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Speckle tracking echocardiography in heart failure development and progression in patients with apneas

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Abstract

Obstructive (OA) and central apneas (CA) are highly prevalent breathing disorders that have a negative impact on cardiac structure and function; while OA promote the development of progressive cardiac alterations that can eventually lead to heart failure (HF), CA are more prevalent once HF ensues. Therefore, the early identification of the deleterious effects of apneas on cardiac function, and the possibility to detect an initial cardiac dysfunction in patients with apneas become relevant. Speckle tracking echocardiography (STE) imaging has become increasingly recognized as a method for the early detection of diastolic and systolic dysfunction, by the evaluation of left atrial and left and right ventricular global longitudinal strain, respectively. A growing body of evidence is available on the alterations of STE in OA, while very little is known with regard to CA. In this review, we discuss the current knowledge and gap of evidence concerning apnea-related STE alterations in the development and progression of HF.

Keywords Obstructive apneas · Speckle tracking echocardiography · Heart failure · Central apneas · Myocardial strain

Introduction

Obstructive apneas (OA) are a common respiratory disorder in the general population, with negative consequences on the cardiovascular system, including a higher risk of development of heart failure (HF) [1–3]. Central apneas (CA), on the other hand, despite a low prevalence in the general population, are extremely frequent in HF, at first as a compensatory mechanism and then furthering its progression [4, 5]. Both OA and CA, through phases of hypoxia, intrapleural pressure swings (especially for OA), low-grade inflammation, and sympathetic overactivation, are known to have negative effects on the heart, leading to adverse remodeling, arrhythmias, and, eventually, life-threatening events [5].

Nonetheless, the diagnosis of apnea-related cardiac alterations promoting HF development or progression is often delayed, especially with regard to OA, as conventional echocardiographic indexes of systo-diastolic impairment have low sensitivity. Speckle tracking echocardiography (STE) has emerged as a feasible tool for the early detection of subclinical diastolic and systolic alterations, with a high accessibility and reproducibility even among different operators [6].

So far, the role of STE has been more substantially used in patients with OA, while very little information is known regarding the potential role of STE in patients with CA.

This review describes the additional value of STE in the assessment of cardiac involvement in patients with apneas, highlighting the role of STE in the early detection of apnea-related cardiac alterations, in the understanding of the pathophysiological mechanisms driving to cardiac damage in patients with apneas, and in the selection of patients with apneas to be treated with specific therapeutic interventions (Fig. 1).

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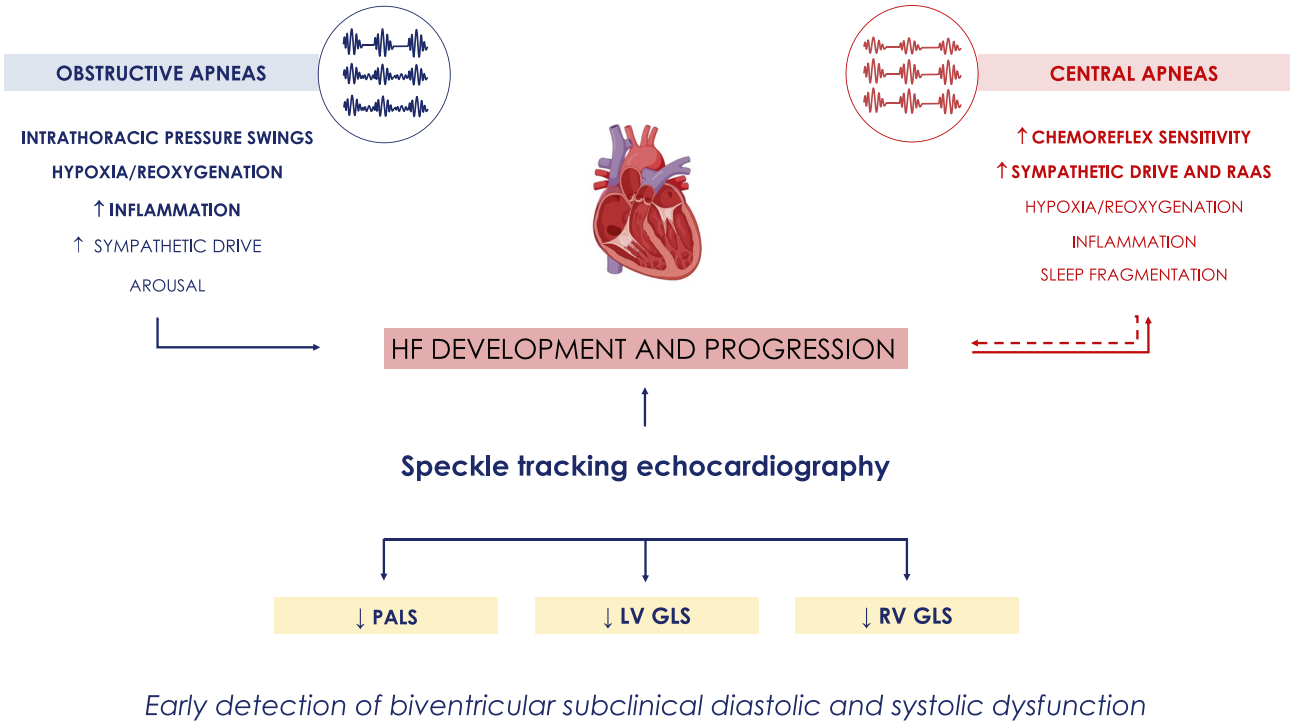

Fig. 1 Obstructive and central apneas, via increased inflammation, cyclical hypoxia/reoxygenation, increased chemosensitivity, increased sympathetic and renin–angiotensin–aldosterone (RAAS) activation, and intrathoracic pressure swings (obstructive apneas), promote heart failure (HF) development and progression. Speckle tracking echocardiography, because of its feasibility and reproducibility, could help to detect subclinical biventricular diastolic and systolic dysfunction, guiding early diagnosis and treatment of HF

Epidemiology, diagnosis, and clinical correlates of obstructive apneas

OA are defined by the absence of respiratory flow for more than 10 s in the presence of a respiratory effort by thoracic and abdominal muscles. The presence of at least five cyclic obstructive events per hour leads to a clinical syndrome characterized by daytime sleepiness, loud snoring, or awakenings [1]. OA can be diagnosed by standard nighttime polysomnography or ambulatory cardio-respiratory monitoring and they are classified according to the apnea/hypopnea index (number of events/hour — AHI) as mild (AHI ≥ 5), moderate-severe (AHI ≥ 15), or severe (AHI ≥ 30) [2]. The estimated prevalence of mild OA is around 15–30% in males and 10–15% in females, while that of moderate-severe OA is approximately 15% and 5%, respectively [7].

