HIGHLIGHTED TOPIC | Physiology of the Aging Vasculature

Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise

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Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol 105: 1342–1351, 2008. First published July 10, 2008; doi:10.1152/japplphysiol.90600.2008.—Understanding the performance of the left ventricle (LV) requires not only examining the properties of the LV itself, but also investigating the modulating effects of the arterial system on left ventricular performance. The interaction of the LV with the arterial system, termed arterial-ventricular coupling (EA/ELV), is a central determinant of cardiovascular performance and cardiac energetics. EA/ELV can be indexed by the ratio of effective arterial elastance (EA; a measure of the net arterial load exerted on the left ventricle) to left ventricular end-systolic elastance (ELV; a load-independent measure of left ventricular chamber performance). At rest, in healthy individuals, EA/ELV is maintained within a narrow range, which allows the cardiovascular system to optimize energetic efficiency at the expense of mechanical efficacy. During exercise, an acute mismatch between the arterial and ventricular systems occurs, due to a disproportionate increase in ELV (from an average of 4.3 to 13.2, and 4.7 to 15.5 mmHg·mL⁻¹·m⁻² in men and women, respectively) vs. EA (from an average of 2.3 to 3.2, and 2.3 to 2.9 mmHg·mL⁻¹·m⁻² in men and women, respectively), to ensure that sufficient cardiac performance is achieved to meet the increased energetic requirements of the body. As a result, EA/ELV decreases from an average of 0.58 to 0.34, and 0.52 to 0.27 in men and women, respectively. In this review, we provide an overview of the concept of EA/ELV, and examine the effects of age, hypertension, and heart failure on EA/ELV and its components (EA and ELV) in men and women. We discuss these effects both at rest and during exercise and highlight the mechanistic insights that can be derived from studying EA/ELV.

left ventricular function; arterial system; exercise; aging; disease

AGING AND CARDIOVASCULAR (CV) diseases, such as hypertension and congestive heart failure (HF), modify the structure and function of both the central arteries and the left ventricle (LV). Left ventricular performance is influenced by the arterial load (33), and arterial properties are, in turn, influenced by left ventricular performance (33, 77). Indeed, the interaction between the LV and the arterial system, known as arterial-ventricular coupling (EA/ELV), is an important determinant of net CV performance (33) and cardiac energetics (74). In this paper, we will review the concept of EA/ELV and its components, effective arterial elastance (EA; a measure of the net arterial load) and left ventricular end-systolic elastance (ELV; a measure of left ventricular performance), and we will discuss the novel mechanistic insights EA/ELV provides into the effects of aging, hypertension, and HF on CV performance at rest and during exercise.

ARTERIAL-VENTRICULAR COUPLING AND ITS COMPONENTS

Traditionally, arterial load was characterized in the frequency domain as impedance spectra (49, 54), whereas left ventricular performance was characterized in the time domain by indexes of pressure and volume (77). This difference hindered the ability to examine the cross talk, or the interactions, between the LV and the central arteries. Studying these interactions required that novel methods be developed, which assess left ventricular and arterial properties in the same domain.

Effective Arterial Elastance

Sunagawa’s pioneering work (77), using a three-element windkessel model in the isolated canine heart, showed that the arterial load could globally be characterized in the time domain as EA (elastance is the change in pressure for a change in volume). EA is not a measure of a specific arterial property; rather, it is an integrative index that incorporates the principal elements of arterial load, including peripheral vascular resistance (PVR), total arterial compliance, characteristic impedance, and systolic and diastolic time intervals (77). EA can, therefore, be considered a measure of the net arterial load that is imposed on the LV. EA is determined from pressure-volume (P-V) loops as the negative slope of the line joining the end-diastolic volume (EDV) and end-systolic pressure (ESP) points (Fig. 1) and can be approximated by the ratio of ESP to stroke volume (SV) (77). ESP can be estimated from the formula $2 \times (systolic \ BP +$
diastolic BP)/3 (37), where BP is blood pressure, or from the formula ESP = 0.9 × systolic BP (37). Kelly et al. (37) showed that EA measured invasively as ESP/SV closely approximated the arterial load obtained from aortic input impedance and arterial compliance data based on a three-element windkessel model [EA = 1.0 × EA(windkessel) − 0.11, SE of estimate = 0.12; coefficient of variation = 0.97, P < 0.001] (37). One limitation of the three-element windkessel model is that it does not include the effects of the reflected pressure waves, which originate from areas of major impedance mismatches or major bifurcations. These reflected waves arrive earlier in the cardiac cycle when the velocity of the pulse wave is increased, as occurs with aging or with hypertension, and they can substantially augment the systolic load on the heart. However, the net effects of the reflected waves are functionally accounted for in P-V loops (37). Thus EA can be considered as a surrogate measure of aortic input impedance whose advantage is that it can be related to measures of ELV, thus allowing the study of arterial and ventricular interactions (see below).

