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CONSENSUS DOCUMENT

The role of ventricular–arterial coupling in cardiac disease and heart failure: assessment, clinical implications and therapeutic interventions. A consensus document of the European Society of Cardiology Working Group on Aorta & Peripheral Vascular Diseases, European Association of Cardiovascular Imaging, and Heart Failure Association

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[Correction added on 21 March 2019, after first online publication: the spelling of Patrizio Lancellotti's name was corrected.]

Ventricular−arterial coupling (VAC) plays a major role in the physiology of cardiac and aortic mechanics, as well as in the pathophysiology of cardiac disease. VAC assessment possesses independent diagnostic and prognostic value and may be used to refine riskstratification and monitor therapeutic interventions. Traditionally, VAC is assessed by the non-invasive measurement of the ratio of arterial (Ea) to ventricular end-systolic elastance (Ees). With disease progression, both Ea and Ees may become abnormal and the Ea/Ees ratio may approximate its normal values. Therefore, the measurement of each component of this ratio or of novel more sensitive markers of myocardial (e.g. global longitudinal strain) and arterial function (e.g. pulse wave velocity) may better characterize VAC. In valvular heart disease, systemic arterial compliance and valvulo−arterial impedance have an established diagnostic and prognostic value and may monitor the effects of valve replacement on vascular and cardiac function. Treatment guided to improve VAC through improvement of both or each one of its components may delay incidence of heart failure and possibly improve prognosis in heart failure. In this consensus document, we describe the pathophysiology, the methods of assessment as well as the clinical implications of VAC in cardiac diseases and heart failure. Finally, we focus on interventions that may improve VAC and thus modify prognosis.

Introduction

The important role of ventricular−arterial coupling (VAC) in the physiology of cardiac and aortic mechanics, as well as in the pathophysiology of cardiac disease has long been recognized. Despite its complexity, several invasive and non-invasive methods have been developed to measure VAC. In this consensus document, we describe the pathophysiology of VAC impairment and the mechanisms that can affect arterial and cardiac function and their relation. Traditional VAC assessment methods are presented, together with novel approaches. Furthermore, we analyse the clinical implications of VAC in arterial hypertension, systemic inflammatory diseases, coronary artery disease (CAD), valvular heart disease, and heart failure (HF). Finally, we focus on invasive and non-invasive interventions that may improve VAC.

Pathophysiology of ventricular−arterial coupling

Heart−vessel coupling is constantly changing to match ventricular end-systolic and arterial elastances, a concept that finds its origins in the pressure−volume (P-V) cardiac function analysis as assessed by cardiac catheterization.[1] By connecting all end-systolic points of a family of P-V loops obtained during various loading conditions, the so-called 'end-systolic pressure−volume relation' (ESPVR) line is retrieved (*Figure 1A*).[1] Suga and Sagawa[1] found this relation to be roughly linear within physiologic ranges, sensitive to inotropic changes, and insensitive to afterload, while the respective line slope has been termed as end-systolic elastance (Ees). Conceptualising the left ventricle as a closed volume, Ees represents the necessary intracavitary pressure to increase its volume by one unit.[1] The intersection between the ESPVR (upper left-hand corner of the P-V loop) and a line drawn from the end-diastolic volume on the horizontal axis identifies a second line. The respective slope represents the end-systolic pressure to stroke volume (SV) ratio, termed as effective arterial elastance (Ea) (*Figure 1B*). It has been shown,
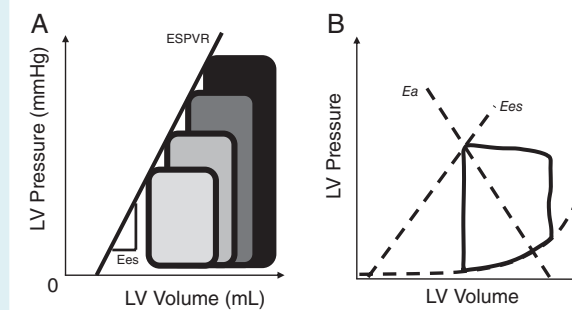

Figure 1 (*A*) Left ventricular (LV) end-systolic elastance (Ees) estimated by pressure−volume loop family, end-systolic point line. By connecting all end-systolic points of pressure−volume loops obtained during various loading conditions, the so-called 'end-systolic pressure−volume relation' (ESPVR) line is retrieved. (*B*) LV Ees estimated as the end-systolic pressure/end-systolic stroke volume ratio and arterial elastance (Ea) estimated as the end-systolic pressure/stroke volume ratio are used to calculate Ea/Ees ratio as a marker of ventricular−arterial coupling using a single pressure volume loop.

based on mechanoenergetic grounds, that stroke work generation is maximal when the Ea/Ees ratio equals 1, while maximal cardiac efficiency is achieved when the Ea/Ees ratio equals 0.5.[2]

Ventricular−arterial stiffening amplifies the elevation of blood pressure (BP) induced by exercise or mental stress and this may further worsen left ventricular (LV) diastolic function and increase cardiac energy costs to provide an adequate output.[3] This may exacerbate the effect of the systemic load on LV diastolic function and elevate cardiac metabolic demand, as well as LV diastolic filling pressures under stress causing HF symptoms, further compromising myocardial reserve in the long term.[3,4]

Although the P-V analysis (*Figure 1B*) provides useful information regarding the operating mechanical efficiency and performance of the ventricular−arterial system when LV ejection fraction is frankly
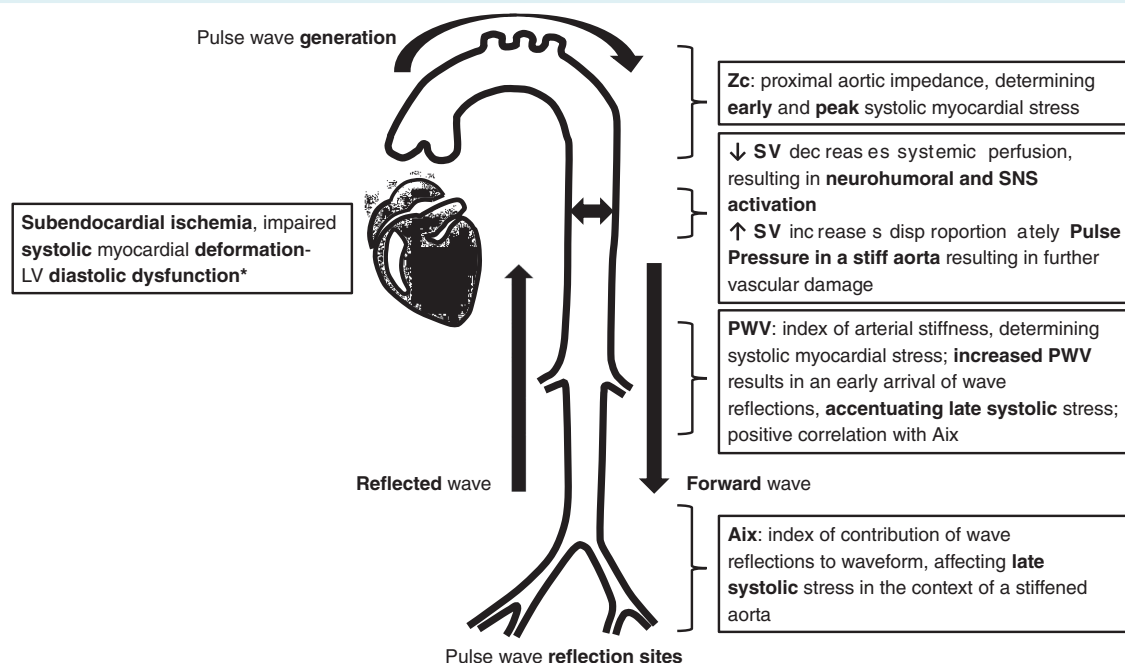
Figure 2 Vascular mechanisms that lead to impaired left ventricular (LV) function. Aix, augmentation index; PWV, pulse wave velocity; SNS, sympathetic nervous system; SV, stroke volume.

abnormal, it is less informative in HF with preserved ejection fraction (HFpEF), as discussed later.

Effects of arterial function on left ventricular structure and performance

The heart ejection generates forward pressure and flow waves, transmitted down the arterial tree, giving rise to reflections which, in a stiffened aorta, arrive early in systole instead of diastole and, thus, increase central systolic BP and reduce diastolic BP, a key determinant of the coronary perfusion gradient.[4] The increase in afterload increases myocardial oxygen demand, and the reduction in coronary perfusion pressure decreases oxygen delivery creating conditions of myocardial ischaemia, further deteriorating LV systolic and diastolic performance (especially during exercise).[4] Furthermore, reflected waves increase late systolic load relative to early systolic load, which has deleterious effects on the myocardium.

In general, arterial load can be expressed as the combination of steady and various pulsatile components. The steady component of afterload (i.e. total peripheral resistance) depends largely on microvascular properties. Pulsatile LV afterload is, in contrast, predominantly influenced by the properties of conduit vessels. Key parameters of pulsatile LV load include the characteristic impedance of the proximal aorta (Zc), the magnitude and timing of wave reflections, and the total compliance of the arterial tree ('total arterial compliance') (for definitions see section 'Markers of arterial function').

Arterial load (arterial compliance, total vascular resistance index, and wave reflections measured in the ascending aorta) and

stiffness [pulse wave velocity (PWV)] are closely related with LV diastolic function, LV mass, and myocardial deformation [e.g. global longitudinal strain (GLS)].[5–8] In fact, LV diastolic dysfunction, LV hypertrophy, abnormal myocardial deformation, and increased aortic stiffness share many epidemiological and pathophysiological features: they predominate in elderly subjects and hypertensives, have a predictive value for morbidity and mortality, and share underlying biochemical mechanisms of remodelling (collagen deposition, increased cellular stiffness, production of advanced glycation end-products in diabetes mellitus). Furthermore, impairment of coronary flow reserve is associated with increased arterial stiffness and myocardial dysfunction in hypertension, inflammatory diseases, and CAD.[6]

Carotid to femoral PWV (cfPWV), aortic characteristic impedance (Zc), and the magnitude and timing of wave reflections during systole summate the impact of arterial load on LV function at systole and diastole[7] that triggers the onset of clinical symptoms,[8] and contributes to cardiovascular events.[9] The vascular mechanisms that may lead to an impaired LV function are summarized in *Figures 2* and *3*. Increased arterial stiffness (as measured by PWV) results in faster pulse wave propagation, earlier reflection and arrival of backward pulse waves during late systole, instead of diastole; thus, early arrival in systole augments central aortic pressure and thus LV afterload and myocardial oxygen demand, and lowers central diastolic arterial pressure and thus coronary perfusion and myocardial oxygen delivery. The imbalance between increased myocardial oxygen demands and reduced coronary perfusion leads to myocardial ischaemia in the absence of coronary stenosis (*Figure 3*).
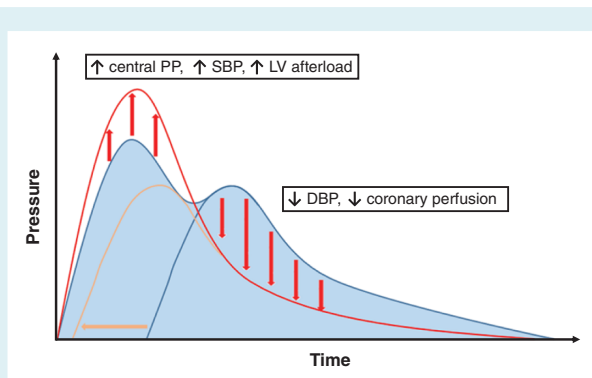
Figure 3 Effects of increased arterial stiffness and the concomitant earlier arrival of wave reflections from the peripheral arteries on central aortic pressure waveform. The pulse wave with blue line indicates augmentation of aortic pressure in diastole by return wave reflections under conditions of normal arterial elastic properties while the aortic systolic component remains unaffected (blue line). The pulse wave with red line indicates augmentation of central aortic pressure in systole by the early arrival of wave reflection (orange line and orange arrow) because of increased arterial stiffness and reduced central diastolic pressure compared to diastolic pressure during the normal (diastolic) arrival of wave reflection (blue line) when arterial elasticity is not impaired. DBP, diastolic blood pressure; LV, left ventricular; PP, pulse pressure; SBP, systolic blood pressure.

