Research Article ISSN 2639-8486

Cardiology & Vascular Research

Pathophysiology of the Arterial, Ventricular, and Atrial Haemodynamic Axis. Potential Clinical Implications

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Received: 23 Apr 2026; **Accepted:** 26 May 2026; **Published:** 06 Jun 2026

Citation: Carlos Alberto Paterno Marchioli. Pathophysiology of the Arterial, Ventricular, and Atrial Haemodynamic Axis. Potential Clinical Implications. Cardiol Vasc Res. 2026; 10(3): 1-7.

ABSTRACT

Arterial hypertension is a complex, multifactorial, and chronic disease, frequently beginning during childhood and adolescence, recognized to be a state of chronic low-grade inflammation, which increases arterial stiffness that in turn produces mitral regurgitation that leads to a progressive left atrial enlargement with the development of ectopic atrial rhythm, and later the new onset of atrial fibrillation. Therefore, the coexistence of arterial stiffness, mitral regurgitation, and ectopic atrial rhythm could be defined as a syndrome of the arterial, ventricular, and atrial hemodynamic axis that can occur even in symptomatic patients who do not fall into the classification of "hypertensive".

The goal of primordial prevention is to maintain the state of cardiovascular health, with a solid population-based strategy that includes non-pharmacological behaviours and effective antihypertensive therapy to prevent cardiovascular complications.

Keywords

Arterial stiffness, Mitral regurgitation, Ectopic atrial rhythm, Atrial fibrillation.

Objective

This study aims to determine whether the coexistence of arterial stiffness, mitral valve insufficiency, and ectopic atrial rhythm in symptomatic patients can be interpreted as an early cardiovascular syndrome within the Arterial, Ventricular, and Atrial Haemodynamic Axis, and after as a precursor to the development of atrial fibrillation.

Background

Arterial hypertension is a complex, multifactorial, and chronic disease, frequently beginning during childhood and adolescence, and it has a significant positive association with adverse cardiovascular outcomes, such as myocardial infarction, stroke, kidney disease, and death [1].

In 2010, 8.8 million adults in the European Union were estimated to suffer from atrial fibrillation, and this number is expected to more than double by the year 2060 [2]. Arterial Hypertension is recognized as a state of chronic low-grade inflammation, elevated levels of inflammatory cytokines, and activation of systemic immunity, which can alter vascular structure and function.

Arterial stiffness

The increase in arterial stiffness is a direct measure of target organ damage, indicating pathological changes in large-artery walls due to cardiovascular risk factors [3].

Abnormalities of left atrial size and function have been previously described in arterial hypertension [4].

It is known that hypertension is the most prevalent independent risk factor for atrial fibrillation in the population and that this is due to atrial enlargement caused by the increased pressure induced in the atrium by left ventricular hypertrophy [5,6].

Both structural remodelling and subsequent electrophysiological

changes by atrial fibrosis constitute an arrhythmogenic substrate for the induction and maintenance of atrial fibrillation.

Arterial Hypertension has been described as a predominantly asymptomatic disease. Still, during the anamnesis, we may find early symptoms, frequently undervalued: headache (prevalent during menses in females), palpitations, sweating, chest pain, breathlessness, throat tightness (prevalent in women), asthenia, mental confusion (prevalent in children). Box 2012 ESH - 2022 ESH 1. In arterial hypertension, the second heart sound is high, even in children and adolescents.

The arterial endothelium contributes to maintaining the balance of cardiovascular function, traditional and emerging risk factors cause functional and structural damage, leading the patient to various stages and degrees of disability that become incompatible with life.

The efficiency of the cardiovascular system depends on the stiffness and geometry of the arteries. The damage to large and small arteries leads to further endothelial dysfunction, reduced vascular compliance, increased vascular stiffness, reduced lumen diameter, and the formation of atherosclerotic plaques [7].

The importance of large-artery stiffening has been further highlighted by the observation that aortic pulse wave velocity, which is inversely related to distensibility, [8] and central augmentation index, a composite measure that depends on the site and degree of wave reflection [9].

Impaired endothelial and smooth muscle cell functions, as well as arterial stiffness, have been previously described in children and adolescents [10].

The augmentation index, which describes the effect of pulse reflection on arterial waveform, is a measure of arterial wall stiffness, a sensitive marker of arterial aging in younger individuals. Increased pulse pressure, a consequence of arterial stiffness, was found to be related to the occurrence of atrial fibrillation. [11]

In addition to traditional and non-traditional risk factors, it can cite the use of hydrochlorothiazide, which increases uric acid and glycemia levels, producing arterial stiffness, and also causes the release of aldosterone through the phenomenon called "escape"[12]. Box 2022 ISH. It is important to add that the effect of estrogen-progestins (Box 2018 ESH – 2017 ESH 3) and systemic inflammatory diseases. Box 2017 ESH 1,2 - 2024 ESH) among the more frequent causes of arterial damage.

