Heart Rate
An Important Confounder of Pulse Wave Velocity Assessment
Pierre Lantelme, Christine Mestre, Michel Lievre, Alain Gressard, Hugues Milon

Abstract—Arterial stiffness is a strong determinant of cardiovascular risk. Pulse wave velocity (PWV) is an index of arterial stiffness, and its prognostic value has been repeatedly emphasized. The purpose of the present study was to assess the effect of heart rate (HR) on PWV. Twenty-two subjects with a mean age of 77.8±8.4 (SD) years and permanent cardiac pacing were studied. In each subject, PWV was measured at 5 different pacing frequencies in the same session (60, 70, 80, 90, 100 bpm), the order of the various frequencies being randomly determined. Furthermore, to test the reproducibility, a repeat measurement of PWV was obtained in one randomly selected frequency. Blood pressure (BP) was measured by conventional means at each pacing frequency. PWV appeared fairly reproducible because no significant difference was disclosed between the 2 measurements obtained at the same HR level (P=0.5) and both measurements were strongly correlated (r=0.87, P<0.001). No significant BP variation was observed during pacing. There was a highly significant effect of HR on PWV estimated by a one-way, within-subjects analysis of variance (P=0.01). This study demonstrates that HR is an important factor in the intraindividual variation of PWV in elderly subjects. This raises methodological concern about the measurement of this parameter. Standardizing PWV for HR level seems mandatory if one wants to interpret PWV changes in clinical trials or in the follow-up of patients. (Hypertension. 2002;39:1083-1087.)

Key Words: arteries ■ atherosclerosis ■ tachycardia ■ compliance ■ heart rate

Pulse wave velocity (PWV) is an index of arterial stiffness and a marker of atherosclerosis. In hypertension and in end-stage renal failure, it has been shown to be a marker of cardiovascular events. Arterial stiffness can be affected by both structural and functional changes. Structural changes involve the composition of the arterial wall; they correspond to vessel damages or adaptations and are important predictors of mortality. They probably represent major goals for therapeutic intervention. Functional changes also affect PWV. For example, the arterial stiffness of a given artery varies as a function of its internal pressure. This effect is important because it accounts, at least partly, for the apparent beneficial effect of blood pressure (BP) lowering on PWV. Also, because BP is highly variable, this BP-PWV relationship weakens the reproducibility of PWV.

There are several other parameters that may vary during PWV measurement, among which heart rate (HR) is of particular importance. Indeed, it can be influenced by both psychological or pharmacological conditions. Of note, in animals, it has been established that arterial distensibility is a function of HR. This has not been so clearly demonstrated in humans, even though Albaldejo et al recently reported, using cardiac pacing in 11 subjects, a nonsignificant trend for an increase of PWV with HR. In cross-sectional studies or in clinical trials, the effect of HR on PWV is often dismissed or even overlooked. Cardiac insufficiency, for example, is associated with an increased PWV, but one can raise the question of the confounding effect of tachycardia in this relationship. This issue is all the more important now that PWV is used in the follow-up of patients or proposed as an intermediate end-point in clinical trials.

The purpose of the present study was to evaluate the importance of HR as a determinant of PWV within individuals. We showed that HR markedly influences the intraindividual variation of PWV in elderly subjects. This raises methodological concerns, and we discuss the need to standardize the measurement of this parameter for HR level.

Methods
Patients were selected from those referred to our cardiology department for pacemaker implantation. Inclusion criteria required that their spontaneous rhythm be below 60 bpm, which usually meant that they had a third degree atrioventricular block or a slow ventricular response with atrial fibrillation. Exclusion criteria were uncontrolled congestive heart failure, recent myocardial infarction, or unstable angina. Using these criteria, 22 patients entered the study. All but 2 patients had a ventricular pacing; these 2 patients had an increase of PWV with HR. In cross-sectional studies or in clinical trials, the effect of HR on PWV is often dismissed or even overlooked. Cardiac insufficiency, for example, is associated with an increased PWV, but one can raise the question of the confounding effect of tachycardia in this relationship. This issue is all the more important now that PWV is used in the follow-up of patients or proposed as an intermediate end-point in clinical trials.

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exclusive permanent atrial pacing (AAIR mode). The protocol was approved by the Institutional Ethics Committee and every subjects gave an informed consent to participate.