Several clinical risk factors are associated with OA, including age, male gender, obesity, and craniofacial and upper airway abnormalities [3, 6]. During sleep, breathing becomes critically dependent upon chemical and mechanical stimuli. In patients with an anatomical predisposition to upper airway collapsability, and especially in obese patients with increased parapharyngeal fat and reduced thoracic and diaphragmatic excursions, reduced muscle tone during sleep promotes obstruction, while in the elderly and in patients with pulmonary comorbidities, increased muscle weakness and hypoglossal nerve dysfunction prevents to overcome the increased upper airway resistance [3, 8]. Moreover, rostral fluid shift occurring in the recumbent position, which is especially relevant in patients with high volume status like HF, also promotes obstruction by increasing neck circumference [8]. Finally, patients with baseline increased chemoreflex gain (high loop gain OA) experience abnormal response to blood gases with secondary ventilatory instability [9]. The repetitive cycles of hypoxia/reoxygenation and hypercapnia lead to increased sympathetic and renin–angiotensin–aldosterone (RAA) system activation and low-grade chronic inflammation, with a variety of detrimental clinical consequences. Indeed, patients with OA are known to experience sleep fragmentation, with disruption of cellular night-time reparative processes and increased risk of dementia and neuropsychiatric disorders, and to have a higher risk of developing insulin resistance and diabetes, polydistrectual atherosclerosis with coronary or cerebral artery disease, systemic and pulmonary hypertension, atrial fibrillation, life-threatening brady- and tachyarrhythmias, and HF [5, 10–12]. Furthermore, the cyclical pressure swings occurring to overcome the obstruction are responsible for intermittently increased afterload with ventricular and atrial stretching. Taken together, all those mechanisms negatively impact on cardiovascular [13] and all-cause mortality [14].

Speckle tracking echocardiography

STE is a non-Doppler-based method that allows to objectively quantify the myocardial strain in standard greyscale bidimensional (2D) and three-dimensional (3D) images [6, 15], with quite high feasibility and reproducibility [16–18]. Left ventricular global longitudinal strain (LVGLS) describes the myocardial shortening of the LV along its base-apex axis, with an accurate and sensitive detection of the alterations of hypoxia-sensitive subendocardial longitudinal fibers [19], while 3D global area strain describes the change of the whole endocardial surface area [15]. Nonetheless, strain can also be obtained by a layer-specific analysis (from endocardium to epicardium) and in the radial and circumferential directions [15, 19].

The LV rotational counterclockwise movement of the LV apex and the clockwise rotation of the base, created by the contraction of its oblique spiral fibers, can also be analyzed by STE. The combination of these two opposite movements identifies the so-called *twisting* during systolic phase and the opposite *untwisting* during diastole. Torsion is evaluated by a normalization of the twisting angle for the LV base-apex length, although it is common to find *twisting* and *torsion* used as synonyms in current literature.

STE is also considered the current gold standard method for the analysis of LA function, which is articulated in three phases: a "reservoir" phase, with active atrial filling, a "conduit" phase, with passive atrial filling, and a "booster pump" phase, with atrial contraction. At the end of LA filling, it is possible to measure the peak atrial longitudinal strain (PALS), a valuable index of atrial compliance [6]. PALS inversely correlated with LA fibrosis assessed by both cardiac magnetic resonance [20] and Masson's trichrome staining in LA tissue samples [21]. LA strain may be used as a surrogate marker of diastolic dysfunction [22] because it is able to accurately predict LV filling pressures [23].

Finally, the analysis of the longitudinal deformation of RV free wall (fwRVLS) has emerged as the most reliable index of RV contractility as, differently from RVGLS that involves interventricular septum tracing as well, it avoids alterations secondary to akinetic septum or paradoxycal septal movements [24, 25].

Apneas before heart failure: strain analysis and early recognition of myocardial damage in obstructive apneas

Left atrial strain and OA: where the story begins

In young healthy adults, a significant change in LA volume index (LAVI) (from 12.9 ± 3.4 to 17.9 ± 4.1 mL/m^2, $p < 0.0001$) has been described after a Mueller maneuver targeted to reach an intrapleural pressure of -40 mmHg, similarly to what is observed in OA [26]. Indeed, patients with OA often present with LA enlargement in diameter, area, and volume, especially in more severe diseases, which is often associated with diastolic dysfunction demonstrated with pulse wave and tissue Doppler imaging [27, 28].

Nonetheless, the conventional echocardiographic parameters are highly dependent on the hemodynamic profile and low sensitivity in conditions like atrial fibrillation [28].

2D STE of the LA is a more sensitive, not angle dependent, precocious marker of diastolic dysfunction, as it is altered even before filling pressures increase (E/e' ratio "grey zone") and before LA enlargement (Fig. 2) [22].

In OA patients, PALS is usually impaired and, while some overlap can be seen between normal breathers and mild OA, the differences are more marked with progressive severity of the disease (Table 1) [29–33]. In a cohort of 162 patients with different severity of OA, PALS was slightly reduced in mild and moderate OA ($30.9 \pm 5.5\%$, normal range 38–40.8%) in presence of a still normal or only mildly increased LAVI (28.1 ± 3.4 mL/m^2) and "gray zone" E/e' ratio values (11.9 ± 3.2) [31]. Interestingly, LA reservoir and conduit function, assessed by STE, decrease with disease progression, while atrial contractile function initially increases and then decreases with more severe OA, possibly as a compensatory mechanism [29]. Therefore, LA strain could be used as a sensitive marker of diastolic dysfunction in OA, independently from increased LA size, which is possibly affected by intrathoracic pressure swings even when filling pressures are still normal [30].

Finally, PALS is a useful tool for atrial dysfunction even in presence of atrial fibrillation, when other markers of diastolic dysfunction lose sensitivity [34]. Given the high prevalence of atrial fibrillation in OA, it is intriguing to speculate that early detection of worsening LA function before the onset of macroscopic alterations might guide therapeutic strategies (e.g., anticoagulation treatment). However, further research is needed to support this approach.

