CLINICAL RESEARCH

Arterial stiffness is associated with left atrial size in hypertensive patients

La rigidité artérielle est associée aux dimensions de l’oreillette gauche chez l’hypertendu

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Summary

Background. — Arterial stiffness is a strong predictor of cardiovascular events and particularly of stroke. A likely explanation is the development of atherosclerotic lesions at the carotid level, favored by increased local stiffness. Another possibility involves cardiac consequences of aortic stiffness and particularly left atrial dilatation with its subsequent risk of atrial fibrillation (AF) and cerebral embolism.

Aims. — The present study investigated the link between arterial stiffness, pulse pressure and left atrial size, a determinant of AF risk.

Methods. — Arterial stiffness was determined from pulse wave velocity (PWV) and pulse pressure (PP). Left atrial size was also measured. Several potential confounders were taken into account including indices of ventricular remodeling and diastolic function (estimated by NT-Pro brain natriuretic peptide (NT-proBNP) levels).

Results. — Three-hundred and ten hypertensive patients, aged 53 ± 13 years, were included. Mean 24-h blood pressure (BP) was 154 ± 20 over 93 ± 13 mmHg. Significant relationships were found between left atrial diameter (LAD) and PWV (r=0.27, P<0.001) and between LAD and 24-h PP (r=0.32, P<0.001). LAD was also correlated significantly, although not always tightly, with left ventricular dimensions, geometry and NT-proBNP. In two different multivariate models, LAD remained significantly correlated with PWV or with 24-h PP, independently of classical determinants like age, gender, body mass index, ventricular remodeling (i.e. dimensions and geometry) and filling pressure.

Conclusion. — These results led us to propose AF as a new possible pathophysiological link between arterial stiffness and stroke. These results also emphasize the cardiac consequences of arterial stiffness which can fuel a new approach to AF prevention.

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KEYWORDS

Arterial stiffness; Pulse wave velocity; Atrial fibrillation; Remodeling
Introduction

Arterial stiffness is a strong independent predictive factor for stroke (1) and is associated with cognitive impairment in the elderly (2). Arterial stiffness involves collagen deposition, fragmentation of elastic tissue and calcifications. It is affected by the amount and density of stiff wall material and the spatial organization of that material (3). Aortic stiffening and the subsequent increase in central pulse pressure (PP) are associated with carotid intima-media thickening (4), atheroma formation (5) and plaque rupture (6). These ‘local’ effects are likely to play a crucial role in the pathophysiology of stroke.

Aortic stiffness also exerts an effect on left ventricular geometry and diastolic function (7). When considering a more advanced stage of heart disease, arterial stiffening increases the risk of heart failure, emphasizing the interplay between vascular mechanics and heart function (8). Because ventricular remodeling is a powerful determinant of left atrial size (9), it is conceivable that arterial stiffness influences left atrial diameter (LAD). Atrial fibrillation (AF), which is closely related to atrial size (10), would then be a potential link between aortic stiffness and stroke.

The aim of the present study was to determine the relationship between arterial stiffness and LAD, independently of important confounders such as left ventricular remodeling and diastolic function. Left ventricular remodeling was assessed from ventricular dimensions [left ventricular diameter (LVD) and left posterior wall thickness (LPWT)] and geometry (relative wall thickness). NT-Pro brain natriuretic peptide (NT-proBNP) was used as a surrogate marker of filling pressure and diastolic function (11). We took into account not only aortic stiffness but also PP, which is influenced by arterial stiffness.

Methods

Three-hundred and sixty-eight consecutive hypertensive patients referred to our cardiology department (Hôpital de la Croix-Rousse, Lyon) for clinical work-up were assessed and 310 of these who had an available LAD determination were included in the study. Patients maintained their usual sodium regimens before and during hospitalization. Whenever possible, any ongoing antihypertensive therapy was discontinued 2 weeks before admission (6 weeks for spironolactone) for hormone measurement purposes. If treatment was deemed mandatory, calcium-channel blockers or central agents were used in most cases. Twenty-four hour blood pressure (24-h BP) measurements and blood collections after overnight recumbency were performed. Standard biological testing included serum creatinine, urinary microalbumin or protein, electrolytes and creatinine. Creatinine clearance was estimated using the Cockcroft formula and expressed as ml/min.

Ambulatory blood pressure recordings

24-h BP recordings were obtained using Diasys (model 200 RS; Novacor) or Spacelabs (model 90207; Spacelabs) monitors that satisfied the criteria of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation (12). Twenty-four hour systolic pressure (SBP), diastolic pressure (DBP) and PP were recorded at 15 min intervals during the day and at 30 min intervals during the night.

Pulse wave velocity measurement

Pulse wave velocity (PWV) measurements were obtained using a Complior device (Complior; Colson, Garges-les-
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Gonesse, France) following a procedure described previously (13). This device has been validated and provides an accurate automatic measurement of PWV (14). Briefly, two transducers were placed at the base of the neck for the common carotid artery and over the femoral artery. The two transducers were positioned so as to record the best signals. The quality of the carotid and femoral pulse waves was checked visually and 25 pulse waves were recorded and stored. The transit time between the carotid and femoral pulse waves was determined automatically by the software. The distance between the two 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 PWV for one given patient.

