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Journal of Hypertension

Identification of cardiac organ damage in arterial hypertension: insights by echocardiography for a comphensive assessment

--Manuscript Draft--

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Abstract:	Arterial hypertension (AH), a widespread disease, whose prevalence increases with age, represents a major risk factor for cardiovascular events, causing damage in several organs, including the heart. In this context, echocardiography has a clear and pivotal role, being able to assess cardiac morphology and detect hemodynamic changes induced by this disease. 2018 ESC/ESH guidelines on arterial hypertension identified main echo parameters such as left ventricular mass, relative wall thickness and left atrial volume, for detecting cardiac organ damage. The present review highlights the advantage of additional echocardiographic parameters such as diastolic

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	measurement and both thoracic and abdominal aortic dimensions. An overlook on aortic valve should also be suggested in order to detect aortic regurgitation and stenosis, both frequent complications in hypertensive patients. In this kind of comprehensive assessment, the combination of standard and advanced echocardiography (speckle tracking echocardiography and, with a lesser extent, three-dimensional echocardiography) could be considered to improve the diagnostic accuracy, stratify prognosis and address management in AH.

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Naples, October 16, 2019

Prof. G. Mancia,
Editor-in-Chief, *Journal of Hypertension*

Dear Prof. Mancia,

On behalf of my co-authors and myself, we submit to your kind attention the revised review **"Identification of cardiac organ damage in arterial hypertension: insights by echocardiography for a comprehensive assessment"** for a possible publication on *Journal of Hypertension.*

The manuscript has been revised according to the criticisms and observations risen by the three reviewers.
The aim of the present review is to present a comprehensive echocardiographic assessment for the identification of early cardiac organ damage in patients affected by arterial hypertension. Thus,we tuned down the title, which now states "Identification of cardiac organ damage in arterial hypertension: insights by echocardiography for comprehensive assessment". Moreover, we highlighted the impact of arterial hypertension on the onset of aortic regurgitation in chapter 6. In addition, even if global longitudinal strain was demonstrated to be able to detect an early systolic left ventricular dysfunction impairment in hypertensive patients, its prognostic impact is controversial in this setting. Accordingly and because of the lack of evidence, we eliminated global longitudinal strain from the list of echo parameters having a prognostic impact on arterial hypertension and also from Table 2.

Enclosed you find the point by point reply to the reviewers.

All authors have read and approved the revised version review and its submission to*Journal of Hypertension*.All authors also affirm that no conflict of interest has to be disclosed.

We hope that our review could be considered suitable now for publication on *Journal of Hypertension*.

Sincerely.

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Reply to Reviewers:

Reviewer #1:

The additional echocardiographic parameters such as left ventricular diastolic measurement and dimensions of both thoracic and abdominal aorta are meaningful for the hypertension, but the low flow low gradient aortic stenosis is not closely related because the high-load hemodynamic state,so the aortic regurgitation is necessary. I think the evaluation of morphological structure of aortic valve is more important for hypertension.

Thank you for your comment. We recognize the important impact of arterial hypertension on aortic valve morphological changes, thus causing both aortic valve regurgitation and stenosis. Aortic valve regurgitation may be due to accelerated AH induced valve deterioration or it could be functional, thus associated to tethering of the leaflets, it depending on the sino-tubular junction/annulus mismatch, because of ascending aorta dilatation. In the new draft of the manuscript we highlighted this concept in chapter 6 (now called: Aortic valve: aortic regurgitation and paradoxical Low flow low gradient aortic stenosis) (see page 15, lines 17-23 and page 16 lines 1-2). We also believe that paradoxical low flow low gradient is a particular type of aortic stenosis, which needs to be carefully searched and detected in the hypertensive setting, because associated with a poor prognosis. Indeed its rate is often underestimated, because its diagnosis is sometimes difficult and characterized by a mismatch between aortic valve area and mean pressure gradient: valve area <1 cm^2 with a peak velocity <4m/s, a mean pressure gradient <40 mmHg and stroke volume index <35 mL/m^2 despite normal LV ejection fraction. LV features of low flow low gradient aortic stenosis include LV concentric geometry and small LV volume, which often represent LV changes induced by AH. These concepts are summarized in the same Chapter 6.

Reviewer #2:

This review describes the potential interest of echocardiography in assessing cardiac damage in hypertension. This review is exhaustive and well written. My main concern is the presentation of this review. "beyond guidelines". Certainly echocardiography allows gathering many information on left ventricular hypertrophy, left ventricular function, atrial volume, aortic size … But the main reason why guidelines have to be cautious is that there is no demonstration that systematic echocardiography could really improve the prognosis of hypertensive patients. So in my opinion you should tune down your conclusion that "The role of echocardiography in the thorough assessment of the hypertensive patient is essential" and the introduction should as well be modified. Echocardiography is very often performed when a hypertensive patient is referred to a cardiologist. Usually the evaluated parameters are LVH, ejection fraction, left atrium diameter and mitral flow. These results usually do not influence the way the patient is treated and I am quite sure that this attitude is not cost effective. But if echocardiography is done, well-motivated or not, it is certainly important to gather the maximum of relevant information on heart and aorta and the interest of this review is to summarize all these points.

We understand your concern. According to your suggestion, we tuned down the title, which now states “Identification of cardiac organ damage in arterial hypertension: insights byechocardiography for comprehensive assessment”. Indeed, we also modified the final part of the introduction (see page 5, lines 17-23) and the conclusions: “The role of echocardiography in the thorough assessment of the hypertensive patient is very useful…” (page 17, lines 19-20).

Actually, the aim of the present review is to present a comprehensive echocardiographic assessment for the identification of early cardiac organ damage in patients affected by arterial hypertension. Moreover, we do believe that the echocardiographic evaluation could influence patients' treatment, for example addressing to surgery patients with aortic valve diseases or aortic dilatation, which are frequent in arterial hypertension and also for establishing correct timing of follow-up. Accordingly, under well defined circumstances, echocardiography could present even a valuable cost/effectiveness ratio in hypertensive patients. We highlight now these concepts in the last part of the conclusions (page 18, lines 10-14).

Minor points:

* In the chapter on LVM measurements you should introduce a word of caution about reproducibility of the results which seriously limits the possibility to follow the evolution of LVM with time and treatment in a single patient.

According to your suggestion, we added a statement about LVM poor reproducibility: "The standard echocardiographic approaches to LVM calculation presume a normal LV shape and have several intrinsic technical limitations including the need of a geometric assumption, frequent difficulties in the assessment due to beam orientation (often inducing off-axis views), and inaccuracy in presence of dilated ventricles or asymmetric hypertrophy. For these reasons, reproducibility of M-mode and 2D derived LVM appears in general to be suboptimal, limiting sometimes the possibility to follow the evolution of LVM over time." (page 7, lines 6-11)

The 3D method for assessing LVM show in our experience important limitations: not possible in many patients, time consuming and poor reproducibility in current practice.

