0005	−0.23	<0.0001	0.38	<0.0001
45–64	−0.28	<0.0001	−0.18	<0.0001	−0.21	<0.0001	0.34	<0.0001
65–84	−0.21	<0.0001	−0.17	0.0001	−0.19	<0.0001	0.31	<0.0001
≥85	−0.15	<0.0001	−0.15	<0.0001	−0.16	<0.0001	0.28	<0.0001

DT, diastolic time; HP, heart period; LVET, left ventricular ejection time; P, probability level; PWV, pulse wave velocity; *r*, linear regression coefficient, dP/dt corresponds to the time derivative of early systolic pressure rise, from the foot of the pressure waveform to the inflection point in the carotid waveforms. dP/dt cannot be determined in the <25 years age group due to the high prevalence of waveforms with the inflection point following the peak-systolic pressure point.

Table 3. *Stepwise regression report with carotid-femoral pulse wave velocity as dependent variable, concerning all 3020 subjects*

Model 1 $r^2 = 0.48$				Model 3 $r^2 = 0.48$			
Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*
Age	0.69	43.2	<0.001	Age	0.68	43.8	<0.001
MAP	0.05	0.2	<0.001	MAP	0.05	0.3	<0.001
HP	−0.11	1.0	<0.001	LVET	−0.12	1.4	<0.001
Sex, male	0.05	0.2	<0.001	Sex, male		0.0	0.6
Model 2 $r^2 = 0.48$				**Model 4 $r^2 = 0.48$**			
Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*
Age	0.68	43.8	<0.001	Age	0.68	43.8	<0.001
MAP	0.05	0.3	<0.001	MAP	0.05	0.3	<0.001
LVET	−0.12	1.4	<0.001	LVET	−0.12	1.4	<0.001
Sex, male		0.0	0.06	Sex, male		0.0	0.06
HP		0.0	0.3	DT		0.0	0.3

DT, diastolic time; HP, heart period; LVET, left ventricular ejection time; MAP, mean arterial pressure. The coefficient β provides a measure of the relative strength of the association independent of the units of measurement. r^2 (%) represents increment expressed as an increased percent.

however, after adding LVET in the model, HP was no longer a significant determinant of PWV. LVET was a significant independent determinant of PWV in all age groups when included instead of (Table 4, *Model 2*), or in addition to HP (Table 4, *Model 3*).

In subjects aged >24 years, dP/dt resulted as an independent predictor of PWV when added to LVET (Table 5).

DISCUSSION

The main and novel contribution of the present study is the finding of a significant and inverse association between carotid-femoral PWV (commonly assumed as an index of aortic stiffness) and LVET (a composite index of left ventricular performance affected by cardiac inotropic function and influenced by preload and afterload) on the background of the major influence exerted by age on arterial rigidity (9, 32). The shorter the LVET, the higher the aortic PWV. Our data clearly show that LVET, which was shown to be related to stroke volume (32, 47), is more closely associated with PWV than HP or DT.

Association between HR (HP) and PWV. A number of cross-sectional studies have shown a significant association between HR and PWV, independent of blood pressure levels (18, 19, 34, 47). On the background of the evidence that HR is an index of sympathetic activity and, to some extent, also of renin-angiotensin-aldosterone system activity (11), it has been suggested that both sympathetic activation and activation of the renin-angiotensin-aldosterone system could increase both HR and arterial stiffness in parallel. This hypothesis, however, has been challenged by Mircoli et al. (26) and Mangoni et al. (23), who showed that the reduction in arterial distensibility associated with tachycardia occurred even in the absence of sympathetic activation. Moreover, the results obtained in subjects with permanent cardiac pacing suggest that the association between PWV and HR is at least partially related to a direct mechanical effect of HR on PWV. Another possible explanation for the relationship between PWV and HR comes from the viscous and inertial properties of the arterial wall: an increase in HR shortens the time available for recoil, which results in arterial stiffening (4, 22). Despite these suggestions, however, the actual mechanisms responsible for the relationship between HR and arterial stiffness are still largely unknown (42).

Associations of PWV with HR, DT, and LVET. A novel contribution of our study to this field is the demonstration that LVET is an independent predictor of PWV, its effect being stronger than that of HP (or DT). Moreover, our study also shows that the role of HP (i.e., 1/HR) as an independent determinant of PWV is variable in different periods of life. HP is well known to be closely and directly related with DT, whereas the relationship between HP and LVET is weaker. However, when HP is replaced by LVET and DT, only LVET results as an independent determinant of PWV, and this relationship is constant at different ages. Our results also show that PWV is more strongly related to LVET than to HP in the youngest subjects, and that this difference disappears with advancing age. This could be explained by the closer relationship between HP and LVET in the elderly.