**Left Ventricular End-Systolic Elastance**

Sagawa et al. (67), in an isolated canine heart model, showed that left ventricular contractility (or end-systolic stiffness) could be indexed by ELV. ELV is determined from the slope of the end-systolic P-V relationship (Fig. 1), which can be obtained from a series of P-V loops recorded while the preload of the heart is altered. An increase in contractility is depicted by an increase in the slope and a shift in the end-systolic P-V relationship to the left, which allows the ventricle to generate more pressure for a given LV volume. ELV can be calculated as ESP/[end-systolic volume (ESV) − V0], where V0 is the x-axis volume intercept of the end-systolic P-V relationship (obtained from the linear extrapolation of the end-systolic P-V relationship). The calculation of ELV assumes that the end-systolic P-V relationship is independent of load, that its slope is linear, and that V0 is insensitive to inotropic influences. Under physiological loading conditions, these assumptions are reasonable approximations (12, 34).

Although ELV is widely regarded as a load-independent index of left ventricular contractility (66, 67), it is also influenced by the geometric and biochemical properties that underlie left ventricular end-systolic stiffness (9). Thus caution should be exercised in interpreting the significance of an elevated ELV, particularly when other measures of left ventricular systolic function are normal (32). It is likely that acute changes in ELV (e.g., with inotropic agents or exercise) reflect acute alterations in left ventricular contractility, whereas baseline values of ELV represent an index that integrates intrinsic left ventricular contractility as well as the modulating effects of the geometric, structural, and functional properties of the LV (32). ELV should, therefore, be considered an integrated measure of left ventricular chamber performance that can be related to an integrated measure of arterial load (i.e., EA).

**Arterial-Ventricular Coupling**

Importantly, EA shares common units with ELV, and their ratio EA/ELV is a measure of the interaction between the LV and the arterial system (77). EA/ELV is an important determinant of net cardiac performance (33) and cardiac energetics (74). Appropriate matching between the LV and the arterial system at rest results in an optimal transfer of blood from the LV to the periphery without excessive changes in pressure; an optimal or near-optimal stroke work (SW); and energetic

\[
\begin{align*}
ESP &= 0.9 \times \text{Systolic BP} \\
EA &= \text{ESP/SV} \\
ELV &= \text{ESP/ESV-V0} \\
EA/ELV &= (\text{ESP/SV})/(\text{ESP/ESV-V0}) \\
E_A/ELV &= \text{ESP-V0/SV} \\
E_A/ELV &= (1/EF)-1 \\
SW &= \text{ESP} \times \text{SV} \text{ (shaded area)} \\
PE &= \text{ESP} \times \text{SV/(V0)}/2 \text{ (hatched area)} \\
PVA &= \text{SW + PE}
\end{align*}
\]
efficiency, i.e., the energy consumed by the heart to achieve the required SW (9). In healthy men and women, in the resting state, mean ± SD values of $E_A/E_{LV}$, $E_A$, and $E_{LV}$ measured invasively are $1.0 ± 0.36$, $2.2 ± 0.8$ mmHg/ml, and $2.3 ± 1.0$ mmHg/ml, respectively (18).

**Noninvasive Measures of Arterial-Ventricular Coupling and Its Components**

The initial studies from Sagawa’s group (67, 77–79) were performed in isolated canine hearts, which were instrumented to obtain P-V loops. Subsequently, $E_A$ and $E_{LV}$ were measured in humans from P-V loops acquired in the cardiac catheterization laboratory (11, 36). However, the invasive nature of these techniques limited their use in humans to a few skilled research groups. Fortunately, noninvasive estimates of $E_A$ and $E_{LV}$ were subsequently developed, which are discussed below (19, 48, 60, 61, 64).

