Narrative paper

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Ventricular–vascular coupling in hypertension: methodological considerations and clinical implications

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The present review is addressed to analyse the complex interplay between left ventricle and arterial tree in hypertension. The different methodological approaches to the analysis of ventricular vascular coupling in the time and frequency domain are discussed. Moreover, the role of hypertension-related changes of arterial structure and function (stiffness and wave reflection) on arterial load and how ventricular–vascular coupling modulates the process of left ventricular adaptation to hypertension are analysed.

The different interplay between vascular bed and left ventricle emerges as the pathophysiological basis for the development of the multiple patterns of ventricular structural adaptation in hypertension and provides a pathway for the interpretation of systolic and diastolic functional abnormalities observed in hypertensive patients. Targeting the therapeutic approach to improve ventricular–vascular coupling may have relevant impact on reversing left ventricular hypertrophy and improving systolic and diastolic dysfunction.

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Keywords: arterial stiffness, effective arterial elastance, hypertension, input impedance, left ventricular hypertrophy, pulse wave analysis, therapy, ventricular–vascular coupling, wave reflection

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Introduction

The heart is anatomically and functionally connected with the vascular system. Structural and functional changes of the arterial tree, changing left ventricular afterload, may modulate left ventricular function and induce adaptive structural modifications. Systolic brachial blood pressure, routinely assessed by sphygmomanometry, is commonly considered to be a good estimate of aortic pressure and thus a surrogate of the load imposed on the left ventricle. This simple assessment, however, provides only a rough estimate of the real aortic pressure, because of transmission delays and wave reflection. Moreover, left ventricular load is a complex entity that comprises both steady and pulsatile elements, such as peripheral resistance, compliance and pressure wave reflection, and cannot be reduced to blood pressure.

Hypertension is characterized by high blood pressure levels. It, however, induces structural and functional modifications of the arterial tree (atherosclerosis, stiffening and enhanced reflection of the pressure wave) that may play a role in increasing arterial load and inducing adaptive structural changes of the left ventricle above and beyond blood pressure itself. According to this view, the different interplay between vascular bed and left ventricle represents the pathophysiological basis for the development of the multiple patterns of ventricular adaptation in hypertension[1] and may have important implications both in the pathogenesis of cardiovascular diseases and in modulating the response to treatment.

The present review is addressed to analyse the components of the arterial load acting on the left ventricle, the methodological aspects of their assessment and their impact on ventricular structure and function in the presence of hypertension. Finally, therapeutic implications of ventricular–vascular coupling will be discussed.

Assessment of ventricular–arterial coupling

The flow–pressure relationship in the time domain

From a functional point of view, the system represented by the left ventricle and arterial vessels can be modelled as a pressure generator located at the origin of a vessel network, which represents the external load.[2] The

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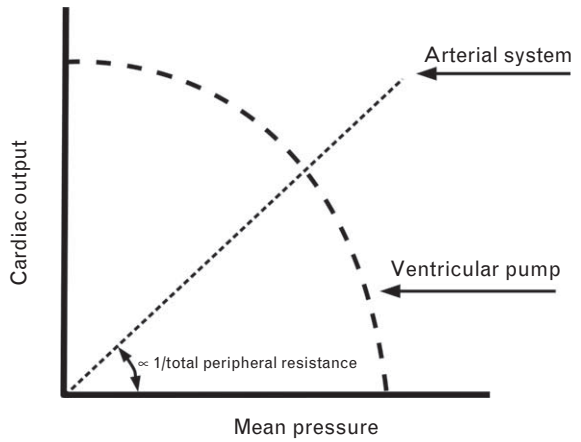
Fig. 1



The left ventricular and arterial pressure–flow relationship in steady-state conditions. Keeping constant the contractile force, the relationship between cardiac output and ejection pressure (load) is inverse and the intercept on the pressure axis represents the maximum pressure level that can be generated during an isometric contraction. Conversely, the relationship between cardiac output and arterial pressure is direct and inversely proportional to total peripheral resistance. In coupling conditions and ventricular–arterial haemodynamic equilibrium, the flow rate and the pressure of ejection are determined by the intersection of the two curves. Modified from references[3] and[4].

interplay between cardiac and arterial functional characteristics determines the amount of flow (i.e. flow rate) that the cardiac pump can generate. Instantaneous pressure/flow relationship can be derived using appropriate models of the ventricular–arterial system.

In steady conditions and in the absence of wave reflections, each element (cardiac pump and external load) can be individually represented by the relationship between the average flow passing through it (the cardiac output) and the average pressure during flow (Fig. 1). Keeping constant the contractile force, the lower is the load (estimated by ejection pressure), the higher is the cardiac output. The intercept of the relationship between cardiac output and ejection pressure on the pressure axis represents the highest level of pressure that can be generated by the cardiac pump during an isometric contraction (heart as 'pressure generator'), whereas the intercept of the same relationship with the other axis represents the maximum cardiac output achievable in the absence of significant afterload (heart as 'flow generator'). On the contrary, the flow entering the arterial system proportionally increases blood pressure, and the slope of this relationship is inversely related to total peripheral resistance. When the cardiac pump and the external load are coupled, their individual mechanical behaviour is in equilibrium at a single point, where the ability of the heart pump to generate flow at a certain pressure exactly balances the pressure required to push the same flow against the arterial load, represented by total peripheral resistance (Fig. 1).

Because the cardiac pump acts intermittently, however, the relation 'mean flow/mean pressure' poorly represents the pulsatile nature of arterial load. It is well known, for example, that the reduction of arterial compliance is associated with increased pulse pressure and that it can lead to a reduction in cardiac output, even in the absence of changes in peripheral resistance.[5] In this regard, it is noteworthy that, just like mean pressure does not accurately represent the behaviour of the arterial tree, it is a poor predictor of cardiovascular events when compared with pulse pressure.[6,7]

The pulsatility of flow is taken into account by the so-called Windkessel model. The basic principle of this model derives from the compliance–resistance combination used in former fire extinguishers to guarantee continuous water flow in pipes. This model has been refined in recent years including up to four elements in order to better characterize the arterial tree. At present, the three-element Windkessel model, which includes the aortic characteristic impedance (Z_c)[8] (see Table 1), is the most widely applied. Although this model allows an accurate representation of the pulsatile pressure–flow relationship in the arterial system, it does not consider wave propagation and reflection that occur at each cardiac cycle and is less accurate in the presence of enhanced wave reflections, such as in hypertension and vascular disease.[8]

