

Ventricular-arterial coupling in heart failure: insights into gender-specific differences

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Summary. The cardiovascular function in physiological conditions depends on a complex interaction between heart performance and vascular system. To describe this situation, the term ‘elastance’ has been devised. Arterial elastance (Ea) is defined as the obstacle that the arterial system opposes to the work of the left ventricle. Ventricular elastance represents heart stiffness and is an important index of myocardial contractility. Considering the interaction between the left ventricle and the arterial system – which is called *ventricular-arterial coupling* (VAC) – information can be obtained about the functional status of the entire cardiovascular system. In physiological conditions, the ventricular-arterial coupling is different in males and females. This is due to the morphological and functional characteristics of the left ventricle, the elastic properties of the aortic wall and the different susceptibility of peripheral resistances to hormonal factors and vasoactive substances. In women, vessel and myocardial stiffness is even more pronounced in pathological conditions. This could explain the gender differences in the pathophysiology and the clinical presentation of heart failure. In fact, the prevalence of heart failure with reduced ejection fraction (HFrEF) is higher in men than in women. Conversely, the latter suffer from heart failure with preserved ejection fraction (HFpEF) more frequently than men, especially after menopause. This suggests that the loss of estrogens, which have an anti-fibrotic and anti-inflammatory activity, could play an important role in the genesis of heart failure in women, increasing left ventricular and vascular stiffness. Hormonal changes can also affect peripheral resistances, and therefore the cardiac load.

Key words. Heart failure, gender differences, ventricular elastance, vascular stiffness, ventricular-arterial coupling.

Accoppiamento ventricolo-arterioso nell'insufficienza cardiaca: approfondimenti sulle differenze genere-specifiche

Riassunto. La funzione cardiocircolatoria in condizioni fisiologiche dipende dall'interazione tra due diversi fattori: la performance cardiaca e il sistema vascolare. Per descrivere questa interazione sono stati conati i termini elastanza ventricolare ed elastanza arteriosa. L'elastanza arteriosa (Ea) è definita come l'ostacolo che il sistema arterioso oppone al lavoro del ventricolo sinistro. L'elastanza ventricolare rappresenta la rigidità del cuore ed è un indice impor-

tante della contrattilità miocardica. Considerando l'interazione tra il ventricolo sinistro e il sistema arterioso, definita accoppiamento ventricolo-arterioso, è possibile ottenere informazioni sullo stato funzionale dell'intero sistema cardiovascolare. In condizioni fisiologiche l'accoppiamento ventricolo-arterioso differisce tra uomini e donne. Questo è dovuto alle caratteristiche morfologiche e funzionali del ventricolo sinistro, alle proprietà elastiche della parete aortica e alla diversa suscettibilità delle resistenze periferiche ai fattori ormonali e alle sostanze vasoattive. Nelle donne, la rigidità dei vasi e del miocardio è ancora più pronunciata in condizioni patologiche. Questo potrebbe spiegare le differenze di genere nella fisiopatologia e nella presentazione clinica dell'insufficienza cardiaca. Infatti, la prevalenza dell'insufficienza cardiaca con frazione di eiezione ridotta (HFrEF) è maggiore negli uomini che nelle donne. Al contrario, queste presentano più frequentemente scompenso cardiaco a frazione di eiezione conservata (HFpEF), specialmente dopo la menopausa. Questo suggerisce che la perdita di estrogeni, che possiedono un'attività anti-fibrotica e antinfiammatoria, giochi un ruolo importante nella genesi dell'insufficienza cardiaca nelle donne, aumentando la rigidità vascolare e ventricolare sinistra. I cambiamenti ormonali possono anche influenzare le resistenze periferiche e quindi il carico cardiaco.

Parole chiave. Insufficienza cardiaca, differenze di genere, elastanza ventricolare, rigidità vascolare, accoppiamento ventricolo-arterioso.