We acknowledge the fact that 3D derived LVM had some limitations: mainly the possible incorrect detection of LV epicardial contours and of LV apex and also the impossibility of obtaining suitable 3D images in patients with inadequate imaging. Thus, the feasibility of 3D assessment is reduced. (page 7, lines 17-21). However, 3D LVM has also several advantages: being validated against cardiac MRI and not needing geometrical assumption. Thus, with technical advancement ("virtual apex", the possibility of obtaining information in a single heart beat) it could represent a good compromise between 2D echo and cardiac MRI. In the hands of trained operators, the technique has a good reproducibility in our experience, but it is also true that further studies are needed to prognostically validate 3D derived LVM in the hypertensive setting.

* Table 1: With the purpose of defining LVH, cut-off would be more adequate than reference range

According to your request, in Table 1 we described the thresholds of normalcy instead of the reference ranges of the parameters used for LV geometrical assessment.

* Table 2. The cut-off defined with the ability to predict cardiovascular events should be presented with sensitivity and specificity. For LVM there are more recent papers than those quoted.

We are unable to present sensitivity and specificity of echo parameter predicting cardiovascular events in arterial hypertension since we should need raw data from the original studies and actually we did not find their report in literature. Accordingly, we reported this limitation in the text (page 17, lines 15-16): "Unfortunately, evidence on sensitivity and specificity of those parameters in predicting CV events is lacking in the hypertensive setting". In Table 2 we addedmore recent studies by Verdecchia P et al. J Am Heart Assoc. 2017;6. pii: e005948, Armstrong AC et al. JACC Cardiovasc Imaging 2012;5:837-48, Gosse P et al. J Hypertens.

2012;30:2403-2409,demonstrating the prognostic impact of LV mass and LV hypertrophy in the hypertensive setting.

For GLS, the lower the better, and probably using the absolute value is less confusing. I am not sure that 20% can be considered as an adequate cut-off. We lack adequate studies in hypertensive patients. Moreover it depends on the software used for its calculation. Quoting Lee and al for GLS is not adequate: only 95 hypertensive patients followed during an average 7 years, 20 events and GLS was not a significant predictor of events.
We understand your concern.Even if GLS was described to detect an early systolic LV dysfunction in arterial hypertension, its prognostic impact is controversial in this setting. Because of the lack of evidence, we eliminated GLS from the echo parameters having a prognostic impact on arterial hypertension and also from Table 2.

* Page 12, I suggest to omit the following comment: It has been proposed that hypertensive heart disease might be divided into four stages, starting with isolated DD (degree I), further progression with DD associated with concentric LVH (degree II), the establishment of clinical signs and symptoms of heart failure (degree III) and finally the occurrence of dilated cardiomyopathy with reduced LVEF (degree IV). [58-59]. This is a conceptual view. There are no strong evidences supporting this progressive evolution and It is probably out of the scope of this review.We eliminated the sentence at issue.

* Fig 3 I suggest to emphasize (for instance with Bold letters) the parameters that must absolutely be present in all echo reports from less important parameters.
According to your suggestion, we highlighted in bold letters the parameters that should be always evaluated in hypertensive patients (Figure 3).

Reviewer #3:

This is an interesting review article that sought to identify target organ damage by echocardiography. However, there are some minor issues to be clarified:

1. For precision, please acknowledge other pioneering randomized studies that have identified changes in diastolic function with anti-hypertensive treatment form Wachtell K et al and Solomon SD et al to name a few.Thank you for your suggestion.The studies by Wachtell K et al and Solomon SD et al are now cited in the references of the new draft of the manuscript.

2. There is limited data that show the incremental prognostic significance of strain imaging. A recent population study by Modin D et al. showed that only left ventricular hypertrophy had incremental prognostic value over clinical risk factors and ECG in hypertensive patients whole global longitudinal strain had incremental prognostic value in nonhypertensive patients. This needs to be clarified.As previously described, even if GLS was demonstrated to be able to detect an early systolic LV impairment in hypertensive patients, its prognostic impact is controversial in this setting. Because of the lack of evidence, we eliminated GLS from the list of echo parameters having a prognostic impact on arterial hypertension and also from Table 2.

Abbreviations:

AAA = Abdominal aorta aneurysm

AH = Arterial hypertension

AF= Atrial fibrillation

BSA = Body surface area

CMR = Cardiac magnetic resonance

CV = Cardiovascular

DD = Diastolic dysfunction

EDV = End-diastolic volume

GLS = Global longitudinal strain

HFpEF = Heart failure with preserved ejection fraction

LA = Left atrium

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVH = Left ventricular hypertrophy

LVM = Left ventricular mass

PWV = Pulse wave velocity

RWT = Relative wall thickness

STE = Speckle tracking echocardiography

TDI = Tissue Doppler imaging

Condensed Abstract

2018 ESC/ESH guidelines on arterial hypertension identified several echocardiographic parameters, like left ventricular mass, relative wall thickness and left atrial volume, for identification of organ damage. The present review highlights the advantage of additional echocardiographic parameters for detecting subclinical organ damage and selecting patients that could be more prone of overt heart failure development. Left ventricular diastolic measurement, both thoracic and abdominal aortic dimensions, and aortic valve diseases measurements could provide an exhaustive view of cardiovascular involvement in arterial hypertension. The combination of standard and advanced echocardiography should be contemplated to address management and stratify prognosis in hypertensive patients.

Identification of cardiac organ damage in arterial hypertension: insights by echocardiography for a comprehensive assessment

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On behalf of Working Groups of Echocardiography and Arterial Hypertension of Italian Society of Cardiology (SIC)

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No conflict of interest to declare

2 Tables

4 Figures

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Abstract

Arterial hypertension (AH), a widespread disease, whose prevalence increases with age, represents a major risk factor for cardiovascular events, causing damage in several organs, including the heart. In this context, echocardiography has a clear and pivotal role, being able to assess cardiac morphology and detect hemodynamic changes induced by this disease. 2018 ESC/ESH guidelines on arterial hypertension identified main echo parameters such as left ventricular mass, relative wall thickness and left atrial volume, for detecting cardiac organ damage. The present review highlights the advantage of additional echocardiographic parameters such as diastolic measurement and both thoracic and abdominal aortic dimensions. An overlook on aortic valve should also be suggested in order to detect aortic regurgitation and stenosis, both frequent complications in hypertensive patients. In this kind of comprehensive assessment, the combination of standard and advanced echocardiography (speckle tracking echocardiography and, with a lesser extent, three-dimensional echocardiography) could be considered to improve the diagnostic accuracy, stratify prognosis and address management in AH.

Key words: Arterial hypertension, Echocardiography, Cardiac organ damage, Left ventricular hypertrophy, Diastolic dysfunction

Condensed Abstract

2018 ESC/ESH guidelines on arterial hypertension identified several echocardiographic parameters, like left ventricular mass, relative wall thickness and left atrial volume, for identification of organ damage. The present review highlights the advantage of additional parameters for detecting subclinical organ damage and selecting patients that could be more prone of overt heart failure development. Thus, diastolic measurement, both thoracic and abdominal aortic dimensions, and aortic valve diseases should be considered for providing an exhaustive view of cardiovascular involvement in arterial hypertension. The combination of standard and advanced echocardiography should be contemplated to address management and stratify prognosis in hypertensive patients.