Mechanisms of the association between PWV and LVET. At least two mechanisms could justify the strong link we observed between PWV and LVET.

First, the relationship between LVET and PWV can be explained by a simple energetic model. At a given HR, if there is a reduction in systolic ejection time, the mechanical work of the left ventricle is carried out in a shorter time, but with greater power. Power (P) represents the work (W) of blood pressure on arterial wall during a given time interval (t) (i.e., $P = dW/dt$). Given that power is proportional to mean blood pressure and to the velocity of traveling waves, an increase in power corresponds to an increase in PWV. Thus for a given value of HP, a reduction in LVET determines an increase in PWV.

This power concept probably relates to time-dependent mechanisms associated with arterial stiffness such as wall viscoelasticity. To provide stronger evidence of the proposed association between left ventricular performance and arterial functional properties, we studied the rate of change of pressure in the initial upstroke, obtained from the dP/dt ratio in the carotid pulse waveform analysis. dP/dt resulted as an independent predictor of carotid-femoral PWV when included in all the considered models (i.e., instead of HP or LVET or even added to LVET) and through each age group.

Second, the observation of a relatively strong link between PWV and LVET through all age groups supports the hypoth-

Table 4. *Stepwise regression report with carotid-femoral pulse wave velocity as a dependent variable. Data are shown subdivided for class of age*

Class of age	MODEL 1				MODEL 2				MODEL 3			
Age: < 25 years	r^2 = 0.09				r^2 = 0.05				r^2 = 0.12			
Subjects: 563	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*
	MAP	0.21	4.4	<0.001	MAP	0.18	3.2	<0.001	MAP	0.17	2.7	<0.001
	Sex, males	0.16	2.4	<0.001	Sex, males		0.0	0.68	Sex, males	0.16	2.6	<0.001
	Age	0.12	1.4	0.004	Age		0.5	0.07	Age	0.11	1.3	0.005
	HP		0.0	0.76	LVET	−0.15	2.1	<0.001	LVET	−0.16	2.3	<0.001
									HP		0.6	0.06
Age: 25 to 44 years	r^2 = 0.16				r^2 = 0.19				r^2 = 0.19			
Subjects: 285	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*
	MAP	0.35	11.1	<0.001	MAP	0.32	8.9	<0.001	MAP	0.32	8.9	<0.001
	HP	−0.12	1.2	0.04	LVET	−0.21	4.0	<0.001	LVET	−0.21	4.0	<0.001
	Sex, males		0.6	0.17	Sex, males		0.2	0.39	Sex, males		0.2	0.39
	Age		0.3	0.34	Age		0.1	0.54	Age		0.1	0.54
									HP		0.3	0.35
Age: 45 to 64 years	r^2 = 0.25				r^2 = 0.26				r^2 = 0.26			
Subjects: 742	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*
	Age	0.30	8.6	<0.001	Age	0.28	7.8	<0.001	Age	0.30	8.2	<0.001
	MAP	0.23	4.8	<0.001	MAP	0.24	5.4	<0.001	MAP	0.23	4.7	<0.001
	HP	−0.24	4.7	<0.001	LVET	−0.23	4.9	<0.001	LVET	−0.14	0.6	0.01
	Sex, males	0.20	3.6	<0.001	Sex, males	0.14	1.8	<0.001	Sex, males	0.17	2.3	<0.001
									HP	−0.12	0.4	0.04
Age: 65 to 84 years	r^2 = 0.18				r^2 = 0.19				r^2 = 0.19			
Subjects: 738	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*
	Age	0.40	14.4	<0.001	Age	0.40	13.9	<0.001	Age	0.40	13.9	<0.001
	MAP	0.15	2.1	<0.001	MAP	0.17	2.5	<0.001	MAP	0.17	2.5	<0.001
	HP	−0.18	3.1	<0.001	LVET	−0.18	3.3	<0.001	LVET	−0.18	3.3	<0.001
	Sex, males	0.13	1.5	<0.001	Sex, males	0.08	0.6	0.02	Sex, males	0.08	0.6	0.02
									HP		0.3	0.09
Age: ≥ 85 years	r^2 = 0.05				r^2 = 0.05				r^2 = 0.05			
Subjects: 692	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*	Variable	β	r^2 (%)	*P*
	MAP	0.17	2.7	<0.001	MAP	0.18	3.2	<0.001	MAP	0.18	3.2	<0.001
	HP	−0.14	2.0	<0.001	LVET	−0.15	2.1	<0.001	LVET	−0.15	2.1	<0.001
	Sex, males		0.0	0.82	Sex, males		0.0	0.67	Sex, males		0.0	0.68
	Age		0.4	0.08	Age		0.5	0.07	Age		0.5	0.07
									HP		0.3	0.11