Heart failure: gender differences

Heart failure is the leading cause of mortality and hospitalization in Western countries.¹ Several epidemiological studies showed that there are gender differences in the presentation of heart failure (HF) among patients. In fact, HF is almost twice as prevalent in women with preserved ejection fraction (HFpEF) than in men. Conversely, men have a higher prevalence of heart failure with reduced ejection fraction (HFrEF).² These discrepancies are due to different structural myocardial features, a different ability to adapt to loads and a different diastolic function. Obesity and diabetes are often associated with this condition.³ Structurally, women have a

smaller left ventricular chamber and a higher ejection fraction.⁴ In addition, their myocardial mass is usually preserved compared to men. In response to age or to an increase in the afterload due to hypertension or aortic stenosis, women tend to develop concentric ventricular hypertrophy while preserving the systolic function, while men tend to present a dilation of the chamber. However, the normalization of the wall stress due to concentric hypertrophy leads to a reduced diastolic compliance. The diastolic stiffness of the chamber increases with age in both sexes, but more in women (both at rest and during exercise), which suggests a greater decline in age-related diastolic function.⁵

After menopause, women show an increase in the incidence of HFpEF. This suggests a close correlation with the estrogen levels. It has been shown that, with age, post-menopausal women tend to have a greater increase in the left ventricular mass, a smaller chamber, a thicker ventricular wall, a less rapid diastolic filling velocity (E) and a lower E/A ratio compared to pre-menopausal women.^{6,7} These findings show that estrogen deficiency is a determinant of structural changes in post-menopausal hearts. Furthermore, a difference in the ventricular filling pattern was demonstrated between post-menopausal women being treated with a hormone replacement therapy (HRT) and those without HRT. HRT, in fact, improves the electrocardiographic parameters and the diastolic function, but not the systolic function. These differences imply that estrogen deficiency is involved in the pathophysiology of structural heart changes in women after menopause. Finally, estrogen deficiency could exacerbate a hypertension-induced diastolic dysfunction.

The effect of age on the left ventricular diastolic function appears to be more pronounced in women. Obesity and insulin resistance are also closely associated with HFpEF, and this association is more pronounced in women.

End-systolic ventricular elastance, arterial elastance and ventricular-arterial coupling

The pathophysiology of heart disease has been extensively studied through the analysis of the pressure-volume curves. In fact, from this analysis it is possible to obtain several information on left ventricle status, arterial load and the adaptation of the heart to the vascular system. To better understand this pathophysiology, reference should be made to the original studies, conducted by Suga and Sagawa.^{8,9} By obtaining pressure-volume curves under different load conditions in experimental models, they defined the properties of the ventricular-arterial system through the concept of end-systolic ventricular elastance (Ees) and arterial elastance (Ea).

Left ventricular end-systolic elastance corresponds to the slope of the straight line deriving from the union of end-systolic points of different cardiac cycles obtained in the same heart at different loading conditions. In other words, this line represents the intracavitary pressure required to increase the heart volume by a unit, an expression of maximum ventricular stiffness. The value of ventricular elastance, given by the angular coefficient of the line ($\Delta P/\Delta V$), was observed to be an index of the contractility of the left ventricle, regardless of preload and afterload conditions. Chen et al. showed that this parameter was an important element in the evaluation of the left ventricular function in decompensated patients.

The arterial elastance is defined as the obstacle that the arterial system opposes to the left ventricle. In other words, when the ventricle ejects a volume of blood into the aorta, the arterial system, which comprises peripheral resistances, total vascular compliance and impedance, opposes to the systolic flow.

In addition, cardiac load can be expressed as the combination of a static and a pulsatile component. The static component of the afterload is represented by the total peripheral resistances, which largely depend on the microvascular properties. Conversely, pulsatility is mainly affected by the properties of the vessels: the impedance of the proximal aorta, the magnitude and timing of the reflection wave generated by cardiac ejection, and the total compliance of the arterial system. The studies of Sunagawa et al. showed that there is a linear relation between the end-systolic pressure (ESP) generated by the left ventricle and the ejection volume (SV) expelled into the aorta. In the pressure-volume loop, the slope of the line expressing this relationship – which is called arterial elastance – defines the characteristics of the arterial system. In fact, a high value of Ea suggests that the ventricle, in order to produce a certain stroke volume, must generate high ventricular pressures. Conversely, if the ventricle is able to generate a high stroke volume with low pressure, it means that the obstacle of the arterial system is low.

Finally, considering the interaction between the left ventricle and the arterial system, information could be obtained on the functional status of the entire cardiovascular system. The relationship between the two systems – which is called ventricular-arterial coupling (VAC) – provides information on the performance and the efficiency of the system. Physics laws state that two objects are said to be coupled when they are interacting with each other, allowing a transfer of energy from the source to the load. The ventricle is a generator of hydraulic energy, which transfers the mechanical energy of the contraction to the blood, under the influence of the arterial system.

