The presence of left atrial (LA) dysfunction is linked to the development of both heart failure and atrial fibrillation (AF). Hypertensive heart disease is an important contributor to both LA dysfunction and AF, and hypertension is present in between 50% and 90% of patients in AF trials. In the early phases of hypertension, LA conduit function is impaired, and there is compensation by increased booster function. Although the association of LA dysfunction with heart failure may be mediated through left ventricular (LV) systolic and diastolic dysfunction, the eventual loss of booster function because of AF is an important precipitant of heart failure. Consequently, it seems logical that controlling hypertension and its LV consequences may be a factor in the prevention of AF. Specifically, because LA dysfunction, wall stretch, and enlargement are a consequence of disturbances of LV hemodynamics, a better understanding of the LV systolic–diastolic coupling may have an important role in protecting the LA.

The historical approach to LV wall stress was that it reflected systolic pressure, wall thickness, and ventricular dimensions. However, this was a simplification of the contributors to wall stress, including failure to account for ventricular shape, tissue properties, and especially the time course of systolic pressure. Exposure of the LV to late systolic load has effects on LV shape, which in turn may be an important interactive link between LV systole and diastole. A recent literature has linked the timing of wall stress to diastolic dysfunction in both community and hypertension-based populations. The implication is that it is inaccurate to calculate systolic wall stress at a single time point.

In this issue of Circulation: Cardiovascular Imaging, Chirinos et al from the University of Pennsylvania have taken the next step, in providing evidence that an abnormal myocardial loading sequence is a contributor to LA dysfunction. In a study of 260 hypertensive patients and 19 normotensive age- and sex-matched controls, information from cardiac magnetic resonance was combined with arterial waveform analysis using carotid tonometry to provide time-resolved ejection-phase myocardial wall stress, based on LV volumes, mass, and aortic flow from phase contrast imaging. LV wall stress was integrated early and late during systole as an index of the temporal variation of myocardial load.

As expected, in comparison with normotensive controls, the ratio of LV wall stress during late to early ejection was greater in the hypertensive group, who also showed a reduction of LA conduit and reservoir function. Tertiles of the ratio of late to early LV wall stress were associated with reduction of LA booster pump function only in the group with the greatest ratio between these entities, whereas reservoir function showed progressive reduction with increasing degrees of late systolic wall stress. Interestingly, LA volume was not significantly different between the tertiles. The presence of peak myocardial wall stress in early systole was associated with better LA function, whereas late systolic wall stress was associated with impairment of LA function. These findings are consistent with experimental and human data showing late systolic load to be associated with a reduction in the rate of fall of LV pressure.

The methodologies used in this study were highly appropriate. Cardiac magnetic resonance allows excellent-quality imaging of the LA and permits feature tracking to measure reservoir, conduit, and booster pump function from atrial strain. The excellent contrast resolution of this modality seems to compensate for the lower temporal resolution than echocardiographic assessment of strain, and this approach seems to be robust. Carotid tonometry offers an estimate of pressure loading over time that cannot be obtained using conventional cuff blood pressure, although the analogy of the arterial pressure profile in the carotid artery and ascending aorta (which is the loading faced by the myocardium) is susceptible to inter-individual differences in systolic blood pressure because of amplification from the aorta to peripheral arterial beds. The only way of avoiding this would be to use invasive blood pressure, which is impractical. Similarly, because of the incompatibility of tonometry equipment with the magnetic field, these measurements were performed in close temporal association, rather than simultaneously with cardiac magnetic resonance.

The observations from this study are important for clinicians at several levels. First, it is a reminder that although LA volume is prognostically important, functional abnormalities are a prelude to adverse remodeling. Thus, assessment of LA function is more sensitive and adds incremental prognostic information to the measurement of LA volume. Indeed, among 971 subjects enrolled in an echocardiographic substudy of the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48), increasingly abnormal LA structure and function were associated with a greater burden of AF and higher stroke risk, but LA dysfunction was present in patients in sinus rhythm, despite the presence of normal LA size. The adaption of strain measurement to the atrium has
increased the feasibility of LA function measurement. The use of this technique provides not only a means of quantifying LA dysfunction but also other parameters such as mechanical dispersion, which may provide evidence of atrial scarring, which is thought to contribute to recurrent AF after ablation.

Second, these results may help us to better understand the efficacy of antihypertensive therapy and risk of AF. Meta-analyses of randomized controlled trials have shown both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are effective in the prevention of AF. Studies showing lack of benefit have generally had an explanation for the observed difference, varying from confounding by higher blood pressure in the treated group, problems with dosing, and discontinuation of the active agents in the course of the trial. Finally, the impact of renin–angiotensin–aldosterone inhibition on the reduction of incident AF was confirmed in the Danish population from 1995 to 2010. These investigators matched patients on monotherapy with angiotensin-converting enzyme inhibitors or angiotensin receptors blockers, β-blockers, diuretics, or calcium antagonists. Hypertensive patients with other diseases predisposing to AF (heart failure, ischemic heart disease, diabetes mellitus, and hyperthyroidism) were excluded. They found that the use of angiotensin-converting enzyme inhibitors and angiotensin receptors blockers were more effective than β-blockers for reducing incident AF, with respective hazard ratios of 0.12 and 0.10, as well as more effective than diuretics (hazard ratio, 0.51 and 0.43) and calcium antagonists (hazard ratio, 0.97 and 0.78). Although these effects have previously been attributed to direct effects on angiotensin I and II receptors in atrial myocardium, it is also conceivable that the AF prophylaxis effect of angiotensin-converting enzyme inhibitors is through their effects on vascular function and unloading of central systolic stress that may not be detectable using standard cuff measured blood pressure.

Third, the results of this study are a reminder of the importance of not only the level of blood pressure but the morphology of the central arterial pressure waveform. Time-varying wall stress is associated with ventriculo-arterial interaction, which has been attributed to wave reflection. However, this remains controversial, and the effect may simply relate to the balance of flow into and out of the aortic reservoir, with a dominant influence of forward (rather than reflected) wave energy. Instantaneous myocardial afterload increases when the resistance to outflow (dependent on multiple factors including peripheral resistance) exceeds inflow (determined by stroke volume and aortic compliance). Various vasoactive agents have effects on ventriculo-arterial interaction, with nitrates exerting their effect through changes in either ventricular ejection or lowering of central aortic blood pressure. Although the effect of nitrates in heart failure with preserved ejection fraction has proven disappointing, there is specific evidence of nitrite effects on conduit arteries. However, the encouraging findings that are being reported with nitrite administration may be counterbalanced by the inconvenience of delivering these agents through parenteral or inhaled techniques.

The recent literature shows increasing evidence that the time course of LV afterload is an important determinant of LV wall stress and, therefore, of systolic–diastolic coupling. This evidence provides clues about how we might more effectively prevent atrial dysfunction, which may impact on heart failure with preserved ejection fraction and AF. What we now need are more effective tools to favorably influence ventriculo-arterial coupling.

Disclosures
None.

References


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