Pressure wave propagation and reflection in the arterial tree

During each cardiac cycle, the flow ejected in the aorta generates a pressure waveform that propagates along the arterial tree with a finite velocity and is reflected at points of abrupt change in impedance.[9] Although there are multiple reflection sites in the upper and lower parts of the body, the reflected waves merge together, appearing as a main reflected wave when they reach the heart.[10] Backward secondary waves, originating from peripheral reflection sites or generated by re-reflection phenomena, are functionally negligible because they occur later and have significantly lower amplitude than the main component. When the reflected wave is optimally timed, as usually occurs in young healthy individuals, the reflected component meets the forward wave in ascending aorta during the early phase of diastole, contributing to coronary perfusion (Fig. 2a). Conversely, when the arterial tree becomes stiffer (as occurs with normal ageing[11] or in hypertension),[11,12] the pulse wave velocity increases and the merging of forward and backward components is timed predominantly in systole. This elevates peak systolic pressure and reduces early diastolic pressure in ascending aorta (Fig. 2b).[13] The 'augmentation pressure' is the absolute increase in systolic pressure owing to the reflected wave, whereas the 'augmentation index' expresses this increment as a percentage of pulse pressure. Recent observations[14,15] suggest that aortic stiffening and increased pulse wave velocity may act differently on augmentation

Table 1 Dictionary of indices of arterial function cited in text

Index	Definition and units
Characteristic impedance (Z_c)	Relationship between pressure change and flow velocity in the absence of wave reflections $\Delta P/\Delta$Vel [(mmHg/cm)/s]
Compliance	Absolute diameter (or area) change for a given pressure step at fixed vessel length $\Delta D/\Delta P$ (cm/mmHg) or (cm^2/mmHg)
Effective arterial elastance (E_a)	Lumped parameter representing the steady and pulsatile components of the arterial load P_{es}/SV (mmHg/ml)
Input impedance (Z_i)	The 'summed' mechanical load imposed by all vessels downstream at a particular point Time-varying pressure/flow relationship in the frequency domain, expressed as modulus [(dynes s)/cm^5] and phase (°) for each harmonic
Peterson's elastic modulus (E_p)	The pressure step required for (theoretical) 100% stretch from resting diameter at a fixed vessel length $(\Delta P \times D)/\Delta D$ (mmHg)
Pulse wave velocity (PWV)	Speed of travel of the pulse wave along an arterial segment Distance/Δt (m/s) PWV is related to Young's elastic modulus by Moens–Korteweg equation ($\mathrm{PWV} = \sqrt{\frac{Eh}{2r\rho}}$) and to characteristic impedance by Waterhammer equation ($\mathrm{PWV} = \frac{Z_c}{\rho}$)
Stiffness index (β')	Ratio of logarithm (systolic/diastolic pressures) to relative change in diameter $\ln(P_s/P_d)/[(D_s - D_d)/D_d]$ (nondimensional)
Total arterial compliance	Relationship between pressure fall and volume fall in the arterial tree during the exponential component of diastolic pressure decay $\Delta V/\Delta P$ (cm^3/mmHg)
Total peripheral resistance (TPR)	Resistance to flow that must be overcome to push blood through the systemic circulation MAP $\times$ 80/CO [(dynes s)/cm^5]
Young's elastic modulus (E)	Elastic modulus per unit area; the pressure step per square centimetre required for (theoretical) 100% stretch from resting length $(\Delta P \times D)/(\Delta Dh)$ (mmHg/cm)

ρ, blood density; CO, cardiac output; D, diameter; h, wall thickness; MAP, mean arterial pressure; P, pressure; P_{es}, end-systolic pressure; r, vessel radius; SV, stroke volume; t, time; V, volume; Vel, velocity.

pressure in younger and older populations. Data from the Anglo Cardiff Collaborative Trial showed in a large population of healthy individuals that in younger individuals, augmentation pressure is, in fact, more related to the magnitude of wave reflection rather than pulse wave velocity, whereas in older individuals augmentation pressure is mainly driven by the earlier return of reflected waves.[14]

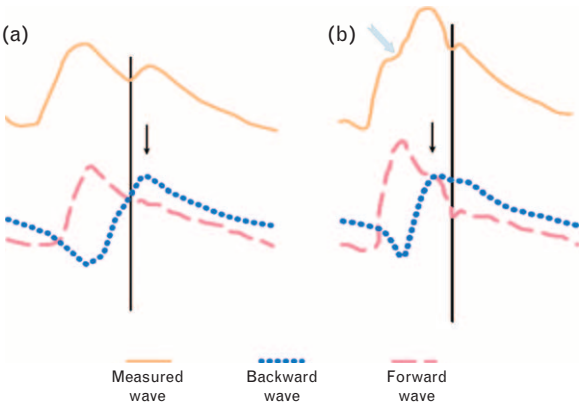
Invasive[16] and noninvasive[17,18] studies have demonstrated that pressure wave reflection, together with the nonuniform elasticity of the arterial tree,[12] is responsible for the progressive increase in systolic and pulse pressure observed moving from central to peripheral districts of the arterial tree. This phenomenon, described by Hamilton and Dow,[19] is known as 'pressure wave amplification' and is due to the early fusion of the reflected wave with the systolic component of the forward wave in points close to the sites of wave reflection. The clinical consequence of pressure wave amplification is that brachial pressure may not be representative of the pressure acting in ascending aorta, especially in young people. Data from the Anglo-Cardiff Collaborative Trial[20] indicate that pressure wave amplification, expressed as the ratio of brachial/aortic pulse pressure, varies from 1.7 in people less than 20 years of age to 1.2 in those more than 80 years of age. When expressed as absolute change (brachial − aortic systolic augmentation pressure), the amplification varies from 20 to 7 mmHg, respectively. The increase in central systolic pressure with ageing is due to the concomitant increase of aortic stiffness and pulse wave propagation speed, resulting in reduction of central–peripheral amplification.[14,21] Therefore, the assessment of central blood pressure estimates more accurately the load actually acting on the left ventricle[22,23] and its effects on left ventricular structure and function.[24,25]

The concept of forward and backward waves travelling along the arterial tree, although widely accepted, has been recently challenged by Tyberg and colleagues.[26,27] Using a modified Windkessel model (the so-called 'reservoir-wave approach'),[28,29] the authors showed that aortic pressure solely depends on the combination of the reservoir function of the proximal aorta and the waveform of aortic flow, which, in turn, is related to the way the left ventricle contracts and relaxes.[26] Using this approach in a canine model, they found that 'backward pressure waves' paradoxically seemed to be propagated in the forward direction[30] and thus the reality of wave propagation phenomena has been questioned.[26] These results have been heavily debated by Westerhof and Westerhof,[27,31] because they are mostly based on a model that incorrectly considers the arterial tree as a single tube. Till now, published data supporting the concept of wave propagation forward and backward in the arterial tree seem overwhelming in comparison to those that oppose this concept. Future research will clarify whether we should look at propagation phenomena in the arterial tree in a different way.