Effects of cardiac function on arterial properties

The left ventricle, aortic valve, aorta, and peripheral arteries should be regarded as interdependent organs placed in a series circuit. The principles of complementarity (all compartments contribute additively to afterload) and competitiveness (one compartment cannot be lowered without raising the other one) reflect their interdependence and the common physiological mechanisms that coordinate their function.[10] During systole, a pulse wave is propagated along the aorta to the periphery stretching the arterial wall. Moreover, capacitance vessels distend to accommodate the increased LV SV during exercise. Furthermore, LV SV reduction does lead to neurohumoral and sympathetic activation, also contributing to vascular dysfunction.

Common biochemical pathways determining arterial and cardiac function

Extracellular matrix and cytoskeleton regulation processes are biochemical pathways that concomitantly affect cardiac and arterial structure and function through replacement or reactive fibrosis. Transforming growth factor-β serves as a biochemical coordinator, activating fibroblasts and myofibroblasts. The fibroblast plays a key role in inflammation, proliferation/apoptosis, angiogenesis (induced by growth factors) and upon stimulation by angiotensin II it produces collagen.[11] Under normal conditions, a balance between extracellular matrix synthesis and degradation exists.

Degradation is the task of matrix metalloproteinases. In the presence of disease or with aging, extracellular matrix synthesis gradually predominates, setting the stage for accelerated fibrosis.[12,13] High galectin-3 levels, a marker of myocardial and vascular fibrosis, predicted impaired VAC.[13]

Endothelial-derived nitric oxide, cytokines, oxidative stress proteins and growth factors determine myocardial microcirculatory function, as well as aortic and peripheral vasoreactivity.[14] Moreover, neurohumoral factors including adipokines, leptin, and sex hormones have also been implicated in the process of ventricular–arterial decoupling by affecting LV hypertrophy, vascular wall hypertrophy, and vasoconstriction.[15,16] For example, ventricular–arterial decoupling was associated with impaired LV performance and was attributed to inflammation in septic shock.[17] The above mechanisms act in parallel to modify arterial and cardiac function in adaptive or maladaptive ways.

Key points

- Reflected waves, which arrive in late systole, increase end-systolic stress and impair diastolic function.
- Changes in LV SV affect vascular function.
- Fibrosis, inflammation and oxidative stress are common biochemical pathways linking impaired ventricular–arterial function.

Methods to assess ventricular–arterial coupling

Although VAC is most frequently assessed in the P-V plane by cardiac catheterization, this approach has important limitations (*Table 1*).[2]

Currently, the most widely used echocardiographic method for the determination of Ea/Ees (normal value 1.0 ± 0.36) is the single-beat method developed by Chen *et al.*[18] Although several methods are available, it remains unclear which provides the most reliable results. According to this method, Ees can be calculated non-invasively by the formula:

$$Ees = (DBP - [End\,(est) \times SBP \times 0.9)] /End\,(est) \times SV$$

$$(normal\ value : 2.3 \pm 1.0\,mmHg/mL)$$

where DBP and SBP are diastolic and systolic arm-cuff BPs, End(est) is the estimated normalized ventricular elastance at the onset of ejection, and SV is Doppler-derived stroke volume. End(est) is described by the following formula:

$$End\,(est) = 0.0275 - 0.165 \times EF + 0.3656$$
$$\times (DBP/SBP \times 0.9) + 0.515 \times End\,(avg)$$

where EF is the basal ejection fraction and End(avg) is derived by a complicated formula:

$$End\,(avg) = 0.35695 - 7.2266 \times tNd + 74.249 \times tNd^2 - 307.39$$
$$\times tNd^3 + 684.54 \times tNd^4 - 856.92 \times tNd^5$$
$$+ 571.95 \times tNd^6 - 159.1 \times tNd^7$$

where tNd is the ratio of pre-ejection period to total systolic period.

We note that this polynomial formula uses the ratio of pre-ejection period to total systolic period raised to multiple powers (up to the seventh) such that small variations or errors in the measurements of time intervals will lead to relatively large changes in the estimated Ees value.

Effective arterial elastance (Ea) can be computed using the following formula[3]:

$$Ea = (SBP \times 0.9)/SV \text{ (normal value : } 2.2 \pm 0.8 \text{ mmHg/mL}).$$

However, a simplified formula frequently used to assess VAC is the following:

$$Ea = ESP/SV, Ees = ESP/ESV$$

where ESP is end-systolic pressure, SV is stroke volume, and ESV is end-systolic volume. Thus, $Ea/Ees = (ESP/SV)/(ESP/ESV)$ and then by eliminating ESP:

$$Ea/Ees = ESV/SV, \text{ which equals to } 1/(EF - 1).$$

It becomes readily apparent that the advantage of the Ea/Ees ratio as a method to provide additional insights about the physiologic status of the ventricular−arterial system is blunted, as it becomes a derivative of LV ejection fraction. Thus, the full formula by Chen *et al.*[18] should be used to calculate Ees and then to be divided to Ea in order to obtain an Ea/Ees ratio that accurately reflects invasive Ea/Ees measures.

Three-dimensional echocardiography or magnetic resonance imaging measure LV volumes more accurately than two-dimensional echocardiography and should be preferred for the calculation of LV (or right ventricular) volumes included in the aforementioned VAC estimation formulas.[19] Finally, in several cardiac diseases (e.g. hypertension, inflammatory diseases, or diabetes), the components Ea and Ees may be similarly impaired, providing an Ea/Ees ratio of around 1; therefore, the extent of physiologic abnormalities should be assessed by the absolute value of each component.[2] The advantages and disadvantages, as described in *Table 1*, pertain to both invasive and non-invasive determinations of the Ea/Ees ratio. However, we should acknowledge that cardiac catheterization provides more accurate measurement of Ea and Ees than non-invasive methods while non-invasive methods are applicable for repeated consecutive studies of VAC, e.g. before and after treatment in daily clinical practice. Thus, we propose the simultaneous measurement of arterial and novel myocardial function markers, as described above, that may provide a more accurate estimation of VAC and its changes in disease or after treatment.

Markers of arterial function

Arterial load depends on the properties of small and large arteries. Indices of the properties of large vessels include aortic characteristic impedance (Zc), aortic distensibility, beta stiffness index, and large artery stiffness (estimated by aortic PWV) (*Table 1*). Finally, other indices 'blend' the effect of small and large arteries, such as central systolic BP and pulse pressure, indices of wave reflections (e.g. augmentation index), brachial−ankle PWV, and total arterial compliance.[20]

Regional arterial wall properties

Characteristic impedance of the proximal aorta (Zc) can be intuitively measured as the slope of the pulsatile pressure−flow relation (where pressure and flow are measured in the same point within the artery) in the absence of reflected waves (*Figure 4A−E*). It is a 'local' arterial property and reflects the interplay between inertial effects and the local storage of blood in the proximal aorta and the load initially experienced by the ventricle upon opening of the aortic valve. It can be measured non-invasively. Two-dimensional guided mode echocardiography of the aortic root to assess aortic root diameter changes between systole (AoS) and diastole (AoD) combined with simultaneous sphygmomanometric measurements of the arterial pressure (PP) at the brachial artery has been used to assess aortic distensibility $(2 \times (AoS - AoD)/(AoD \times PP))$,[21] though this index was initially measured invasively. A stiff and narrow aorta leads to high Zc and low aortic distensibility, whereas a distensible, wide aorta to a low Zc and increased aortic distensibility. The local stiffness parameter beta can also be calculated according to the formula $Beta = \ln (Ps/Pd)/(Ds - Dd/Dd)$, where Ps and Pd are systolic and diastolic BP in the brachial artery measured by an automated sphygmomanometer, and Ds and Dd are the maximal and minimal diameters of the right common carotid artery measured by ultrasonic high resolution wall tracking[22] or of the aorta by echocardiography.[21]

Large artery stiffness

Carotid to femoral PWV, which is the velocity of the pulse as it travels from the heart to the carotid and femoral artery, remains the most commonly used non-invasive method and is considered as the 'gold standard'. cfPWV is usually measured using surface tonometry probes at the right common carotid and right femoral artery. The transit time is the time of travel of the wave over these sites. The distance (D) covered by the waves is usually assimilated to the skin distance between these two recording sites; PWV is calculated as $PWV = D/Dt$ (m/s).[20] Brachial−ankle PWV capitalizes on the concept that measurements over a longer arterial length may provide additional information.[20]

Central haemodynamics/wave reflections

Pressure and flow waves are generated with each heartbeat and are propagated towards the periphery where they are reflected backwards, merge with the antegrade wave and amplify it. As a result, peripheral BPs are higher compared to central (aortic) BPs. Central BPs are more relevant than peripheral ones, as the heart, brain and kidneys are directly exposed to them. Central haemodynamic indices are either central BP parameters and derivatives (central systolic BP, pulse pressure, augmented pressure and amplification), or indices that quantify timing and magnitude of wave reflections (obtained by pulse wave analysis in the frequency domain and wave separation analysis). A frequently used central augmentation index is measured non-invasively by arterial tonometry and is calculated as $100 \times$ peak central systolic BP/central pressure at the inflection point and represents the pressure boost that is induced by the return of the reflected waves at the aorta.[20] Central pulse wave recordings are obtained by cardiac catheterization or non-invasively by arterial tonometry or oscillometry devices (*Figure 4A*). Furthermore, the newly developed techniques of pressure−flow (*Figure 4A−E*) and wave separation analysis (*Figure 4F−G*) may offer more insight into the assessment of vascular haemodynamics in various disease states by measurement of both forward and backward compression and expansion pulse wave. Wave reflection assessment by wave separation analysis is based on the principle that reflected waves add to forward pressure and subtract from forward flow distorting the linear relationship between the increase in pressure and the increase in flow that is seen in early systole when the pulsatile pressure−flow relation is governed by aortic root Zc (*Figure 4E* and *G*). Several lines of evidence support the importance of late systolic load from wave reflections

Table 1 Advantages and disadvantages of ventricular–arterial coupling assessment modalities