Abbreviations:

AAA = Abdominal aorta aneurysm

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LVEF = Left ventricular ejection fraction

LVH = Left ventricular hypertrophy

LVM = Left ventricular mass

PWV = Pulse wave velocity

RWT = Relative wall thickness

STE = Speckle tracking echocardiography

TDI = Tissue Doppler imaging

1. Introduction

Arterial hypertension (AH) is one of the major contributors to the global burden of disease, showing a high prevalence which progressively increases as the age advances, reaching a value >60% in the population aged 60 years or over. [1] It is an important cardiovascular (CV) risk factor since it is independently associated with the occurrence of major CV events, including myocardial infarction, heart failure, peripheral artery disease, ischaemic and haemorrhagic stroke [2,3] and atrial fibrillation (AF) as well. [4] Subclinical target organ damage involves heart, brain, kidney, eyes, and is considered a marker of pre-clinical CV disease. [5] In order to avoid irreversible organ damage, it is important to promptly diagnose cardiac organ damage and to initiate an early and effective treatment to reduce the progression towards overt involvement. In this view, echocardiography plays a central role in detecting subclinical cardiac remodelling, which develops as a result of pressure overload. These changes include left ventricular (LV) concentric remodelling and hypertrophy (LVH), diastolic dysfunction (DD) and left atrial (LA) enlargement, all factors predisposing to heart failure. The detrimental effect of AH on aorta and its elastic properties induces a progressive wall stretching and increased arterial stiffness, which is a predictor of both aortic valve and aortic vessel disease.

The latest ESC/ESH guidelines [6] on AH recommend the use of echocardiography in presence of electrocardiographic abnormalities, suggesting the assessment of standard echo parameters such as LV mass (LVM), relative wall thickness (RWT) and LA volume, for the definition of organ damage. The present review aims to underline the possible advantage of using additional parameters, including aortic dimension and cardiac function, obtainable from standard and advanced echocardiography that could provide a wider view of CV involvement and identify subclinical organ damage in patients affected by AH.

2. Left ventricle

Left ventricle is directly affected by systemic AH. Elevated blood pressure is responsible for increased LV afterload, which implies that the left ventricle must develop a higher pressure in order to guarantee adequate cardiac output and peripheral organ perfusion. In response to AH, LV wall stress increases, LV walls become thicker and LVM greater, due to interposition of interstitial fibrosis among cardiomyocytes. The echocardiographic assessment is a cornerstone in this kind of evaluation, it corresponding to the detection of LV geometric patterns and diagnosis of LVH.

2.1 Left ventricular hypertrophy

Echocardiographic derived LVH has proven to be a strong predictor of mortality in both the general population and in patients affected by AH. [7] Furthermore, the regression of LVH during anti-hypertensive treatment is a good predictor of improved prognosis. [8-10] Accordingly, an exhaustive quantification of LVM in hypertensive patients is of paramount importance. As reported in the ASE/EACVI Chamber Quantification recommendations [8,11], LVM can be determined by linear measurements of septal and posterior wall thickness, and of LV internal cavity dimension, all at end-diastole, by using 2D guided M-mode echocardiography or directly by 2D echocardiography [8]. These approaches imply the assumption of a geometric model and the use of the following formula:

$$LVM = 0.8 \times 1.04 \times [(IVST + LVID + PWT)^3 - LVID^3] + 0.6\ g$$

where IVS is the interventricular septal thickness, LVID is LV internal diameter and PWT is the infero-lateral wall thickness. LVM determined by this formula has been successfully validated against heart cardiac autopsy [12]. LVM can be calculated also by 2D echocardiography by using area-length formula and the truncated ellipsoid formula. [13] The indexation of LVM is mandatory,

because it allows comparisons among subjects with different body sizes. In the hypertensive setting, LV mass is usually indexed for body surface area (BSA) or for height raised to allometric powers such as 2.7 [14] or 1.7 [15]. As reported in the ESC/ESH guidelines [6,11], the indexation for height has advantages over indexing to BSA, in order to avoid the underestimation of the rate of LVH in overweight/obese subjects. [16]

The standard echocardiographic approaches to LVM calculation presume a normal LV shape and have several intrinsic technical limitations including the need of a geometric assumption, frequent difficulties in the assessment due to beam orientation (often inducing off-axis views), and inaccuracy in presence of dilated ventricles or asymmetric hypertrophy. For these reasons, reproducibility of M-mode and 2D derived LVM appears in general to be suboptimal, limiting sometimes the possibility to follow the evolution of LVM over time [17-18]. Conversely, the novel 3D reconstruction of LVM potentially represents a more reliable method for the assessment of LVM since does not need a geometric assumption and allows to obtain its direct calculation, even in patients with abnormal LV shape [19]. 3D echo derived LVM has been validated against cardiac magnetic resonance (CMR), i.e. the gold standard imaging technique for the evaluation of this parameter [20-22] but is less expensive and more widely applicable in the clinical practice than CMR. Some limitations of 3D LVM computation shall be acknowledged: mainly the possible incorrect detection of LV epicardial contours and of LV apex and also the impossibility of obtaining suitable 3D images in patients with basically 2D inadequate imaging. Thus, at the present time, both the feasibility and reproducibility of 3D LVM determination are still suboptimal. Nevertheless, technical advancement in temporal and spatial resolution allows to acquire suitable 3D echo images, with the possibility of amplifying LV apex region (“virtual apex”), which is the most critical part of the assessment. [23]

Table 1 summarizes the cut-off values of abnormalcy of LVM with the different techniques. The knowledge of the cut-off points by using the different imaging techniques should be carefully considered. Notably, the cut-off points of LVM derived from standard echocardiography are prognostically validated, whereas those obtainable by 3D echo is not. CMR derived LVM and LVH were demonstrated to be prognosticators in AH [24].