Primary Mitral regurgitation

Leonardo da Vinci intuited that the cardiac valves were key to the functioning of the heart, and sought to connect what he considered to be inseparable: bodily structures and their functions.

Mitral regurgitation tends to increase with age [13]. It is the most frequent left-sided valve disease in the community and the second most common in patients hospitalised in the United States [14].

The magnitude of mitral regurgitation depends on the impedance to empty the left ventricle. Mitral regurgitation leads to increased left ventricular preload and reduced afterload, and results in progressive left atrial enlargement.

These structural and functional changes in the left atrium are associated with atrial fibrillation. After thousands of years that had been developed of the mitral valve, it isn't possible that minimal regurgitation from childhood and adolescence is currently interpreted as "non-pathological', "physiologic", "haemodynamically insignificant", also it is attributed that it "starts from birth" or named "para-physiologic effect", "observation non communicable", etc. Box 2020 ESH/ISH – 2021 ESC - 2025 ESH.

Ectopic atrial rhythm and Atrial fibrillation

The left atrium's essential function is modulating left ventricular filling via its different reservoir, conduit, and contractile functions.

Left atrial function, assessed through volumetric changes or myocardial deformation techniques, has also been linked to paroxysmal atrial fibrillation.

The atrium appears to be more sensitive to the hypertrophic effect of Angiotensin II, causing the increased heterogeneity of the electrical conduction speed and the reduced refractoriness, a determining factor in the onset of an arrhythmia after triggering caused by pulsating blood flow.

The left atrium, left ventricle, and arteries behave as a continuous cavity separated by two valves, and the increased pressure of one is immediately transmitted to the upstream structure. The increase in left atrial volume/pressure is related to an increased risk of atrial fibrillation.

Therefore, both the increase in systolic and diastolic pressure values and central haemodynamic parameters could be the cause of the appearance of atrial extrasystoles even in youth.

The electrophysiological characteristics of the arrhythmias, such as ectopic atrial rhythm, and atrial fibrillation, depend on the underlying structural heart disease [15].

Ectopic atrial beats were interpreted as electrical remodeling due to increased wall tension, even without the presence of an increase in atrial diameter and volume, as a final consequence initiated in the arterial-ventricular-atrial couple through mechanical incontinence of the mitral valve. Box 2022 ESH 2 - 2025 ESH.

A pathophysiological explanation may be that the arterial stiffness, increases with age, resulting in increased pulse pressure and increased pulsatile load on the heart, [16] promoting LVH, [17] left ventricular diastolic dysfunction, [18] and increased left atrial

size, [19] possibly leading to fibrosis and electrical remodelling in the left atrium and eventually, atrial fibrillation.

In Medicine, clinical data are always sovereign

On the third-to-last page of the book "Don Quixote de la Mancha," the author Miguel de Cervantes Saavedra writes that the protagonist, in his final moments, "fainted very often". Perhaps the "ingenious hidalgo" was experiencing episodes of "atrial fibrillation"?

Material and Methods

In this study, 265 patients aged 18 and over, of both sexes, were registered, who had presented 3 characteristics: arterial stiffness, minimal mitral regurgitation, and wandering atrial rhythm and/or brief episodes of atrial fibrillation.

The patients were distributed into groups by sex and age in decades.

The youngest patients had never received therapy, and for those of older patients, therapy was not sufficient.

Central systolic blood pressure, central pulse pressure, and the augmentation index are dependent on the speed of wave travel, the amplitude of reflect wave, the reflectance point, and the duration and pattern of ventricular ejection. One of the major clinical applications is in pathophysiological studies.

The SphygmoCor was used to measure the quality of the arteries, device PVX software version 9.0 (AtCor-Medical, Australia), a validated pulse wave analysis system that employs the high-fidelity technique of non-invasive applanation tonometry of the radial artery and an appropriate computer software for pressure wave analysis with a generalized transfer function that assesses the central augmentation index as a surrogate value of the arterial wall stiffness, according to established protocols according to normal ranges by gender and age. The Central Haemodynamic Parameters, such as Central Aortic Pressure, End-Systolic Pressure, Mean Arterial Pressure, Pulse Pressure, and Augmentation Pressure, were measured in mmHg. The Augmentation Index, is the ratio AP/PP and can be corrected for a heart rate of 75, and was measured in percentage. Also, the difference between normal levels and observed values of Augmentation Index was measured.