Echocardiography

M-mode echocardiograms were recorded with a commercially available echocardiograph (Vingmed System Five and VIVID Five; General Electric) with the patient lying in left lateral position (15). The transducer was placed in the third or fourth intercostal space. Two-dimensional mode examination allowed selection of the best parasternal line. LAD, LVD, and LPWT were measured. A reliable interventricular septum thickness was obtained less frequently precluding left ventricular mass calculation. LVD and LPWT were used as indicators of ventricular mass. Relative wall thickness (RWT = 2 x LPWT/LVD) was calculated and provided an estimation of left ventricular geometry, also known to influence LAD (9).

NT-Pro brain natriuretic peptide measurement

Plasma NT-proBNP was measured by electrochemiluminescence using an Elecsys 2010 NT-proBNP assay (Roche Diagnostics) according to manufacturer’s instructions. The range of values was 5-35000 pg/ml and the coefficient of variation was between 1 and 2.5%.

Statistical analysis

Values are expressed as means ± SD. Because of their skewed distribution, the natural logarithms of PWV and NT-proBNP were used for statistical tests. Statistical analysis was performed with the Statistica 5.1 software package (Statsoft Inc, Tulsa). Associations between variables were tested by univariate regression (Pearson’s coefficient of correlation “r”) and by forward stepwise multiple linear regression analysis with mean substitution in the case of missing variables. Multivariate analyses were restricted to those patients with an available stiffness marker (i.e. PWV or 24-h PP, depending on that used in the model). A P value <0.05 was considered significant.

Results

Characteristics of the overall population

The demographic characteristics of the whole group are shown in Table 1. Mean age was 53 ± 13 years, 166 were male, and the majority (75%) received anti-hypertensive treatment. 24-h BP was 154 ± 20 and 93 ± 13 mmHg for SBP and DBP, respectively, for the whole group. LAD was 39 ± 6 mm. Arterial PWV was 12 ± 3 m/s and 24-h PP was 62 ± 14 mmHg.

Correlates between atrial size, ventricular remodeling and arterial stiffness in univariate analysis

LAD was significantly associated with age (r=0.23, P<0.001), 24-h SBP (r=0.22, P<0.001), body mass index (r=0.44, P<0.001) and creatinine clearance (r=0.14, P<0.05), but not with 24-h DBP. LAD was significantly larger in men than in women (P<0.001) and in treated vs. untreated subjects (P<0.001). As shown in Fig. 1, LAD was correlated with indices of left ventricular mass (LVD, LPWT), and was also correlated significantly, although not tightly, with left ventricular geometry (r=0.15, P<0.05) between LAD and RWT. Finally, atrial size was slightly dependent on filling pressure (r=0.12, P<0.05 between LAD and NT-proBNP expressed as its logarithm).

Both PWV and 24-h PP were correlated with LAD (Figure 1). Some indices of ventricular remodeling (LPWT and RWT) were correlated with PWV (r=0.25, P<0.001; r=0.23, P<0.01, respectively) while LVD was not. Similar findings were obtained with 24-h PP (r=0.32, P<0.001 between LPWT and 24-h PP; r=0.26, P<0.001 between RWT and 24-h PP; no significant relationship between LVD and 24-h PP).

Independent relationships between arterial stiffness and LAD

Because of potential confounders, the relationships between LAD and arterial stiffness were also studied in multivariate analyses including all variables significantly associated with LAD in a univariate mode as independent factors. Table 2 shows that LAD remained significantly

<table>
<thead>
<tr>
<th>Number</th>
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<tr>
<td>Age(years)</td>
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</tr>
<tr>
<td>Male/Female(n)</td>
<td>310</td>
</tr>
<tr>
<td>Treatment(yes/no)</td>
<td>310</td>
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<tr>
<td>24-h systolic blood pressure(mmHg)</td>
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<tr>
<td>24-h diastolic blood pressure(mmHg)</td>
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<tr>
<td>Body mass index(kg/m²)</td>
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<tr>
<td>Creatinine clearance(ml/min)</td>
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<td>Left atrial diameter(mm)</td>
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<td>Left posterior wall thickness(mm)</td>
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<td>NT-Pro brain natriuretic peptide(pg/ml)</td>
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<tr>
<td>24-h pulse pressure(mmHg)</td>
<td>297</td>
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<tr>
<td>Pulse wave velocity(m/s)</td>
<td>237</td>
</tr>
</tbody>
</table>

Values for continuous variables are means ± SD.
correlated with PWV (used here as a Log value, \( P<0.05 \)) independently of usual determinants such as age, gender, body mass index, ventricular remodeling (i.e. dimensions and geometry) and filling pressure. Similarly, Table 3 shows that LAD remained correlated with 24-h PP \( (P<0.05) \) independently of these determinants.