The evaluation of differential diagnosis for LVH is important in order to exclude other possible causes of increased LV parietal walls, such as hypertrophic cardiomyopathy. Regional strain could be helpful in this context. Patients with hypertrophic cardiomyopathy present a more impaired regional longitudinal strain, particularly in apical segments, compared to hypertensive-LVH. [23, 25] The assessment of regional strain is also useful for differentiating myocardial effects of AH from infiltrative diseases, as cardiac amyloidosis, being characterized by a regional impairment of longitudinal function which spares the apical segments ("apical sparing") [26], and storage cardiomyopathy, such as Anderson Fabry disease. [27]

2.2 Left ventricular geometry

In the early stages of AH, LV geometry remains generally normal, but as consequence of increased afterload, the shape of the left ventricle is prone to morphological changes [28]. The standard echocardiographic definition of LV geometry presumes the use of LVM and RWT; the latter is commonly determined as the ratio between twice the posterior wall thickness and LV diastolic diameter at end-diastole [29]. Adopting these two parameters, four geometrical patterns are described: normal geometry, concentric remodelling, concentric LVH - which consists in uniformly increased LV wall thickness, an increased LVM with normal cavity size [8, 30] - and eccentric LVH, characterized by increased LV cavity size and LVM with normal LV wall thickness (**Figure 1**). More recently, Khouri et al proposed a new classification of LV geometry patterns,

considering also LV dilatation. [30] By using this novel classification, survival was similar between hypertensive patients with eccentric LVH and normal LVM, whereas it was progressively reduced as LV dilatation occurred, achieving the lowest rate in patients with concentric LVH and LV dilatation. [31-33]

An accurate evaluation of LV geometry is essential for the patient's risk stratification, to guide anti-hypertensive therapy and to identify a target organ damage [6]. However, due to the above mentioned limitations of 2D assessment, this approach can be even improved by using LVM/end-diastolic volume (EDV) ratio, a novel index which has been firstly introduced by CMR. [34]: higher the ratio greater the thickness to cavity ratio of the left ventricle. This ratio was also found to correlate with myocardial fibrosis and outcome in hypertensive patients [34]. The feasibility of this index has been recently shown by using 3D-echocardiography [34, 35]. 3D echo derived LVM/EDV ratio was also able to detect a higher rate of LV concentric geometry in comparison with 2D assessment; 3D LV mass/EDV ratio identified also patients with low stroke volume in the context of LV remodelling due to AH. [34] This aspect is particularly relevant since it might reveal an early functional impairment beyond the information carried by LV geometry alone Accordingly, the use of 3D echo could be a good compromise between 2D echo and CMR in characterizing subclinical organ damage in AH. **Table 1** shows the main parameters and their cut-off points of abnormalcy used for assessment of LV geometry by echo techniques.

2.3 Left ventricular function

Currently 2D echocardiographic derived LV ejection fraction (LVEF) is the most frequently used parameter for the assessment of LV systolic function. Nevertheless, LVEF suffers the limit of geometric assumption, it has poor reproducibility (day-to day variability of about 10%) [36-37] and therefore it is able to detect LV dysfunction only in clinically overt stages. [38] In addition, LVEF is

deeply influenced by load conditions and changes of LV geometry [39, 40], both critical points in hypertensive patients [41]. Accordingly, LVEF is poorly accurate for detecting subclinical LV dysfunction in the clinical setting. In the 1980s this concept was firstly highlighted by the calculation of midwall fractional shortening, an index which, incorporating half part of the myocardial wall, allows to identify early LV systolic dysfunction in presence of LV concentric geometry, when LVEF is still normal [39]. To date, the assessment of myocardial mechanics can be much more easily performed by using pulsed Tissue Doppler imaging (TDI) or, better, speckle tracking echocardiography (STE), depending on the available level of technology [41]. TDI has demonstrated the diagnostic capability of differentiating between physiological and pathological LVH. [42] STE is angle-independent and very reproducible, being also relatively operator independent. It allows quantifying the different directional components of myocardial deformation such as longitudinal, circumferential and radial strain, and LV twisting as well. Although all these strain components well correlate with LVEF, global longitudinal strain (GLS) appears to be superior because of its largely better feasibility and reproducibility (about 6%). [43] Moreover, despite being load dependent similarly to LVEF, GLS can be altered independently on changes of LV geometry. [44] Accordingly, a decline in GLS, has been shown to be evident even in presence of LVEF, being useful to identify preclinical stages of LV involvement in AH [45]. GLS has been found to be also associated with both the degree of LV filling pressures and the extent of myocardial fibrosis in uncomplicated hypertensive patients. [46-50] Preliminary experience showed the potential usefulness of 3D strain rate imaging in AH [51]. However, this technique is not ready yet to be used in the clinical practice, due to its limited availability and feasibility.

3. Diastolic function

In early stages of AH, LV diastolic dysfunction (DD) generally occurs long before LVEF is compromised [52]. Persisting elevated blood pressure levels promotes LV DD through various mechanisms, including increased afterload, myocardial ischemia [53], and myocardial fibrosis, which constitutes the main determinant of diastolic properties' alteration, it being characterized by an altered myocardial relaxation that interferes with normal LV diastolic filling. [54]

According to the latest ASE/EACVI recommendations on diastolic function [54], when LVEF is above 50%, and any myocardial disease (e.g., presence of LVH, ischaemic or significant valvular heart disease) is excluded, recommendations suggest the use of four variables to determine the presence of DD (septal e' <7 or lateral e' <10 cm/s, average E/e' >14, tricuspid regurgitation systolic jet velocity >2.8 m/s, LA maximum volume index >34 ml/m^2) (**Figure 2**) On the contrary, in presence of myocardial disease, even in presence of normal LVEF, recommendations suggest to apply the same algorithm used for patients with reduced LVEF to estimate LV filling pressures degree (**Figure 3**) [54]. Thus, if LVH is present or not, the second or the first algorithm should be used respectively.

Interestingly, DD is strongly related with LV longitudinal systolic dysfunction, and it might occur even before the development of LV concentric geometry [55]. This implies that subtle systolic dysfunction might be responsible for an increase in LV filling pressures, which is a strong predictor of both prognosis and clinical functioning [56]. It has to be stressed that AH generally clusters with other CV risk factors [56], and diabetes mellitus, impaired renal function, aging and obesity augment the progression of DD in these patients. [57] Furthermore, DD tends to improve during anti-hypertensive treatment [58-60], which makes it a valuable tool to test therapy efficacy, since it is also easily assessed through the echocardiographic exam.

3.1 The role of hypertensive-induced DD in heart failure

AH is one of the main risk factor for the development of heart failure, in particular in presence of preserved LVEF (HFpEF). Traditionally, HFpEF pathophysiology was explained by several conditions that induced an increased LV work due to high afterload, while emerging models have highlighted the role of systemic pro-inflammatory changes determined by different comorbidities, including AH. [61, 62] In fact, one of the first signs of an increased LV afterload corresponds to DD. When this pressure overload is sustained over time, diastolic function appears more impaired, LV remodelling becomes progressively decompensated, and HFpEF ensues.[63-64]

4. Left atrium

LA is the other cardiac chamber affected by the pressure overload that accompanies AH. In fact, when DD has developed, the contribute of LA to LV filling becomes essential, therefore LA pressure tends to progressively increase, [65] which then leads to a gradual LA dilatation. It has been proven that LA enlargement is proportional to the severity of DD and to the duration of the hemodynamic overload [66], representing the memory of chronic increase of LA pressure in AH. As a matter of fact, an increase of LA size frequently occurs in hypertensive patients, and besides DD, it appears to correlate also with obesity, older age and particularly with a clear-cut LVH [67] LV geometry and mechanics are important factors influencing LA afterload.