The flow–pressure relationship in the frequency domain: the aortic input impedance

The flow–pressure relationship and the ventricular vascular coupling can be assessed in the frequency domain

Fig. 2



Forward and backward waves and morphology of pressure waveforms. The pressure wave generated by left ventricular contraction (red, interrupted line) travels towards the periphery of the arterial tree, where it is reflected. The backward wave generated by reflection (blue, dotted line) merges with forward wave, modifying the morphology of the measured pressure waveform (orange, continuous line). In central aorta, when pulse wave velocity is normal, reflected wave merges with forward wave in diastole, increasing early diastolic pressure and myocardial perfusion (a). When pulse wave velocity increases (e.g. in hypertension), the reflected wave merges with the forward wave in late systole. This can be seen as an inflection in the ascending branch of the measured waveform (arrow) and an increase in systolic pressure (b). Augmentation pressure expresses the absolute increase in pressure, whereas augmentation index expresses this increase relative to measured pulse pressure.

by aortic input impedance. In general, vascular impedance expresses the relationship between pressure and flow in a given vessel. It is calculated in the frequency domain from the ratio between the corresponding harmonic components of pressure and flow waves, derived by Fourier analysis (Fig. 3). Input impedance is a complex entity and is represented graphically by 'modulus' (amplitude of pressure harmonics divided by amplitude of corresponding flow components) and 'phase' (phase shift between flow and pressure harmonic components), as a function of the frequency of the harmonics (Fig. 4). Aortic input impedance is considered to be the most accurate estimate of left ventricular afterload, because it includes both static and pulsatile components of arterial load.[12]

The input impedance profile is similar in all major arteries. Modulus is relatively high at zero frequency (resistive component, calculated by average pressure and average flow), and then decreases with increasing frequency to a minimum, after which it usually increases up to a local maximum before falling again (Fig. 4). Phase is initially negative, then becomes positive approximately at the minimum of the modulus, and then again becomes negative. The frequency at which modulus reaches its minimum depends on the distance of the arterial ends: it is greater in the femoral artery than in abdominal aorta and is minimal in the ascending aorta. The average modulus at high frequencies corresponds to aortic characteristic impedance[33,34] and thus reflects aortic stiffness. Oscillations in impedance moduli around characteristic impedance are related to wave reflections. Changes in vascular properties are reflected by patterns of impedance. Vasodilation, which is accompanied by decrease of vascular resistance, reduces the resistive component of impedance, determines the disappearing of the lesser peak of the modulus and attenuates the fluctuations of phase.[35,36] Conversely, vasoconstriction is accompanied by the increase of resistive component of impedance without further noteworthy modification of modulus and phase components.[35,36]

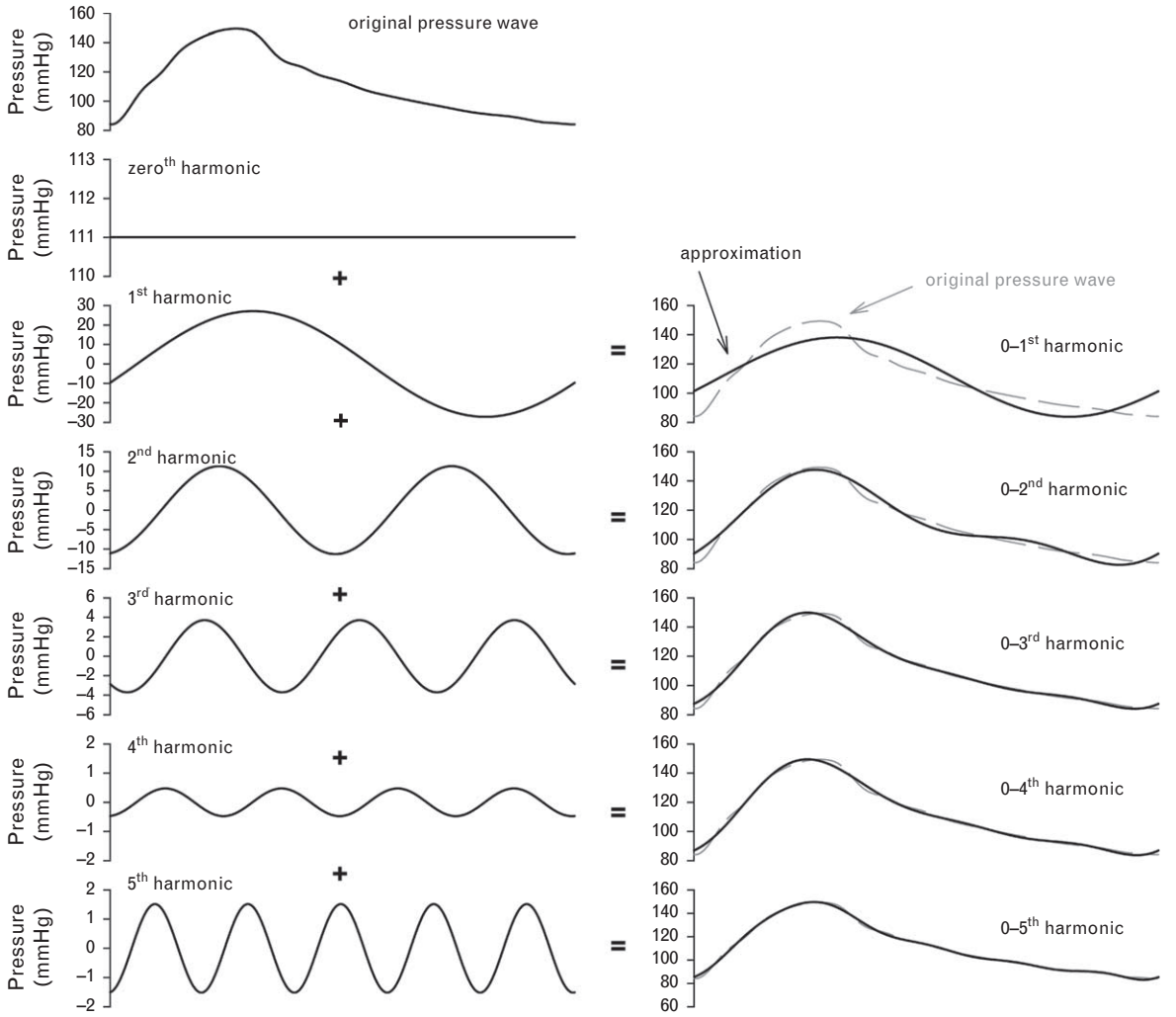
Aortic input impedance is a well established index of left ventricular afterload in both animals[37,38] and humans,[39,40] and it is used to assess ventricular–arterial coupling.[22,41] The complexity of its calculation and interpretation and its inherent invasiveness, however, greatly limits its use in clinical practice. The limitation due to invasiveness has been overcome using Doppler flowmetry (for estimating flow in the ascending aorta) and carotid arterial tonometry (for estimating central aortic pressure).[42] From these noninvasive parameters, modulus and phase of aortic input impedance can be calculated. Kelly and Fitchett[42] demonstrated good correspondence between impedance values obtained using this method and those obtained invasively.

The use of approximated triangular flow waveform for impedance and wave reflection calculation has been proposed by Westerhof *et al.*[43] This approach further simplifies the assessment of arterial function allowing an easier application in clinical research. Recently, Qasem and Avolio[44] applied this approach to derive a model for predicting pulse wave velocity only from carotid pulse wave decomposition in a group of 46 patients. Application of this model in a separate group of 44 patients provided good agreement.[44] Data from the large population (>2500 patients, 35–55 years old) of the ASKLEPIOS Study,[45] however, did not confirm the accuracy of this approach when compared with Doppler aortic flowmetry. Moreover, derived measures of wave reflection showed only modest correlation with reference values.[45] According to these data, the simplified approach for flow wave reconstruction (the 'triangular approximation') could not be recommended for assessing pressure/flow relationship.