HP, heart period; LVET, left ventricular ejection time; MAP, mean arterial pressure. The coefficient β provides a measure of the relative strength of the association independent of the units of measurement. r^2 (%) represents increment expressed as an increased percent.

esis that carotid-femoral PWV, mainly considered as a marker of aortic stiffness, may be also significantly influenced by left ventricular performance and hemodynamic status. Because LVET depends on the capability of the left ventricle to eject blood and thus on left ventricular inotropic function and loading conditions (9, 10, 31), an alteration in any of these variables may influence LVET.

Thus taking into account both these two plausible mechanisms, the relationship between LVET and PWV should not be considered only as a result of a direct modulation of arterial distensibility induced by HP changes. Conversely, our data suggest that this relationship could rather be the result of a mutual interaction between left ventricular ejection function and aortic and large artery distensibility. It can be hypothesized that with advancing age when age progressively becomes the most powerful predictor of PWV, the inverse relationship between LVET and PWV may be an epiphenomenon of an age-related increase in large artery stiffness contributing to an increased aortic impedance that ultimately tends to limit ejection duration. On the contrary, in the youngest subjects with distensible arteries, PWV shows a prevalent association with MAP and LVET, suggesting a stronger dependence of PWV on left ventricular performance than on aortic stiffness (38).

Left ventricular ejection duration was also shown to be the strongest independent direct correlate of carotid augmentation index (AIx), commonly considered to be a composite index of arterial stiffness, wave reflection, and peripheral resistance, both in baseline conditions and during dobutamine infusion (42). The same study confirmed the previous observation of an inverse correlation between AIx and HR, and reported a direct correlation of AIx with left ventricular systolic strain rate, an

Table 5. *Stepwise regression report with carotid-femoral PWV as a dependent variable, and dP/dt included as an independent variable*

Variable	β	r^2 (%)	*P*
Age 25–44 years; Subjects 187 (r^2 = 0.26)			
MAP	0.26	4.8	<0.001
LVET	−0.23	4.0	0.002
dP/dt	0.18	2.1	0.021
Age	−0.16	2.3	0.02
Sex, males		1.0	0.10
Age 45–64 years; Subjects 682 (r^2 = 0.25)			
MAP	0.15	1.6	<0.001
LVET	−0.18	2.7	<0.001
dP/dt	0.17	1.8	<0.001
Age	0.25	5.6	<0.001
Sex, males	0.17	2.7	<0.001
Age 65–84 years; Subjects 686 (r^2 = 0.23)			
MAP	0.10	0.8	0.01
LVET	−0.14	1.9	<0.001
dP/dt	0.23	4.9	<0.001
Age	0.36	10.8	<0.001
Sex, males	0.07	0.5	0.05
Age ≥85 years; Subjects 660 (r^2 = 0.11)			
MAP	0.11	1.2	0.01
LVET	−0.13	1.7	0.003
dP/dt	0.26	6.7	<0.001
Age		0.5	0.09
Sex, males		0.0	0.70

index of left ventricular systolic function. However, the relation between AIx and strain rate disappeared after adjusting for heart rate changes. Quite interestingly, even in this study (42) when heart rate was used instead of ejection duration, the prediction of AIx by the model became weaker. Thus ejection duration appears to be a more powerful determinant than heart rate for both AIx and PWV.

A final relevant finding of our work is that the determinants of PWV are different at different ages. As clearly shown in Fig. 2, if we consider the role of HR only as determinant of PWV, it is negligible in young people, appearing only in adults. On the other hand, the role of LVET is constant and homogeneous throughout life. Indeed, both in very young and in very old subjects, mean blood pressure and left ventricular ejection time, reflecting left ventricular performance and peripheral resistance, are both less powerful determinants of pulse wave speed along the arterial tree.