While 2018 ESC/ESH guidelines propose to identify LA dilation computing LA size as LA volume indexed to height powered to 2 [6,68], the current ASE/EACVI echocardiographic recommendations on diastolic function suggest that LA size should be assessed by measuring LA volume indexed for BSA, a measure that is highly validated and commonly used in the clinical practice. [11, 54] LA antero-posterior diameter, measurable in the parasternal long-axis view,

preferably using the 2D mode, despite largely applied in the past, does not accurately represent the size of this chamber which is tridimensional. LA volume should be preferably assessed through the biplane disk summation technique, since it is characterized by fewer geometric assumptions, rather than through the area-length method. [11] In both cases, LA endocardial borders are traced in the apical four- and two- chamber views. 3D-echocardiographic assessment of LA volume has been shown promising results, it being more accurate in comparison with CMR. [67] Also 3D echo derived LA phasic volumes have been demonstrated to correlate with hypertensive organ damage (a LA active stroke volume index of 5.9 ml/m^2 predicted end-organ damage with a sensitivity of 82% and a specificity of 92%) [69] and with the severity of hypertensive retinopathy. [70] However, these experiences are preliminary and 3D echo of LA volume should not be considered in the routinely assess of AH.

STE could also help to assess LA function. A reduced LA strain was found in patients with suboptimal control of blood pressure [71], it occurring before the onset of clear-cut LA dilatation [72] and independently on LV longitudinal dysfunction. [73] In addition, when AH is complicated by paroxysmal AF, STE-derived LA reservoir, conduit and pump function are early impaired. [74]

5. Aorta

Current ESC/ESH guidelines on AH put emphasis on the importance of evaluating arterial stiffness [6,75] but not examining the aortic size at both ascending and abdominal level. Arterial stiffness can be used to define asymptomatic organ damage in AH and is a substrate for the development of resistant hypertension. It refers to the elastic properties of the aorta, which affect vessel dimension, pressure and blood flow across every cardiac cycle [75]. It is also known to be a

predictor of adverse CV outcomes. [76] ESC/ESH guidelines propose the carotid-femoral pulse wave velocity (PWV) as the gold standard to assess arterial stiffness [6,77]: the stiffer the arteries, the higher the PWV. Therefore, correctly diagnosing and treating patients at the beginning of the disease could prevent this further complication by limiting the aortic damage [78-79]. However, this tool is not currently used in the clinical practice.

Although aorta is greatly affected by chronically elevated blood pressure, it is not frequently evaluated in the routine echocardiographic work up of hypertensive patients. Nevetherless, several studies demonstrated that AH accelerates the aging dependent enlargement of thoracic aorta and particularly affects ascending aorta and aortic arch. This process can induce a progressive dilatation and loss of shape of sino-tubular junction, causing aortic regurgitation. [80] Functional classification of aortic root abnormalities responsible for aortic regurgitation provides information for surgical management. This information can be useful for targeting the optimal time and strategy for aortic valve-sparing surgery in ascending aorta aneurysms [81]. Hypertensive induced ascending aorta dilation is also associated with both increased LVM and arterial stiffness. [82-83] It is conceivable that AH could lead to a progressively increased mechanical stress on the aortic wall, which in turn induces elastin fragmentation, and finally aortic dilatation. [83] Although a certain degree of controversy exists about the effect of AH on the aortic root [84-86], recent studies seem to demonstrate that elevation in diastolic blood pressure influences the aortic root dilation, also in relation with the AH disease duration. [87]

According to these findings, the aortic diameters of hypertensive patients should be determined at different levels with 2D echocardiography from the parasternal long-axis view. According to the latest ASE/EACVI recommendations, [8] the aortic annulus should be measured using the inner edge-to-inner edge, whereas it should be preferred the leading edge-to-leading

edge convention for measuring the aortic root and the ascending aorta. Notably, the ascending aorta distensibility appears to be a non-invasive predictor of outcome and might therefore be helpful for guiding the optimal anti-hypertensive treatment. [88] Recently, TDI has been used to estimate the motion of the aortic wall; [89] the velocity values, expressing the aortic elasticity, were found to be lower in hypertensive patients than in the normal population of the same age. [90] In particular, the anterior wall motion velocity of the ascending aorta has been proven to be a predictor of LV geometry and function. [91]

Also the abdominal aorta should be explored by ultrasound in hypertensive patients. AH is one of the main risk factor for the development of abdominal aorta aneurysm (AAA). The prognostic role of abdominal aorta evaluation has been recently investigated in patients awaiting for endovascular repair of AAA [92], the dilation of abdominal aorta being independently associated with long-term mortality in this cohort of patients. [93] These findings highlight the possible screening power of abdominal aorta ultrasound assessment, which could be even performed by using hand-held echocardiography [93]. Diameter measurements should be performed in the plane perpendicular to the arterial axis, to avoid any overestimation of the actual diameter.

6. Aortic valve: aortic regurgitation and paradoxical Low flow low gradient aortic stenosis

AH may induce a mechanical damage on the aortic valve, causing abnormally high stress on aortic leaflets, turbulent flow and endothelial injury, and subsequent progression towards alteration in aortic valve morphology, causing both aortic regurgitation and stenosis [94]. Therefore, the evaluation of aortic valve morphology and function represent a valuable point in echo providing information. Aortic valve regurgitation may be due to accelerated AH induced valve deterioration or it could be functional. In this second circumstance, functional aortic

regurgitation is mainly associated to tethering of the leaflets, it depending on the sino-tubular junction/annulus mismatch, as a consequence of ascending aorta dilatation [81, 95]. AH and aortic stenosis are often concomitant diseases, particularly in the elderly patients [95-97]. Accordingly, the echocardiographic assessment of aortic valve area and gradients is extremely useful for detecting and monitoring the progression of aortic stenosis in AH [98]. A particular type of aortic stenosis, the paradoxical low flow low gradient aortic stenosis, has been typically described in hypertensive patients. It is characterized by a mismatch between aortic valve area and mean pressure gradient: aortic valve area is severely reduced in presence of low mean pressure gradient. The diagnosis of paradoxical low flow low gradient aortic stenosis is performed when valve area <1 cm^2 with a peak velocity <4m/s, a mean pressure gradient <40 mmHg and stroke volume index <35 mL/m^2 despite normal LVEF. LV features of low flow low gradient aortic stenosis include LV concentric geometry and small LV volume [98]. It is conceivable that the hypertensive heart, characterized by deep remodelling with the presence of LV small diameters, LV concentric geometry, high ventricular wall stiffness and reduced LV stroke volume, could not be prone to bear the impact of aortic stenosis. Thus, paradoxical low flow low gradient aortic stenosis is associated with poor prognosis. [99] In some cases it is often difficult to perform a differential diagnosis between paradoxical low flow low gradient aortic stenosis and pseudo-severe aortic stenosis. Evaluation of calcification degree with Agatston calcium score by multi-slice computed tomography may be helpful in this setting and can resolve the diagnosis [98]. Based on the above mentioned evidences, a thorough echocardiographic assessment in patients affected by AH should not overlook valve evaluation.