Cardiac work, potential energy and performance

In physics, work is defined as a force causing the displacement of an object, and is measured in joules. The heart is a pump that develops a force used to move a certain volume of blood during a systole. From the analysis of the pressure-volume curves, it is possible to calculate the cardiac work (or stroke work), assuming that the curve of the cardiac cycle has a rectangular shape. From this approximation, it is evident that the stroke work (SW) is the result of the product of base (EDV-ESV) and height (ESP) (Figure 1). To accomplish this work, however, the heart must convert its potential energy into the kinetic energy necessary to contraction. The potential cardiac energy (PE) is represented by the area subtended by the end-systolic elastance line relation.

Finally, it is possible to calculate the performance, which is the ratio between the work done and the energy supplied to the system during the energy-conversion process. The performance – or efficiency – is therefore obtained from the ratio between the systolic work and the potential energy spent to perform it.

Some studies have shown that stroke work is maximum when E_a/E_{es} is equal to about 1, whereas maximum cardiac efficiency is reached when the ratio is equal to 0.5.¹⁰ In fact, studies by Burkhoff and Sagawa showed that, for maximum efficiency, arterial elastance must be half of the ventricular one (coupling = 0.5).^{11,12} In these conditions, the heart produces an EF equal to 60%, which is the value of a healthy heart.

Invasive and non-invasive methods for the calculation of elastance

The gold standard for the estimation of elastance, described by Kono et al, is an invasive method that involves the insertion of catheters in the ventricle to obtain pressure and volume measurements at different beats (multiple beats), by modifying the ventricular preload.¹³

To make this evaluation simpler, and not dependent on invasive studies, methods on a single-beat model have been developed for a non-invasive estimation of elastance.

The first study that reports this technique was conducted by Senzaki et al in 1996,¹⁴ but only later its validity was demonstrated for the first time by Chen et al, who compared the single-beat method with the values obtained with the invasive method.¹⁵

Today, the calculations of end-systolic ventricular elastance, arterial elastance, ventricular arterial coupling, SW, PE and LV efficiency are more commonly performed in a non-invasive way, by means of an echocardiogram.

The formulas for the calculation of the parameter derived from pressure-volume loop are reported in Table 1.

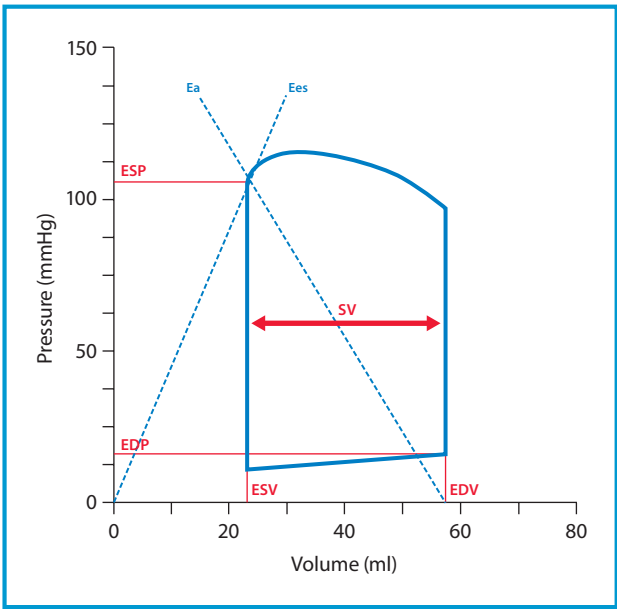


Figure 1. The stroke work (SW) is the result of the product of base (EDV-ESV) and height (ESP).

Table 1. Measurement of the parameters derived from a pressure-volume loop of the left ventricle

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| End-systolic pressure (ESP) = systolic blood pressure x 0.9 |
| Arterial elastance (E_a) = ESP/stroke volume |
| End-systolic LV elastance (E_{es}) = ESP/end-systolic volume |
| End-diastolic LV elastance (E_{ed}) = EDP/end-diastolic volume |
| Ventricular-arterial coupling (VAC) = E_a/E_{es} |
| Stoke work (SW) = ESP x SV |
| Potential energy (PE) = ESP x ESV/2 |
| Pressure-volume area (PVA) = PE + SW |
| LV work efficiency = 100 x SW/PVA |