Pulse Wave Velocity Measurement
Pulse wave velocity (PWV) was measured using a Complior device (Colson) following the manufacturer’s recommendations. This device has been validated and provides an accurate automatic measurement of PWV.10 Briefly, 2 transducers were placed, one at the base of the neck for the common carotid artery and one over the femoral artery. The 2 transducers were positioned so as to record the best signals. The quality of the carotid and femoral pulse waves was visually checked, and 25 pulse waves were recorded and stored. The transit time between the carotid and the femoral pulse waves was automatically determined by the software. The distance between the 2 recording sites was measured, allowing PWV to be calculated as the ratio of the distance to the transit time. The 25 measurements were averaged to provide the PWV value for one given heart rate (HR) level.

Study Protocol
The study was performed at least 48 hours after pacemaker implantation. The pacemaker was set in the SSI mode. Five different HR levels (60, 70, 80, 90, and 100 bpm) were programmed in a random order, and PWV was measured at each of them. Furthermore, with the aim of testing the reproducibility, a repeat measurement of PWV was obtained in one randomly selected frequency. Conventional blood pressure (BP) was measured in the lying position with a mercury sphygmomanometer at each pacing frequency.

Statistical Analysis
All analyses were performed using the Statistica 5.1 software package (Statsoft Inc). Values are expressed as mean±SD. Reproducibility of PWV measurements was tested using the paired t test, Spearman’s correlation, and Bland and Altman plot. The effect of HR on BP and PWV was tested by a one-way, within-subjects analysis of variance with a repeated measurement factor. Each PWV determination at one particular HR level was set as an independent variable with a repeated measurement factor of 5 levels. A post hoc analysis with a least significant difference test was performed to determine which HR levels led to significant changes in PWV. A probability value <0.05 was considered to indicate statistical significance.

Results
The characteristics of the patients are presented in the Table. In particular, mean age was 77.8±8.4 years and 59% were males. About one third of the subjects had hypertension or diabetes. Almost half had an overt cardiac disease (ischemic, valvular, or dilated cardiomyopathy). Diuretics were the most common drugs used in the overall group of patients, as well as in the subgroup of hypertensives (75%). The other antihypertensive treatments were renin angiotensin system inhibitors (62.5%), calcium antagonists (25%), and beta blockers (12.5%). A reliable estimation of PWV was obtained in all subjects.

When considering the relationships between PWV and either BP or age at each HR level in a univariate mode, we found a significant correlation (1) between PWV and age in all cases, (2) between PWV and systolic BP in all cases but one (ie, at 100 bpm), and (3) between PWV and diastolic BP in all cases but 2 (ie, at 80 and 100 bpm). In a multiple regression analysis, age was the major determinant of PWV variance, being significantly and independently correlated with PWV at each HR level (P=0.003, P=0.05, P=0.004, P=0.01, and P=0.01 at 60, 70, 80, 90, and 100 bpm, respectively).

Reproducibility of PWV
The repeat measurement of PWV at one randomly chosen frequency for each subject allowed testing of the reproducibility of PWV assessment. The average difference between the 2 measurements performed at the same pacing frequency was −0.3 m/s with a SD of 1.8 m/s as shown in a Bland-Altman plot of the differences between the 2 measurements against their means (Figure 1). The first measurement did not differ significantly from the second (P=0.5), ruling out a systematic drift, and the correlation between the 2 measurements was highly significant (r=0.87, P<0.001) (Figure 1).

Effect of HR Changes on BP and PWV
The effect of HR on BP is illustrated in Figure 2 (top). Systolic and diastolic BP remained stable on average (not significant for HR effect by one-way analysis of variance). PWV increased gradually with HR (Figure 2, bottom). PWV values (mean±SD) were 13.7±3.1, 13.7±2.6, 14.2±3.6, 14.6±3.7, and 15.1±4.3 m/s at 60, 70, 80, 90, and 100 bpm, respectively. The effect of HR on PWV was highly significant (P=0.01 for HR effect by one-way analysis of variance). The average difference between PWV at 100 and 60 bpm was 1.36±2.9 m/s. One patient had a very high PWV and a very pronounced HR effect on PWV. Even after excluding this patient from the analysis, the HR effect studied by one-way analysis of variance remained statistically significant (P<0.05). A post hoc test showed that significant differences in PWV were observed between 100 bpm and both 60 bpm (P=0.006) and 70 bpm (P=0.004) and between 90 bpm and both 60 bpm (P=0.04) and 70 bpm (P=0.03).