8. **Echocardiographic parameters having a prognostic impact in AH**

An appropriate diagnosis of AH and correct assessment of CV risk are essential to initiate antihypertensive treatment. Echocardiography is a very helpful tool in this context, not only for the evaluation of organ damage, but also for defying the prognostic profile of a given hypertensive patient. LVH and LV geometric pattern provide important prognostic information [7]. LV concentric hypertrophy is associated with an increased rate of mortality and CV events, even after adjusting for other CV risk factors including LVM, and showing the greatest mortality risk in patients with suspected coronary artery disease [7,100,101]. Also increased LA volume is a prognostic indicator of CV morbidity and mortality, and a LA volume greater than 34 ml/m^2 was associated with poor prognosis including death, heart failure, AF, and ischemic stroke [102-103]. The most consistent evidence regards LA volume rather than LA area and LA antero-posterior diameter [104-106]. LA dilation is also expression of DD and increased LV filing pressures. Accordingly, DD and in particular E/e' ratio have been shown to be strong predictors of heart failure and CV events, independently on several confounders including LVM [54,55]. **Table 2** shows the main echocardiographic parameters predicting poor prognosis in patients affected by AH. Unfortunately, evidence on sensitivity and specificity of those parameters in predicting CV events is lacking in the hypertensive setting.

9. Conclusions

The role of echocardiography in the thorough assessment of the hypertensive patient is very useful, since it allows the measurement of several parameters that correlate with organ damage. **Figure 4** summarizes the echocardiographic parameters that should be evaluated in hypertensive patients. Besides LVH and LA enlargement identified from current ESC/ESH guidelines on AH to detect cardiac injury, multiple echocardiographic parameters, such as GLS, LA

strain and diastolic evaluation could identify an early heart impairment. The evaluation of LV and LA function, rather than the simple measure of their dimensions, has given promising results in early detection of cardiac dysfunction, which might help identifying patients that can benefit from a more aggressive treatment and a closer follow-up. Also the evaluation of DD is extremely important, because it can occur before the development of LV geometry changes. Moreover, in a complete overview on AH induced cardiac impairment the assessment of aortic dimension and aortic valve function should not be overlooked. In this context, the combination of standard and advanced echocardiographic techniques should be carefully considered in order to diagnose subclinical cardiac organ damage, stratify prognosis and address management at the best.

In this view, based on a preliminary clinical assessment, the echocardiographic evaluation could gather the maximum of relevant information on heart and aorta by influencing patients' treatment, and also establishing correct timing of follow-up. Accordingly, under well defined circumstances, echocardiography could present even a valuable cost/effectiveness ratio in hypertensive patients.

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Legend of Figures

Figure 1. Schema showing different LV geometry based on the LVM index and RWT.

LV= left ventricular, LVM= left ventricular mass, RWT= relative wall thickness.

Figure 2. Diagnostic algorithm for diastolic dysfunction in hypertensive patients with normal LVEF and absence of myocardial disease.

LA= left atrium, LV= left ventricular, LVEF= left ventricular ejection fraction, LVH= left ventricular hypertrophy, TR= tricuspid regurgitation.

Figure 3. Diagnostic algorithm for diastolic dysfunction in patients with reduced LVEF or normal left ventricular ejection fraction and concomitant myocardial disease.

LA= left atrium, LV= left ventricular, LVEF= left ventricular ejection fraction, LVH= left ventricular hypertrophy, TR= tricuspid regurgitation.

Figure 4. Picture showing the echo parameters useful in the evaluation of the hypertensive patient. In bold letters the parameters that should always be assessed in hypertensive patients.

EDV= end-diastolic volume, GLS= global longitudinal strain, LA= left atrium, LV= left ventricular, LVEF= left ventricular ejection fraction, LVM= left ventricular mass, PWV= pulsed wave velocity, RWT= relative wall thickness, TDI= tissue Doppler imaging, TR= tricuspid regurgitation.

Table 1. Parameters used for assessment of left ventricular geometry

Method	Parameter	Thresholds of normalcy		References
Echo Linear method	LV mass (g)	Women ≤162	Men ≤ 224	1) Lang RM et al. Eur J Echocardiogr. 2006 Mar;7(2):79-108. [13] 2) Ilercil A et al. J Am Soc Echocardiogr 2001;14:601e11. [107]
	LV mass/BSA (g/m^2)	Women ≤ 95	Men ≤ 115	1) Lang RM et al. Eur J Echocardiogr. 2006 Mar;7(2):79-108. [13] 2)Devereux RB et al. Circulation 1997;96: 1416e23. [108]
	LV mass/height (g/m)$^{2.7}$	Women ≤ 45	Men ≤ 49	1) Lang RM et al. Eur J Echocardiogr. 2006 Mar;7(2):79-108. [13] 2)de Simone G et al. J Am Coll Cardiol. 1992;20:1251–60. [109]
	LV mass/height (g/m)$^{1.7}$	Women ≤ 60	Men ≤ 81	Chirinos JA et al. Hypertension. 2010;56:91-98. [15]
	Relative wall thickness (cm)	Women < 0.42	Men < 0.42	1) Lang RM et al. J Am Soc Echocardiogr. 2015;28:1-39.e14. [8] 2)Ganau A et al. J Am Coll Cardiol 1992; 19:1550–1558. [110]
Echo 2D method	LV mass (g)	Women ≤150	Men ≤200	1)Lang RM et al. J Am Soc Echocardiogr. 2015;28:1-39.e14. [8] 2) Park SH et al. J Am Soc Echocardiogr 1996;9:119-228.[111]
	LV mass/BSA (g/m^2)	Women ≤ 88	Men ≤ 102	Lang RM et al. J Am Soc Echocardiogr. 2015;28:1-39.e14. [8]
	LV mass/height (g/m)$^{2.7}$	Women ≤ 47	Men ≤ 50	de Simone G et al. Am J Hypertens 2005;18:191-196. [14]
Echo 3D method	LV mass (g)	Women ≤ 130	Men ≤ 170	Mizukoshi K et al. J Am Soc Echocardiogr. 2016 Jan;29(1):51-61. [112]
	LV mass/BSA (g/m^2)	Women ≤ 80	Men ≤ 88	Mizukoshi K et al. J Am Soc Echocardiogr. 2016 Jan;29(1):51-61. [112]
	LV mass/EDV ratio	Women < 1.23	Men < 1.22	Lembo M et al. J Hypertens. 2018;36:1697-1704. [34]
MRI method	LV mass (g)	Women ≤ 146	Men ≤ 186	Maceira AM et al. J Cardiovasc Magn Reson. 2006; 8:417-426. [113]
	LV mass/BSA (g/m^2)	Women ≤77	Men ≤ 93	Maceira AM et al. J Cardiovasc Magn Reson. 2006; 8:417-426. [113]
	LV mass/EDV ratio	Women < 1.0	Men < 1.12	Rider OJ et al. Eur Heart J. 2013;34:292-299. [114]

BSA= body surface area, EDV= end diastolic volume, LV= left ventricular

Table 2. Echocardiographic parameterspredicting poor prognosis in patients affected by arterial hypertension, their cut-off values of normalcy and references.