As noted above, $E_A$ can be calculated as ESP/SV. SV can be readily measured noninvasively (e.g., by echocardiography or gated blood pool scans) (25, 73). Chen et al. (17) found that the calculation of ESP from $0.9 \times$ brachial systolic BP reasonably approximated ESP measured invasively: the correlation coefficient between the two variables was 0.75, and the regression line had a slope of 1.01 ($P < 0.0001$).

Importantly, the equation $E_A = ESP/SV$ can be algebraically rearranged to show that $E_A$ is proportional to the sum of HR (heart rate) × PVR and [(ESP − mean arterial pressure)/SV], suggesting that the main determinants of $E_A$ include HR, a resistive component (PVR), and a stiffness component (change in pressure/change in volume) (20).

For the noninvasive assessment of $E_{LV}$, two approaches have been developed. The first is based on the equation noted above ($E_{LV} = ESP/ESV − V0$), and assumes that V0 is negligible compared with ESV. Thus, by measuring ESV noninvasively (e.g., by echocardiography or by gated blood pool scans) and by calculating ESP as $0.9 \times$ systolic BP, $E_{LV}$ can be noninvasively estimated.

The second noninvasive approach to assess $E_{LV}$ attempts to derive the slope of the end-systolic P-V relationship without altering the loading conditions of the heart. This approach takes advantage of the finding that, under physiological loading conditions, the time-varying elastance curves, from which the end-systolic P-V relationships are derived, are fairly independent of loading conditions, left ventricular contractile state, and HR, particularly when they are normalized to peak amplitude (end-systolic stiffness) and time to peak amplitude (70). As a result, the end-systolic P-V relationship can be estimated from a single heartbeat (70). This method requires the measurement of systolic and diastolic BPs, ejection fraction (EF), and SV, pre-ejection period, and total systolic ejection period on Dopper echocardiography. This single-beat elastance approach has been validated against invasively measured $E_{LV}$ with a correlation coefficient of 0.81 ($P < 0.001$) [single-beat $E_{LV} = 0.78 \times E_{LV}$ (invasive) + 0.55, SE of estimate = 0.6] (17).

From these noninvasive determinations of $E_A$ and $E_{LV}$, the $E_A/E_{LV}$ ratio can be calculated. The noninvasively obtained values of $E_A/E_{LV}$ closely approximate those obtained invasively (21, 65). $E_A/E_{LV}$ is inversely related to EF [$E_A/E_{LV} \approx (1/EF) − 1$] (20). The advantage of $E_A/E_{LV}$ over EF is that examining the components of $E_A/E_{LV}$ allows us to evaluate whether alterations in $E_A/E_{LV}$ are due to alterations in arterial properties, left ventricular properties, or both. Importantly, the ability to noninvasively assess $E_A/E_{LV}$ has expanded the range of clinical trials and the scope of conditions in which $E_A/E_{LV}$ could be investigated. For example, $E_A/E_{LV}$ has been examined in epidemiological studies (61) and in studies evaluating the effects of exercise (50).

**Scaling of Effective Arterial Elastance and Left Ventricular End-Systolic Elastance**

Because body size is an important determinant of CV structure and function, adjusting for body size (or for left ventricular mass) is often needed when CV variables are being characterized or compared among groups. Moreover, there is no consensus as to the best strategy for normalizing $E_A$ or $E_{LV}$. Both SV and ESV vary directly with body size. Thus some investigators have scaled SV to body surface area (BSA) (5, 50, 65), whereas others have scaled $E_A$ (i.e., ESP/SV) to BSA (61). For $E_{LV}$, a broader spectrum of scaling variables has been utilized, including BSA (29, 47), BSA to the power 1.19 (24), body mass (28), left ventricular mass (7), left ventricular EDV (30), and left ventricular mass/EDV (42). For the most part, the scaling technique has consisted of dividing $E_{LV}$ by the variable of interest. However, this approach does not necessarily provide adequate adjustment for the variable of interest, because $E_{LV}$ may not necessarily be linearly related to the variable. Instead, a preferred approach might be the allometric scaling method (6, 26, 52), whereby $E_{LV}$ is divided by the variable of interest raised to a scalar exponent, which is derived from an equation that linearly relates the two. In the following sections, CV variables that are normalized to body size will be depicted by the suffix “I” (e.g., $EAI$ and $E_{LV}I$).