VAC assessment modality	Advantages	Disadvantages

Ea/Ees	• Widely used with extensive published data
	• Relatively simple and intuitive
	• Characterizes mechanical indices that relate to energetics (only when EF < ∼40%):
	  • External mechanical energy
	  • Potential energy
	  • Energetic efficiency
	• Allows us to discern the determinants of stroke volume and EF
		• Cardiac catheterization for pressure–volume loops
		• Echocardiography provides an approximation of Ea/Ees and its components
		
		Disadvantages of Ea:
		• It is not a pure index of arterial load because it is prominently influenced by heart rate
		• It is mostly dependent on resistance and is insensitive to changes in pulsatile arterial load
		• It is not a measure of arterial stiffness or total arterial compliance
		• Its derivation did not account for wave reflection or transmission
		• It does not discern the temporal pattern of load (loading sequence) which is an important determinant of diastolic dysfunction, maladaptive LV remodelling and heart failure risk
		
		Disadvantages of Ees:
		• Non-linearity of the ESPVR
		• It demonstrates afterload dependency
		• It demonstrates some preload dependency
		• It does not assess myocardial properties (only 'chamber' properties)
		• Little validation of single-beat non-invasive methods beyond the original derivation study
		
		Disadvantages of Ea/Ees:
		• It does not characterize (and neglects) LV loading sequence
		• In HFpEF, it may be normal because both Ea and Ees are increased
		• Ea/Ees derived by the simplified formula (ESV/SV ratio) is related mathematically to EF (1/EF − 1) and thus may not add substantial information to EF measurement

Arterial stiffness markers		
Total arterial compliance	• Assessment of the compliance of the whole arterial tree • Measured non-invasively	• Depends non-linearly on arterial pressure • It is size-dependent • There are systematic differences between different methods, making it difficult to standardize • Required expertise is high • Limited prognostic and therapeutic data
Pulse wave velocity	• Solid pathophysiological background • Can be measured non-invasively in a standardized manner at a low cost, requiring low expertise • Significant prognostic and therapeutic data • Reference values established	• It depends on arterial pressure • It represents a part of arterial system (segmental arterial stiffness)
Central aortic haemodynamics/wave reflections (central SBP, Aix)	• Solid pathophysiological background • Can be measured non-invasively • Prognostic data are available • Reference values established	• Estimations are based on assumptions and algorithms • More prognostic and therapeutic data are needed

Table 1 Continued

VAC assessment modality	Advantages	Disadvantages
Characteristic impedance of the proximal aorta (Zc)/aortic distensibility	• Solid pathophysiological background • It can be measured non-invasively	• It is dependent on blood pressure and aortic size • Increased cost for the equipment • Significant expertise needed for its estimation • Limited prognostic and therapeutic data
Valvulo—arterial impedance (Zva)	• Solid pathophysiological background • It can be measured non-invasively • Prognostic data are available • Reference values are available	• It is dependent on blood pressure and loading conditions • Technical limitations of Doppler echocardiographic measurements of LV stroke volume and pressure gradient

Cardiac function markers

Internal linear dimensions

M-mode	• Reproducible • High temporal resolution • Wealth of published data	• Beam orientation frequently off axis • Single dimension, i.e. representative only in normally shaped ventricles
2D	• Facilitates orientation perpendicular to the ventricular long axis	• Lower frame rates than M-mode • Single dimension, i.e. representative only in normally shaped ventricles

Volume assessment

2D	• Corrects for shape distortions • Less geometrical assumptions compared with linear dimensions	• Apex frequently foreshortened • Endocardial dropout • Blind to shape distortions not visualized in the apical two- and four-chamber planes
3D	• No geometrical assumption • Unaffected by foreshortening • More accurate and reproducible compared to other imaging modalities	• Lower temporal resolution • Less published data on normal values • Image quality dependent

Myocardial function markers

Tissue Doppler imaging	• High temporal resolution • Established prognostic value of E',S' and E/E' • Incorporated in all echo systems • Reference values established	• Angle-dependent, affected by noise • Assessment of longitudinal and radial deformation • Time consuming for strain analysis • Moderate reproducibility/inter and intra-observer variability for strain analysis
Speckle tracking modalities	• Angle-independent • Assessment of longitudinal, radial and circumferential deformation • Assessment of LV twisting—untwisting properties • Established prognostic value for GLS • RV assessment • Pressure—strain loops to assess myocardial work index • Good reproducibility/inter and intra-observer variability • 3D imaging is available • Normal values available	• Vendor dependent • Dependent on good 2D image quality • Limited studies on clinical value of 3D strain and myocardial work index by 2D strain
Time-resolved wall stress curve	• Calculation using a central pressure waveform derived non-invasively and time-resolved LV geometric information derived from echocardiography or cine MRI characterization of the myocardial loading sequence	• Limited studies on clinical value
PWV to GLS ratio	• Established prognostic value for PWV and GLS • Sensitive markers of arterial and myocardial function	• Limited studies on clinical value in hypertensives

2D, two dimensional; 3D, three dimensional; Aix, augmentation index; Ea, arterial elastance; Ees, left ventricular elastance; EF, ejection fraction; ESPVR, end-systolic pressure–volume relation; ESV, end-systolic volume; GLS, global longitudinal strain; LV, left ventricular; MRI, magnetic resonance imaging; PWV, pulse wave velocity; RV, right ventricle; SBP, systolic blood pressure; SV, stroke volume; VAC, ventricular–arterial coupling.
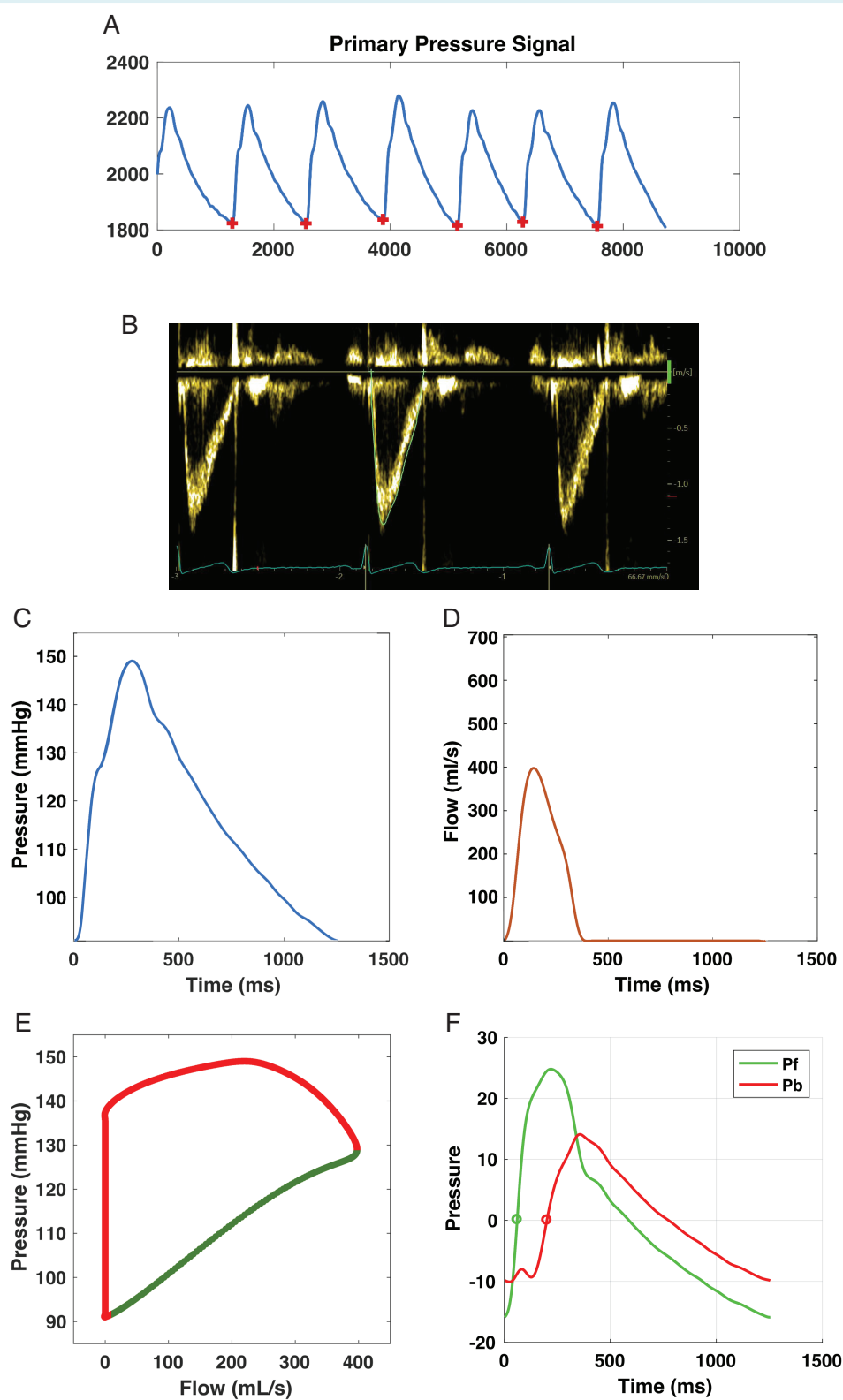
A
Primary Pressure Signal