Left and right ventricular global longitudinal strain and obstructive apneas: where the story goes

Patients with OA often do not experience LV systolic dysfunction, at least in the first phases of the disease. However, subtle differences in LVEF between mild and moderate-severe OA can be observed (Table 2), raising the interest for sensitive markers of early systolic dysfunction (Fig. 2).

The analysis of GLS during a Mueller maneuver in healthy individuals demonstrated a relevant decrease of both LV and RV strain (from -17.0 ± 1.6 to $-14.5 \pm 2.2\%$, $p < 0.0001$ and from -22.0 ± 3.1 to $-17.2 \pm 2.5\%$, $p < 0.0001$, respectively) [35]. Similar observations were made in healthy subjects

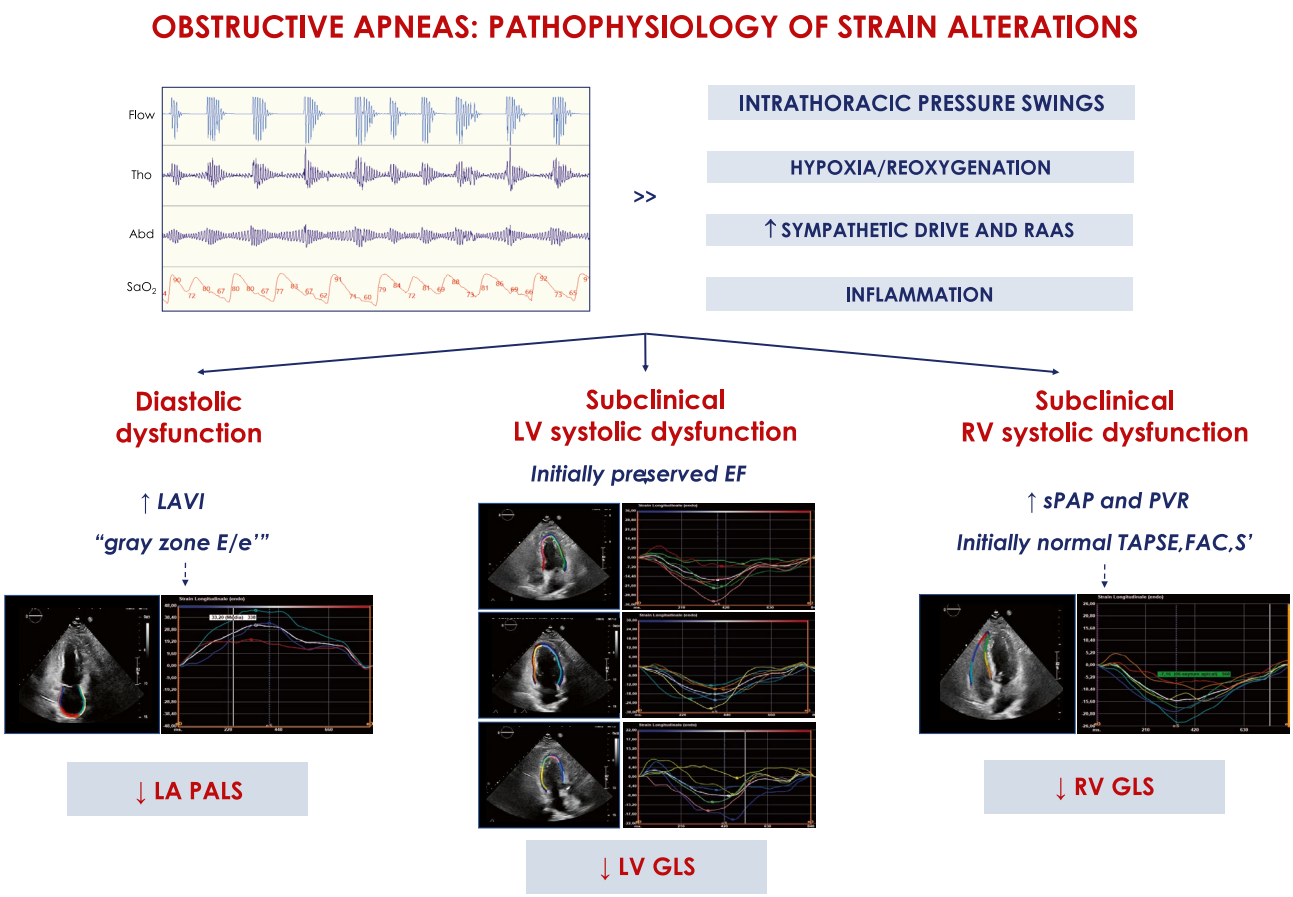

Fig. 2 Obstructive apneas: pathophysiology of strain alterations. Cyclical intrathoracic pressure swings, hypoxia/reoxygenation, increased sympathetic drive and renin–angiotensin–aldosterone system (RAAS) activation, and inflammation induce diastolic dysfunction, with reduced peak atrial longitudinal strain (PALS) and left atrial volume index (LAVI), even if filling pressures are still within normal or "gray zone" range (LVEDP, left ventricular end diastolic pressure; PCWP, pulmonary capillary wedge pressure). The same mechanisms also promote left ventricular (LV) systolic dysfunction with reduced global longitudinal strain (GLS) and increased systolic pulmonary artery pressure (sPAP) and pulmonary vascular resistances (PVR) with subsequent right ventricular (RV) dysfunction with GLS, even if conventional echocardiographic indexes are still within the normal range

after a voluntary end-expiratory apnea in normoxic but not hyperoxic conditions, suggesting a potential contribution of chemoreceptor-induced sympathetic discharge on acute changes of heart mechanics [36].

GLS values are lower in patients with OA, especially in those with moderate and severe disease, when compared to healthy controls (Table 2) [29, 37–45], while the relationship is less clear in patients with mild OA, where LVGLS values are partly in overlap with those of healthy controls [38, 39]. Nonetheless, GLS is strongly correlated with AHI, with correlation coefficients ranging from −0.56 to −0.77 across different studies [29, 39, 41], and AHI and nocturnal desaturation were found to be independent predictors of reduced GLS at multivariable analysis in different studies [45, 46]. Interestingly, epicardial and midwall longitudinal strain, as well as circumferential strain, are also reduced in OA, suggesting a possible damage not only of the subendocardium but also of cardiac muscle and epicardial tissue [41]. In fact, 3D global area strain calculated with 3D STE, which is a composite of longitudinal and circumferential strain, showed the highest correlation with AHI in 78 normotensive OA patients ($r = -0.80$, $p < 0.0001$) [39]. Further studies are needed to investigate the time and severity-related impact of OA on different cardiac layers, possibly also to tailor therapeutic interventions.