**Arterial-Ventricular Coupling and Its Components During Exercise**

Exercise provides a powerful tool to examine the response of the CV system to stress and to assess its functional reserve. During exercise, the goal of the CV system is to prioritize cardiac efficacy over energetic efficiency (50). It uses a complex combination of alterations in HR, LV contractility, preload (EDV and SV), and afterload to ensure adequate blood supply to the tissues.

Few studies have examined the changes in $E_A/E_{LV}$ and its components during exercise. In adult dogs, Little and Cheng (43) reported that $E_A/E_{LV}$ decreased by ~25% from rest to submaximal exercise. In healthy human subjects undergoing supine cycle ergometry, Asanoi et al. (3) observed that $E_A/E_{LV}$ decreased by 35 and 54% at workloads corresponding to 30%, 50, 65, whereas others have scaled $E_A$ (i.e., ESP/SV) to BSA (61). For $E_{LV}$, a broader spectrum of scaling variables has been utilized, including BSA (29, 47), BSA to the power 1.19 (24), body mass (28), left ventricular mass (7), left ventricular EDV (30), and left ventricular mass/EDV (42). For the most part, the scaling technique has consisted of dividing $E_{LV}$ by the variable of interest. However, this approach does not necessarily provide adequate adjustment for the variable of interest, because $E_{LV}$ may not necessarily be linearly related to the variable. Instead, a preferred approach might be the allometric scaling method (6, 26, 52), whereby $E_{LV}$ is divided by the variable of interest raised to a scalar exponent, which is derived from an equation that linearly relates the two. In the following sections, CV variables that are normalized to body size will be depicted by the suffix “I” (e.g., $EAI$ and $E_{LV}I$).

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approximately three times higher than to a similar change in arterial stiffness (16, 69). In contrast, during exercise, arterial stiffness has a progressively and intensity-dependent greater impact on $E_A$ than PVR (57, 58), such that $E_A$ (on average) increases during exercise, paralleling the increase in arterial stiffness, despite a reduction in PVR (57).

Some of the methodological issues pertaining to the noninvasive assessment of $E_A/ELV$ and its components during exercise should be highlighted. At rest, the single-beat elastance approach is regarded as the preferred noninvasive method to measure $ELV$ (17). However, the single-beat elastance approach may be technically challenging during exercise, because of the difficulties in measuring cardiac volumes and systolic time intervals with echocardiography during exercise (63). If imaging modalities other than echocardiography are available for measuring ESV and SV during exercise (e.g., gated blood pool scans), then estimating $ELV$ from the formula $ELV = ESP/ESV$ may be more feasible. However, the noninvasive measurement of $ELV$ from ESP/ESV has, in turn, its own limitations. 1) It assumes that $V_0$ is negligible compared with ESV. $V_0$ has not been well characterized in humans, particularly during exercise. In healthy adult dogs, Little and Cheng (43) found that, although the absolute values of $V_0$ did not significantly change during exercise, $V_0$ as a percentage of ESV increased by 9%. In contrast, in healthy subjects, Starling (74) found that $V_0$, both in absolute values and as a percentage of ESV, did not appreciably change during dobutamine infusion. 2) The formula used to noninvasively estimate ESP (ESP = 0.9 × systolic BP) has not been validated during exercise. In this regard, methodologies that use radial applanation tonometry may be of help as they allow noninvasive and accurate estimations of central SBP at rest and during exercise, at least in the supine position and at low intensities of exercise (71, 72).

In the subsequent sections, we will examine the effects of age, hypertension, and HF on $E_A/ELV$ and its components, both at rest and during exercise, and we will highlight important sex differences when appropriate. Advancing age, hypertension, and HF all result in alterations in $E_A/ELV$ and its components, both at rest and during exercise. These changes are summarized in Table 1.