Ventricular-arterial coupling in patients with heart failure

Ventricular-arterial coupling in heart failure with reduced ejection fraction

In heart failure with reduced ejection fraction, when the cardiac function decreases E_{es} is reduced, and tissue hypoperfusion occurs. This causes the activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, in an attempt to increase the intravascular volume and the arterial load, in order to counterbalance the reduced systemic perfusion. However, the increase in E_a leads to an enormous increase in the E_a/E_{es} ratio, with a decoupling which leads to a

reduction in the efficiency of the cardio-vascular system. This creates a condition that predisposes to a further worsening of the cardiovascular function.^{16,17}

Ventricular-arterial coupling in heart failure with preserved ejection fraction

In the case of HFpEF, the underlying problem is an increase in the stiffness of the ventricular walls, that causes an altered diastolic relaxation. It manifests itself with an increase in wall stress.¹⁸ These alterations are accompanied by an increase in ventricular size, with a shift to the left of the pressure-volume relation curve.

In addition, HFpEF is a common condition in elderly subjects, and is associated with a high burden of comorbidities (especially hypertension, obesity and diabetes), which are partly responsible for the stiffness of the arterial system. The increase in arterial stiffness results in a more rapid propagation of the pressure wave, and in an earlier reflection wave that occurs at the end of the systole, instead of during the diastole. This results in an increase in central aortic pressure, which in turn causes an increase in the afterload and in oxygen demand. At the same time, there is a reduction in central diastolic blood pressure, and therefore of coronary perfusion. This imbalance leads to myocardial ischemia in the absence of coronary stenosis, which deteriorates the diastolic performance of the left ventricle. Again, the increase in impedance – and therefore in arterial pressure – is associated with an increase in left ventricular afterload, which in turn causes a hypertrophic concentric adaptation, that leads to diastolic dysfunction. In the heart failure with preserved ejection fraction, both E_a and E_{es} increase, resulting in a normal ventricular-arterial coupling value (Figure 2).¹⁸

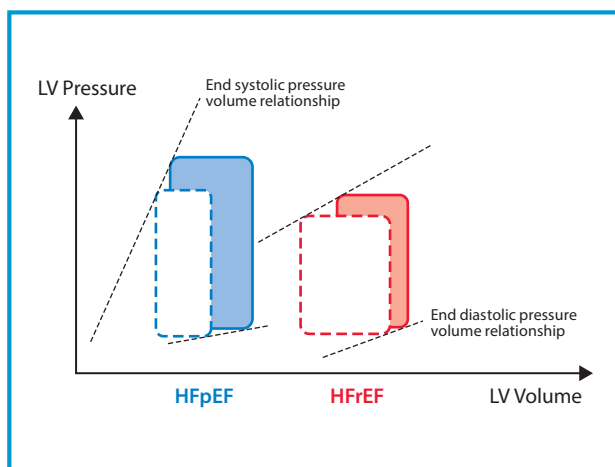


Figure 2. In the heart failure with preserved ejection fraction, both arterial elastance (E_a) and end-systolic ventricular elastance (E_{es}) increase, resulting in a normal ventricular-arterial coupling value.

Gender differences in ventricular-arterial coupling in heart failure

Over the years, several authors tried to explain the gender differences identified in heart failure patients through the analysis of the volume-pressure curves. As already described above, the prevalence of HFpEF in women is greater than in men, in whom HFrEF is more prevalent.

In HFpEF, the underlying problem is the increase in the stiffness of the ventricular walls, which causes an altered diastolic relaxation and an increase in wall stress. In the study conducted by Coutinho et al, women suffered from a high arterial stiffness, as evidenced by a higher aortic impedance and a lower arterial compliance versus men.¹⁹ It has also been suggested that aortic stiffness and pulsatile load during an early systole may decrease the efficiency of the cardiovascular system in women, leading to diastolic dysfunction.²⁰ The increase in impedance – and therefore in arterial elastance – is associated with an increased left ventricle afterload, which leads to concentric adaptations, that in turn cause the development of diastolic dysfunction. In fact, it has been widely demonstrated that women have smaller ventricular chambers and a reduced diastolic function.⁴ Furthermore, a stiff vascular system determines a greater heart systolic stress, that can cause microvascular abnormalities leading to organ damage.²¹ It has been also shown that women have a greater prevalence of microvascular dysfunction, which is closely related to HFpEF.²²

Redfield et al demonstrated that arterial stiffness is greater in women and that the linear association with age is steeper in women than in men.²³ In the same study, they showed that women, under the same conditions, presented a greater end-systolic and end-diastolic ventricular elastance at rest than men. A greater age-related increase in E_{es} in women than in men is also present. Essentially, in men, against a similar increase in both variables, arterial-ventricular coupling remains unchanged.