Parameter	Thresholds of normalcy	References
LVM	**LVM/height$^{2.7}$ (g/m$^{2.7}$) ≤50 men, ≤47 women** **LVM/BSA (g/m^2) ≤115 men, ≤95 women**	1) Levy D et al. N Engl J Med. 1990;322:1561-1566.[7] 2) Ghali JK et al. J Am Coll Cardiol. 1998;31:1635-1640. [101] 3) Armstrong AC et al. JACC Cardiovasc Imaging 2012;5:837-48.[115] 4) de Simone G et al.AM J Hypertens 2005;18: 191-196. [14] 5) Krumholz HM et al. J Am Coll Cardiol. 1995;25:879–884.[100] 6) Gosse P et al. J Hypertens. 2012;30:2403-2409.[116] 7) Verdecchia P et al. J Am Heart Assoc. 2017;6. pii: e005948.[32]
RWT	**<0.42**	1) Ghali JK et al. J Am CollCardiol. 1998;31:1635–1640.[101] 2) Gaasch WH et al. J Am CollCardiol. 2011;58: 1733–1740 [28]
LA size	**LA volume index <34 ml/m^2** **LA AP diameter (cm) <4.0 men, <3.8 women**	1) Abhayaratna WP et al. J Am CollCardiol. 2006;47:2357–2363. [117] 2) Verdecchia P et al. Hypertension 2003; 41:218–223 3) Gardin JM et al. Am J Cardiol 2001;87:1051–1057.
Diastolic function	**First or second algorithm according to recommendations** **septal e' ≥7 or lateral e' ≥10 cm/s,** **average E/e' <14,** **tricuspid regurgitation systolic jet velocity <2.8 m/s,** **LA volume index<34 ml/m^2**	1) Aljaroudi W et al. Circulation 2012;125:782-8. [118] 2) Bella JN et al. Circulation 2002;105:1928-33. [119] 3) Dini FL et al. Int J Cardiol. 2013;168:3351-3358. [55] 4) Oh JK et al. J Am Coll Cardiol. 2006; 47:500–506. [64]

AP = Antero posterior, BSA = Body surface area, LA = Left atrial, LVM = Left ventricular mass, RWT = Relative wall thickness.

Figure 1

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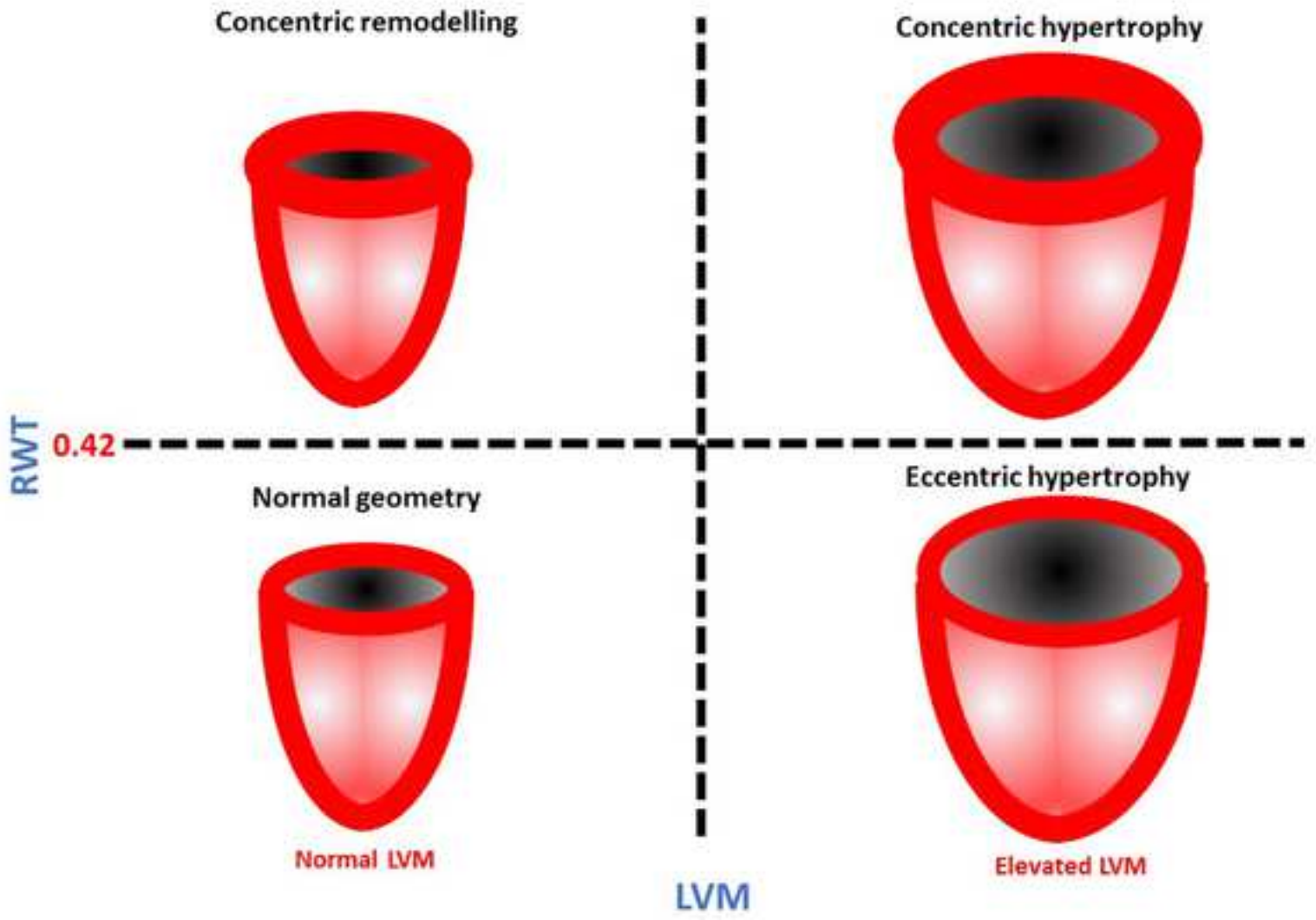