Arterial and ventricular elastance

A relatively simple model for the analysis of ventricular–arterial coupling was proposed by Sunagawa *et al.*[46] in the early 1980s. In this model, the left ventricle is represented as an elastic chamber that during cardiac cycle increases its stiffness to a maximum, reached at end systole.[47] At a constant inotropic state, the end-systolic points of left ventricular pressure–volume loops recorded during acute preload or afterload changes describe the end-systolic pressure–volume relationship. Under these

Fig. 3

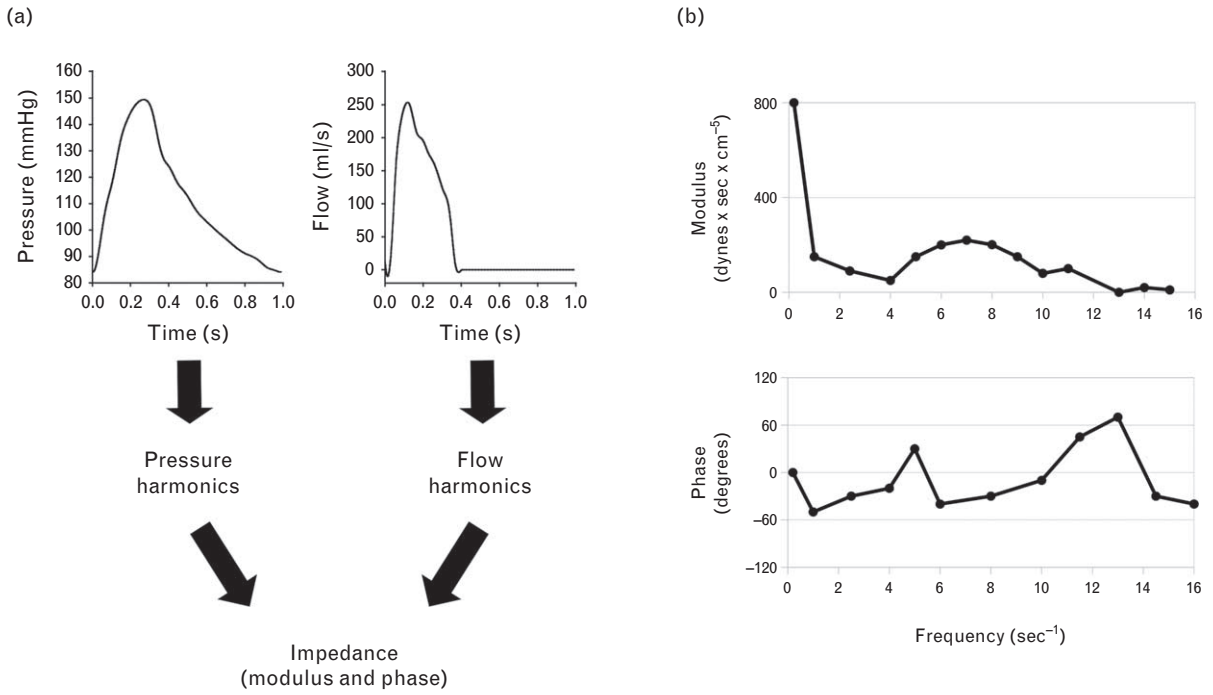


Fourier decomposition of a pressure wave. Following Fourier analysis the pressure (and flow waves) can be represented as the sum of sinusoid waves (harmonics). Note the decreasing amplitude of higher harmonics and their phase shift. Reproduced from Swillens and Segers.[32]

conditions, left ventricular end-systolic elastance (E_{lv} or E_{es}) can be thus quantified by the slope of the straight line that connects the end-systolic points of the pressure–volume relationship. E_{lv} is widely regarded as a load-independent index of left ventricular contractility, but it is influenced by the geometric and biochemical properties that underlie left ventricular stiffness. Greater left ventricular mass, smaller internal dimensions and concentric geometry[48] increase left ventricular elastance and should be taken into account when comparing patients with different characteristics.[49,50] In order to obtain body size–independent and geometry-independent estimates of E_{lv}, several indexations have been proposed, but one universally accepted is still lacking. Hayward and colleagues[49] showed only weak correlation between body surface area and E_{lv} while left ventricular internal dimensions better normalized this parameter. Discussion on strengths and weaknesses of the different approaches for normalization of E_{lv} is beyond the scope of this review, and the reader is addressed to more specific reviews.[50,51]

The arterial load can be similarly assessed in terms of effective arterial elastance (E_a) from the slope of the relationship between end-systolic pressure and stroke volume (SV).[46,52] E_a is a lumped parameter that integrates both static and pulsatile components of arterial load and has been considered a reliable index of aortic input impedance.[53] The ability of E_a, however, to represent the pulsatile component of arterial load has been questioned,[54] because it can be approximated by the ratio between total peripheral resistance (R) and heart cycle length (T).[52] If this was true, E_a should have no relationship with the pulsatile component of the arterial load. Mathematical models[55] and human studies[56] have however demonstrated that arterial stiffness and pulsatile components of arterial load, although with a significantly