In women, on the other hand, a slightly reduced VAC occurs with age, due to a greater increase in E_{es} compared to E_a .²⁴

This increase in ventricular elastance is accomplished through an increase in contractility and through a cardiac remodeling that represents an adaptation to the increase in arterial stiffness, in order to normalize the left ventricle systolic stress and maintain optimal SV and mechanical efficiency. However, the stiffening of the heart-vessel system causes an increase in the sensitivity of systolic pressure to volumetric changes. This could partially explain the exercise intolerance and the predisposition to heart failure (Figure 3). These changes introduce the mechanism of diastolic dysfunction, which is characterized by the inability of the heart chambers to dilate in order to accommodate volumes of blood, due to the increased rigidity of the ventricular walls.

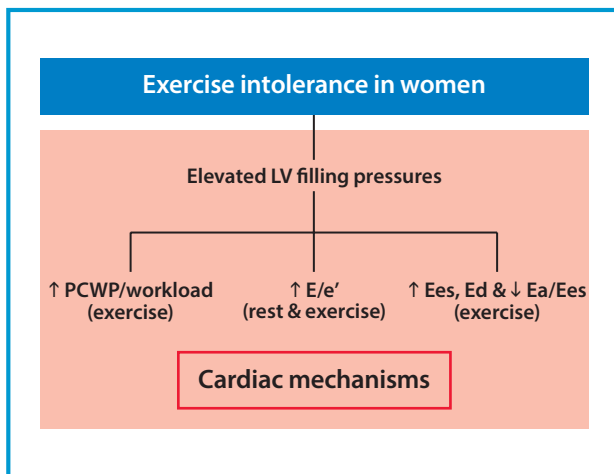


Figure 3. Exercise intolerance in women.

It has already been reported that older women present a greater proximal aorta stiffness compared to younger women or to men of the same age.²⁵ This contributes to increase the arterial elastance. A reliable indicator of the arterial system stiffness is the central aortic pulse pressure (APP), an invasively-obtained hemodynamic parameter which has been independently associated with E/e values.²⁶ This has been demonstrated in elderly females, but not in elderly males, which explains the relationship between the greater arterial elastance and the higher ventricular end-diastolic pressure found in females. Gender differences in ventricular-arterial coupling have traditionally been attributed to hormonal variances, with particular reference to estrogens.²⁷ Before menopause, the estrogen receptors – active in the large central arteries – show anti-inflammatory properties and vasoprotective effects. Therefore, the loss of estrogens after menopause could lead to a profibrotic and proinflammatory milieu.²⁸ The loss of estrogenic action in women could play a role in the increase in arterial stiffness and the decrease in elasticity. It can be concluded that ventricular-arterial coupling is similar in the two sexes, despite women having increased E_{es} and E_a , due to a greater stiffness, which is however counterbalanced by a greater sensitivity of the system to any variations of the standard conditions. With age, VAC will tend to decrease more in women than men, due to a greater ventricular stiffness, rather than to arterial stiffness. Ventricular elastance – which represents a load-independent contractility index of the left ventricle – is also affected by the geometric and biochemical properties underlying the stiffness of the left ventricle. In fact, women – who have higher values of ventricular elastance than men – have been shown to develop higher left ventricular hypertrophy and to maintain a better systolic function than men, in response to a pressure overload.

Elastance differences in men and women have also been studied in other pathological conditions.²⁹⁻³¹ In patients with hypertension, several studies have shown that ventricular and arterial elastance values in men are approximately 60-90% higher than in normotensive patients. The increase in afterload is in fact balanced by an increase in ventricular mass, which leads to an increase in ventricular size, in order to maintain an optimal systolic ejection. This parallel increase, therefore, ensures an almost unchanged VAC. In hypertensive woman, on the other hand, a decrease in VAC of about 23% occurs, due to a greater increase in E_{es} compared to E_a . This greater increase in ventricular stiffness, compared to arterial stiffness, is explained by a greater adaptation to high pressures in the woman's vessels, but also by a greater susceptibility of the ventricle to hypertension.³² Other studies focused on the behavior of arterial-ventricular coupling during exercise, and on the differences between sexes.³³