### Table 1. Summary of the alterations in arterial-ventricular coupling and its components with age, hypertension, and heart failure at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>At Rest</th>
<th>At Peak Exercise</th>
<th>Reserve</th>
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<tbody>
<tr>
<td>$E_A/ELV$</td>
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<td>$E_A/ELV$</td>
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<td>Old vs. young</td>
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<td>HTN vs. NT</td>
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<td>Women</td>
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<tr>
<td>SHF vs. healthy controls</td>
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<tr>
<td>Men and Women</td>
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<tr>
<td>HFpEF vs. healthy controls</td>
<td>$\leftarrow$</td>
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<td>Men and Women</td>
<td>$\leftrightarrow$</td>
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Arrows indicate directionality of the comparison.  
$E_A$, effective arterial elastance; $ELV$, LV end-systolic elastance; $E_A/ELV$, arterial-ventricular coupling; HTN, hypertensive; NT, normotensive; SHF, systolic heart failure; HFpEF, heart failure with a preserved ejection fraction.

### AGE

**Arterial-Ventricular Coupling and Its Components at Rest**

Aging influences the structural and functional properties of both the arterial system and the LV. With advancing age, the central arteries dilate, and their walls become thicker and stiffer (51). $E_A$ increases with advancing age in individuals without known CV diseases (18, 21, 65). For example, in 2,042 individuals from Olmsted County, Minnesota, Redfield et al. (61) observed an age-associated increase in $ELV$ in both men ($r = 0.28$, $P < 0.001$) and women ($r = 0.28$, $P < 0.001$) (Fig. 2). Similar results were obtained in a subset of the population ($n = 623$) that was free from CV diseases (61). The age-associated increase in $ELV$ was principally attributed to the age-associated increase in arterial stiffness, because pulse pressure increased with age, whereas PVR and HR did not change.

Advancing age is also associated with alterations in left ventricular structure and function. Most notably, there is a reduction in myocyte number in men, but not in women, and there is an increase in left ventricular wall thickness and collagen deposition (40, 55). These alterations are accompanied by an increase in resting $ELV$ with advancing age (18, 21, 61). For example, healthy 75-yr-old men and women had a $\approx 10\%$ ($P < 0.01$) and $\approx 15\%$ ($P < 0.01$) higher resting $ELV$, respectively, compared with their 55-yr-old counterparts (Fig. 2) (61). These findings are unlikely to be due to differences in left ventricular chamber size, as similar results were obtained when $ELV$ was normalized to left ventricular EDV (61). Sex-related differences were also noted, whereby $ELV$ was higher in women than in men at all ages and increased more steeply with advancing age (61). Other markers of left ventricular systolic function, such as stress-corrected fractional shortening (61), circumferential end-systolic stress/ESV index (8), and preload-recruitable SW (30), have also been shown to be higher in women than in men. In addition, female rats have an enhanced systolic function compared with male rats (14, 81), suggesting that the higher $ELV$ in women may reflect a higher left ventricular systolic function.

Because a higher $ELV$ represents a steeper slope of the end-systolic P-V relationship, it results in an increased sensi-
tivity of systolic pressure to changes in volume (36). Kass et al. (35) reported, in an isolated canine heart model, larger reductions in ELV after a myocardial infarction in hearts with a higher resting ELV. This greater mechanical vulnerability to an ischemic insult may help to explain why older individuals, who have an increased ELV [particularly older women and hypertensive (HTN) subjects, see below] experience worse outcomes following a myocardial infarction.

Even though EA and ELV both increase with advancing age, their ratio, EA/ELV, remains relatively unchanged across the age spectrum in men (18, 21, 50), suggesting that the increases in EA and ELV are matched. In contrast, EA/ELV declines slightly with advancing age in healthy women (61), reflecting a disproportionate increase in ELV compared with EA. This suggests a greater impact of aging on ventricular vs. arterial properties in women compared with men. Furthermore, women have a higher resting EA, and an even higher resting ELV than men (50, 61), but a lower resting EA/ELV, suggesting that the sex differences in EA/ELV are predominantly related to sex differences in ventricular properties. These sex differences in EA and ELV persist even after adjusting for age, body size, and HR (61).