Finally, GLS increment under effort is also impaired in OA patients when compared to controls (Δ LVGLS $15.8 \pm 3.4\%$ vs. $25.4 \pm 4.1\%$, $p < 0.001$), and it is mirrored by a higher increment in filling pressures and systolic artery pressure (sPAP) [44]. Therefore, GLS under effort should be considered as a potential marker of early diastolic and systolic dysfunction in those patients.

Besides LV systolic dysfunction, OA are also associated with progressive RV systolic dysfunction, which is aggravated by hypoxia and chemoreflex-induced increased systolic pulmonary artery pressure (sPAP). Nonetheless, the

Table 1 Comparison of indexes of left atrial and diastolic function in healthy subjects and in patients with obstructive apneas

Study	Population	Subjects (*n*)	AHI (events/h)	E/e'	LAVI (mL/m^2)	PALS (%)
Altekinet al. 2012 [29]	Healthy	21	-	6.9 ± 1.7	26.0 ± 4.4	38.1 ± 6.9
	Mild OA	20	10.7 ± 2.6	6.9 ± 1.9	29.0 ± 4.8	36.4 ± 3.3
	Moderate OA	19	20.5 ± 2.6*[a]	8.6 ± 2.4	34.2 ± 6.9*[a]	35.4 ± 4.6
	Severe OA	19	58.1 ± 16.3*[a¶]	10.3 ± 1.5*[a¶]	42.3 ± 5.1*[a¶]	30.5 ± 3.3*[a¶]
Kim et al. 2012 [30]	Healthy	24	2.9 ± 1.4	9.1 ± 4.3	21.3 ± 7.2	55.1 ± 13.6
	OA	25	19.7 ± 11.6*	10.8 ± 2.8*	34.7 ± 8.9*	42.9 ± 10.2*
Vural et al. 2014 [31]	Healthy	45	35.4 ± 4.1	6.5 ± 2.2	24.3 ± 6.4	35.4 ± 4.1
	Mild OA	22	34.0 ± 2.3	8.4 ± 3.4*	23.5 ± 3.5	34.0 ± 2.3
	Moderate OA	27	30.9 ± 5.5*[a]	11.9 ± 3.2*[a]	28.1 ± 3.4*[a]	30.9 ± 5.5*
	Severe OA	68	29.3 ± 6.0*[a¶]	12.0 ± 3.8*[a¶]	37.8 ± 7.1*[a¶]	29.3 ± 6.0*[a]
Cetin et al. 2017 [32]	Non-severe OA	26	8.9 ± 9.8	8.5 ± 2.8	25.7 ± 4.3	33.9 ± 5.0
	Severe OA	29	61.1 ± 21.0*	12.2 ± 3.2*	40.7 ± 7.1*	28.5 ± 5.6*
Wan et al. 2020 [33]	Healthy	50	3.0 ± 0.9	7.2 ± 2.2	21.9 ± 3.4	39.3 ± 5.5
	OA	62	48.5 ± 9.2	7.8 ± 2.2	24.5 ± 5.1*	34.1 ± 8.1*

AHI, apnea–hypopnea index; *OA*, obstructive apneas; *LAVI*, left atrial volume index; *PALS*, peak atrial longitudinal strain. *$p < 0.05$ vs. healthy, [a]$p < 0.05$ vs. mild OA, [¶]$p < 0.05$ vs. moderate OA

current indexes of systolic RV dysfunction display a low sensitivity and specificity, mainly because of the difficult RV anatomy. Therefore, RV dysfunction is often missed or discovered late in severe stages of the disease (Table 3). In this respect, RVGLS and fwRVLS could represent useful indexes. Several studies, albeit small, have addressed the alterations of RV strain in OA (Table 3) [39, 46–50]. Despite differences in cut-off values, RVGLS and fwRVLS appear reduced in patients with OA, especially in moderate and severe disease, and in RV apical segments, differently from other phenotypes of cardiac hypertrophy [46–50]. Similarly, 3D parameters of RV function are more closely associated with OA severity, with RV volumes and desynchrony increasing and 3D ejection fraction decreasing in the more advanced stages of the disease [48].

Interestingly, the lowest values of RV 2D and 3D strain have been found in populations studied at high altitude (1500 to 3000 m) [47, 50]. Therefore, a potential contribution of hypoxia and chemoreflex-induced sympathetic overactivation on sPAP and RV function can be hypothesized.

Patients with OA, in fact, often show higher values of sPAP when compared to healthy individuals [28]. GLS is affected by increased RV afterload, and it correlates both with sPAP and AHI ($r = -0.46$, $p < 0.0001$ and $r = -0.26$, $p = 0.035$, respectively) at sea level [41], and more strongly with AHI at high altitude ($r = -0.65$, $p = 0.01$) [50]. When OA patients were stratified according to sPAP (cut-off value 30 mmHg), those with increased sPAP show the lowest values of fwRVLS (25.1 ± 7.0 vs. 17.8 ± 4.8, $p < 0.001$) [49], while TAPSE, albeit slightly reduced in OA, was still within normal range.

Torsion, OSA, and hypertension: a twisted relationship

OA are highly prevalent in hypertension, being the most frequent secondary cause of resistant hypertension [51–54], despite the strong influence of different confounding variables including age, obesity, and metabolic syndrome [11]. Subjects with concomitant hypertension and OA typically show a non-dipping or even reverse-dipping pattern, with negative prognostic consequences [55]. Increased LV afterload, as in hypertension per se, induces mechanical compensatory changes within the heart with increased epicardial-to-endocardial fibers thickening to preserve systolic function, resulting in increased LV mass and enhanced LV torsion [56]. Indeed, normotensive patients with OA demonstrate a 15% increase in LV mass, and some authors have highlighted a higher LV twist in normotensive OA, more pronounced in severe OA (14.8 ± 4.2° in controls vs. 15.7 ± 4.3° in mild OSA vs. 21.3 ± 5.1° in severe OSA, $p < 0.001$) [37]. However, other authors have reported a slight increase in LV torsion in mild and moderate OA, but not in severe OA (15.6 ± 1.5° vs. 16.1 ± 1.9° vs. 16.5 ± 1.6° vs. 14.8 ± 1.6°, $p < 0.001$) [42]. These differences could be ascribed to a higher prevalence of hypertension (around 20%) and lower levels of LVGLS (−18.4 ± 2.7 vs. −15.6 ± 5.6) in the second cohort, which could subtend initial systolic dysfunction with eccentric remodeling and, therefore, reduced torsion in the later stages of disease. Nonetheless, no information is so far available on the additive and independent effect of hypertension and OA on LV mass and torsion.