Main Characteristics of the Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
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</tr>
<tr>
<td>Males/females, n</td>
<td>13/9</td>
</tr>
<tr>
<td>Smokers/nonsmokers, n</td>
<td>9/13</td>
</tr>
<tr>
<td>Diabetes/no, n</td>
<td>9/13</td>
</tr>
<tr>
<td>Hypertension/no, n</td>
<td>8/14</td>
</tr>
<tr>
<td>Atrial fibrillation/no, n</td>
<td>7/15</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
</tr>
<tr>
<td>Ischemic disease, n (%)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Valvular disease, n (%)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy, n (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other cardiac disease, n (%)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>No cardiopathy, n (%)</td>
<td>8 (36)</td>
</tr>
</tbody>
</table>

Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers, n</td>
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</tr>
<tr>
<td>RAS inhibitors, n</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Diuretics, n</td>
<td>16 (73)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>3 (14)</td>
</tr>
</tbody>
</table>

Plus-minus value is mean±SD; n indicated number of subjects; RAS, renin angiotensin system.
PWV obtained for consecutive HR values were not statistically different.

The slopes of the individual regression lines of PWV on HR varied considerably between subjects as indicated by the large standard deviation: 0.07 m/s for an average of 0.04 m/s. None of the factors tested (age, systolic BP, diastolic BP, pulse pressure, or PWV at 60 bpm) seemed to account for such variability.

Discussion

The present study shows that HR exerts a significant influence on PWV assessment in elderly subjects. This raises an important methodological concern for the use of PWV in clinical trials or for the follow-up of individuals.

A fundamental physical property of the arterial wall is elasticity. Arterial stiffening favors an increase of systolic BP and pulse pressure, both of which have been shown to be independent predictors of mortality. Several indices can be used to assess arterial stiffness. Among them, PWV is widely used, and its prognostic value has been established by epidemiological studies in hypertension and in end-stage renal failure. The major advantages of PWV are practicality and the absence of serious technical limitations.

Arterial elasticity is impaired with hypertension and aging. Accordingly, it has been repeatedly found that PWV is positively correlated with BP and age. Our results on a small sample of subjects are consistent with these well-established findings. At each HR level, age and, to a lesser extent, BP appeared as important determinants of PWV variance. Associations have been reported with important risk factors for atherosclerosis, such as blood glucose. As to serum cholesterol, the association has been found by some
but not by all authors. However, the clinical use of PWV is compromised by a poor reproducibility. This is not surprising because arterial stiffness can be affected by other factors than structural changes of arterial wall. In particular, a curvilinear relationship has been described between pressure and vessel diameter, stiffness being higher at high BP and lower at low BP. Therefore, BP changes probably represent an important limitation in arterial distensibility assessment by PWV. In our experimental conditions, no BP change was observed with changing HR, and we observed a fairly good reproducibility of PWV measurement, with a mean difference between 2 repeat measurements of 0.3±1.8 m/s (P=0.5). Such value is very similar to those previously reported: the average difference was 0.32±0.69 m/s in Yasmin’s study and 0.07±1.17 m/s in Wilkinson’s study.

Our findings indicate that HR may also have an effect on PWV independent of BP level. This hypothesis is in line with some epidemiological evidence obtained from cross-sectional studies showing a significant and independent association between HR and PWV. Of course, these results do not suffice to demonstrate that HR has a direct effect on PWV within individuals. Using atrial pacing, Mangoni et al have shown that arterial distensibility increased in parallel with increased HR in rats. In humans, the relationship between HR and PWV has not been fully elucidated. Siché et al measured PWV during exercise and showed a trend for PWV to increase with HR. However, this study was confounded by the changes in BP or in sympathetic tone that occur during exercise. Recently a similar nonsignificant positive trend between HR and PWV was found by Albaladejo et al using cardiac pacing. However that study lacked statistical power, with only 11 subjects included and 3 HR levels tested. In addition, the 3 HR levels were not predetermined but had only to lie between 40 and 130 bpm. To our knowledge, our experiment is the first to establish unequivocally a significant effect of HR on PWV in humans and to provide an estimation of it. The major strengths of our study are (1) a design that allowed the examination of the intraindividual variation of PWV, each subject being his/her own control; (2) a range of HR values limited to what is usually observed in routine clinical practice; (3) pacing at 5 predetermined frequencies in a random order to allow for carryover effects; and (4) standardized conditions of PWV measurement and no change in either systolic or diastolic BP. This lack of BP change was probably due to the narrow range of HR variation compared with other studies. One can also assume that, because of the rapid changes in HR, the neurohumoral status was unchanged.