Fig. 4



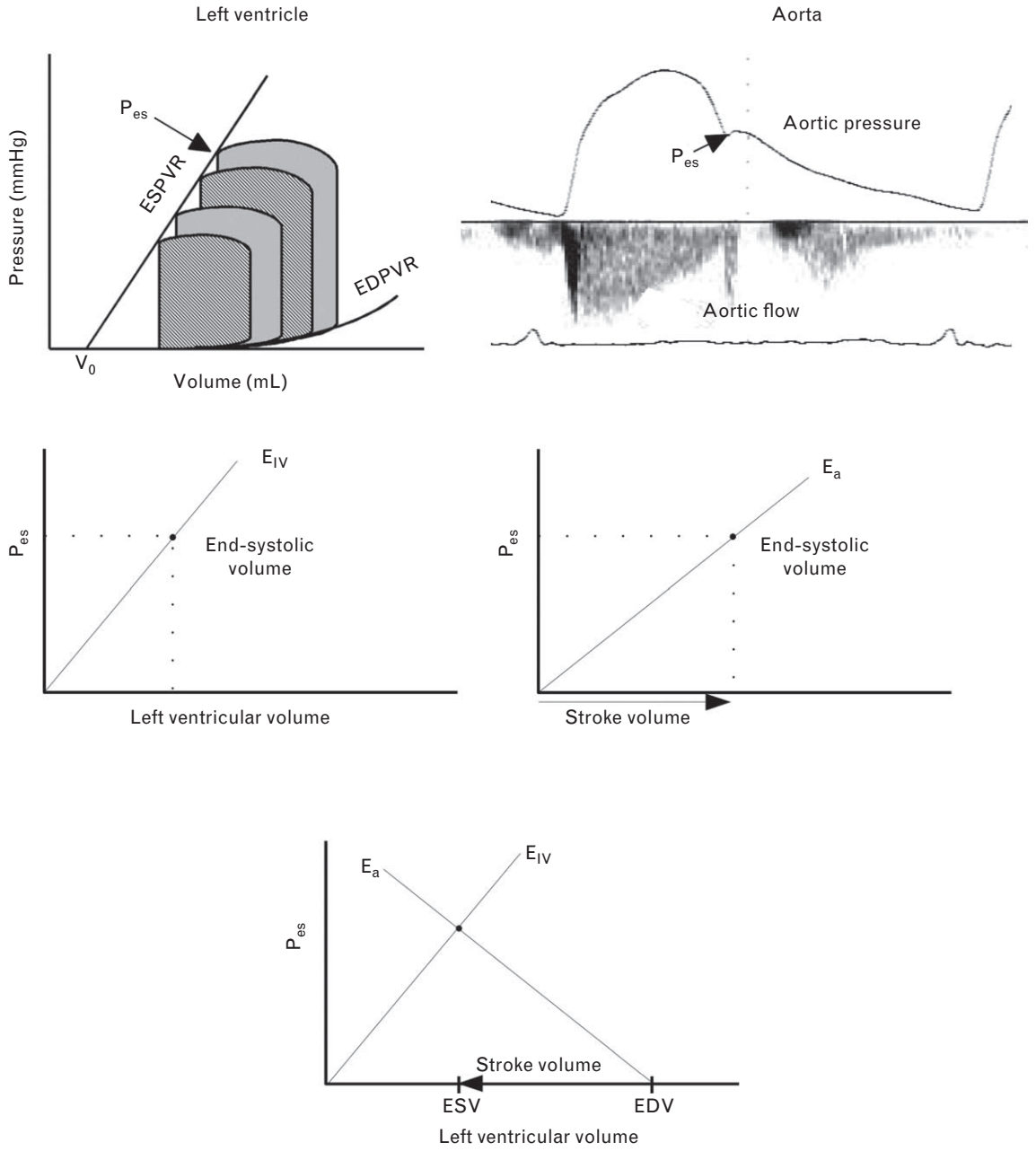
Calculation of aortic input impedance. (a) Pressure and flow waveforms are simultaneously recorded and harmonic components derived by Fourier analysis. From amplitude and phase of corresponding harmonics, impedance modulus and phase are derived. (b) Graphic representation of aortic input impedance. Both modulus and phase are plotted against frequency of harmonics. Modulus at 'zero' harmonics (nonoscillatory behaviour) corresponds to total peripheral resistance. The average modulus at high frequencies corresponds to aortic Z_c. Random oscillations in impedance moduli around Z_c are attributable to wave reflections. The first minimum of impedance modulus and the first zero crossing of phase are related to the distance of the effective reflecting site of pressure waves.[33,34]

lesser extent than total peripheral resistance, play a role in determining the effective arterial elastance. Data obtained from patients undergoing cardiac catheterization showed that the sensitivity of E_a to a change in R/T was 2.5 times higher than to a similar change in arterial stiffness.[56] The R/T ratio, however, significantly underestimated E_a, especially in hypertensive patients, and this bias was most strongly related to arterial stiffness. Accordingly, data from a clinical population of hypertensive patients showed significant relationship between the effective arterial elastance and arterial stiffness.[57]

The different interplay of SV, peripheral resistance, aortic stiffness, wave reflections and heart rate on effective arterial elastance may influence its values and give normal E_a values also in the presence of high blood pressure.[58] In fact, while high total peripheral resistance and marked aortic stiffening may elevate E_a,[58] in the presence of only modest increments of peripheral resistance and/or reduction of characteristic impedance due to hypertension-induced increase of aortic diameter,[59] normal E_a values could be observed also in hypertensive patients.[58] Because SV is influenced by body size, arterial elastance is also directly related to body size. In order to compare absolute values of arterial elastance in heterogeneous populations, indexation of arterial elastance for body surface area is needed.[57]

Using left ventricular and arterial elastances, ventricular–vascular coupling can be easily analysed as the ratio of these two entities[52] and the SV for a given left ventricular diastolic volume can be derived from the intersection of the two relations[60] (Fig. 5). Using this model, Sunagawa *et al.*[52] have shown that the left ventricle generates the maximum external work for a given load when arterial and ventricular elastances are equal. If we consider work efficiency, however, expressed by the ratio between the work generated by the heart during ejection and the oxygen consumption,[61,62] maximal left ventricular external work does not correspond with maximal efficiency for a given load condition.[63] Accordingly, Sasayama and Asanoi[60] demonstrated that in normal individuals ventricular elastance was nearly twice larger than arterial elastance, warranting maximal mechanical efficiency. Conversely, in patients with moderate heart failure, with ejection fraction of 40–59%, ventricular elastance was almost equal to arterial elastance, affording maximal stroke work from a given end-diastolic volume. Finally, in patients with severe heart failure, and ejection fraction less than 40%, ventricular elastance was less than half of

Fig. 5

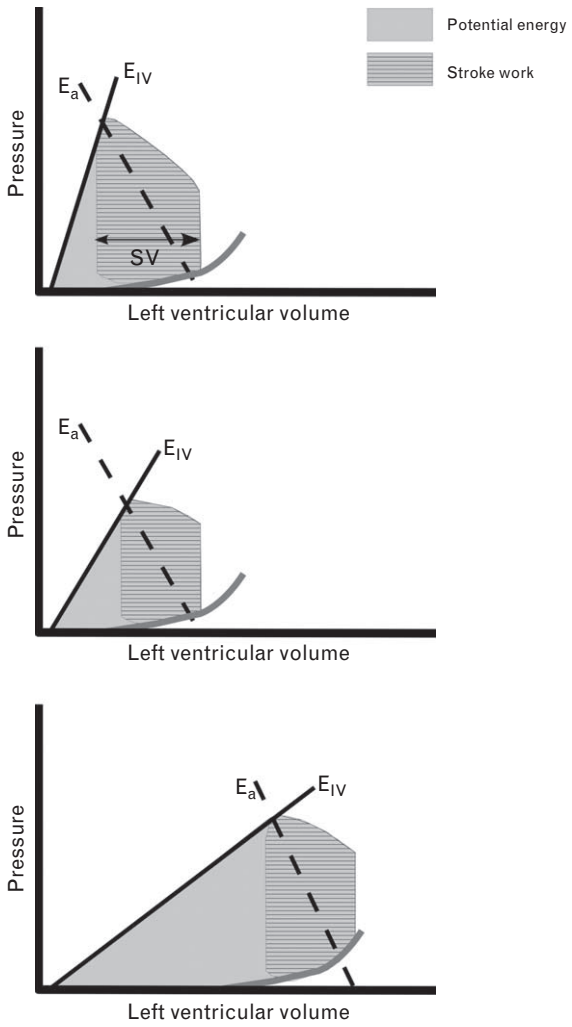


Schematic illustration of the framework of analysis for coupling of the ventricle with the arterial load. The mechanical characteristics of the left ventricle are expressed by the end-systolic pressure (P_{es}) vs. volume relationship (left, upper and middle panels). The mechanical characteristics of the arterial system are expressed by the arterial end-systolic pressure (P_{es}) vs. stroke volume (SV) relationship (right, upper and middle panels). This, in turn, can be transformed into the P_{es}–left ventricular volume relationship. Coupling of left ventricle and arterial tree is expressed at end systole from the intersection between these two P_{es}–left ventricular volume relationship lines (bottom panel). Modified from Sunagawa *et al.*[52]

arterial elastance, which resulted in increased potential energy and decreased work efficiency (Fig. 6). Ventricular–arterial coupling is normally set towards higher left ventricular work efficiency, whereas in patients with moderate cardiac dysfunction ventricular and arterial properties are matched in order to maximize stroke work at the expense of work efficiency.[60,64]