Table 2 Comparison of indexes of left ventricular systolic function in healthy subjects and in patients with obstructive apneas

Study	Population	Subjects (*n*)	AHI (events/h)	LVEDD (mm)	LVEF (%)	LVGLS (%)
Altekin et al. 2012 [29]	Healthy	21	-	-	64.2 ± 3.7	−25.6 ± 2.2
	Mild OA	20	10.7 ± 2.6	-	64.2 ± 3.8	−23.9 ± 3.9
	Moderate OA	19	20.5 ± 2.6[a]	-	63.7 ± 5.4	−21.3 ± 2.6*[a]
	Severe OA	19	58.1 ± 16.2[a¶]	-	63.2 ± 3.2	−16.9 ± 2.7*[a¶]
Cho et al. 2012 [37]	Healthy	35	2.93 ± 1.44	46.0 ± 3.8	65.5 ± 3.0	−20.6 ± 2.0
	OA	25	19.7 ± 11.6*	49.6 ± 3.8*	64.4 ± 4.2	−16.5 ± 1.9*
Vitarelli et al. 2013 [38]	Healthy	35	3.8 ± 1.1	-	62 ± 8	−21.9 ± 2.8
	Mild OA	19	15.4 ± 2.2*	-	60 ± 7	−21.2 ± 2.5
	Severe OA	23	59.4 ± 9.3*	-	59 ± 7	−18.4 ± 2.7*
Wang et al. 2016 [39]	Healthy	30	2.7 ± 1.2	46 ± 4	67 ± 7	−18.2 ± 1.7
	Mild OA	26	10.5 ± 3.2*	47 ± 5	65 ± 7	−17.8 ± 1.5
	Moderate OA	29	18.7 ± 5.6*[a]	49 ± 5*	61 ± 9*	−15.9 ± 1.4*[a]
	Severe OA	23	57.2 ± 12.6*[a¶]	50 ± 4*[a]	59 ± 8*[a]	−14.8 ± 1.5*[a¶]
D'Andrea et al. 2016 [40]	Healthy	45	-	48.2 ± 3.8	58.4 ± 6.5	−16.8 ± 5.1
	OA	55	35.1 ± 15.4	49.4 ± 4.7	56.2 ± 5.5	−11.5 ± 4.1*
Zhou et al. 2016 [41]	Healthy	19	-	4.67 ± 0.37	65.7 ± 3.3	−21.7 ± 2.5
	Mild OA	20	-	4.71 ± 0.39	66.1 ± 4.7	−21.2 ± 2.8
	Moderate OA	16	-	4.70 ± 0.41	64.2 ± 3.4	−19.0 ± 3.7
	Severe OA	24	-	4.72 ± 0.37	63.8 ± 2.9	−17.5 ± 5.8*[a]
Varghese et al. 2017 [42]	Healthy	31	-	-	65.2 ± 3.4	−19.0 ± 1.6
	Very severe OA	31	74.3 ± 13.2	-	66.2 ± 3.5	−15.0 ± 1.8*
Vural et al. 2017 [43]	Healthy	45	2.8 ± 1.0	-	63.9 ± 2.7	−22.3 ± 4.0
	Mild OA	22	9.3 ± 3.2	-	63.5 ± 3.1	− 20.0 ± 2.3
	Moderate OA	27	24.9 ± 3.9	-	63.8 ± 2.6	−17.2 ± 2.0*
	Severe OA	68	57.3 ± 20.4	-	62.7 ± 4.1	−15.6 ± 5.6*[a]
D'Andrea et al. 2020 [44]	Healthy	35	2.2 ± 2.4		57.4 ± 5.5	−18.4 ± 3.3
	OA	55	41.4 ± 27*		56.5 ± 6.2	−13.4 ± 3.8*
Ma et al. 2021 [45]	Mild OA	97	5.3 ± 4.2	46.3 ± 5.3	68 .0± 6.0	−20.1 ± 2.4
	Moderate to severe OA	147	42.2 ± 20.6*	48.4 ± 4.3*	66.0 ± 5.0*	−18.2 ± 2.1*

AHI, apnea–hypopnea index; *OA*, obstructive apneas; *LVEDD*, left ventricular end diastolic diameter; *LVEF*, left ventricular ejection fraction; *LVGLS*, left ventricular global longitudinal strain. *$p < 0.05$ vs. healthy, [a]$p < 0.05$ vs. mild OA, [¶]$p < 0.05$ vs. moderate OA

Biventricular function after CPAP: is strain analysis a magnifying glass?

The American Academy of Sleep Medicine recommends continuous positive airway pressure (CPAP) for the treatment of symptomatic OA or OA associated with other comorbidities like hypertension [57]. The beneficial effects of CPAP on outcomes of atrial fibrillation, myocardial infarction, HF, and cardiovascular mortality have been demonstrated in meta-analysis of observational studies, but not of randomized-controlled trials [57–59]. Various differences in patients' selection, impact of comorbidities, and especially compliance to therapy can account for those discrepancies. Therefore, the implementation of strain evaluation for patients' selection and follow-up after CPAP initiation could be a useful tool.

Several studies have addressed the impact of CPAP on strain values, especially in moderate and severe OA (Table 4) [31, 38, 40, 43, 48, 60–62]. The positive effect of CPAP on RV and LVGLS has been consistently reported across different studies, despite the diverse populations and duration of the treatment, even in presence of unchanged conventional echocardiographic indexes of LV and RV systolic function (Table 4). Recently, the effect of CPAP on STE was evaluated in 52 patients with OA in the first 1:1 randomized, double-blind, sham-controlled study. At 3 months' time point, LVGLS significantly improved in patients randomized to CPAP (−18.0 ± 2.5% sham vs. −20.0 ± 2.1% on CPAP; $p = 0.004$), while EF did not change. CPAP also improved RV dimensions and fractional area change (46.9 ± 6.7% sham vs. 51.3% ± 7.9% on CPAP; $p = 0.038$),

Table 3 Comparison of indexes of right ventricular systolic function in healthy subjects and in patients with obstructive apneas