Arterial-Ventricular Coupling and Its Components During Exercise

It is well known that there is an age-associated deficit in CV performance at peak exercise that is evident from age-associ-
ated reductions in HR, EF, and oxygen consumption at peak exercise (41). Najjar et al. (50) reported that the decline in \( E_{AI}/E_{LV} \) from rest to peak upright bicycle exercise is blunted in older (>60 yr) compared with younger (<40 yr) healthy men and women (Fig. 3A). This blunted \( E_{AI}/E_{LV} \) response was attributed to a blunted increase in \( E_{LV} \) during exercise in older compared with younger individuals (Fig. 3C), as the

**Fig. 4.** \( E_{AI}/E_{LV} \) (A), \( E_{AI} \) (B), and \( E_{LV} \) (C), measured at rest in normotensive (NT) and systolic hypertensive (SH) men and women. \( E_{AI}/E_{LV} \) does not differ at rest between NT and SH men due to tandem increases in \( E_{AI} \) and \( E_{LV} \) in SH vs. NT men. In contrast, resting \( E_{AI}/E_{LV} \) is lower in SH women vs. NT women, due to a disproportionate increase in \( E_{LV} \) vs. \( E_{AI} \). * \( P < 0.05 \), ** \( P < 0.01 \), *** \( P < 0.001 \), comparing NT to SH after adjusting for age. [From Chantler et al. (15).]

**Fig. 5.** The change in \( E_{AI}/E_{LV} \) (A), \( E_{AI} \) (B), and \( E_{LV} \) (C) in NT (solid symbols) and SH (open symbols) men (solid lines) and women (dashed lines). At rest, \( E_{AI}/E_{LV} \) is similar between NT and SH men and is lower in SH vs. NT women (\( P < 0.01 \)). \( E_{AI}/E_{LV} \) decreases during exercise in both NT and SH men and women (\( P < 0.01 \)). There are no differences between NT and SH men and women at 50% maximal workload (MWL) or at peak exercise. At rest, \( E_{AI} \) is higher in SH vs. NT men and women (\( P < 0.001 \)). \( E_{AI} \) increases during exercise in both NT and SH men and women (\( P < 0.05 \)). However, only SH men have a higher \( E_{LV} \) at 50% MWL and at peak exercise vs. NT men (\( P < 0.001 \)), as no differences are found between NT and SH women at 50% MWL or at peak exercise. [Modified from Chantler et al. (15).]
increase in $E_A$ during exercise did not differ between young and older subjects (Fig. 3B) (50). Consequently, advancing age is associated with a smaller $E_A/E_LV$ reserve ($E_A/E_LV$ peak − $E_A/E_LV$ rest) and $E_LV$ reserve ($E_LV$ peak − $E_LV$ rest) (50). Thus examining $E_A/E_LV$ and its components during exercise provides additional insights into the age-associated deficits in EF reserve and suggests that it is due to age-associated deficits in left ventricular contractile reserve, more so than to age-associated differences in arterial properties.

Najjar et al. (50) also observed age by sex interactions in $E_A/E_LV$ in their normotensive (NT) cohort. In younger (<40 yr) individuals, peak $E_A/I/E_LV$ was lower in men than in women, whereas in older (>60 yr) individuals, peak $E_A/I/E_LV$ was higher in men than in women (Fig. 3A). This was attributed to an age by sex interaction in $E_LV$, whereby, at peak exercise, $E_LV$ was higher in younger men vs. younger women, but did not differ between older men and women (Fig. 3C). As for $E_A$, it was higher in both young and old men compared with women (Fig. 3B).

Only one study has examined the effects of exercise training on $E_A/E_LV$ and its components during exercise. In 26 patients with coronary artery disease, Rinder et al. (62) found that 12 mo of aerobic endurance exercise training lead to a 37% increase in $E_LV$ and a 23% decrease in $E_A/E_LV$ during handgrip exercise performed at 30% of maximal voluntary contraction. However, the change in $E_A$ during handgrip exercise remained unaltered after the exercise training.