B

C

D

E
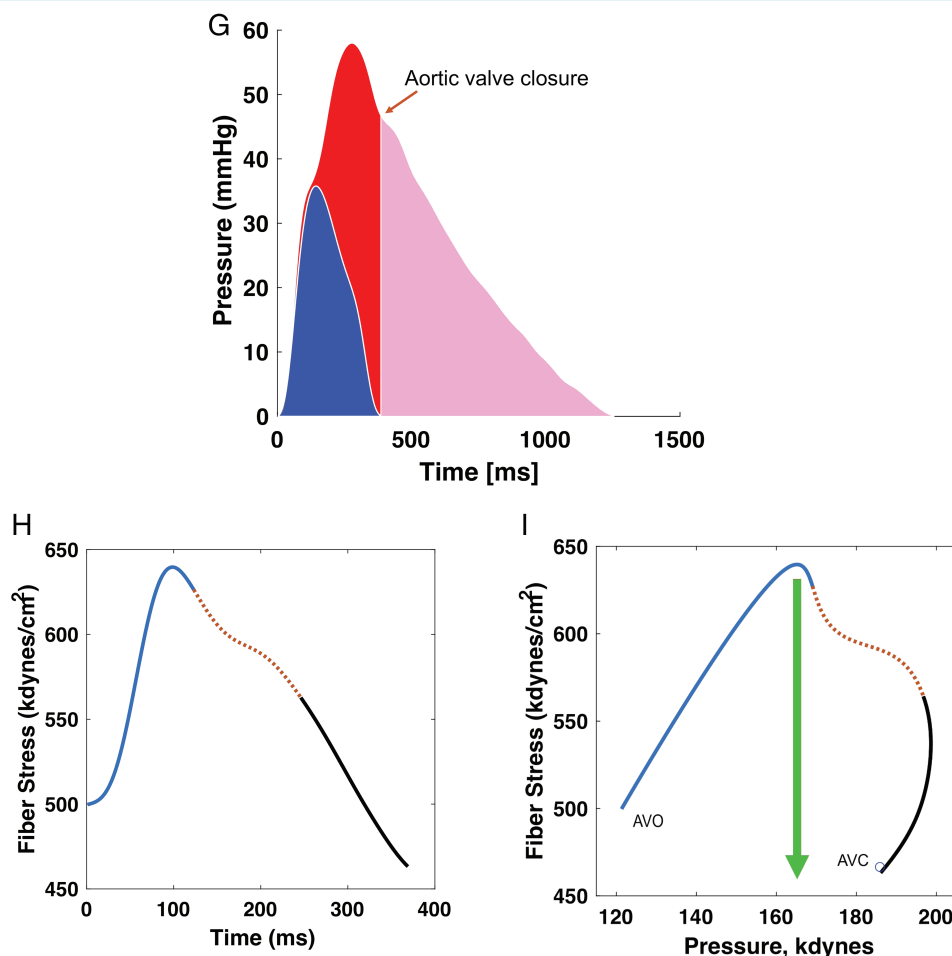
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Figure 4 Analyses of central pressure−flow relations and myocardial wall stress. (*A*) Arterial tonometry recording. (*B*) Pulsed wave Doppler flow velocity recording of the left ventricular outflow tract; this velocity envelope can be multiplied by the left ventricular outflow tract cross-sectional area to obtain volume outflow from the left ventricle, which equals aortic inflow. (*C* and *D*) Signal-averaged pressure and flow waveforms. (*E*) Pressure−flow loop showing the linear early systolic pressure−flow relation (green segment); the slope of this line approximates the aortic characteristic impedance (Zc), which equals the ratio of pulsatile pressure/pulsatile flow in the aortic root in the absence of wave reflections; a deviation (upward shift) from this linear relation occurs upon the arrival of the reflected wave, which increases pressure and reduces flow (red segment in the pressure−flow loop). (*F*) Wave separation analysis which decomposes the pressure waveform into its forward (Pf) because of left ventricular contraction and backward (Pb) components because of wave reflection at peripheral arterial sites (e.g. points of branching or change in arterial wall diameter). (*G*) Measured pressure in systole vs. product of flow time aortic root Zc (blue area) that denotes the pressure in aortic root during left ventricular systolic contraction if wave reflections were absent; the red area denotes the 'excessive' pulsatile pressure because of the arrival of wave reflections from the peripheral arteries, which is above that required to 'accommodate' observed flow through the aortic root if reflections were absent. The early arrival of wave reflections in systole occurs when pulse wave velocity is increased because of a stiff aorta; the pink area represents the diastolic component of the central aortic pulse wave starting after the inflection point that indicates the aortic valve closure (AVC) (arrow). (*H*) Time-resolved myocardial wall stress in the same subject, obtained via a combination of arterial tonometry and speckle tracking echocardiography; myocardial wall stress at each time point during ejection is computed to generate a time-resolved stress curve; notice the early systolic myocardial wall stress peak, with lower values of wall stress during late systole. (*I*) Ejection-phase pressure−stress plot showing that the lower wall stress values in late systole are related to a mid-systolic shift of the pressure−stress relation (green arrow) which favours lower stress values in late systole despite rising pressure. This mechanism may protect the myocardium against wave reflections, but is impaired in the presence of a low ejection fraction or left ventricular concentric remodelling, and may be overcome when there is excessive wave reflection magnitude. AVO, aortic valve opening.

Table 2 Studies presenting the independent value of markers of arterial stiffness as predictors of cardiovascular events and incident heart failure

Source	Year	Population	Design	Parameter	Endpoint	Follow-up duration (median, years)
Chirinos et al.[9]	2012	Primary care population	Prospective observational	PPA, RM	CV mortality and HF incidence	7.6
Aisu et al.[24]	2017	Risk factors for HF	Retrospective observational	PWV	Hospitalization for new-onset HF	4.9
Chester et al.[25]	2017	Primary care population	Prospective observational	RM	Incident HF	11.2
Chirinos et al.[26]	2014	Chronic kidney disease	Prospective observational	PWV, SBP, PP	Hospitalization for new-onset HF	3.5
Ohyama et al.[27]	2017	Primary care population	Prospective observational	PWV	Incident HF	10
Pandey et al.[28]	2017	Primary care population	Prospective observational	PWV	Incident HF	11.4
Said et al.[29]	2018	Primary care population	Prospective observational	ASI, PP	All-cause, CV and non-CV mortality	2.8
Tsao et al.[30]	2015	Primary care population	Prospective observational	PWV	Incident HF	10.1
Feistritzer et al.[87]	2017	Acute STEMI	Prospective observational	PWV	MACCE including incident HF	1.2

ASI, arterial stiffness index; CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; MACCE, major adverse cardiac and cerebrovascular events including death, non-fatal myocardial reinfarction, new-onset congestive HF, and stroke; PP, pulse pressure; PPA, pulse pressure amplification; PWV, pulse wave velocity; RM, reflection magnitude; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

as a determinant of maladaptive LV remodelling, diastolic and systolic dysfunction, and HF risk (*Table 2*).[7–9,12,13]

Normal values for PWV (< 10/ms) and central systolic BP (< 130 mmHg) have been described[23] and their predictive value for incident cardiovascular mortality and HF has been demonstrated (*Table 2*).[24–31]

Numerous methods have been suggested to estimate total arterial compliance based on the Windkessel (elastic reservoir) model; most require both accurate pressure and flow wave recording at the aorta and are hampered by practical and technical (mainly related to complexity), as well as theoretical limitations (including not accounting for wave reflections).[20] The SV over pulse pressure method has been reintroduced recently and it requires accurate and reproducible echocardiographic measurement of cardiac output; however this ratio is shown to overestimate compliance and further standardization of the measurement is required[20] (*Table 1*).

Markers of myocardial performance. Novel echocardiography techniques have permitted the evaluation of myocardial deformation in systole and diastole by use of tissue Doppler imaging, two-dimensional, and recently three-dimensional speckle tracking[32] (*Table 1*). Studies have shown impaired myocardial deformation (e.g. GLS < 20%) in the presence of normal ejection fraction in patients with hypertension, diabetes, CAD, valvular heart disease and HF.[31,33] Myocardial deformation markers have been related with myocardial fibrosis,[34] arterial stiffness,[31,35] natriuretic peptides,[8] exercise capacity,[36] symptoms of HF,[36] and have a prognostic value in valvular heart disease[37] and in HF with reduced and preserved ejection fraction.[2] Thus, these myocardial deformation markers may be surrogate markers of impaired myocardial function.

Novel markers to assess ventricular–arterial coupling. Arterial load should always be interpreted by considering interactions between arteries and the left ventricle as a pump[3,4] and also between myocardial elements and instantaneous LV geometry and the time-varying load imposed by the systemic circulation. Wall stress represents the time-varying mechanical load experienced by the contractile elements

in the myocardium (myocardial afterload) and is related to the amount of force and work the muscle does during a contraction.

In axisymmetric ventricles, average LV myocardial fibre stress can easily be approximated by the formula developed by Arts et al.[38]:

$$Fiber\ \sigma = \frac{P}{\frac{1}{3}\ln\left(1 + \frac{V_w}{V_{lv}}\right)}$$

When assuming rotational symmetry and homogeneity of mechanical load in the wall, the dimensionless ratio of muscle fibre stress [sigma (σ) fiber] to LV pressure (P) appears to depend mainly on the dimensionless ratio of cavity volume (V_{lv}) to wall volume (V_w) (ln denotes natural logarithm) and is quite independent of other geometric parameters.

This method can be applied non-invasively to calculate time-resolved ejection-phase fibre stress using a central pressure waveform and time-resolved LV geometric information (derived from echocardiography or cine magnetic resonance imaging)[2] (*Figure 4A–D*). A time-resolved wall stress curve allows for characterization of the myocardial loading sequence, which can be expressed as a ratio of the stress-time integral in late vs. early systole. A high late-to-early systolic stress time integral ratio has been shown to be associated with reduced indices of myocardial systolic contraction and diastolic relaxation[7,8] and left atrial dysfunction,[31] providing a link between wave reflections and the reported risk of incident HF in the general population[4,9,25] (*Figure 4H–I*).

New echocardiography software construct arterial pressure–LV longitudinal myocardial strain curves by speckle tracking echocardiography and measure the area of the pressure–strain loop, termed as myocardial work index (*Figure 5*). The software calculates the constructive and the wasted myocardial work.[39] Further studies are required to assess the performance of this method for physiologic and clinical evaluations as this method neglects the work performed in the circumferential direction. Shear wave generation using an ultrasonic burst focused on the myocardium is a novel promising assessment method of myocardial elasticity.[40] Finally, the ratio of cfPWV to LV GLS appears to be a novel promising marker to assess VAC in hypertensives.[41]
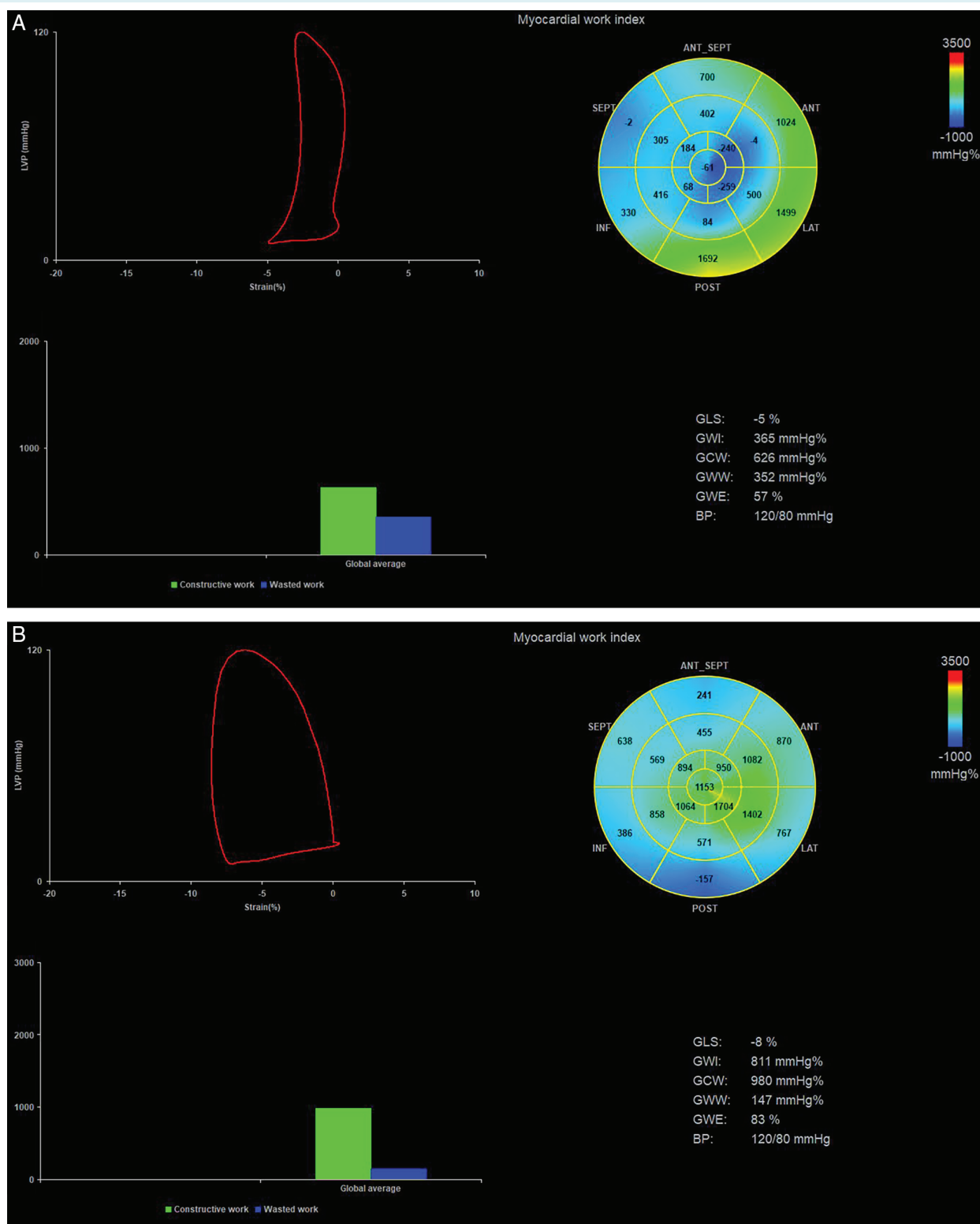
Figure 5 Myocardial work index comprises a novel method of ventricular–arterial coupling estimation derived by pressure–left ventricular longitudinal myocardial strain loop during one cardiac cycle by speckle tracking echocardiography. (*A*) Before and (*B*) after cardiac resynchronization therapy (CRT). Note the larger area of the pressure–strain loop after CRT compared to baseline, indicating an improved myocardial work during systole after CRT. The bull's eye shows the myocardial work index in each one of the 17 left ventricular wall segments. (Echocardiography images provided as courtesy by Dr I. Ikonomidis, Echocardiography Department, Attikon Hospital, NKUA, Athens, Greece).