Study	Population	Subjects (*n*)	AHI (events/h)	RV diameter (mm)	TAPSE (mm)	S' (cm/s)	sPAP (mmHg)	RVGLS (%)	fwRVLS (%)
Kepez et al. 2009 [46]	Healthy	22	2.5 ± 2.0	2.6 ± 0.1	-	13.9 ± 3.1	-	-	−35.8 ± 7.6
	Mild to moderate OA	45	15.0 ± 13.0*	2.7 ± 0.3	-	13.0 ± 2.4	-	-	−29.8 ± 8.9
	Severe OA	40	46.0 ± 42.0*	2.6 ± 0.2	-	13.3 ± 2.4	-	-	−25.7 ± 7.5
Güvenç et al. 2015 [47]	Healthy	26	23.0 ± 4.5	30.6 ± 4.4	22 ± 3	16.5 ± 3.1	30.9 ± 6.5	-	−18.5 ± 7.3
	OA	41	53.4 ± 18.5*	31.1 ± 5.3	22 ± 4	15.2 ± 4.7	38.4 ± 8.6*	-	−13.1 ± 8.3
Vitarelli et al. 2015 [48]	Healthy	30	3.8 ± 1.4	-	23 ± 6	12.6 ± 2.5	22 ± 3	−24.2 ± 3.4	−25.6 ± 5.5
	Mild OA	10	7.1 ± 1.9*	-	21 ± 3	11.9 ± 2.9	25 ± 6	−23.6 ± 3.7	−23.7 ± 4.1
	Moderate OA	8	19.8 ± 2.7*	-	18 ± 4*	9.2 ± 3.3*	35 ± 11*	−22.9 ± 3.8	−20.5 ± 4.1*
	Severe OA	19	58.9 ± 9.1*	-	16 ± 4*	7.8 ± 3.3*	46 ± 11*	−19.1 ± 3.7*	−18.2 ± 4.9*
D'Andrea et al. 2016 [40]	Controls	45	-	37.8 ± 4.5	23.8 ± 2.5	-	24.8 ± 11.3	−17.6 ± 5.6	48.8 ± 10.6
	OA	55	35.1 ± 15.4	39.8 ± 5.4	22.6 ± 2.2	-	35.8 ± 14.4*	−13.8 ± 5.2*	38.5 ± 4.6*
Buonauro et al. 2017 [49]	Healthy	29	-	23.1 ± 11.6	23.3 ± 3.8	13.5 ± 2.2	23.2 ± 3.5	−22.8 ± 3.3	−25.7 ± 3.2
	OA	59	42.0 ± 24.3	32.5 ± 6.1*	23.5 ± 3.3	13.1 ± 2.6	27.3 ± 8.1*	−20.9 ± 4.9*	−22.6 ± 7.2*
Chu et al. 2020 [50]	Healthy	31	2.6 ± 1.0	30.0 ± 3.9	20.7 ± 2.3	13.2 ± 2.5	29.6 ± 4.7	−23.1 ± 3.8	−25.7 ± 2.9
	OA	71	44.3 ± 17.2*	30.5 ± 3.3	20.0 ± 2.2	13.6 ± 2.4	42.7 ± 8.4*	−18.8 ± 5.9*	−22.8 ± 3.4*

AHI, apnea–hypopnea index; *fwRVLS*, free wall right ventricular longitudinal strain; *OA*, obstructive apneas; *RV*, right ventricular; *RVGLS*, right ventricular global longitudinal strain; *sPAP*, systolic pulmonary artery pressure; *TAPSE*, tricuspidal annular plane systolic excursion. *$p < 0.05$ vs. healthy, [a]$p < 0.05$ vs. mild OA, [¶]$p < 0.05$ vs. moderate OA

as well as RVGLS (−18.5 ± 4.4% sham vs. −20.3 ± 4.4% on CPAP, $p < 0.05$) [62].

However, the duration and compliance to CPAP therapy has not been systematically evaluated, nor data are available in responders vs. non-responders and on the consequent effects on cardiac function. Studies designed to investigate those questions are of great clinical interest, especially in light of the controversial effects of CPAP on cardiac hemodynamics. Patients with subclinical RV systolic dysfunction might be, in fact, more sensitive to the hemodynamic changes on the RV [40, 60], and the net effects of altered preload and afterload in the long term are not completely clarified. Therefore, RV strain could be a useful index to assess the chronic effects of CPAP on right heart function.

Finally, few but positive results on early improvement of diastolic function with CPAP are available. In patients compliant to the therapy (5.7 ± 1.2 h/night), a reduction in LAVI was seen after 12 weeks of treatment, and was sustained even after 24 weeks of therapy. This beneficial anatomical improvement was accompanied by an increase in reservoir and conduction atrial strain (29.3 ± 6.4% vs. 31.7 ± 6.5%, $p < 0.05$ and 12.9 ± 3.3% vs. 15.1 ± 3.6%, $p < 0.05$, respectively) [31], a result recently confirmed in a randomized, double-blind, sham-control trial after 3 months [62]. Notably, positive effects on LA function could also subtend a higher efficacy of catheter ablation of atrial fibrillation in the maintenance of stable sinus rhythm after 1 year in patients treated with CPAP compared to controls [63, 64]. Further research on the impact of those indexes to guide pharmacological and device therapy are therefore of great clinical interest.

Apneas after heart failure: can speckle tracking echocardiography have a role in patients with HF and central apneas?

Once HF ensues, CA become more prevent, affecting around 60% of patients with HF and reduced ejection fraction (HFrEF) and 40% of patients with preserved ejection fraction (HFpEF) [4, 65–67].

As LV dysfunction progresses, CA can be found also at daytime in around 30% of patients, and in the upright position in around 15% [68–71].

Differently from OA, the absence of thoracic and abdominal movements during apneas does not impact on intrathoracic pressures, while increased chemosensitivity to hypoxia and hypercapnia, increased plant gain (the lung contribution to ventilation) and prolonged circulatory time are the main pathophysiological triggers of CA [68–71]. Nevertheless, the intermittent cycles of hypoxia/reoxygenation induce sympathetic and RAAS overactivation and inflammation, which is further aggravated by increased chemoreflex activation per se, worsening HF progression and arrhythmic burden and negatively impacting on survival [4, 66–71].