**HYPERTENSION**

**Arterial-Ventricular Coupling and Its Components at Rest**

The prevalence of hypertension markedly increases with advancing age, such that it affects 66% of individuals over 60 yr of age (56). Hypertension is an important risk factor for mortality, stroke, and HF (23, 31). The age-associated changes in arterial and left ventricular structure and function are accentuated in the presence of hypertension. HTN patients exhibit greater carotid wall thickness (2), central arterial wall stiffness (1), and reflected waves (53) than NT subjects, even after adjusting for age. Furthermore, hypertension is associated with LV remodeling and fibrosis (46).

Few studies have examined the impact of hypertension on $E_A/E_LV$ and its components. Cohen-Solal et al. (20) showed that HTN individuals have a 60 and 95% higher $E_A$ and $E_LV$, respectively, compared with NT controls. Saba et al. (64) found that HTN individuals have a 23 and 29% higher $E_A$ and $E_LV$, respectively, compared with NT controls. However, $E_A/E_LV$ did not differ between HTN and NT men (20, 64), suggesting that the increases in $E_A$ and $E_LV$ in HTN men was matched. In contrast, $E_A/E_LV$ was ∼23% lower in systolic HTN compared with NT women (15), a finding that persisted even after adjusting for age (Fig. 4A). The lower $E_A/E_LV$ in systolic HTN women was due to a disproportionate increase in $E_LV$ (Fig. 4B) compared with $E_A$ (45 vs. 16%) (Fig. 4C), suggesting an adaptation by these women to limit the impact of systolic hypertension on the vasculature or, alternatively, a more pronounced impact of systolic hypertension on ventricular vs. arterial elastance.

**Arterial-Ventricular Coupling and Its Components During Exercise**

Only one study has examined the effects of systolic hypertension on the changes in $E_A/E_LV$ and its components during exercise. $E_A/I/E_LV$ did not differ between NT and HTN men and women at 50% of maximal workload or at peak upright bicycle exercise (Fig. 5) (15). In men, this was because $E_A$ and $E_LV$ were proportionally higher at peak exercise in HTN compared with NT, whereas, in women, this was because $E_A$ and $E_LV$ did not differ at peak exercise between HTN and NT. Thus $E_A/I/E_LV$ reserve did not differ between HTN and NT men, but it was 61% lower in HTN compared with NT women, because HTN women have a lower $E_A/I/E_LV$ at rest. This was accompanied by a 60% lower $E_A$ reserve in HTN compared with NT women (15).

**HEART FAILURE**

**Arterial-Ventricular Coupling and Its Components at Rest**

HF is a syndrome that is characterized by an inability of the heart to pump a sufficient amount of blood to meet the demands of the metabolizing tissues, or can do so only at the expense of elevated filling pressures (30a). We will only provide a brief summary of the alterations in $E_A/E_LV$ and its components in HF, as insights they provide into the pathophysiology of HF and response to treatments have recently been reviewed (9, 27).

Systolic HF. HF patients with systolic dysfunction are characterized by a diminished resting EF and left ventricular contractility (5). Systolic HF patients have a downward and rightward shift of the end-systolic P-V relationship (Fig. 6) and thus a reduced $E_LV$ (range 0.6–2.6 mmHg·mL⁻¹·m⁻²) (5). Systolic HF patients have an augmented $E_A$ (range 1.7–3.7 mmHg·mL⁻¹·m⁻²) due to a decrease in SVI and to increases in HR and PVR (5). The increase in $E_A$ and decrease in $E_LV$ result in marked, up to three- to fourfold, increases in $E_A/E_LV$ (range 1.3–4.3) (5, 68). This suboptimal coupling reflects diminished CV performance and efficiency of the failing heart.

HF with a preserved EF. Approximately 40% of patients with HF have an EF ≥50% (59). These individuals are classified as HF patients with a preserved EF (HFP EF). HFP EF is more prevalent in older women than men (39), and systolic HTN is the most common risk factor for this syndrome (39). HFP EF patients have an 18 and 20% higher resting $E_A$ and $E_LV$, respectively, compared with healthy controls (42). One study found that patients with HFP EF had a disproportionately higher $E_LV$ than $E_A$ compared with young and old NT controls, and thus a lower $E_A/E_LV$ (36). However, in a larger sample population, Lam et al. (42) noted that patients with HFP EF had matched increases in $E_A$ and $E_LV$; thus their $E_A/E_LV$ did not differ from $E_A/E_LV$ of NT controls or individuals with HTN but without HF. These conflicting findings may be due to differences in patient selection and group comparisons with which the HFP EF patients were compared, or to the heterogeneity among patients classified as having HFP EF. For example, Maurer et al. (45) noted that some patients with HFP EF who were NT had values of $E_A$ and $E_LV$ that did not differ from those of healthy NT controls.
Arterial-Ventricular Coupling and Its Components During Exercise