In general, it has been shown that, during exercise, ventricular-arterial coupling tends to decrease because of a greater increase in E_{es} compared to E_a .^{34,35} The increase in E_a during exercise is due to an increased stiffness of the vessels in stress conditions. Stiffness has the greatest impact on E_a compared to the total peripheral resistances, which in these conditions decrease, but without affecting the total value of E_a . However, this decrease in the E_a/E_{es} ratio during exercise occurs to a lesser degree in the elderly than in the young, and this is explained by a smaller increase in ventricular size in the elderly. This proportionally smaller reduction in VAC in old age produces a deficit in contractile reserve.³⁶ In addition, the fall of E_a/E_{es} during exercise is observed more frequently in women, probably due to an increase in E_{es} secondary to a greater increase in the reflected wave.^{34,37} At the same time, arterial compliance is lower in women, which leads to greater increases in arterial elastance during exercise. This is confirmed in another study conducted in endurance sports (i.e. sports continued for a prolonged time), where a reduction in ventricular-arterial coupling values was observed only in females.³⁸ It has also been reported that in young people VAC during exercise is lower in males than in females, due to a greater ventricular elastance. On the contrary, in the elderly VAC during exercise is higher in men than in women, because of a larger sensitivity to afterload, which results in a greater increase in ventricular size.³⁶

Other studies have shown that, in patients with HFpEF, the ventricular-arterial coupling is altered, due to a reduction in the contractile reserve and to an abnormal vasodilation.³⁹ In HFpEF, VAC decreases during exercise less than in healthy subjects, leading to a smaller increase in the ejection fraction. In addition, heart rate increases less than in healthy subjects. This uncoupling

also leads to an altered oxygen consumption, and therefore to a reduction in cardiac efficiency.⁴⁰

A recent study investigated the hemodynamic differences between HFpEF female and male subjects. Compared to men, women had a lower left ventricular diastolic reserve, which plays a central role in the pathophysiology of HFpEF. This was explained by a higher PCWP increase in response to workload, and also by a greater increase in PCWP indexed for stroke volume variations during exercise.⁴¹

In the same study, there were gender differences in the vascular system, which was less compliant at rest and during exercise, together with a trend toward higher values of arterial and systemic vascular resistance in women with HFpEF compared to men. This is in agreement with the data from other studies, which showed a greater age-related stiffness in women than men.²³

On the contrary, HFrEF is characterized by a decrease in Ees and an increase in Ea values, due to an increase in impedance, heart rate and total peripheral resistances. These changes in elastance cause an abnormal increase in the Ea/Ees ratio, which manifests itself with a reduction in the efficiency of the cardiovascular system.

In conclusion, in normal physiological conditions, ventricular-arterial coupling is different in men and

women. This is due to the morphological and functional characteristics of the left ventricle, the elastic properties of the aortic wall and the different susceptibility of the peripheral system to hormonal factors and vasoactive substances. These gender-related differences are also present in heart failure, suggesting a central role of the interaction between ventricle and vascular system in the genesis and manifestation of this syndrome.

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Key messages

- Heart failure (HF) is almost twice as prevalent in women with preserved ejection fraction than in men.
- Left ventricular systolic elastance is an index of myocardial contractility. Arterial elastance (Ea) is the obstacle that the arterial system opposes to the left ventricle. Ventricular-arterial coupling – the relation between Ea and end-systolic ventricular elastance (Ees) – provides information on the functional status of the cardiovascular system.
- In heart failure with reduced ejection fraction (HFrEF), the increase in Ea, due to the activation of the renin-angiotensin-aldosterone system (RAAS), leads to an enormous increase in the Ea/Ees ratio, with a decoupling which leads to a reduction in the efficiency of the cardio-vascular system.
- In HFpEF, the increase in arterial stiffness results in an earlier reflection of the pressure wave that occurs at the end of the systole, instead of during the diastole, causing hypertrophic concentric adaptation and diastolic dysfunction.
- Estrogen deficiency is a determinant of the structural changes in the cardiac and vascular system, since it plays a role in the genesis of heart failure in women.
- Arterial stiffness is higher in women. This leads to concentric adaptations of the left ventricle, which cause a greater increase in ventricular stiffness, compared to arterial stiffness and diastolic dysfunction.

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