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The influence of arterial stiffness in heart failure: a clinical review

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Vascular aging in large arteries plays an important role in contributing to cardiovascular morbidity and mortality.[1] Structural changes include an increase in wall thickness, intima-media thickening ratio is widely attributed to sub-clinical atherosclerosis and it is independently associated with future cardiovascular events.[1]

The most marked functional change in large arteries with age consists in a real "stiffening". Arterial stiffness, assessed using pulse wave velocity (PWV), is also a strong independent predictor of cardiovascular events;[1] it plays an important role in terms of age-related increase in systolic blood pressure and pulse pressure,[2] which are both components of blood pressure closely associated with cardiovascular risk in middle-aged or elderly subjects.

The aetiology of arterial stiffening should be related to degenerative/calcified processes; conversely, the thickening of the walls should be much more related to the atherosclerotic processes. However, it is not clear in which way both processes are correlated and deranged. Recently, the Consensus Document[3] on the ventricular-arterial coupling in cardiac disease, recognized PWV as the gold standard non-invasive examination able to study the large arterial stiffness. Furthermore, the document explored the meaning of arterial stiffness in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), considering extremely useful the analysis of the ventricular-arterial coupling in managing therapy.

The aim of this review consists in analyzing the clinical meaning of the arterial stiffness in heart failure patients.

THE PULSE WAVEFORM ANALYSIS AND PWV MEASUREMENT: CENTRAL BLOOD PRESSURE MEASUREMENT AND PULSE VELOCITY

The measurement of arterial stiffness parameters was normally evaluated using non-invasive diagnostic tools for the clinical evaluation of central arterial pressure. The devices normally deduce the central wave-shaped aortic pressure from the pulsations of the brachial artery cuffs. The pulse waveform analysis provides key parameters that include central systolic pressure, central pulsation pressure and arterial stiffness indices, such as increased pressure and increased index.[4–6] The reflected wave causes a visible notch (inflection point) and an rise (augmentation) in late systolic pressure (Figure 1). Augmented pressure (AP), expressed in mm Hg, is calculated, as the increase in blood pressure, following the inflection point and is partially related to the effects of wave reflection on the aortic blood pressure curve.[4] The augmentation index (AI) is the ratio between the augmentation pressure and the pulse pressure and it is typically expressed as the percentage. The growth in central systolic blood pressure and the increase indices have been reported as indicators of cardiovascular risk. Measurements ought to be performed on a supine patient in a quiet environment, having avoided smoking in the hour before the examination or abusing vasoactive substances (coffee) and having kept intact its pharmacological therapy. The heart-rate adjusted augmentation index (AIx75) was measured at the level of the carotid artery by obtaining ten high quality pulse wave measurements with automatic