In summary, the measurement of novel myocardial and arterial function markers may be used to describe and quantify VAC in various disease states.

Key points

- The measurement of novel myocardial and arterial function markers may describe and quantify VAC, particularly if the traditional Ea/Ees approximates 1, despite the suspicion or presence of overt cardiovascular disease (such as in HFpEF).
- Comprehensive assessments of VAC in future studies should include proper measurements of pulsatile load and VAC (wave reflections, Zc, wave intensity and wave power analyses), rather than relying entirely on P-V analyses.
- Other novel markers, such as myocardial work index, may be informative and compensate for some of the classic method limitations, but further clinical evidence of the utility of this approach is required.

Clinical implications of ventricular–arterial coupling

Ventricular–arterial coupling in hypertension, diabetes, and systemic diseases

The association between myocardial and arterial function markers has been used to describe and quantify VAC in hypertension,[41,42] diabetes,[43] and inflammatory diseases.[44,45] More specifically, combined ventricular and arterial stiffening has been demonstrated in HFpEF patients and hypertensives.[3] The investigators found an inverse correlation between total arterial compliance and Ees, independently of body surface area and SV. Additionally, both hypertensive and HFpEF patients had reduced Ea/Ees (<0.6) compared to healthy controls.[3,42]

Furthermore, in untreated patients with arterial hypertension, central augmentation index (measured by arterial tonometry) and aortic distensibility have been related with abnormal markers of LV diastolic function as assessed by Doppler echocardiography,[45] while PWV has been associated with E/E' and E'/A' as assessed by tissue Doppler imaging.[46]

Moreover, an interrelation between conduit arterial stiffness and subendocardial dysfunction as assessed by tissue Doppler imaging in patients with diabetes, hypertension, or ischaemic dilated cardiomyopathy has been found.[22] Additionally, in a study cohort of hypertensives and diabetics, it has been shown that early diastolic velocity (E') by tissue Doppler imaging varies inversely with Zc, Ea, and PWV.[6] Late systolic load, as assessed by augmentation index and arterial compliance, had the strongest association with E'. Similar associations were found between vascular markers and systolic mitral annulus velocity (S').[7] In morbidly obese subjects, an inverse relationship between isovolumetric relaxation time and aortic distensibility (both assessed by echocardiography) was observed, while weight reduction after bariatric surgery improved BP, aortic distensibility and LV diastolic dysfunction.[47]

In a study including 320 hypertensive patients, increased PWV was found to be related with abnormal LV longitudinal strain, reduced LV untwisting and peak untwisting velocity as assessed by speckle tracking echocardiography.[48] In this study, impaired LV myocardial deformation and untwisting were associated with reduced exercise capacity.[48] Interestingly, increased PWV was also associated with reduced coronary flow reserve,[46] which in turn was related to abnormal myocardial deformation in hypertensives.[48] A similar association between arterial stiffness and myocardial deformation was found in chronic kidney disease patients.[49] Similarly, in the context of type 1 diabetes mellitus, a negative correlation between PWV and left atrial strain has been underlined.[50] Furthermore, in type 2 diabetics, increased PWV and central aortic pressure were associated with impaired LV longitudinal deformation and untwisting before and after 6 months of antidiabetic treatment.[51]

Thus, in hypertension and diabetes there is a close link between arterial stiffness and myocardial deformation, which appears to be a harbinger of HFpEF, if left untreated.

Interventions to improve ventricular–arterial coupling in arterial hypertension

Antihypertensive treatment improved VAC, arterial stiffness, and LV systolic and diastolic function in 527 patients with early stage hypertension.[52] In the above study, changes in the Ea/Ees ratio were inversely correlated with those in ejection fraction, stroke work index, LV efficiency and changes in mitral E/e'. It has also been shown that improved Ea/Ees after 6 months of antihypertensive monotherapy is related with improved LV function and regression of LV hypertrophy, with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and dihydropyridine calcium antagonists having the most favourable effect on this index.[53]

Indeed, the various antihypertensive drug classes have differential effects on pulsatile and central haemodynamics; ACE inhibitors, ARBs, calcium-channel blockers, and some vasodilating β-blockers are more effective in this regard, compared to diuretics and some non-vasodilating β-blockers.[54−56] ACE inhibitors represent the first drug class for which a clear advantage over β-blockers was demonstrated in terms of effects on central BP, arterial stiffness and wave reflections. Also ARBs and dihydropyridines were demonstrated to be able to reduce PWV and improve central aortic haemodynamics.[55,56] Conversely, the majority of studies have shown that diuretics have a neutral effect on arterial stiffness and central haemodynamics.

The differential effects of calcium-channel blockers on arterial stiffness may be related to better prognosis as shown by the CAFÉ-ASCOT study (*Table 3*).[54−56] Evidence showing that an improvement in wave reflection will lead to a reduction in cardiovascular events was provided by the CAFÉ study,[54] where, despite a similar reduction in peripheral systolic BP, a calcium-channel blocker regimen (amlodipine with perindopril added as required) was more effective in lowering central systolic BP, and reduced future cardiovascular events compared to a β-blocker regimen (atenolol with bendroflumethiazide-K as required). It should be

noted that the majority of patients received a combination of amlodipine with perindopril or atenolol with diuretic (only 26% on monotherapy) and thus, the difference in cardiovascular events and central haemodynamics should be related only to treatment combinations and not to individual drugs. Additionally, antihypertensive drug classes that have more pronounced effects on arterial stiffness and wave reflection, are the same that cause significant regression of LV hypertrophy.[55]

The effects of LCZ696 [angiotensin receptor-neprilysin inhibitor (ARNI): sacubitril/valsartan] on aortic stiffness were evaluated in elderly patients with systolic hypertension and pulse pressure > 60 mmHg. At week 12, sacubitril/valsartan reduced central aortic systolic pressure to a greater extent than olmesartan by −3.7 mmHg. After 52 weeks, more patients required add-on antihypertensive therapy with olmesartan (47%) vs. sacubitril/valsartan (32%).[57]

Pulse wave velocity and augmentation pressure were significantly and progressively reduced by renal denervation in patients with resistant hypertension, especially in hypertensive patients with more elevated PWV at baseline.[58] After renal denervation, actual PWV measures were lower than the predicted age- and mean BP-corrected values, suggesting that this intervention might exert BP-independent effects on arterial stiffness. Additionally, renal denervation diminished cardiac systolic work load as evident by shorter ejection duration and reduced systolic BP load after the procedure, suggesting a substantial effect on VAC.

Similarly, in type 2 diabetics, treatment with glucagon-like peptide-1 (GLP-1) caused a greater reduction of PWV, central aortic pressure and wave reflections, and greater improvement of LV longitudinal deformation and LV twisting-untwisting than metformin after 6 months of treatment, likely through reduction of oxidative stress burden as assessed by the reduction of protein carbonyls and malondialdehyde.[51] Indeed, in the above study, the reduction of malondialdehyde after 6 months of GLP-1 treatment was associated with the respective reduction of PWV which, in turn, was related with improved LV GLS.

Key points

- Myocardial dysfunction and vascular stiffness are present in newly diagnosed hypertensives and diabetics.
- Both may contribute to reduced exercise capacity and HF symptoms.
- There are treatment options that may improve both myocardial dysfunction and vascular stiffness and thus improve VAC.

Ventricular–arterial coupling in systemic inflammatory disease

Atherosclerosis, subclinical LV dysfunction, and increased risk of cardiovascular events characterise rheumatoid arthritis (RA), systemic lupus erythematosus, ankylosing spondylitis, psoriasis, gout, and medium- and large-vessel vasculitides.[21,59,60] With regard to VAC, systemic inflammatory processes and oxidative stress may

cause an increase in arterial stiffness, leading to increased Ea in parallel to myocardial stiffening causing an increased Ees.[44]

In a trial examining 80 patients with RA, the investigators demonstrated that reduced systemic arterial compliance was related to reduced LV longitudinal strain and strain rate and abnormal LV twisting and untwisting velocity as assessed by speckle tracking echocardiography.[59] Similarly, an increased PWV was associated with reduced LV longitudinal strain in psoriatic patients.[60] Furthermore, in a patients with Adamantiades−Behcet's disease, reduced aortic distensibility was associated with prolonged deceleration time, an established marker of LV diastolic dysfunction.[21]

Interventions to improve ventricular–arterial coupling in inflammatory disease

Anti-inflammatory treatment has been shown to alleviate ventricular−arterial decoupling. In a double-blind, crossover study of RA patients, injection of anakinra [a recombinant interleukin (IL)-1 receptor antagonist] resulted in improved systemic arterial compliance and systemic vascular resistance, improved E/E', in parallel with improved indices of LV myocardial deformation and twisting as assessed by speckle tracking. Interestingly, the improvement in vascular and myocardial deformation markers was greater in the group of patients with coexisting CAD who showed a higher inflammatory burden.[60] Administration of tocilizumab (an IL-6 antagonist) has been shown to reduce PWV,[61] improve cardiac function, and reduce LV mass in RA.[62] Moreover, anti-tumour necrosis factor-α therapy resulted in reduced PWV after a 3-month follow-up period in patients with inflammatory arthropathy.[63] Additionally, the Physical Activity in RA (PARA) trial has shown that moderate intensity physical activity resulted in increased E/A and a trend towards decreased PWV and augmentation index,[64] suggesting the reversal of ventricular−arterial decoupling. Finally, in psoriatic patients, novel biological agents reduced arterial stiffness, central aortic pressure and wave reflections, and improved LV longitudinal deformation and LV twisting-untwisting within 4 months, through inflammatory and oxidative stress burden reduction.[65]

Key points

- Systemic inflammation concomitantly impairs arterial and myocardial function.
- Anti-inflammatory treatment improves arterial stiffness in parallel with myocardial stiffness contributing to reversal of ventricular−arterial decoupling.