Based on the studies of Sunagawa, this model has been applied to assess ventricular–arterial coupling in normal individuals,[49,65,66] in the elderly[22,67] and in pathological conditions such as heart failure,[64,68] valvular diseases,[69,70] ischaemic heart disease[71,72] and hypertension.[58,73,74] Other studies were conducted also during pharmacological interventions,[75,76] in cardiac transplant[77,78] and even

Fig. 6



Ventricular–vascular coupling in different conditions. In normal individuals (upper panel), E_{lv} exceeds E_a. In this condition, left ventricular mechanical efficiency is optimal, because the resulting ratio between stroke work (area described by left ventricular pressure–volume loop) and potential energy (grey area) is maximized. In patients with mild left ventricular systolic dysfunction (middle panel), E_{lv} and E_a tend to equalize, keeping maximized the stroke work at the expenses of a lower mechanical efficiency. Patients with severe left ventricular systolic dysfunction (lower panel) show a very compromised mechanical efficiency. Acceptable stroke work and arterial pressure are maintained keeping high left ventricular volumes, and E_a exceeds E_{lv}.

in conditions of absence of gravity.[79] Recent data suggest also the application of this model for risk stratification of patients undergoing stress echocardiography, because an impaired E_a/E_{lv} ratio reserve during stress was associated with a higher prevalence of adverse outcomes at follow-up.[80]

The main limitation of this approach is related to left ventricular elastance calculation, which needs acute modifications of left ventricular load.[81] Considering negligible the value of V_0 (the theoretical ventricular volume at zero pressure), ventricular elastance has been estimated from a single beat[58,67,73,82,83] without considering V_0. The assumption of V_0 equal to 'zero' substantially reduces the E_{lv} and the ratio E_a/E_{lv} to a function of the ejection fraction $[E_a/E_{lv} = (1/\text{LVEF}) - 1]$[84] and could lead to the wrong assumption that ejection fraction and E_{lv} are interchangeable in this analysis (LVEF= Left Ventricular Ejection Fraction). Although ejection fraction and E_{lv} are directly related, this assumption is not correct, because it is known that V_0 can be considerably different in patients with normal or depressed left ventricular function.[64,85] In an attempt to overcome these limitations, new approaches have been proposed to calculate from a single beat reliable estimates of both V_0 and end-systolic ventricular elastance.[86,87]

Wave intensity analysis

In the last years, a new approach, the 'wave intensity analysis', has been proposed for the assessment of ventricular–arterial coupling.[88,89] Wave intensity considers changes in pressure and velocity at any point in the arterial tree as a result of interaction between forward-travelling and backward-travelling wavelets carrying energy from the heart and vasculature, respectively. Wave intensity is defined as dP/dU, where dP and dU represent instantaneous rates of change in pressure and flow. As with aortic input impedance, wave intensity analysis thus provides information on magnitude and direction of propagating wavelets,[90,91] with the advantage of performing the analysis in the time domain. Another potential advantage of wave intensity analysis is the possibility offered by modern ultrasound machines of automatic calculation, combining the information derived from Doppler and echo-tracking data.[92] The algorithm of automated calculation is based essentially on the assumption that the observed changes of arterial diameter are linearly correlated with changes of blood pressure.[93] It is well known, however, that changes of arterial diameter follow pressure changes with a variable hysteresis,[94] and therefore this assumption could lead to an unpredictable bias. Moreover, the clinical applicability of this approach to the assessment of ventricular–arterial coupling, although promising, still needs to be demonstrated in wide populations.

Impact of arterial structure and function on ventricular load in hypertension

Structural and functional changes of conductance arteries and arterial load

Hypertension induces structural (atherosclerosis, myointimal thickening) and functional (increased stiffness) changes of the arterial tree that can change left ventricular load. Atherosclerosis may modify pressure wave propagation and reflection along the arterial tree. Animal studies[95,96] have shown an increase of pulse wave velocity after induction of atherosclerosis with lipid-rich diet. Large population studies, however, did not show a significant impact of dyslipidemia on pulse wave velocity

after correcting for age and blood pressure.[97] Accordingly, no significant correlation between cholesterol levels and local (carotid Young's elastic modulus and β stiffness index)[98] or systemic (total arterial compliance)[99] indices of arterial stiffness was found in populations with a high prevalence of atherosclerosis. Conversely, central pulse pressure and augmentation index have been found increased in patients with hypercholesterolemia.[100] Interestingly, preliminary data obtained in a population of familial hypercholesterolemic patients showed an earlier return of reflected waves, even in the absence of increased pulse wave velocity.[101] This suggests that atherosclerosis, inducing new proximal sites of wave reflection, may shorten the effective length of the arterial tree, contributing to the increase of load imposed on the left ventricle. Additional studies, however, are needed in order to assess the impact of atherosclerosis on wave reflection and ventricular–vascular coupling in human populations.

Approximately 30% of hypertensive patients develop carotid intimal–medial thickening.[102,103] The chronic cyclic stress of the vessel wall due to high blood pressure promotes muscular cell proliferation and increases wall thickness[104] with a mechanism tending to wall stress normalization. Accordingly, in hypertensive patients, the relative wall thickness of carotid arteries is increased,[103] whereas Young's elastic modulus, which normalizes the stress/strain relation for wall thickness,[105] is not significantly different from normotensive patients.[106]

Several studies have shown that in hypertension arterial stiffness is increased and age-dependent changes of the vessel wall are more marked. This increase of 'operative' stiffness is related to both structural changes and passive stretching of the arterial wall. When elastic fibres are completely elongated, further increments in distending pressure cause recruitment of inelastic collagen fibres. Thus, in hypertensive patients the 'operative' stiffness (measured by Peterson's elastic modulus or pulse wave velocity) is usually increased, whereas stiffness tends to be normal when measured by Young's elastic modulus (which takes into account arterial wall thickening) or stiffness index β' (which takes into account the nonlinearity of arterial pressure–distension relationship).[57,103] For this reason, increments of arterial stiffness should be interpreted as secondary to structural changes of the arterial wall only after considering distending pressure. Reliable comparisons of stiffness parameters between normotensive and hypertensive patients should also be performed at reference pressure levels.[107,108]