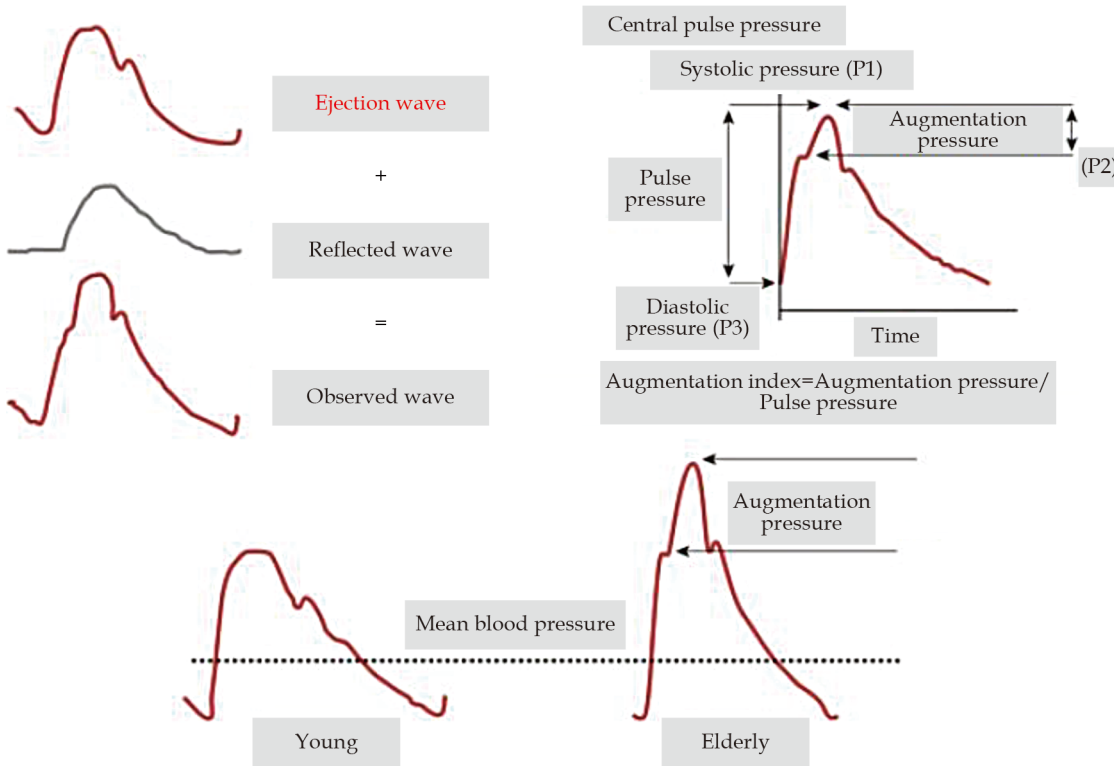

Figure 1 The curves of blood pressure and their components.

calculation of AIx, using the manufacturer's proprietary software and after normalizing to a heart rate of 75 beats per minute.[7] It represents the pressure boost that is induced by the return of the reflected waves at the aorta.

The measurement of the wave velocity of the pulse waveform of the arterial pulse moves from the descending aorta to the femoral artery. The velocity of the arterial pulse wave is detected by the carotid and femoral arterial impulses simultaneously measured in a non-invasive manner. It is considered the gold standard metric of aortic stiffness.[4–6] The carotid pulse is measured through the tonometer, while the femoral pulse is measured through the pulsations with a cuff placed around the thigh. PWV values in normal ranges depend on the age of the examined subjects, but can be considered within 9–10 m/s. Obviously, an increment in the wave velocity of the carotid and femoral impulses indicates an increase in aortic stiffness, or a damage to the target organ. The 2018 European Society of Cardiology Guidelines underlined as a threshold of 10 m/s for PWV was reported as clinically correlated to an increased cardiovascular risk.[8]

THE INFLUENCE OF ARTERIAL STIFFNESS IN HEART FAILURE

Nowadays, the role of the aortic stiffness values in heart failure (HF) patients is under debate. Moreover, the prognostic meaning of different degree of PWV/AIx75 in those patients has not been elucidated yet.

Data coming from the Health ABC Study,[9] that followed for more than eleven years 2,290 subjects, demonstrated as the determination of PWV after additional adjustment for other traditional risk factors has not been statistically associated with the risk of developing systolic or diastolic HF.

Besides, in fifty young advanced systolic HF patients a neutral effect by PWV in predicting cardiac death/hospitalization for HF emerged, concluding as the determination of PWV did not add value to a traditional/strong prognostic markers; as invasive cardiac output, pulse pressure (PP) and age.[10]

In their clinical review, Weber and Chirinos[4] recently highlighted that central pressure and wave reflections are both related to the left ventricular late systolic afterload, ventricular remodelling, diastolic dysfunction and the risk of new-onset HF.