Ventricular–arterial coupling in valvular heart disease

Aortic stenosis

In patients with aortic stenosis (AS), the left ventricle is often facing a double load: a valvular load imposed by AS and an

Table 3 Effect of different antihypertensive drug classes on aortic stiffness, wave reflection and central blood pressure

Antihypertensive drugs	Aortic PWV/aortic stiffness	Wave reflection	Central systolic pressure	Augmentation index	Carotid stiffness
Diuretics	↓/↔	↔	↔	↔↓	↓/↔
β-blockers	↓				
Without vasodilating effects	↓	↓/↔	↓	↓	↔
With vasodilating effects	↓	↓	↑	↑	↓/↔
α-blockers	↔	↓			NA
Calcium-channel blockers	↓				
Dihydropyridines	↓/↔	↓	↓	↓	↓/↔
Non-dihydropyridines	↓	↓			↓
ACE inhibitors	↓	↓	↓↓	↓↓	↓
Angiotensin II receptor blockers	↓	↓	↓	↓	↓/↔
Aldosterone antagonists	↓/↔	↓			NA
Nitrates	↔	NA	↓↓	↓↓	NA

ACE, angiotensin-converting enzyme; NA, not available; PWV, pulse wave velocity; ↑, increased; ↓, decreased; ↓↓, marked decrease; ↔, no change.
Adapted from Nilsson et al.[55] and Boutouyrie et al.[56]

arterial load caused by a decrease in systemic arterial compliance (or an increase in systemic vascular resistance) in the context of existing co-morbidities (e.g. age, smoking, hypertension, diabetes) (Figure 6).

Briand et al.[66] proposed two practical indexes, systemic arterial compliance (SAC) and valvulo–arterial impedance (Zva) to assess the effects of aortic wall properties on LV function in AS. SAC index is the ratio of SV indexed to body surface area/pulse pressure: $SAC \cong SVi/PP$. In their study, 40% of patients with severe AS had markedly reduced arterial compliance (SAC index < 0.6 ml/m^2/mmHg) associated with LV dysfunction.[66]

Valvulo–arterial impedance represents the total haemodynamic load opposing LV blood ejection into aorta, combining both valvular and vascular factors, and can be a used as a surrogate marker of VAC. Zva is obtained non-invasively by calculating the LV pressure (sum of systolic pressure and the mean pressure gradient obtained by continuous wave Doppler) divided by SV/m^2: $Zva \cong LV$ pressure/SVi (mL/m^2/mmHg); thus, it represents the cost in mmHg for each systemic mL of blood pumped by the left ventricle during systole. A value > 4.5 mmHg/mL/m^2 indicates a severely increased total afterload. Interestingly, Zva was superior to valve area or gradients to predict outcomes.[62] Finally both $Zva \geq 4.9$ mmHg/mL/m^2 and LV GLS $\leq 15.9\%$ independently predicted outcome in asymptomatic moderate to severe AS (aortic valve area ≤ 0.6 cm^2/m^2) patients.[67]

Arterial hypertension and stiffness may also alter VAC and, thus, accelerate symptoms in AS. In a series of 193 AS patients,[68] symptoms occurred earlier in the subset of hypertensive patients, despite a larger valve area. Moreover, Weisz et al.[69] demonstrated that in patients with moderate to severe AS and preserved LV ejection fraction, increased carotid and aortic stiffness was independently associated with elevated LV filling pressures, B-type natriuretic peptide (BNP) levels, and symptoms.

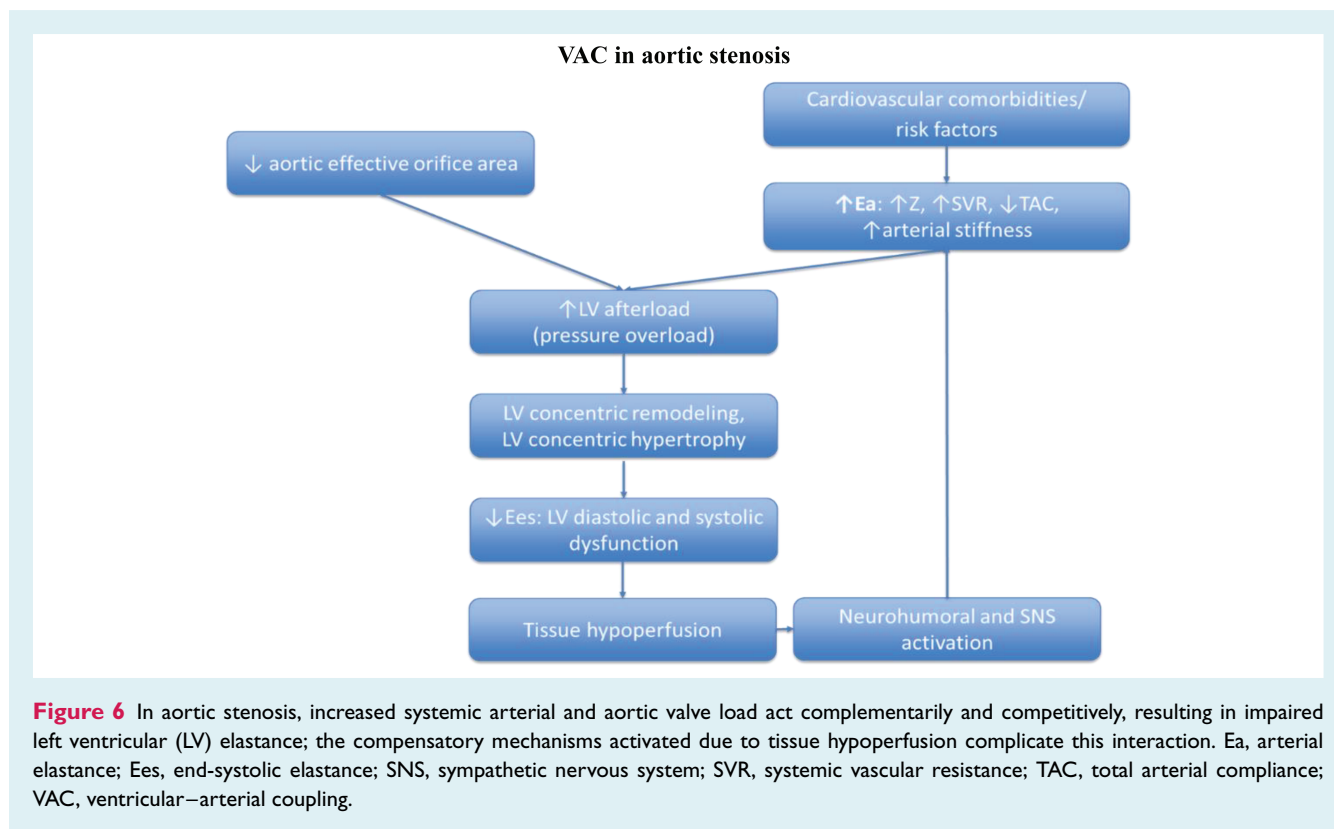Ventricular–arterial coupling and Zva have also important prognostic implications in patients with paradoxical low-flow, low-gradient AS. These patients are typically elderly, hypertensive, with stiff aorta, elevated arterial afterload despite similar end-systolic wall stress[70] and high Zva. Additionally, in patients with low-flow, low-gradient AS, Zva was associated with lower aortic mean gradient.[70] Moreover, higher Zva is associated with impaired longitudinal LV systolic function[71] and lower survival.[72,73] Zva, like Ea, has limitations because the complex pulsatile afterload cannot be lumped in a single parameter. Studies utilizing proper assessments of pulsatile LV afterload in AS are needed.

Aortic regurgitation

Wilson et al.[74] found in asymptomatic chronic aortic regurgitation patients that reduced aortic distensibility was related with increased LV volumes, systolic wall stress and LV mass, and led more rapidly to aortic valve replacement (AVR). In another study,[75] 20 patients with non-stenotic biscuspid aortic valve had reduced aortic elasticity and LV hypertrophy compared to controls.

Interventions to improve ventricular–arterial coupling

Arterial hypertension and stiffness may alter VAC and, thus, accelerate symptoms in AS and deteriorate prognosis in patients with paradoxical low-flow, low-gradient AS. Thus, in patients with coexisting hypertension, increased markers of arterial stiffness and/or impaired markers of VAC and AS, effective treatment of hypertension with medication which has been also shown to improve arterial wall properties may delay the occurrence or reduce the intensity of symptoms. AVR may acutely impact VAC[76] and promote the recovery of mid- and long-term LV contractility[77] and LV GLS.[78] However, surgical manipulations of the aorta may impair perfusion and induce inflammation of the aortic wall, resulting in reduced aortic elastance and consequently

Figure 6 In aortic stenosis, increased systemic arterial and aortic valve load act complementarily and competitively, resulting in impaired left ventricular (LV) elastance; the compensatory mechanisms activated due to tissue hypoperfusion complicate this interaction. Ea, arterial elastance; Ees, end-systolic elastance; SNS, sympathetic nervous system; SVR, systemic vascular resistance; TAC, total arterial compliance; VAC, ventricular−arterial coupling.

to ventricular−arterial decoupling.[77] The early post-AVR deterioration of aortic elastance is usually followed by a progressive improvement for up to 1 year.[79] In the case of transcatheter aortic valve replacement (TAVR), the aortic root is only minimally manipulated. The acute decrease of LV pressure overload following TAVR[80] results in an early reduction of valvular load as well as improved LV energetics, as demonstrated by VAC normalization.

However, VAC is not always improved post-TAVR. The post-procedural decrease in afterload results in an abrupt decrease of LV pressure and contractility (i.e. Ees), with a consequent VAC disruption.[80] Moreover, the relief of valvular obstruction acutely increases SV and thus in the context of a stiff, non-compliant aorta, may cause a disproportionate increase of systolic aortic BP, posing an excessive afterload to the left ventricle. Therefore, arterial load (i.e. Ea) is increased, negatively affecting LV efficiency[81] and blunting the haemodynamic benefits of TAVR. Thus, the pre-procedural state of aortic elasticity, myocardial function and VAC may affect the response to TAVR.

Mitral regurgitation

In chronic severe organic mitral regurgitation, there is a progressive deterioration of LV contractile state (i.e. Ees reduction), which leads to VAC impairment that is prevented neither by stable Ea, nor by vasodilator therapy.[82] Thus, in chronic mitral regurgitation, the progressive deterioration of VAC and pump efficiency suggests the potential progression to clinically overt cardiac dysfunction requiring mitral valve surgery.[82] In 175 patients with functional mitral

regurgitation and dilated or ischaemic cardiomyopathy (LV ejection fraction < 45%),[83] there was a significant association between PWV and functional mitral regurgitation in the ischaemic group.