Figure 2

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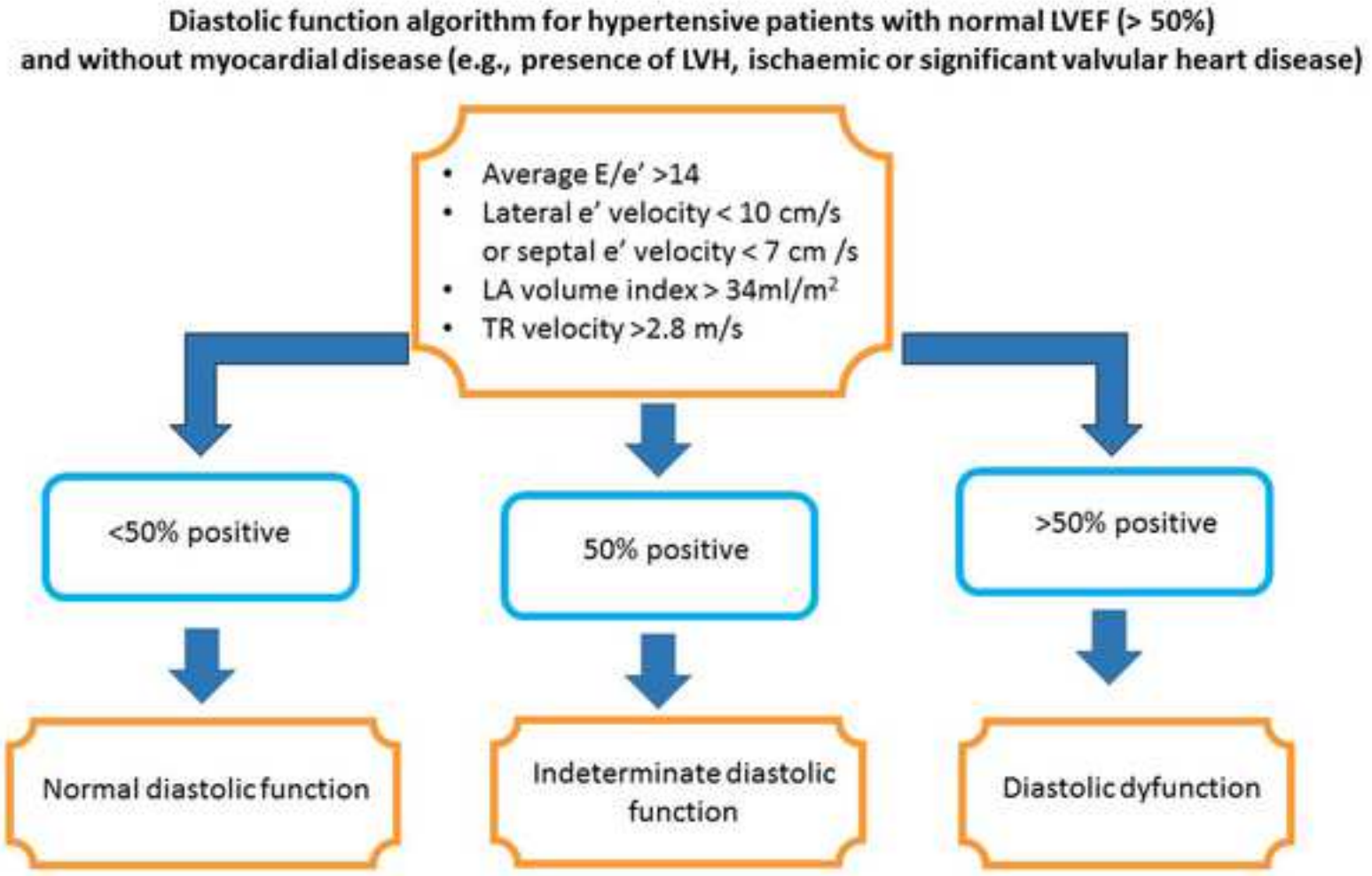


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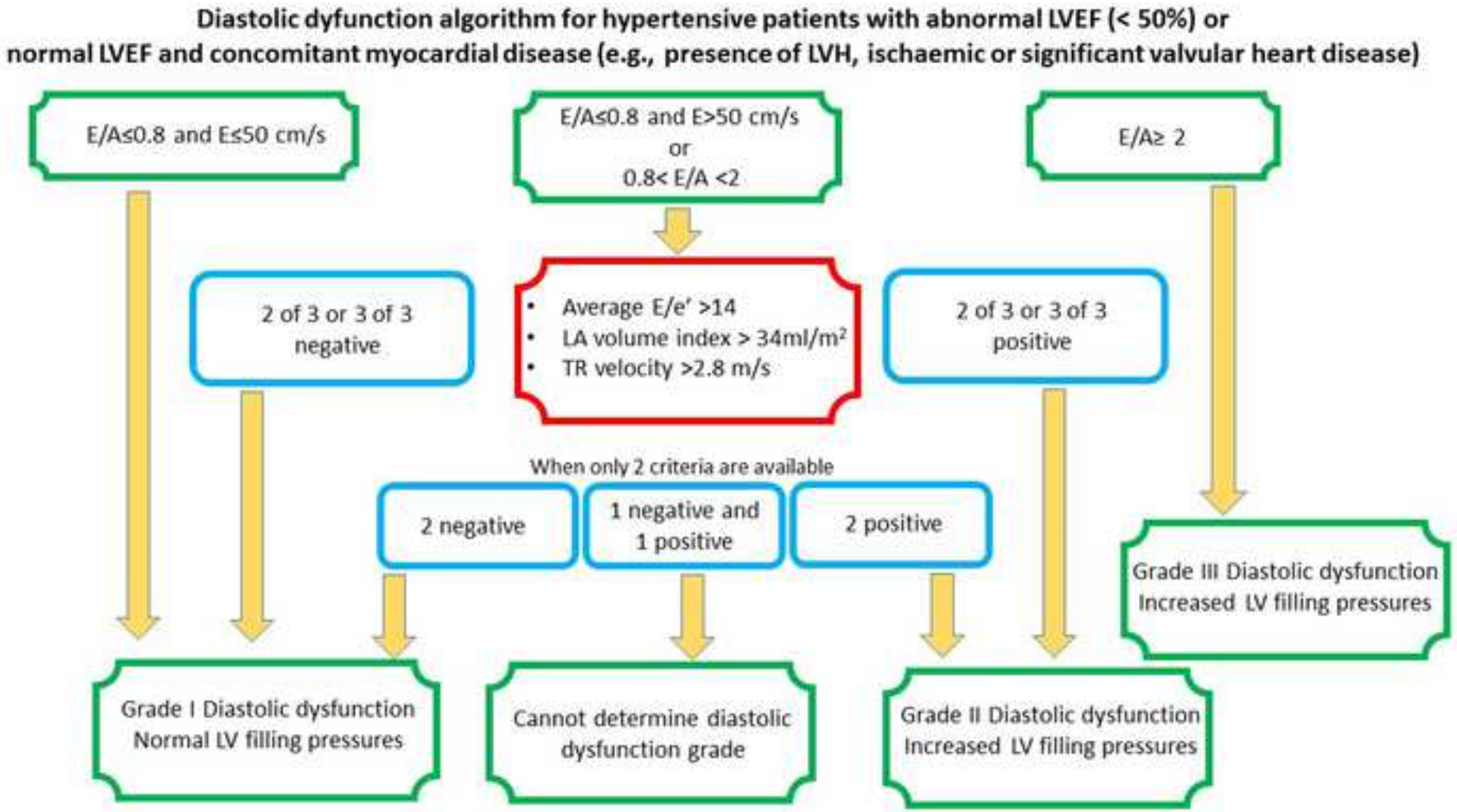


Figure 4

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