Wave reflections increase the ventricle load in the last part of the systolic cycle, which might cause left ventricle remodeling and myocardial dysfunction. The effect of wave reflection on myocardial load is modulated by contraction pattern and the time course of myocardial wall stress. Left ventricles in which the mid-systolic shift in the pressure-stress relation is impaired (due to a reduced ejection fraction, concentric geometric remodeling and/or reduced early systolic ejection fraction) fail to protect cardyomyocities against the load induced by wave reflections in late systole, a period of vulnerability to load. This may represent a vicious cycle that might determine the development and progression of HF (Figure 2).[6] Furthermore, left ventricular hypertrophy, a marker of organ damage in hypertension, is an important intermediate step from hypertension to HF.[11] Left ventricular mass seemed to be more correlated to PP than to mean arterial pressure, confirming the importance of the pulsatile phenomena and the measurement of it.[12] In advanced HFrEF patients, a low brachial PP is due to a poor left ventricle function and has been associated with a worse prognosis. In less severe degree of HFrEF, PP seemed to be more reflective or arterial stiffness, increased pulsatile afterload worsening the hemodynamic conditions. In acute decompensation patients, Sung, *et al.*[13] demonstrated the adverse prognostic value of wave reflections in 80 acute HF patients in a short-term follow-up (six months). Regnault, *et al.*,[14] in the EPHESUS study, studying 306 post-myocardial infarction HF patients with systolic dysfunction [left ventricular ejection fraction (LVEF) < 40%] showed as an higher PP correlated with a lower events rate as well as an increased PWV was associated with a negative prognosis. Similarly, the measurement of PWV, as an expression of arterial stiffness, has been associated with an increment of HF hospitalization and cardiovascular mortality in chronic, stable HFpEF.[15] Nägele, *et al.*[7] in 74 stable HF patients documented a significant increase in PWV in HF patients in comparison to healthy controls and cardiovascular risk factor (CVRF) patients, not evidencing, however, none difference in AIx75 between groups ($P = 0.51$ and $P = 0.9$, respectively). More recently,[16] we documented in 59 HF patients as PWV proved to be different in comparison with CVRF/healthy population. Moreover, with similar age, CVRF subjects had higher brachial systolic pressure and central systolic pressure than HF patients, that might influence the result obtained for PWV, confirming the strict dependence of PWV on central/brachial blood pressure. PP is a parameter determined by cardiac function and arterial stiffness through wave reflections. Large-artery stiffness, influenced by aging, diabetes mellitus, atherosclerosis and renal failure, is the main determinant of PP. In our clinical experience, central/brachial PP was not different in the three population, confirming the results of Regnault, *et al.*[14]