Other indices have been used to assess arterial elasticity in humans. Among them, the augmentation index (AI) is obtained by analysis of the pressure waveform, and it has been found positively correlated with PWV. Surprisingly, however, Wilkinson et al recently showed a negative relationship between AI and HR. In fact, PWV and AI are not interchangeable indices because AI depends not only on arterial stiffness per se (reflected by PWV) but also on other parameters, such as the pattern of ventricular ejection, the vascular tone, or the absolute systole duration. Indeed, variations of AI may occur without any parallel changes in PWV.

In our study, the average effect of a 40 bpm increase in HR on PWV was 1.36 m/s, which can be considered a limited variation. In fact, each 1 m/s increase of PWV has been shown to increase the risk of all-cause mortality by 39% in end-stage renal disease patients. Reciprocally, Guérin et al showed that the PWV variation following a drug-induced BP decrease was also related to outcome in hemodialysed patients. In their study, the adjusted relative risk for all-cause mortality for a PWV decrease of 1 m/s was 0.71 (95% CI, 0.60–0.86). Globally, in these high-risk subjects, a 1 m/s PWV variation is clinically relevant. However, in hypertensive patients, such variation is probably less significant because Laurent et al have recently shown that the odds ratio for a 5 m/s PWV increase was 1.51 for cardiovascular mortality.

The determinants of HR-induced PWV variations have already been questioned. A first hypothesis that is frequently put forward involves the change in sympathetic tone that usually goes with an increase of HR. This hypothesis has been elegantly addressed by Mircoli et al by comparing the stiffening effect of tachycardia in sympathectomized and control rats. They showed that the variation of arterial distensibility that accompanies tachycardia occurred even in the absence of a functional sympathetic nervous system. They also showed that there might be a differential effect of sympathetic influence on elastic-type versus muscle-type arteries. However, HR variation, by design, was not due to a change in sympathetic tone in our study, which therefore, could not explain the tachycardia-induced rise in PWV.

Mechanical arterial properties are determined not only by elastic, but also by viscous and inertial, components of the vessel wall. Tachycardia shortens the time available for recoil, which results in vessel stiffening. This represents the most plausible explanation for our results in that, because of our very controlled experimental conditions, HR was the only parameter that significantly varied.

Our results have methodological implications. As previously proposed, arterial stiffness should be assessed in isobaric conditions. In light of our results, a proper comparison of arterial stiffness assessment using PWV should also be performed, theoretically, at a similar HR level, especially when the aim is to assess the effects of antihypertensive agents that interfere with HR. This could be taken care of by an appropriate correction of PWV for HR.

In this respect, our study has limitations related to patients’ characteristics. First of all, they were elderly subjects, which might have amplified the overall PWV/HR relationship because age is indeed known for its effect on arterial compliance. Secondly, as a group, they were heterogeneous with regard to cardiovascular status and type of ongoing treatment, whereas both cardiac dysfunction and treatment have been shown to affect PWV. This likely contributed to the observed important interindividual variability of the PWV/HR relationship. Such a variability prevented us from using the average effect for establishing a correction factor for HR. Finally, the sample size did not permit analyses in
relevant subgroups, such as diabetic, hypertensive, or dyslipidemic patients.

In conclusion, the effect of HR variation on PWV within individuals cannot be dismissed. This HR-related variation of PWV may be limiting for the use of PWV as an intermediate end point in clinical trials, especially those devoted to the evaluation of the effects of antihypertensive drugs. Further studies are needed to determine precisely what kind of correction should be applied to take account of this HR effect and whether such correction is also required in younger individuals.

Perspectives

PWV has recently come to the attention of the scientific world as a marker of atherosclerosis and cardiovascular risk. This marker is, however, affected by BP variations and, as demonstrated in the present study, by HR. HR level should then be taken into account when interpreting PWV changes. This means either trying to determine a correction factor in larger groups of subjects of various age or considering as significant only large variations of PWV or variations that are not paralleled with changes in HR.

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References


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