It should be noticed that changes in aortic wall thickness, stiffness and diameter due to hypertension may have different impact on stiffness parameters. In fact, whereas pulse wave velocity is relatively insensitive to diameter, characteristic impedance is extremely sensitive to diameter changes. Thus, if operating diameter decreases by 10% with no change in wall properties, pulse wave velocity will increase by 5%, whereas characteristic impedance will increase by 25%.[59] The complex interplay between hypertension-induced aortic distension, which reduces characteristic impedance, and passive stiffening due to recruitment of collagen fibres could thus provide contrasting results when aortic stiffness and ventricular load are assessed with different parameters.[109,110]

Elasticity of large arteries is influenced by polymorphisms of genes coding for elastin,[111] collagen,[112,113] fibrillin[114] and the renin–angiotensin system.[115,116] All these genetic variants can affect the structural and functional characteristics of the arterial tree and have significant impact on arterial load. For instance, Medley and colleagues[114] demonstrated that different fibrillin genotypes are associated with modifications of aortic impedance and different levels of central and peripheral blood pressure. Similarly, Tarasov and colleagues[113] found a significant association between genetic variants of type 4 collagen and pulse wave velocity in the SardiNIA population study.

Finally, hypertension-induced endothelial dysfunction may play a role in determining arterial stiffness and ventricular load. It is known that nitric oxide and endothelin contribute to the regulation of vascular tone and their action may influence arterial distensibility[117] and pulse wave velocity.[100,118] The relationship between endothelial dysfunction and vascular stiffening, however, may also be the opposite (i.e. vascular stiffening contributing to endothelial dysfunction), as some studies[119] have shown. The activation of renin–angiotensin–aldosterone system (RAAS) in endothelial cells and vascular smooth muscle reduces the production of nitric oxide, leading to endothelial dysfunction, changed vascular smooth muscle cell function and arterial stiffening.[120] The sympathetic nervous system is also involved in this process, because RAAS, through angiotensin II, facilitates neuronal transmission within sympathetic ganglia. This favours, in turn, norepinephrine release by sympathetic nerve terminals, enhancing α-mediated vasoconstriction in arterioles.[121]

Pressure wave reflection and arterial load

The pressure waveform recorded in central arteries reflects both cardiac pump and arterial characteristics, providing information on arterial load. The amplitude of the reflected wave, evaluated in terms of augmentation index, has been shown to be related to aortic impedance.[23] Therefore, the increase in amplitude of reflected waves, or their earlier return to the central districts, increases the load imposed on the left ventricle and reveals suboptimal ventricular–arterial coupling. The change of load conditions due to early wave reflection increases myocardial oxygen consumption,[122,123] whereas the concomitant decrease in diastolic blood pressure reduces coronary perfusion.[124] This unfavourable

combination impairs the blood supply/demand ratio of the left ventricle and facilitates the onset of myocardial ischaemia.[125,126] The early return of reflected waves to central arterial districts can therefore be figured as a poorly timed intra-aortic balloon pump, which increases left ventricular afterload and myocardial oxygen consumption while simultaneously reducing diastolic pressure in ascending aorta and, as a consequence, coronary perfusion.[13]

The clinical impact of pressure wave reflection is not limited to left ventricular load and coronary perfusion. Pressure wave amplification may be influenced by hypertension and hypertension-induced arterial damage. Patients with major cardiovascular risk factors, such as hypertension, diabetes, hypercholesterolaemia, smoking or established cardiovascular disease, have lower pressure wave amplification, independent of confounding factors such as age, sex, height and heart rate.[20] Aside from physical changes in the arterial wall attributable to these cardiovascular risk factors, an acute increase in mean blood pressure may increase arterial stiffness and pressure wave reflections, thus leading to acutely reduced amplification.[127] There is increasing evidence that antihypertensive drugs may have different effects on central and peripheral pressure by increasing or reducing pressure wave amplification.[127] The discrepancy between brachial and central pulse pressure may account for the finding that in untreated patients with essential hypertension, regression of left ventricular mass index after 1 year of drug treatment was independently associated with increase of pressure wave amplification, but not with reduction in brachial pulse pressure.[128]

Impact of arterial load on left ventricular structure and function in hypertension

Arterial load and left ventricular structure

Arterial load acts on left ventricle, modulating its adaptive responses. Ganau *et al.*[1,129] have shown that the adaptation of the left ventricle to arterial hypertension is polymorphic and is in relation to the different characteristics of the haemodynamic load. More specifically, left ventricular concentric remodelling reflects a condition of reduced volume load (denoted by decreased SV),[130] whereas volume overload is typically associated with the development of eccentric hypertrophy. Moreover, whereas concentric geometric patterns are characterized by high peripheral resistance, in eccentric hypertrophy peripheral resistance is not significantly increased.[1]

The pulsatile load, measured in terms of amplitude of pressure wave reflection (augmentation index or augmentation pressure), is an additional stimulus to left ventricular hypertrophy in humans, independent of blood pressure and peripheral resistance.[25,131] This finding was also confirmed in experimental models in which the arterial load was changed by aortic banding at two different levels.[132] In a group of rats with distal aortic banding, besides a marked elevation of left ventricular pressure, a strong reflection component of aortic impedance was observed and a significant increase in left ventricular mass occurred. On the contrary, in a group of animals with proximal aortic banding, the pressure elevation was similar compared with the previous group and a marked elevation of aortic characteristic impedance was observed. In the latter group of animals, however, left ventricular mass did not increase significantly.[132] This study confirms the role of reflected waves as an independent stimulus to myocardial hypertrophy and suggests that arterial stiffness *per se* has little influence on left ventricular mass. Accordingly, Roman *et al.*[133] observed in hypertensive humans that higher arterial stiffness, as assessed by carotid β' stiffness index, was not associated with increased left ventricular mass, whereas a significant direct relationship between arterial stiffness and left ventricular relative wall thickness was found. Moreover, data from a small study suggest that the reduction of left ventricular mass due to antihypertensive treatment is, at least in part, related to modification in amplitude and timing of reflected waves.[134]

Interestingly, hypertensive patients with elevated effective arterial elastance have about three-fold greater (30 vs. 9%) prevalence of concentric ventricular geometry than hypertensive patients with arterial elastance in the normal range.[58] Higher effective arterial elastance was related with not only relatively smaller left ventricular cavity size but also larger relative wall thickness in a small sample of a general population.[135] Further studies should be performed to confirm these observations in wider populations.