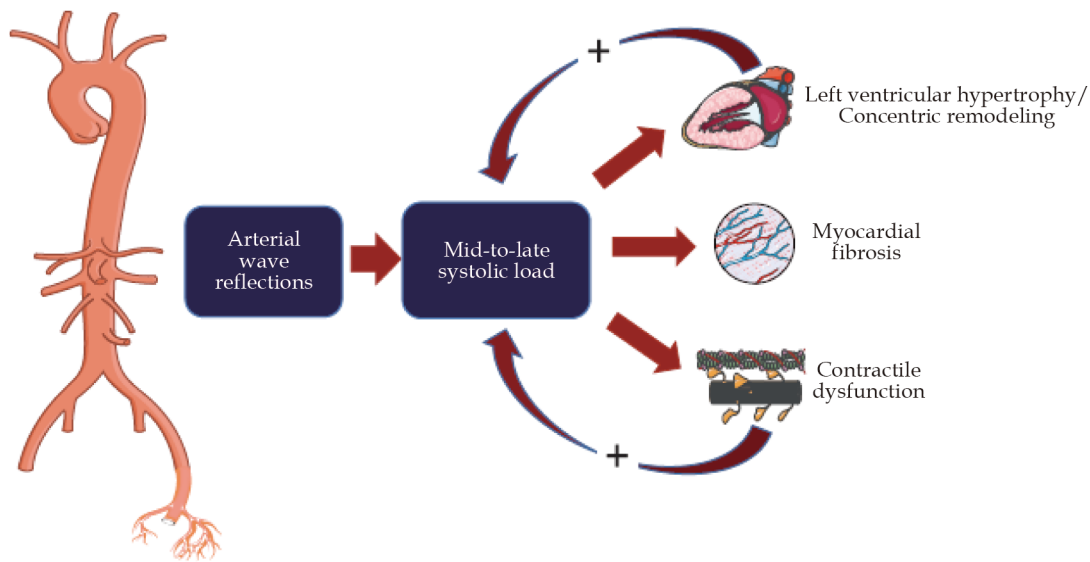

Figure 2 Wave reflections increase late systolic ventricle load, which might determine left ventricle remodeling and myocardial dysfunction. Modified from Chirinos, *et al.*[6]

in which PP being negatively associated with prognosis, but should not be considered a marker of aortic elasticity for its dependence to left ventricular function.

Furthermore, a significant difference in the values of AIx75 between the group of HF patients versus CVRF and healthy group emerged (22% *vs.* 34% and 32%, respectively), being significantly reduced in the decompensated patients. The possible explanation should be researched in the formula that determines the AI (augmentation pressure/pulse pressure). According to this formula, we deduce that a lower ratio is determined by the variations in the numerator or denominator value. Since the denominator (pulse pressure) is similar in the two groups (55 mm Hg in the HF group, 60 mm Hg in the CVRF group), it can be hypothesized that what decreased was the augmentation pressure in the HF patients. These data allow hypothesizing that the reduction/delay of the arrival of the reflected wave could enter into the determinism of the left ventricular remodelling, since the arrival of the reflected wave creates an additional obstacle to the ejection of the left ventricle. Besides, considering our results, in the HF patients, more than the PWV, should be measured the AIx75, in order to evaluate the systolic delay of the wave reflections. Finally, in HFpEF patients, Chirinos, *et al*.[17] recently demonstrated a distinct phenotypic profile in diabetic versus non-diabetic patients, with pronounced aortic stiffening. In fact, the difference in PWV was calculated in 3 m/s respect the non-diabetic counterparts that seemed to be equivalent to several decades of aging in the arterial tree. According to the presence of an adverse pulsatile hemodynamic profile and the presence of more pronounced left ventricle hypertrophy, diabetes mellitus should be considered a determinant of left ventricle structure and arterial stiffness in HFpEF patients.

THE STRICT LINKAGE BETWEEN RENAL FUNCTION, ARTERIAL STIFFNESS AND HEART FAILURE

It is well known that the renal dysfunction is one of the strongest predictors of adverse outcome in admitted[18] or ambulatory HF patients[19] . In admitted HF patients, the ADHERE registry highlighted that in-hospital mortality risk increased considerably in patients with urea nitrogen ≥ 43 mg/dL and plasma creatinine ≥ 2.75 mg/dL, being the renal dysfunction together with systolic blood pressure an essential part of the ADHERE risk tree stratification.[18] In out-patients with HF followed in dedicated clinics, urea nitrogen and serum creatinine are significantly correlated with cardiac deaths and hospital readmissions at 6-month follow-up (r = 0.35, P = 0.0001; r = 0.27, P = 0.0001, respectively).[19] On the other hand, renal failure as well as aging, are two of the main determinants of the arteriosclerosis characterized by direct structural changes including elastin fragmentation and medial calcification that increased the arterial stiffness.[20] In renal failure, indeed, a combination of active process adding a reduction in calcification inhibitors occurred, deranged calcium and phosphate metabolism and determining a calcification of intima and media of the vessel wall.[20] The results coming from the Chronic Renal Insufficiency Cohort (CRIC) Study[21, 22] demonstrated the validity of the PWV measurement in chronic renal disease patients and the predictive value at 5-year follow-up. In the CRIC population, the quartile of participants presenting a PWV of 10.3 m/s underwent to end-stage renal disease with a 37% of increase in comparison to patients with a PWV of 7.7 m/s even after adjustment for demographic, mean artery blood pressure and diabetes. The hypothesizing mechanism seemed to be related to the penetration of the energy within the pulse wave deeply into a low-resistance tissue like the kidney where the excess of energy might be transmitted into pressure-sensitive tissue like the glomerulus resulting, at the end, in a loss of function.[23] Furthermore, the meta-analysis of Sidibe, *et al*.[24] clearly evidenced as arterial stiffness, measured with PWV, and wave reflection, calculated with AIx, ameliorated in end-stage renal disease after 3–12 months successful renal transplantation. Moreover, in renal failure patients, evaluation of PWV in 150 non-dialysis renal disease patients, demonstrated an early onset of elevated aortic stiffness and increased rate of progression over a year in those patients in comparison to non-renal disease patients.[25]