Systolic HF. The baseline alterations in $E_A/E_{LV}$ and its components in patients with systolic HF are also evident during exercise (22). Indeed, $E_A$, $E_{LV}$, and $E_A/E_{LV}$ do not appreciably change during exercise in systolic HF patients, whereas they markedly change in healthy subjects (22). Thus the limited capacity of systolic HF patients to augment their CV function during times of stress (such as exercise) involve marked deficits in both LV and arterial elastance reserves.

HF with a preserved EF. To date, there are no studies that have examined the change in $E_A/E_{LV}$ or $E_A$ during exercise in HFpEF. Borlaug et al. (10) examined the change in $E_{LV}$ and EF in HFpEF during upright bicycle exercise. Compared with HTN controls with LV hypertrophy, HFpEF patients had a threefold smaller increase in $E_{LV}$ and a reduced ability to lower their PVR and increase their HR during exercise (10). They also had a 50% smaller increase in EF during exercise as EF is inversely related to $E_A/E_{LV}$ (20), this suggests that the change in $E_A/E_{LV}$ during exercise in HFpEF may also be severely blunted. Since female sex and systolic hypertension are risk factors for HFpEF (39), and as the pathophysiology of HFpEF involves a limited CV reserve (38), the diminished $E_A/E_{LV}$ reserve observed in systolic HTN women (15) suggests that they may be exhibiting signs of subclinical (Stage B) HF. This raises the possibility that they may be on a trajectory to progressive exercise intolerance and perhaps functional limitations.

CARDIAC ENERGETICS

$E_A/E_{LV}$ is an important determinant of cardiac energetics (13, 74). From P-V loops, total mechanical energy can be quantified as the pressure-volume area (PVA), which is composed of SW (shaded area in Fig. 1) and potential energy (hatched area in Fig. 1) (76). PVA and myocardial oxygen demand are linearly related (75); therefore, PVA has been used as an index of the oxygen cost of performing a given SW (74). Thus the amount of SW performed by the LV and the amount of oxygen the LV consumes while performing this SW vary with the loading conditions imposed on the LV and the contractile state of the LV (76).

$E_A/E_{LV}$ in the range of 0.6–1.2 in the resting state (9) is thought to represent the optimal interaction between the arterial and LV systems (74) and confers the near-optimal balance between mechanical efficacy and energetic efficiency (74). Interestingly, this range is also observed across species (44, 80), suggesting that it has been conserved through mammalian evolution.

During exercise, energetic efficiency is sacrificed in favor of cardiac efficacy to augment CV performance. To date, very few studies in humans have examined the impact of age, hypertension, and HF on cardiac energetics during exercise. Chantler et al. (15) found that HTN women, but not men, had a higher SWI and PVA at peak exercise compared with NT controls. Furthermore, an exaggerated increase in $E_A$ during exercise, as noted in older women (50) and in women with hypertension (60), increases the pulsatile load on the LV, which may increase the cardiac energy costs to provide blood flow by raising myocardial oxygen consumption.

CONCLUSIONS

Examination of the alterations in $E_A/E_{LV}$ and its components, $E_A$ and $E_{LV}$ with aging, hypertension, and HF at rest and during exercise is often overlooked, yet it can yield mechanistic insights into the pathophysiology of these conditions and how they differ between men and women. Future studies should examine the effects of lifestyle changes (e.g., physical conditioning), other medical conditions (e.g., diabetes), and the various classes of medications used to treat hypertension and HF on $E_A/E_{LV}$ and its components, $E_A$ and $E_{LV}$. Furthermore, longitudinal studies are needed to evaluate whether alterations in $E_A/E_{LV}$, $E_A$, and $E_{LV}$ provide any prognostic information for adverse outcomes, such as HF.

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Review

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