Furthermore, the preservation of VAC after mitral clip implantation has been associated with an increase in forward SV, despite a reduced ejection fraction.[84]

Mitral stenosis

A study[85] of patients with severe mitral stenosis undergoing percutaneous balloon valvuloplasty and healthy subjects, demonstrated that mitral stenosis induced an increase in arterial stiffness that was improved after percutaneous balloon valvuloplasty.

Key points

- VAC assessment possesses diagnostic and prognostic value in valvular heart disease, over and above stenosis, regurgitation, or ejection fraction quantification.
- Systemic arterial compliance and Zva can specifically describe the haemodynamic consequences of AS.
- Zva and LV GLS offer prognostic information in AS even when asymptomatic.
- Impaired VAC may be the cause of symptoms in AS, despite a large aortic orifice.
- The pre-procedural state of VAC in the context of increased aortic stiffness may compromise the beneficial effects of AVR.

- Deteriorating VAC may suggest cardiac dysfunction in organic mitral regurgitation.
- Mitral clip implantation in functional mitral regurgitation may preserve VAC.

Ventricular–arterial coupling in coronary artery disease

Coronary artery disease shares common pathophysiological processes with aortic stiffening.[59,86] The severity of CAD has been associated with impaired markers of arterial stiffness.[86] The presence of significant CAD may negatively affect LV systolic function particularly in the longitudinal axis. Additionally, an increase of the arterial load due to increased aortic stiffness may also affect LV performance.[29] Increased PWV was related with reduced coronary flow reserve in CAD patients even after successful revascularization[5] and with elevated N-terminal pro BNP (NT-proBNP) post-myocardial infarction (*Table 2*).[87] Myocardial strain imaging (LV GLS < 20%)[7,27] has shown to detect subclinical dysfunction in CAD patients and represents a more sensitive method of identifying LV performance.[21] Increased aortic stiffness impairs LV function, mainly in the longitudinal axis, through inappropriate VAC with mechanisms discussed in detail above (*Figure 2*). Thus, non-invasive measurement of VAC can provide comprehensive assessment of LV performance and may also be incremental to LV ejection fraction in the characterization and clinical management of CAD patients. In 891 patients with suspected or known CAD who had negative stress echocardiography (mean LV ejection fraction 47%), it was shown that patients with impaired VAC reserve (measured as the change in Ea/Ees between peak stress and rest) had increased rates of all-cause mortality, compared with patients with more preserved VAC reserve.[88] Additionally, among 41 patients with ischaemic cardiomyopathy (LV ejection fraction $47 \pm 13\%$), those with an Ea/Ees ratio < 1.47 had better survival than patients with higher (more impaired) Ea/Ees ratios (≥ 1.47).[89] Furthermore, increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions, and various markers of arterial stiffness have been associated with adverse outcome in CAD.[86]

Key points

- There is evidence suggesting the use of LV GLS, VAC assessment, or aortic stiffness markers to refine risk stratification of CAD patients.

Ventricular–arterial coupling in heart failure

Heart failure with reduced ejection fraction

In the context of HF with reduced ejection fraction (HFrEF), as cardiac function primarily declines and LV elastance (e.g.

Ees) decreases, systemic tissue hypoperfusion occurs. The renin–angiotensin–aldosterone system and the sympathetic nervous system are consequently over-activated, in an attempt to increase intravascular volume and arterial load, and counterbalance the impaired systemic perfusion; thus, Ea is increased. The increased Ea along with the direct cardiotoxicity of sympathetic over-activation and the increased myocardial oxygen demands of hyper-dynamic circulation create a vicious circle predisposing to further worsening of cardiovascular function and syndrome progression (*Figure 7*).

Indeed, in a cohort of 466 patients with HFrEF, VAC (Ea/Ees) was strongly associated with New York Heart Association (NYHA) functional class, increase in natriuretic peptides, and adverse clinical outcomes.[90]

A reduced GLS[91] and/or a small GLS increase after stress echocardiography (< 19%)[92] have been demonstrated to be independent prognosticators of mortality in HFrEF. Furthermore, markers of arterial stiffness (pulse pressure, PWV, central systolic BP) have been found to be independent predictors of outcome in HFrEF.[93]

Interventions to improve ventricular–arterial coupling in heart failure with reduced ejection fraction

Ventricular–arterial coupling may also be useful to assess response to various therapeutic approaches in chronic HF. *Table 4* summarizes various therapeutic strategies having beneficial effects on VAC in HFrEF.[53,57,59,65,94–107]

In a prospective clinical trial, 38 patients with HFrEF underwent aggressive titration of vasoactive HF medications (ACE inhibitors, carvedilol, nitrates, MRAs) with assessment of central aortic waveforms.[94] Clinical response to treatment was assessed using the 6-min walk test, which increased in 25 patients and decreased or remained unchanged in 13. Patients with clinical improvement after therapy displayed higher baseline aortic pressure wave pulsatility (central pulse pressure, reflected pressure wave, and reservoir pressure) than patients without improvement. After treatment, aortic pressure pulsatility decreased only in patients with functional improvement. These differences in arterial load at baseline and on therapy were not apparent from conventional brachial artery cuff pressure assessments. Thus, central aortic waveform analysis may allow an individualized treatment regimen for patients with HFrEF.

In a study including 877 elderly patients with HF (age ≥ 65 years, NYHA class $\geq$ II, LV ejection fraction ≤ 45 %), treated with β-blockers, underwent Doppler echocardiography before and after 12 weeks of treatment.[95] VAC, as assessed by Ea/Ees, improved after treatment. Ea decreased from 2.73 ± 1.16 to 2.40 ± 1.01, resulting in a near-optimization of VAC ratio [from 1.70 ± 1.05 (1.46) to 1.50 ± 0.94 (1.29)]. A similar VAC response was evident in patients with ischaemic and non-ischaemic HF and was related with lower degree of HF functional class (NYHA) after β-blocker administration. The strongest predictor of VAC alteration was the LV ejection fraction increase. Thus, the beneficial effect of β-blockers in elderly HF patients may have been achieved, at least partly, by VAC optimization, associated with cardiac contractility improvement.
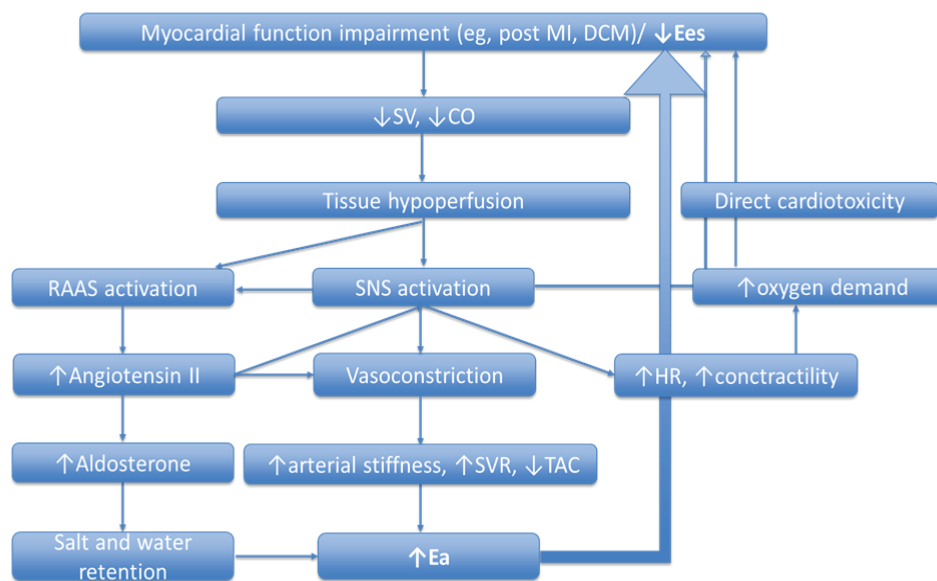
Figure 7 In the heart failure with reduced ejection fraction model of ventricular−arterial decoupling, a primary reduction of left ventricular elastance results in a compensatory increase of systemic arterial elastance (Ea); their interaction creates a vicious circle. CO, cardiac output; DCM, dilated cardiomyopathy; HR, heart rate; MI, myocardial infarction; RAAS, renin−angiotensin−aldosterone system; SNS, sympathetic nervous system; SVR, systemic vascular resistance, SV, stroke volume; TAC, total arterial compliance; VAC, ventricular−arterial coupling.

Eplerenone improves endothelial function and vascular compliance in HFrEF patients, while having beneficial effects on their exercise capacity, quality of life, and prognosis. Moreover, this agent exerts anti-fibrotic action, alleviating cardiac remodelling and LV stiffness.[96]

Ivabradine (I_f inhibition) lowers heart rate and improves cardiac function and prognosis in HFrEF.108 Ivabradine altered haemodynamics in the murine aorta by increasing the magnitude of shear stress.[97] This change was accompanied by endothelial nitric oxide synthase induction and vascular cell adhesion molecule-1 suppression. Thus, ivabradine creates local mechanical conditions that trigger protective anti-inflammatory responses in the arterial wall.[97] Moreover, IL-1 inhibition by anakinra has been shown to improve exercise capacity in HFrEF patients after 12 weeks of treatment[98] as well as to improve arterial load, coronary flow reserve and LV myocardial deformation in CAD patients with coexisting RA.[61]

Steendijk *et al.*[99] described the VAC and mechanical efficiency improvement that is induced by cardiac resynchronization therapy in relation with the observed improvements in clinical and functional status. Another study[100] highlighted value of myocardial strain−BP loops (reflecting the VAC status) to calculate myocardial work index non-invasively and thus to predict the long-term clinical response to cardiac resynchronization therapy (*Figure 5*).