Atrial arrhythmias were recorded with 24-hour Holter monitoring. Main attention was paid to differentiating them from sinus rhythm, reporting them as isolated wandering supraventricular extrasystoles, in brief phases of ectopic atrial rhythm, or definitively atrial fibrillation.

Minimal mitral regurgitation was detected using the Doppler effect of the echocardiogram.

Results

Comparing both sexes, a similar age was observed in the two groups.

The body mass index rises at higher levels of overweight in both sexes.

The waist circumference/height ratio was higher than normal levels in both sexes, indicating abdominal obesity.

The systolic and diastolic pressure values were higher than those indicated in the latest guidelines on hypertension [20].

Also, it was a higher value than those obtained in a personal study (121/73 mmHg), which did not observe brief phases of atrial fibrillation [21] Table 1.

Table 1: Age, anthropometric values, systolic and diastolic blood pressure.

	n	Age	BMI	WC/H	SBP	DBP
Women	142	62.7	29.2	0.61	140.5	81.3
Men	123	63.0	28.8	0.60	139.1	82.9

BMI: Body Mass Index. WC/H: Waist Circumference/Height. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure.

The central haemodynamic parameters reached higher than normal levels in both sexes. Obviously, the difference in the augmentation index, between the observed value and the normal level, was higher than normal, because the patient's entry must present arterial stiffness (Table 2).

Table 2: Central Haemodynamic Parameters.

	CAP	ESP	MAP	PP	AP	Diff AIx
Women	132.2	119.9	103.0	49.7	19.2	5.5
Men	129.6	118.3	102.3	45.3	13.9	5.3

CAP: Central Aortic Pressure. ESP: End-Systolic Pressure. MAP: Mean Arterial Pressure. Diff-AIx: Difference between normal levels and observed values of the Augmentation Index.

The average systolic and diastolic pressures per decade increase with age; it can be observed that among women, the most significant increase occurs after age 40 and coincides with the increase in atrial fibrillation episodes. Instead, in men, the more significant increase in blood pressure is observed after age 60 and

Table 3: Mean of Systolic/Diastolic Blood Pressure by age.

	Age	18-30	31-40	41-50	51-60	61-70	71-80	81-92
	n	8	9	14	26	36	33	16
Women	Systolic	112.8	118.3	137.9	132.5	144.7	143.1	159.8
	Diastolic	69.4	77.8	85.9	81.3	84.1	79.2	78.7
	n	6	4	14	24	29	33	13
Men	Systolic	124.5	130.0	133.6	132.2	142.6	145.5	139.6
	Diastolic	79.3	85.8	88.0	85.1	84.6	79.1	80.0

also coincides with the increase in atrial fibrillation (Tables 3, 4). According to the latest guidelines on hypertension, women in the 18-30 years age group fall into the "Non-elevated blood pressure" group, while the other three groups (from 31-40 years to 51-60 years) belong to the "Elevated blood pressure" class. Men from the 18-30 years age group to the 51-60 years age group belong to the "Elevated blood pressure" class too.

Only after the age of 70 years, both sexes were classified as "Hypertension" (140/90 mmHg). No cases of atrial fibrillation were observed up to age 30, but a few cases of ectopic atrial rhythm started. Ectopic atrial rhythm increases slowly until the age of 50 years, in the next decades, a great increase was observed until the age of 80 years, after which it decreases.

The presence of atrial fibrillation begins after the age of 30 years, slowly increasing up to 60 years. After age 61 and up to age 80, it increases considerably. A significant decrease was found in the last decade. A similar evolution was observed in both sexes (Table 4).

Added (outside of the adult sample)

In the total patients' registry, only 4 children/adolescents had the Arterial, Ventricular, and Atrial haemodynamic axis syndrome. This is an observation of its early appearance in life (Table 5).

Table 5: Children and adolescents <18 years.

Years	10	11	12	16
Female		1	1	
Male	1			1

Discussion

The evidence from this study is that in early stages of so-called arterial hypertension, an association with the contemporaneous presence of arterial stiffness, mitral insufficiency, and ectopic atrial beats can be observed, as a haemodynamic axis syndrome is developed into the internal space of the three chambers: arteries, the left ventricle, and the left atrium, separately by two valves, in symptomatic patients.