Impact of arterial load on left ventricular function

Diastolic function

Change of arterial load may profoundly influence left ventricular diastolic function. Experimental data demonstrate the functional coupling between the left ventricle and the arterial tree not only during the systolic phase but also in diastole.[136] This is probably mainly related to the impact of reflected pressure waves on myocardial fibre relaxation process and on coronary perfusion.[137]

Several observations in different populations reported the dependence of ventricular diastolic function on timing and amplitude of reflected pressure waves.[137,138] Therefore, the reduction of E-wave amplitude and the inversion of *E*/*A* ratio, commonly observed at transmitral Doppler examination in hypertensive patients, may be an expression of the physiological response of myocardial fibres to an abrupt overload generated by the early return of reflected pressure waves (load dependence of myocardial relaxation).[139] When diastolic function is assessed by tissue Doppler, E' also results inversely associated with vascular load, and this association is most pronounced for late systolic load, which is mediated predominantly by systolic wave

reflections.[140] These data imply that the changed transmitral flow pattern, commonly observed in the elderly and in hypertensive patients (both characterized by increased pressure wave reflection and late systolic pressure peak), is not necessarily due to structural stiffening of myocardial tissue, but can be a functional and thus potentially reversible change. Similarly, the higher prevalence of diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) in women could be related to both enhanced wave reflection[141] and higher arterial stiffness.[142,143] Therefore, therapies designed to reduce late systolic vascular loading and arterial stiffening may be useful for treating patients with diastolic dysfunction or failure.

Systolic function

The effects of pressure wave reflection on left ventricular systolic function have been studied mainly on animal models.[24] These studies have shown that the increase of the pulsatile load, due to the early return of reflected waves, significantly reduces the efficiency of myocardial contractility. Kelly *et al.*[24] in a canine model in which pulsatile load was increased using a Dacron bypass showed that the change in load was associated with a mild reduction of ejection fraction (from 50 to 43%), whereas the cardiac energetic cost of delivering a given SV, estimated by oxygen consumption, increased by 20–40%. These data were confirmed by Zannoli *et al.*,[144] who showed that the early return of the reflected waves is associated with reduced flow and external cardiac work.

The operational contractile function of the left ventricle, assessed as midwall fractional shortening, is reduced in hypertensive patients with left ventricular concentric hypertrophy.[145,146] Accordingly, in hypertensive patients with elevated arterial elastance, among whom prevalence of left ventricular hypertrophy and concentric geometry is high, a significant reduction of midwall fractional shortening has been observed.[58] Nevertheless, ventricular pump function, assessed in terms of ejection fraction and endocardial fractional shortening, was preserved.[58] Similarly, Nitenberg *et al.*[74] showed in a population of hypertensive patients with left ventricular hypertrophy that peak ventricular elastance was increased in absolute terms but, after correction for left ventricular mass, it was significantly depressed. These data suggest that, despite the loss in contractility, the increase of left ventricular mass and elastance, balancing the elevation of arterial load, helps in keeping the E_a/E_{lv} ratio within the normal limits. Accordingly, Borlaug *et al.*[48] showed that after correction for end-systolic stress, left ventricular midwall fractional shortening is normal or ever increased in uncomplicated hypertensive patients, providing a normal ventricular–vascular coupling also in the presence of elevated afterload. Data from other populations also confirm the observation of normal ventricular–arterial coupling in hypertensive patients with a high prevalence of left ventricular hypertrophy.[68] According to this view, concentric left ventricular hypertrophy may represent an adaptive mechanism that increases E_{lv}, keeping normal ventricular–vascular coupling. A similar mechanism occurs in the elderly, in whom, despite a marked elevation of E_a, ventricular–vascular coupling tends to be normal.[84,147] In this case, the compensatory increase of E_{lv} is favoured by the age-induced increase of left ventricular concentric geometry.[147,148]

A changed ventricular vascular coupling and the consequent combination of reduced contractility and diastolic dysfunction may represent the pathophysiological basis of the progression to HFpEF, which is highly prevalent in hypertensive populations.[149] Accordingly, although E_a/E_{lv} ratio could be still normal in these patients at rest,[48] an abnormal ventricular–vascular coupling can be revealed during exercise.[50,150]

Overall, these data suggest that in conditions characterized by high arterial load (E_a) such as hypertension and ageing, the development of left ventricular hypertrophy and/or concentric geometry preserves left ventricular pump function (ejection fraction) and, increasing left ventricular elastance, optimizes ventricular vascular coupling (E_a/E_{lv} ratio ≤ 1). This occurs at an energy cost lower than nonhypertrophic hearts, in which the ejection work is achieved by an increase in contractility, which is energetically more expensive.[74] This is detrimental, however, in the long term, because it favours the development of HFpEF.

Therapeutic implications

Whereas hypertension is associated with an increased risk of cardiovascular events, blood pressure lowering reduces the hypertension-attributable cardiovascular risk. This is in part related to slowing target organ damage progression, but could also be related to improvement of ventricular–vascular coupling. Blood pressure normalization, independently of the drug used, reduces effective arterial elastance and the coupling ratio, allowing better left ventricular mechanical efficiency and lesser oxygen consumption.[151,152] The various classes of antihypertensive agents, however, act differently on pressure wave reflection and impedance modulus: after short-term administration, whereas vasodilators, calcium channel blockers and angiotensin-converting enzyme inhibitors (ACEIs) improve all the haemodynamic changes, β-blockade appears deleterious.[153] Moreover, the beneficial action of ACEIs compared with β-blockers lasts in the long term.[153] The beneficial effect of ACEIs seems to be related to a reduction of wave reflections. This is potentially attributable to chronic reverse remodelling of the small arteries leading to reduced reflection coefficients.[127] Class-specific effects of drugs on central haemodynamics (with special regard to β-blockers) may explain, at least in part, the difference in mortality and left ventricular structure that was observed in the

CAFÉ,[154] REASON[155] and LIFE[156] trials. Therefore, β-blockers may be suboptimal as first-line therapy in hypertension, especially in patients with increased pulse pressure. It should also be considered that, compared with β-blockers, vasodilating drugs exert a favourable effect on pressure wave amplification. This means that for the same reduction of brachial pulse pressure, they reduce central pulse pressure more than β-blockers.[127]

Finally, reduction of arterial stiffness could be a therapeutic target in order to reduce pulsatile vascular load. Diuretics and ACEIs have been shown to reduce arterial wall thickening and improve arterial compliance through reduction of operative stiffness.[157] This mechanism, however, could be reasonably extended to all antihypertensive drugs. Newer pharmacological approaches have been evaluated for the reduction of arterial stiffness[158,159] and improvement of ventricular vascular coupling but are still not available in the clinical practice.

Conclusion

The assessment of ventricular vascular coupling is crucial for the understanding of several aspects of hypertension, from ventricular adaptation to therapeutic strategies. The old, reductive concept that hypertension acts on left ventricle only as pressure overload has been widely reconsidered. Moreover, the role of pulsatile components of arterial load and wave reflection emerged as critical in modulating the hypertension-induced left ventricular structural and functional modifications. As a consequence, therapeutic strategies for treating hypertension need to consider the impact of drugs on the different components of arterial load in order to favour the regression of left ventricular hypertrophy and improve systolic and diastolic function.

Although often questioned, the E_a/E_{lv} model appears as more suitable for the assessment of ventricular vascular coupling in wide study populations. Its applicability in the daily clinical practice, however, is still far away. Possibly, in the near future, the automated calculation of wave intensity could provide reliable insights of the ventricular vascular interaction also in the daily clinical practice.

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