Lastly, cardiopulmonary rehabilitation on top of optimal treatment is associated with VAC and LV mechanical efficiency optimization in HFrEF patients with systolic HF. This beneficial effect is potentially multi-factorial, including significant improvements in arterial compliance, peripheral resistance, wave reflections, skeletal muscle oxidative function, and arterial−venous oxygen difference.[101]

Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction is a common condition in the elderly and is associated with a high burden of co-existing co-morbidities (especially arterial hypertension and diabetes).[44] Arterial stiffening contributes to the pathophysiology of HFpEF via arterial−ventricular mismatching, particularly with exertion, afterload-induced diastolic dysfunction, and subendocardial ischaemia.[9,20,22] Additionally, in acute hypertensive HF, abnormal VAC can lead to acute pulmonary congestion. In HFpEF, impairment of VAC is related to inflammatory and mechanical overload caused by arterial hypertension and other co-morbidities; thus abnormal VAC may be considered a primary mechanism for the clinical deterioration of HF (*Figure 8*). As LV and arterial elastances increase in parallel, the classic Ea/Ees ratio is insensitive to abnormal VAC states in HFpEF. Thus, either each component of the ratio should be examined separately or novel markers of VAC assessment, as described above, should be utilized. Weber[4] demonstrated that HFpEF is characterized by increased arterial stiffness and wave reflections, which increase the late systolic pulsatile load of the left ventricle. Among the novel markers proposed to assess the ventricular−arterial interaction, an increased PWV, a marker of arterial stiffness, is a major determinant of abnormal LV GLS, a

Table 4 Main effects of medical therapy on ventricular–arterial coupling in chronic and acute heart failure patients

Therapeutic approach	Main effect
HFrEF	
Vasodilators[94]	Reduction of central pressures and afterload
β-blockers[95]	Improvement of ventricular–arterial interaction
MRAs[96]	Reduction of cardiac fibrosis and improvement of endothelial/vascular function
Ivabradine[97]	Vascular stiffness alleviation
Anakinra (IL-1 receptor antagonist)[98]	Reduction of inflammation and oxidative stress and improvement of exercise capacity, arterial load and LV myocardial deformation
CRT[99,100]	Improvement of VAC and cardiac remodelling
Exercise training[101]	Improvement of arterial compliance and LV mechanical efficiency
HFpEF	
Sodium restriction[102]	Improvement of arterial elastance and VAC
Anti-hypertensive therapy (RAAS inhibitors)[53,103]	Improvement of cardiac and vascular stiffness
Ivabradine[97]	Improvement of vascular stiffness, anti-fibrotic properties
Anakinra (IL-1 receptor antagonist)[59]	Reduction of inflammation and oxidative stress and improvement of vascular function, coronary flow reserve and LV myocardial deformation
Ustekinumab (IL-12 receptor antagonist)[65]	
ARNI (sacubitril/valsartan)[57]	Reduction of central pressures and afterload
Acute heart failure	
IV vasodilators (IV nitrates)[103]	Reduction of preload and afterload/improvement of filling pressures
Serelaxin[104–106]	Reduction of afterload, organ protection, improvement of vascular function
Levosimendan[107]	Vasodilatation with positive lusitropic properties, improvement of right ventricular–pulmonary arterial coupling

ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IL, interleukin; IV, intravenous; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; VAC, ventricular–arterial coupling.

sensitive marker of LV dysfunction, and is associated with reduced aerobic exercise capacity in hypertensive heart disease[48] while a reduced LV GLS (< 16%), has been shown to predict mortality following hospitalization for HFpEF.[102]

Interventions to improve ventricular–arterial coupling in heart failure with preserved ejection fraction

Table 4 also describes therapeutic interventions that may restore VAC in HFpEF. Furthermore, in hypertensives with HFpEF, a sodium-restricted diet was associated with favourable changes in LV diastolic function, Ea, and VAC.[109]

Nitric oxide is an important regulator of muscular artery tone and the magnitude of wave reflection. Orally administered inorganic nitrates (which are direct precursors of nitric oxide via the nitrate–nitrite–nitric oxide pathway) have been shown to reduce wave reflections and increase exercise capacity in HFpEF.[110] However, the recent INDIE-HFpEF[111] trial failed to demonstrate any improvement in peak oxygen uptake (VO$_2$) with use of inhaled sodium nitrite with short half-life (~35–40 min) and pronounced drug fluctuations, which are an important barrier to its efficacy. The negative results of this and previous studies[112] highlight the need for more studies that use other outcome measures (besides VO$_2$) to evaluate the efficacy of nitric oxide donor agents in patients with HFpEF (e.g. cardiac function markers, biomarkers, and/or hospitalizations for HF). However, these results may also indicate that the use of inhaled sodium nitrite with its short half-life in not an effective treatment in this clinical setting. In contrast to inorganic

nitrite, orally administered inorganic nitrate has a longer half-life (~5–8 h) and does not seem to commonly induce hypotension with single or continued administration.[113,114]

In a diabetic HFpEF mouse model, ivabradine administration improved vascular stiffness, LV contractility, and diastolic function.[115] Additionally, short-term treatment with ivabradine increased exercise capacity, due to improved LV filling pressure response to exercise[116] in humans, though others had failed to demonstrate meaningful improvement in VO$_2$.[117]

Recently, the novel combination ARNI (sacubitril/valsartan) led to a significant improvement of central aortic and brachial pressures in elderly patients with systolic hypertension,[57] while effectively reduced NT-proBNP and circulating pro-fibrotic markers in HFpEF patients in the PARAMOUNT trial, suggesting beneficial effects of the drug on VAC.[118] PARAGON-HF is an ongoing trial that investigates the effect of ARNI on major cardiovascular outcomes in HFpEF.

In acute hypertensive HF, intravenous nitrates[103] or the new agent serelaxin effectively reduced afterload, as well as pulmonary congestion by way of vascular stiffness alleviation and VAC optimization[119] (*Table 1*). Although serelaxin improved 180-day mortality in phase II RELAX-AHF,[104,105] this benefit on adverse outcome was not confirmed in the following phase III RELAX-AHF-2 study in a larger patient cohort.[106] Thus, the neutral results of trials such as NEAT-HFpEF (mean age 69 years, 57% women, objective evidence of HF, LV ejection fraction > 50% and reduced self-reported activity levels), INDIE-HFpEF [mean age 68 years,
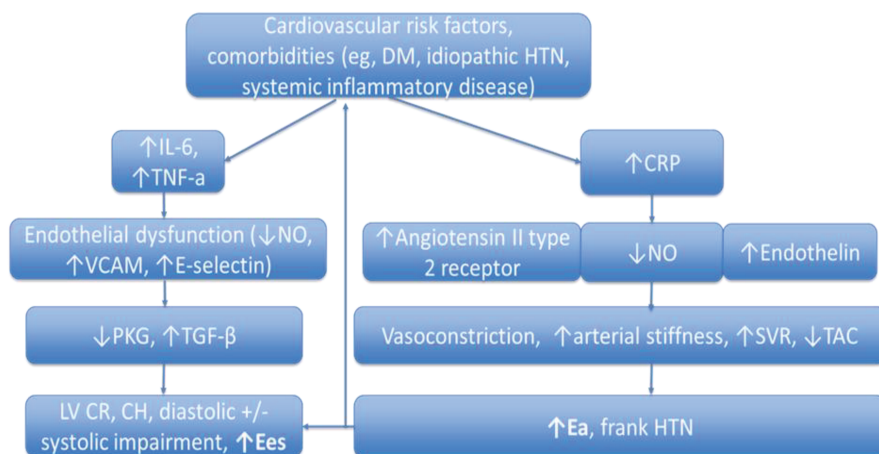
Figure 8 In the heart failure with preserved ejection fraction model of ventricular–arterial decoupling, cardiovascular co-morbidities and risk factors induce pro-inflammatory and pro-fibrotic cascades that concomitantly impair left ventricular and systemic arterial elastance; further damage results from their interaction. CH, concentric hypertrophy; CRP, C-reactive protein; DM, diabetes mellitus; HTN, hypertension; IL-6, interleukin-6; LV CR, left ventricular contractile reserve; NO, nitric oxide; PKG, protein kinase-G; SVR, systemic vascular resistance; TAC, total arterial compliance; TGF-β, transforming growth factor-β; TNF-a, tumour necrosis factor alpha; VCAM, vascular cell adhesion molecule.

68% women, objective evidence of HF, LV ejection fraction > 50% and reduced exercise capacity (peak VO$_2$ ≤ 75%)], and RELAX-AHF-2 (mean age 73 years, 40% women, hospitalized for acute decompensated HF, mean LV ejection fraction of 40%) on cardiovascular risk reduction[106,111,112] have raised questions regarding the utility of targeting afterload reduction, the timing of intervention,[104] and the drug of choice to improve vascular function and, thus, outcomes in HFpEF or acute decompensated HF.

In patients with right-sided HF due to LV dysfunction or primary pulmonary hypertension, the inodilator levosimendan increases cardiac output by restoring right ventricular–pulmonary arterial coupling and decreasing pulmonary vascular resistance.[107] Finally, treatment with IL-1 or IL-12 inhibitors has shown beneficial effects on arterial load, myocardial deformation and NT-proBNP, suggesting an improvement of VAC in inflammatory disease.[59,65]

Although endurance exercise training improves exercise capacity in older patients with HFpEF, it does not appear to have a significant effect on markers of endothelial function and arterial stiffness.[120,121]

Key points

- Abnormal VAC is implicated in the pathophysiology of left and right HF clinical deterioration.
- Different patterns of abnormal VAC are recognized in HFrEF vs. HFpEF.
- Restoration of VAC may be a new therapeutic target in HF and pulmonary hypertension.
- More mechanistic and VAC-guided therapy clinical trials are needed in this field.

Ventricular–arterial coupling in pulmonary hypertension

The right ventricle undergoes adaptive changes in response to increased pulmonary artery pressures. Initially, the compensatory increased contractility and hypertrophy suffice to match the respective right ventricular afterload. Eventually, however, ventricular–arterial decoupling ensues with an increased Ea/Ees ratio.[122] Right ventricular–pulmonary arterial coupling may independently predict transplantation-free survival of patients with pulmonary hypertension.[123] Although data regarding humans are limited, a number of pulmonary hypertension pharmacotherapies (e.g. drugs inducing pulmonary vasodilatation) have demonstrated beneficial effects on right ventricular–arterial coupling in animal models.[124]

Key points

- Abnormal VAC is involved in the pathophysiology of right HF in pulmonary hypertension. Studies should further examine whether improvement of VAC by treatment will also improve symptoms and prognosis in pulmonary hypertension.

Conclusion

Fibrosis, inflammation and oxidative stress are common biochemical pathways linking impaired ventricular–arterial function. Increased arterial stiffness/wave reflections are associated with various maladaptive structural and functional LV changes, contributing

to the development of HF. VAC assessment possesses independent diagnostic and prognostic value in cardiac disease and may be used to refine risk stratification. Traditionally, VAC is assessed by the non-invasive measurement of the Ea/Ees ratio. With disease progression, both Ea and Ees may become abnormal and the Ea/Ees ratio may approximate normal values (∼1). Therefore, the measurement of each component of this ratio or of novel, more sensitive markers of myocardial (e.g. GLS) and arterial function (e.g. PWV) may describe and quantify VAC. Treatment guided to improve VAC through improvement of both or each one of its components (Ea, arterial stiffness, central BP and/or myocardial elastance and deformation) may delay the progression to HF and possibly improve prognosis. More mechanistic and VAC-guided large-scale clinical trials are needed in this field.

Gaps in evidence

There are still several unanswered questions related to the study of VAC in cardiac disease. The optimal marker that will be easy to use in daily clinical practice to assess VAC and myocardial work efficiency and to monitor the effects of treatment is not yet established.

The effects of pre-procedural VAC on valve interventions such as TAVR and mitral clip or cardiac resynchronization therapy device implantation and its utility to assist patient selection or assess response to intervention have not been fully defined.

The effects of nitric oxide donors on vascular and myocardial function using new endpoints besides exercise capacity (e.g. myocardial function markers, hospitalizations, mortality), as well as dose or duration of this treatment should be examined.

The appropriate type, dose and duration of anti-inflammatory treatment to improve VAC in systemic inflammatory diseases, CAD, and HF, as well as the association of VAC improvement with improved functional status and reduced cardiovascular outcomes are not clarified. Finally, the drug, dosage, duration and, more importantly, the timing of treatment targeting afterload reduction especially in acute HF in order to have a beneficial effect on adverse cardiovascular events are not known.

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