Study limitations. This study analyzed the associations between cardiac and arterial parameters derived simultaneously from pressure waveform analysis obtained by applanation tonometry. From its design this cross-sectional study cannot draw any conclusions about the direction of these associations (i.e., we cannot establish cause-and-effect relationships).

In the different models we used, LVET explains between 2 and 5% of the variance in PWV. Although this is relatively small, this contribution is consistently significant in the different models. In addition, it is very unusual to detect variables that have a much stronger determinism in the variations of PWV with the exception of age. Actually, under specific conditions characterized by significant changes in heart rate on the same population, the change in heart rate should be taken into serious consideration when analyzing the data. For example, exposure to high altitudes or sports activity may cause considerable increases in heart rate and significantly affect PWV values.

Conclusions. Carotid-femoral PWV as well as hemodynamic indices derived from arterial pressure waveform analysis are influenced by multiple mechanisms involving arterial structure and function and left ventricular performance. These associations are influenced by age. Interestingly, the association of PWV with LVET appears stronger than that with HR in all age groups. Despite the complexity in the relationship between LVET and PWV, taking into account data derived from the literature, it is plausible that in particular in the elderly, LVET depends on arterial stiffness rather than being its determinant; a marked arterial stiffness causing a reduction in left ventricular ejection duration, secondary to an increased after-load.

Our results support the emerging evidence that both in clinical practice and in clinical research, not only HR but also cardiac systolic function-related variables should be regularly

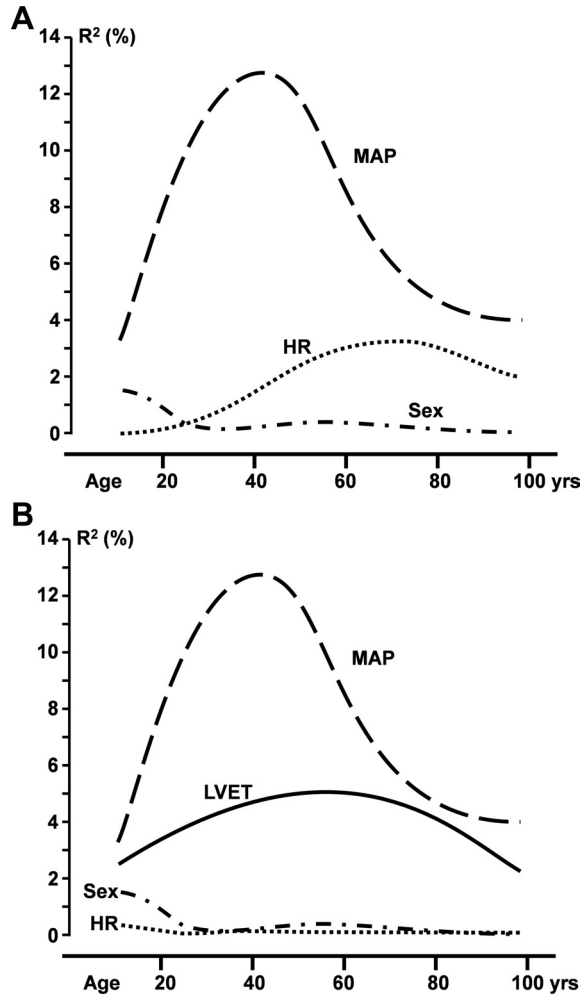

Fig. 2. Role of major determinants of pulse wave velocity (PWV) through age decades. *A*: mean arterial pressure (MAP), gender, and heart rate (HR) have been considered. *B*: the role of HR changes after insertion of ventricular ejection time (LVET). Data are the results of subdividing all subjects for class of age and weighing up the r^2 increment in stepwise regression analysis into each class of age.

taken into account when interpreting arterial function indices; namely, carotid-femoral PWV.

DISCLOSURES

Paolo Salvi is a consultant for DiaTecne s.r.l., manufacturer of systems for analyzing the arterial pulse. All other authors have no conflicts to report.

AUTHOR CONTRIBUTIONS

Author contributions: P.S., C.P., and A.B. conception and design of research; P.S. performed experiments; P.S., C.P., and C.L. analyzed data; P.S., C.P., G.M.S., C.L., G.P., and A.B. interpreted results of experiments; P.S. prepared figures; P.S., C.P., G.M.S., G.P., and A.B. drafted manuscript; P.S., C.P., G.M.S., C.L., G.P., and A.B. edited and revised manuscript; P.S., C.P., G.M.S., C.L., G.P., and A.B. approved final version of manuscript.

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