The nomination of Arterial Hypertension or High Blood Pressure doesn't reflect the great dimension of the illness that should be named Cardiovascular, Endocrine-Metabolic, Environmental, and Unhealthy Behaviour disease, and should not be considered only the systolic and diastolic values as a prevalence over the illness to evaluate the patient.

Consolidating this idea, the concept of Ryohei Ono is highlighted, bringing together chronic inflammation, metabolic factors, and comorbidities [22].

Although admitted patients should have stiff arteries, patients in the first 3 decades did not fall under the classification of "Hypertension".

The pathophysiology of the arterial, ventricular, and atrial hemodynamic axis syndrome initially is paucisymptomatic. When symptoms do begin, they are frequently misinterpreted as "stress", "panic attack", "anxious state", etc., which can delay diagnosis and early therapy.

"Elevated blood pressure" is not a "gray zone" because symptomatic patients with an arterial, ventricular, and atrial haemodynamic axis syndrome should be considered as a pathological state.

Therefore, the increase in pressure values would depend primarily on increases in cardiovascular volume, which would cause greater intra-atrium pressure and the appearance of ectopic atrial rhythms and ultimately the onset of atrial fibrillation. When the disease begins to develop from an early age the patient could have "normal" systolic-diastolic values; therefore, their identification is still difficult. This systemic clinical disease would be preceded by a haemodynamic syndrome produced from an initial arterial stiffness, secondary mitral regurgitation, and finally ectopic atrial beats, offering the opportunity to anticipate the diagnosis of "arterial hypertension" and its early therapeutic control with the aims to avoid severe complications.

Table 4: Presence of Atrial Fibrillation, Ectopic Atrial Rhythm, and their association, according to sex and age.

Pathology	Sex/Age	18-30	31-40	41-50	51-60	61-70	71-80	81-93	n
EAR + AF	Women	8	9	14	26	36	33	16	142
	%	5.6	6.3	9.9	18.3	25.4	23.2	11.3	
	Men	6	4	14	24	29	33	13	123
	%	4.9	3.2	11.4	19.5	23.6	26.8	10.6	
EAR	Women	8	8	8	16	18	11	4	73
	%	11.0	11.0	11.0	21.9	24.6	15.0	5.5	
	Men	6	2	12	18	10	11	5	64
	%	9.4	3.1	18.8	28.1	15.6	17.2	7.8	
AF	Women	0	1	6	10	18	22	12	69
	%		1.4	8.7	14.5	26.0	31.9	17.4	
	Men	0	2	2	6	19	22	8	59
	%		3.4	3.4	10.2	32.2	37.3	13.5	

EAR: Ectopic Atrial Rhythm. AF: Atrial Fibrillation.

The space defined by the walls of the arteries, the left ventricle, and the left atrium has three compartments in a continuous axis that are haemodynamically interconnected and separated by two valves; therefore, a pathology starting in the arteries should produce a repercussion in the other two chambers. Due to a contemporaneous presence of metabolic, endocrine, and inflammatory elements that initially act on the arterial wall, they can produce an initial endothelial dysfunction and sodium/water retention; therefore, it is possible to arrive at structural remodeling of the left ventricle, developed by a high end-systolic pressure, with a dyssynchrony of the mitral apparatus, with the development of an initial minimal mitral regurgitation. Moreover, an increase in volume/pressure inside the atrium can cause electrical and mechanical dysfunction, leading to the presence of an ectopic atrial rhythm, brief phases of atrial fibrillation, or the new onset of atrial fibrillation.

Recognizing this syndrome is not simple. First, the classical sphygmomanometer does not provide information about arterial stiffness; therefore, non-invasive instruments are necessary to obtain data from the pulse wave and its reflection. Second, the minimal mitral regurgitation (pathological) is frequently interpreted as benign, inconsequential, or without hemodynamic value. Finally, in the reports of the 24-hour Holter monitoring, the differences between sinus and atrial ectopic extrasystoles are rarely reported, therefore deprived of criticality, and have thus been largely neglected.

The great increase in blood pressure in women after the age of 40 years occurs, and the appearance of episodes of atrial fibrillation at the same age too. Similar acts succeeded in men but after the age of 60 years.

According to this study, it appears that women develop Atrial Fibrillation earlier than men, which would indicate the need to make an early diagnosis and start therapy.

Is recommended to begin preventive treatment for atrial fibrillation before the age of 30 to absolutely avoid the new onset of atrial fibrillation, even if the systolic and diastolic values are not high. Box 2023 ESH. But, episodes of the ectopic atrial rhythm were evident even in youth, it is important to consider that before the age of 18 years, information and non-pharmacological measures should be planned to avoid the development of the arterial, ventricular, and atrial haemodynamic axis syndrome.