The role of STE is becoming increasingly recognized in HF independently from EF, holding prognostic and diagnostic significance, especially to guide therapeutic interventions

Table 4 Effects of continuous positive airway pressure on apneas and echocardiographic indexes of left ventricular function

Study	Subjects (*n*)	Treatment duration (m)	Average CPAP use (h)		AHI (events/h)	E/e'	LAVI (mL/m^2)	PALS (%)	LVEF (%)	LVGLS (%)	TAPSE (mm)	RVGLS (%)
Haruki et al. 2010 [60]	14	3	-	*Before* *After*	56 ± 19 *vs* 5 ± 8*	-	-	-	-	− 20.9 ± 2.3 *vs* − 21.3 ± 1.9*	-	-
Hammerstingl et al. 2013 [61]	82	6	6.5 ± 1.1	*Before* *After*	31.4 ± 26.8 *vs* 5.6 ± 7.1*	11.0 ± 6.2 *vs* 10.1 ± 3.6	-	-	60.7 ± 8.4 *vs* 63.2 ± 7.2*	-	24.8 ± 5.9 *vs* 24.3 ± 5.9	− 16.9 ± 7.5 *vs* − 17.6 ± 8.5*
Vitarelli et al. 2013 [38]	15	4	6.0 ± 0.5	*Before* *After*	58.6 ± 9.4 *vs* 4.1 ± 1.8*	-	-	-	58 ± 8 *vs* 59 ± 7	− 18.3 ± 2.2 *vs* − 20.2 ± 2.4*	-	-
Vural et al. 2014 [31]	28	6	5.7 ± 1.2	*Before* *After*	-	12.0 ± 2.5 *vs* 9.8 ± 1.5*	38.3 ± 7.6 *vs* 34.1 ± 7.9*	29.3 ± 6.4 *vs* 31.7 ± 6.5*	-	-	-	-
Vitarelli et al. 2015 [38]	15	4	-	*Before* *After*	57.9 ± 9.1 *vs* 4.2 ± 1.6*	-	-	-	-	-	15 ± 4 *vs* 17 ± 4	− 19.3 ± 4.6 *vs* − 20.7 ± 4.8*
D'Andrea et al. 2016 [40]	53	6	-	*Before* *After*	35.1 ± 15.4 *vs* 5.1 ± 8.2*	8.2 ± 0.4 *vs* 5.5 ± 0.5*	-	-	56.2 ± 5.5 *vs* 60.2 ± 5.1*	− 11.5 ± 4.1 *vs* − 14.8 ± 4.5*	22.6 ± 2.2 *vs* 22.8 ± 2.6	− 13.8 ± 5.2 *vs* − 14.6 ± 6.2*
Vural et al. 2017 [43]	28	6	5.7 ± 1.2	*Before* *After*	-	12.0 ± 2.5 *vs* 9.8 ± 1.5*	38.3 ± 7.6 *vs* 34.1 ± 7.9*	-	61.5 ± 4.1 *vs* 61.8 ± 3.3	− 15.5 ± 6.9 *vs* − 18.8 ± 3.6*	-	-
Kim et al. 2019 [62]	26	3	4.6 ± 1.2	*Before* *After*	64.2 ± 20.5 *vs* 3.5 ± 1.0*	8.9 ± 2.4 *vs* 8.9 ± 2.4	26.5 ± 5.8 *vs* 26.6 ± 5.2	37.3 ± 9.8 *vs* 43.0 ± 9.1*	66 ± 5 *vs* 65 ± 6	− 17.8 ± 2.1 *vs* − 20.0 ± 2.1*	-	− 18.5 ± 4.4 *vs* − 20.3 ± 4.4*

AHI, apnea–hypopnea index; *OA*, obstructive apneas; *LAVI*, left atrial volume index; *LVEF*, left ventricular ejection fraction; *LVGLS*, left ventricular global longitudinal strain; *PALS*, peak atrial longitudinal strain; *RVGLS*, right ventricular global longitudinal strain; *TAPSE*, tricuspidal annular plane systolic excursion. *$p < 0.05$ before vs. after CPAP treatment

[72, 73]. Nonetheless, little is known about its applications in patients with HF and CA. When compared to patients with HFrEF and no CA, patients with CA both at nighttime and daytime have lower EF and TAPSE, secondary to chronic hypoxia, inflammation, and elevated precapillary and post-capillary pulmonary pressures [66, 74–76]. In accordance, very depressed values of LV and RV strain have been described in patients with HFrEF and CA (−8.7 ± 3.4% and −12.0 ± 4.2, respectively) [77].

On the other hand, patients with HFpEF and CA do not show differences in conventional echocardiographic indexes of LV and RV function, but they have depressed values of both LVGLS and RVGLS (−15.0 ± 4.3 and −14.6 ± 3.8, respectively) [77]. Nonetheless, a systematic assessment of LV and RV strain in HF and CA has never been performed, and worse values compared to HF patients without apneas can only be hypothesized (Fig. 3).

Finally, both LV and RVGLS did not improve after treatment with adaptive servoventilation in a sub-analysis of the CAT-HF trial both in HFrEF and in HFpEF patients when compared to medical therapy [77]. However, this study was not powered for the evaluation of the efficacy of mechanical ventilation on strain parameters, nor differences between presence or absence of CA. Nonetheless, after the results of the SERVE-HF trial, that demonstrated a worse prognosis in HFrEF patients with CA treated with adaptive servoventilation [78], concerns have been raised regarding the effects on non-invasive ventilation on the right heart, which could be greatly affected in patients with initial or subclinical RV systolic dysfunction. Therefore, the assessment of RV function with the more sensitive 2D and 3D strain parameters might help in the therapeutic decision-making for the use of mechanical ventilation (especially in HFpEF) or for other emerging treatments for CA, such as phrenic nerve stimulation [79] or drugs [80–82],