Although the CRIC Study did not enrol HF patients, the most common non-fatal cardiovascular

outcome resulted hospitalization for HF.[22] The hazard ratio for the risk of hospitalization for HF proved to increase from 1.95 in the lowest tertile of PWV (< 7.8 m/s) to 3.01 for the higher tertile (> 10.3 m/s) as far as the tertile of central blood pressure > 50.8 mm Hg demonstrated an augmented risk of 2.45 times.[23] Moreover, data coming from the same CRIC Study[26] confirmed, as even after adjustment for multiple confounders, PWV remained an independent predictor of HF hospitalization together with brachial systolic pressure and PP.

In our previous experience,[16] based on data coming from fifty-nine HF patients, PWV demonstrated a positive moderately significant correlation with creatinine (r = 0.33, P = 0.01), red blood cell distribution width (r = 0.31, P = 0.02), N-terminal pro B-type natriuretic peptide (r = 0.28, P = 0.049), brachial systolic pressure (r = 0.33, P = 0.01), central systolic pressure (r = 0.29, P = 0.02) and a negative moderately significant correlation with estimated glomerular filtration rate (r = −0.40, P = 0.002). The AIx75 showed a positive, weakly significant correlation with creatinine (r = 0.27, P = 0.04), sodium (r = 0.28, P = 0.04), central PP (r = 0.43, P = 0.001) and a negative significant correlation with estimated glomerular filtration rate (r = −0.33, P = 0.01). Dividing our population according LVEF (HFrEF = 30/59 pts, mid-range HF = 16/59 pts and HFpEF = 13/59 pts, respectively), the median of PWV (10.8 m/s, 10.1 m/s and 10.5m/s, respectively) and the AIx75 (21%, 24.5% and 25%, respectively) did not change significantly (P = 0.7 and P = 0.6, respectively) among subgroups. The analysis of PWV and AIx75 divided for left ventricular diastolic function (0 = normal, type 1–2–3) did not show significant differences (P = 0.45 and P = 0.73, respectively) as well. The strongest correlation was revealed between the values of PWV/AIx75 and the value of renal filtrate. This data confirms that the presence of renal failure plays an important role in the development of both HF and vascular damage even with an increase in aortic stiffness.

Finally, in the meta-analysis of Vlachopoulos, *et al.*,[27] based on seventeen studies (18,777 patients followed for more than seven years), confirmed the strong predictive value of PWV in evaluating total mortality and cardiovascular events underlining as the predictive value of PWV proved to be larger in subjects with renal disease. More precisely, for an increase in aortic PWV of 1 m/s, the risk of development cardiovascular events or died increase by more than 10% to 40%, according to the presence of higher risk disease state (as renal dysfunction).

CONCLUSIONS

In conclusion, it can be affirmed that in HF patients the influence of arterial stiffness should be clarified yet. In previous clinical experience, PWV and the value of AIx could be considered in the determinism of HF. However, in severe degree of systolic HF, the reduction of cardiac output might reduce the role of PWV in predicting prognosis in those patients. Brachial/central PP should not be considered a marker of aortic elasticity in HF patients. In the search for a prognostic meaning in HF patients, aortic stiffness seems to be particularly related to renal dysfunction and extremely important in the prognostic setting.

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