To achieve this status is important to know that at the 2015 ESC Congress (London) it was said that “Lower Blood Pressure, fewer episodes of Atrial Fibrillation occur”. At the 2022 ISH Congress (Kyōto), Prof Shibata entitled his conference: “Occur Treat High Blood Pressure with Mineralocorticoid Receptor Antagonists as first line?”

In this study, the End-Systolic Pressure was higher than normal, indicative of an increase in the residual cardiovascular volume, important for producing high stretching of the atrial wall that can originate electrical and mechanical remodeling, and in turn, the appearance of atrial arrhythmias.

In a previous work by the author treating arterial hypertension with the ARB + MRA association, it was observed that practically no episodes of brief phases of atrial fibrillation were observed [23] Box 2020 ESC. The decrease in patients with atrial fibrillation after the age of 80 could be deduced as an important cause of death, considering the sum of possible comorbidities at that age. Also, it was observed that the proportion of ectopic atrial rhythm and atrial fibrillation across the decades overlapped in both sexes.

In the other hand, the natural history after cerebrovascular events in patients with patent foramen ovale remains insufficiently defined. The causal relationship between patent foramen ovale and stroke has been controversial. [24] Closure of a patent foramen ovale for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy [25]. It has been suggested that occlusion of the patent foramen ovale before age 40 would be appropriate to prevent the onset of atrial fibrillation. Furthermore, the occurrence of atrial fibrillation after patent foramen ovale closure has been described, attributing its possibility to the device used.

Medicine has taught us:
Jane may also be at Ann’s house

In this study of the arterial, ventricular, and atrial haemodynamic axis syndrome, it was observed that atrial fibrillation appeared at the same age as patent foramen ovale; therefore, it would be important to determine the main cause of atrial fibrillation in young patients.

According to the principles of Medicine:
“The best treatment of Atrial Fibrillation is the Prevention”.
Prevention is the wisdom that avoids health from turning into illness.
Education is the mother of Prevention.

Superior doctors prevent the disease
Mediocre doctors treat the disease before the evidence
Inferior doctors treat the full-blown disease
Qin Shi Huáng Dì Nei Ching (2600 BC) - 1st Chinese Medical Text

Conclusions

The presence of an arterial, ventricular, and atrial haemodynamic axis syndrome could be considered to arise from cardiovascular, endocrine-metabolic, environmental, and behavioural disease, even at young ages, which would allow for the early initiation of preventive measures to prevent the onset of atrial fibrillation, even though the blood pressure values do not fall under the latest Guidelines of the "Hypertension" classification.

BOX

Posters presented by the author

2012 ESH - Relation between angiotensin receptor blocker candesartan cilexetil treatment and chronic migraine on central haemodynamic parameters.

2017 ESH 1 - Comparison of the detrimental effect of psoriasis and rheumatoid arthritis measured on central haemodynamic parameters in prevalent overweight-obesity and hypertensive population.

2017 ESH 2 - The polycystic ovary syndrome increases levels of augmentation index similar than women with systemic diseases as psoriasis and rheumatoid arthritis.

2017 ESH 3 - Residual harmful effect by the use of oral contraceptive pill measured according to central haemodynamic parameters.

2018 ESH - Assessment of the central haemodynamic parameters during oestrogen-progesterone therapy in women with polycystic ovarian syndrome.

2020 ESC - Angiotensin receptor blockers and mineralocorticoid receptor antagonists therapy reach better central haemodynamic parameters and avoid the episodes of atrial fibrillation.

2020 ESH-ISH - What does the finding of minimal mitral regurgitation mean?

2021 ESC - Is the minimal mitral regurgitation a marker of high blood pressure, and can predispose to the appearance of atrial fibrillation?.

2022 ISH - The use of hydrochlorothiazide for the treatment of hypertension increases the cardiovascular risk according to the central haemodynamic parameters.

2022 ESH 1 - The importance of the symptoms for diagnosing and treating of hypertension in children, adolescents and young-aged, assessed with applanation tonometry.

2022 ESH 2 - What is the significance and the meaning from finding a wandering atrial rhythm?

2023 ESH - Early diagnosis of hypertensive disease in youth with normal systolic and diastolic blood pressure levels.

2024 ESH - Systemic diseases are a group of inflammatory illnesses that can damage the arterial wall assessed according to non-invasive arterial tonometry.

2025 ESH - Minimal mitral regurgitation and electrical abnormalities of the atrium could develop from arterial stiffness, assessed by non-invasive arterial tonometry.

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