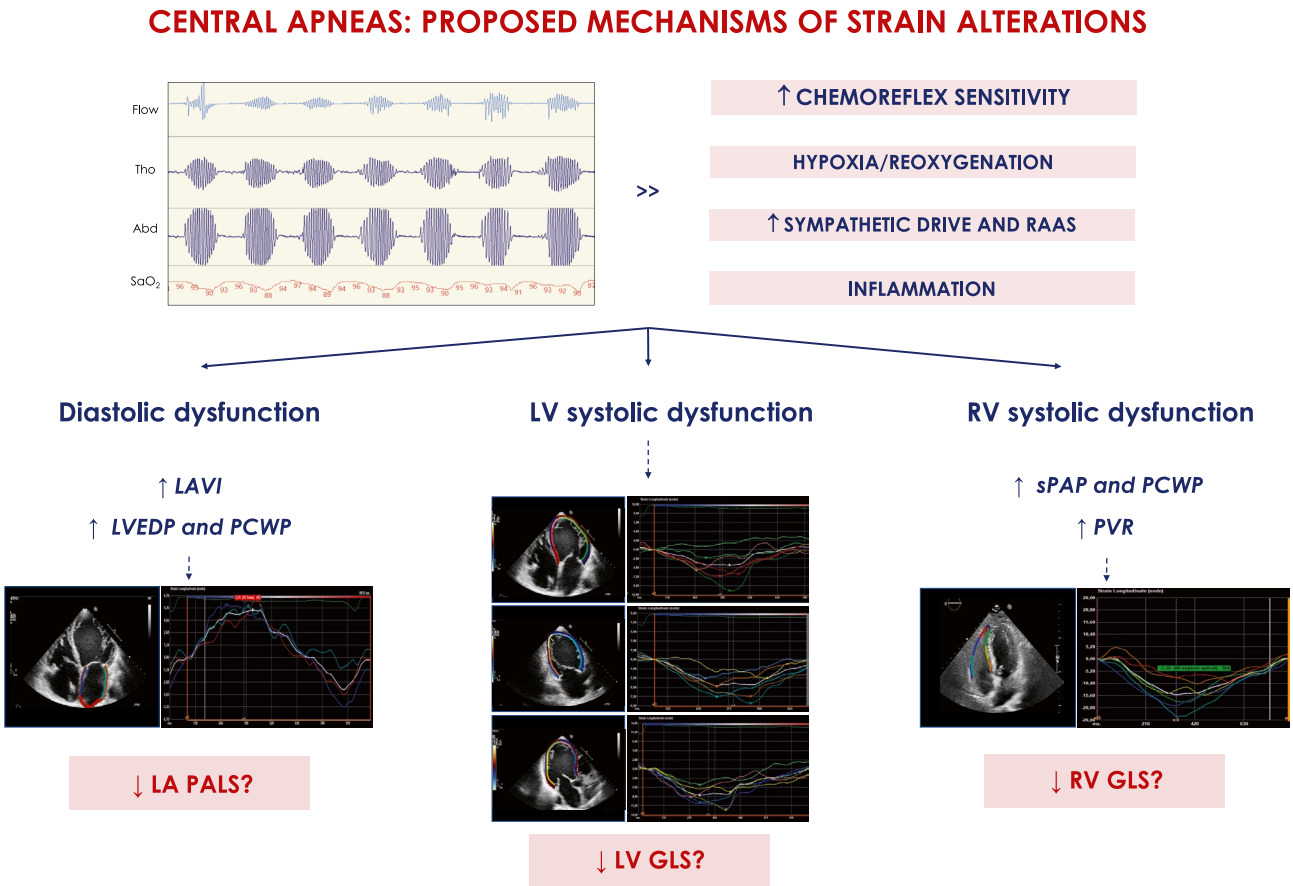

Fig. 3 Central apneas: proposed mechanisms of strain alterations. Increased sympathetic drive and renin–angiotensin–aldosterone system (RAAS) activation, inflammation, chemoreflex overactivation, and chronic intermittent hypoxia promote diastolic dysfunction, with increased left atrial volume index (LAVI) and filling pressures (LVEDP, left ventricular end diastolic pressure; PCWP, pulmonary capillary wedge pressure), possibly reducing peak atrial longitudinal strain (PALS). Similarly, CA induce left ventricular (LV) systolic dysfunction, with a plausible impact on global longitudinal strain (GLS). Finally, chemoreflex and hypoxia mediated increased pulmonary vascular resistances (PVR) and systolic pulmonary artery pressure (sPAP), together with increased PCWP, negatively impact on right ventricular (RV) function, potentially reducing RVGLS

as well as to detect early signs of RV dysfunction once the treatment is initiated.

Finally, with regard to atrial function, LA enlargement and diastolic dysfunction are greater in patients with HF and disordered breathing when compared to normal breathers [66, 83], and LAVI was found to be the only predictor of disordered breathing at multivariable analysis (OR 3.4 95% CI 1.2–9.3, $p < 0.05$) [84] [66].

Whether increased LA volume and pressure are a cause or a consequence of CA is still a matter of debate. Increased LA pressure promoted tachypnea and increased both heart rate and respiratory rate in free healthy dogs [85], while at the same time increasing CO_2 chemosensitivity, one of the main mechanisms promoting ventilatory instability in HF (Fig. 3). Nonetheless, the link between LA dimensions and function is less clear. When addressing the three functions of the LA separately with vectorial echocardiography, in a subgroup of patients from the ADVENT-HF study (HFrEF, mean LVEF $28.5 \pm 8.7\%$), all three were markedly depressed in CA patients when compared to OA, despite similar LA volumes. LA function deteriorated with a more severe CA burden, N-terminal fraction of pro-Btype natriuretic peptide, and central apnea index (but not obstructive apnea index) were independent predictors of poorer atrial function at multivariable analysis [86].

Nevertheless, a more comprehensive evaluation of LA strain has never been performed in HF and CA, which would be useful to give insight into the differences in LA mechanics in patients with HF and apneas, with higher accuracy than other markers of LA dilatation and, potentially, contribute to the early detection of beneficial effects of novel therapeutic strategies.

Conclusions

OA and CA are highly prevalent respiratory disorders that are tightly associated with increased cardiovascular comorbidities (especially hypertension and diabetes) and with the development (OA) and progression (both OA and CA) of HF. STE is an emerging non-Doppler-based method for the early detection and quantification of myocardial dysfunction, and it has the advantage of being both feasible and reproducible. OA, especially moderate and severe OA, have a detrimental impact on cardiac anatomy and function, and the assessment of LV, RV, and LA strain has granted the opportunity of the detection of subclinical alterations that ensue before that of commonly evaluated echocardiographic indexes and before the onset of HF and in light of therapeutic interventions. The relationship of CA with progressive cardiac systolic and diastolic dysfunction is also well established. However, the evaluation of strain alterations in this population has been rarely performed. Nonetheless, the assessment of echocardiographic strain in both OA and CA may allow to shed a light onto their complex pathophysiological background and represents a valuable tool for the early detection and follow-up of cardiac alterations before and after the onset of HF, as well as for the the evaluation of OA and CA treatment efficacy and/or side effects.

Declarations

Conflict of interest The authors declare no competing interests.

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