**Discussion**

Our results show that arterial stiffness and subsequent PP are significantly correlated with atrial size, even after adjustment for major confounders including left ventricular remodeling and filling pressure. This suggests that arterial stiffness per se may contribute to left atrium enlargement and thus, to the risk of AF and stroke.

Cerebrovascular diseases represent a major health problem. In the USA, 700 000 people suffer a stroke annually, a disease known for its high rate of mortality and disability (16). Stroke risk is highly dependent on BP (17) but also on arterial stiffness (1). Aortic stiffening and the subsequent increase in central PP are associated with carotid intima-media thickening (4), atheroma formation (5) and plaque rupture (6), providing a pathophysiological link between vascular mechanics and cerebrovascular events.

However, arterial stiffness also influences cardiac remodeling. Indeed, carotid stiffness is an independent determinant of left ventricular remodeling (18). In addition, aortic stiffness has a major impact on diastolic function (7). In this respect, our study confirms the relationship between parameters of left ventricular remodeling (LVD, LPWT and RWT) and arterial stiffness. NT-proBNP, used as a surrogate marker of diastolic dysfunction (11, 19), was also correlated with arterial stiffness, a finding in line with previous reports (7). Because of the close interplay between left atria, left ventricular remodeling (9) and diastolic function (20), the relationship between arterial stiffness and LAD is not surprising. It is further supported by the capacity of an ACE-inhibitor to improve left atrial structural remodeling and vascular compliance in parallel (21).

Nevertheless, as an independent relationship it provides a potential link between stiffness and AF, which represents another mechanism of stroke. Indeed, a rather extensive adjustment was performed to determine that aortic stiffness was independently associated with LAD. This included, as adjustment variables, left ventricular diameter, posterior wall thickness, relative wall thickness (because of its important role in atrial remodeling (9)) and NT-proBNP (as a surrogate marker of filling pressure), in addition to other confounders (age, body mass index, etc).

Some limitations to this study should be discussed. First, we may not have adjusted for all confounders and especially for systolic function. However, ventricular geometry has a greater effect on LAD than left ventricular end-systolic stress (9). Second, we did not use Doppler indices of diastolic function. The use of NT-proBNP was appropriate though, since its performance to detect diastolic dysfunction is as good as that of tissue Doppler imaging (11); in addition, used as a continuous variable, it is probably more powerful for statistical testing than the categorical definition in 3 or 4 stages of diastolic function based on Doppler estimates. Third, we did not directly address the issue of a
link between stiffness and AF and rather used LAD as a surrogate marker of the risk of AF (10). In this regard, the literature is pretty scant and controversial. Reiffel et al. (22) did not report any association between arterial stiffness and AF in a small group of hypertensive and normotensive subjects. On the other hand, several recent therapeutic trials have shown that treatments reducing arterial stiffness (23, 24) prevent the occurrence of AF both in hypertensives (25) and in heart failure patients (26).

Finally, we used brachial PP and not central PP. Peripher al PP, most often measured at the site of the brachial artery, does not fully reflect central PP, measured at the carotid site. Indeed, in peripheral arteries, reflection sites are closer than in central arteries, and reflected waves travel faster on peripheral arteries than on central arteries, which are less stiff in young subjects. Thus, according to the “amplification phenomenon”, the amplitude of the pressure wave is higher in peripheral arteries than in central arteries, and brachial PP overestimates central PP in young subjects. However, these discrepancies are probably attenuated in our study patients, who had an average age of 53 years.

One issue which is left open is the mechanism by which stiffness could directly influence atrial remodeling, bypassing the “ventricular effect”. This question is largely a matter of speculation and requires caution because of the limitations highlighted above. There is, however, a rapidly growing number of papers in the literature on the participation of genes, particularly those involved in matrix proteins, in the thickening process (27). For example, Medley et al. (28) showed that matrix metalloproteinases are potential candidates to explain arterial wall remodeling, especially MMP3 and MMP9 genes. Interestingly, Nakano et al. (29) found a similar role for one of these genes (MMP9) as a candidate for atrial remodeling during AF. Other genes involved in cell-matrix connections, like integrins, provide additional examples, being activated during vascular and atrial remodeling (3, 30). In light of these findings, one might speculate that, for some reason and maybe simply because of age, similar genes are up-regulated both in the atria and vessel wall, contributing to a concomitant remodeling of both, possibly on top of mechanical effects.

Inflammation may also be involved since it has been shown that arterial stiffness was related to an increased level of C-reactive protein as well as of other markers like IL-6 and TNF-α (23, 32). Stiffening at the vascular level may trigger an inflammatory process, a condition associated with a greater occurrence of AF (32).

In conclusion, these results provide a new possible pathophysiological link between arterial stiffness and stroke, and consequently may open the way for a new approach to AF prevention. This concept has recently been illustrated by the LIFE trial, which showed that the drug regimen producing the most important decrease in left atrial size had the greatest effect at preventing AF (33).

References


