Peer Review File

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**Review Comments:**

**Reviewer A:**

The authors tried to explore and assess myocardial structure, function, and tissue characteristic changes of LV remodeling in patients with OSA by CMR method, and concluded that LV remodeling mainly with cellular hypertrophy is earlier than LV systolic dysfunction in patients with OSA. The characteristics and composition of myocardial tissue may contribute to the preserved LV systolic function. This study is very interesting, the main commons as follows.

**Comment 1:** Since subjects in the control group also had symptom, only compared the CMR indices between OSA and controls may be not enough, suggest to add a third group of healthy controls as references.

**Reply 1:** Thank you very much for this suggestion. We have now added Table 2 and Table 4 as the healthy controls' data supplements in the revised manuscript. The reason why we didn't add these data is that a group with AHI < 5 events/h is always recommended as the control group in OSA study.

**Changes in the text:** we showed healthy control group data in Table 2 and Table 4 in the revised manuscript.

**Comment 2:** Many OSA patients had hypertension, therefore the ECV comparison between OSA and controls cannot draw the conclusion as in the paper.

**Reply 2:** Thank you very much for this suggestion, which we take seriously. Here are some of our considerations for the comment. First of all, the etiology and pathogenesis for OSA makes it more frequently associated with cardiovascular complications and metabolic abnormalities. It is reported that the comorbid OSA in hypertensive patients is up to 30% to 50% and the frequency of obesity in OSA is even up to 60%. Disentangling obesity and hypertension from OSA-related effects on cardiac outcomes is really a challenge. Secondly, until now, there has not been a CMR research which focused on a relatively "purely" OSA group without the confounding factors influence. Therefore, it is very difficult to conduct a comprehensive contrast-enhanced CMR study in OSA. More importantly, regard to OSA pathogenesis, we incline to consider patients with OSA and hypertension or obesity as a whole, which represent OSA population more really. So, we performed multiple linear regression analysis to determine the association between OSA and LV remodeling parameters and showed positive results. Meanwhile, we modified our conclusion in Abstract and Conclusions section in the revised manuscript. we have modified our text as advised (see Page 5, Line 79-81; see Page 16, Line 318-321; see Page 22, Line 462-465).

**Changes in the text:** "LVMI is elevated in OSA with a normal left ventricular ejection fraction, mainly with cellular hypertrophy. Cellular hypertrophy without focal fibrosis in OSA may be Our main finding." (See Page 5, Line 79-81);

"Our main finding was that patients with OSA have elevated LVMI, which is mainly derived from the expansion of the cellular compartment. We also noted that LV subclinical systolic function was slightly decreased in these patients, whereas LVEF was preserved." (See Page 16, Line 318-321);

"LV remodeling in OSA with preserved LVEF is prominent with cellular hypertrophy which may retreat after proper clinical management. Longitudinal analyses and long-term follow-up of OSA with CMR scans are required for a comprehensive understanding of the LV remodeling process." (See Page 22, Line 462-465)

**Comment 3:** Besides systolic strain indices, please add diastolic strain index in the analysis.

**Reply 3:** Thank you very much for the comment. Since all CMR image analyses were performed with the commercially software (Version 3.2, Medis, Leiden, the Netherlands), which couldn't provide LV diastolic strain parameters as CVI42 did. However, we think you may be interested to the LV diastolic function, so, we display the left atrial function data instead. And the results are shown in the following table. Considering the result of this analysis does not add to any new conclusions in our study, it is not put into the manuscript. However, we're sincerely looking forward to your further opinion about it and we'll follow your suggestion. Thank you!

| | All OSA (n=32) | Non-OSA (n=19) | P[1] value | Mild-moderate OSA(n=13) | Severe OSA (n=19) | P value |
|---|---|---|---|---|---|---|
| LAVI (ml/m$^2$) | | | | | | |
| LAVImax | 34.8(28.8,42.6) | 37.7(31.8,38.5) | 0.546 | 34.8(32.5,40.1) | 34.3(27.1,46.6) | 0.819 |
| LAVIpre-a | 23.0(18.6,28.0) | 22.8(20.4,25.4) | 0.984 | 25.1(22.1,27.1) | 22.1(16.1,28.6) | 0.296 |
| LAVImin | 12.6(9.9,16.4) | 12.3(11.8,14.6) | 0.682 | 12.7(11.7,14.8) | 11.5(9.5,18.8) | 0.905 |
| Reservoir function | | | | | | |
| LA total EF (%) | 62.1(59,68.7) | 62.4(60,68.2) | 0.938 | 63.1(59,70.4) | 61.2(58.6,66.6) | 0.936 |
| εs (%) | 28.9(25.5,32.1) | 29.5(26.9,32.7) | 0.612 | 27.2(23.8,31.8) | 30.2(26.1,32.4) | 0.493 |
| SRs ($s^{-1}$) | 1.4(1.2,1.6) | 1.4(1.2,1.5) | 0.892 | 1.3(1.2,1.7) | 1.4(1.3,1.6) | 0.868 |
| Conduit function | | | | | | |
| LA passive EF (%) | 34.0±8.4 | 35.7±6.2 | 0.440 | 30.5±8.7 | 36.3±7.6 | 0.080 |
| εe (%) | 16.4±4.3 | 16.6±3.3 | 0.850 | 15.1±4.8 | 17.4±3.7 | 0.266 |
| SRe ($s^{-1}$) | -1.2±0.5 | -1.2±0.4 | 0.918 | -1.0±0.6 | -1.3±0.3 | 0.202 |
| Booster pump function | | | | | | |
| LA active EF (%) | 45.2±8.0 | 42.8±5.3 | 0.239 | 49.6±7.5$^{\#}$ | 42.3±7.0$^{\Delta}$ | **0.006** |
| εa (%) | 12.5(11.6,15.6) | 13.2(11.5,14.0) | 0.808 | 13.4(12,15.5) | 12.1(11.3,15.7) | 0.495 |
| SRa ($s^{-1}$) | -1.2(-1.4, -1.0) | -1.2(-1.4, -1.0) | 0.508 | -1.2(-1.7, -1.0) | -1.2(-1.4, -1.0) | 0.747 |

**Table Comparison of global left atrial function.** LA volume and function were analyzed using commercial postprocessing software (QStrain, Medis Suite 3.2, Leiden, the Netherlands), and the detailed analysis method was described in Yang et al. study (1). Data are mean ± SD for normally distributed continuous variables, median (IQR) for skewed variables. P[1] denotes comparation between all OSA and the non-OSA group; p denotes comparation within the non-OSA, the mild-moderate OSA and the severe OSA groups.

Abbreviations: OSA, obstructive sleep apnea; LAEF, left atrial emptying fraction; LAVImax, left atrial maximum volume index; LAVIpre-a, left atrial pre-atrial contraction volume index; LAVImin, left atrial minimum volume index; εs, total strain; εe, passive strain; εa, active strain; SRs, peak positive strain rate; SRe, peak early negative strain rate; SRa, peak late negative strain rate.

**Changes in the text:** No changes in the manuscript.

**Reviewer B:**

Key finding seems to be no LME and GLS but increased ECV. How does the negative LGE and GLS compare to the literature? What is the clinical relevance or implication of the findings reported in the study? What is the advantage over echo?

Small pilot study with new findings reported. If the authors can address the clinical relevance or implication, might be worth to consider publication.

**Comment 1:** How does the negative LGE and GLS compare to the literature?

**Reply 1:** Thank you very much for the suggestion. We have now added some information in our text as advised (see Page 17, Lines 342-351; see Page 21-22, Lines 436- 446).

**Changes in the text:** "A PubMed database search showed only four studies related to cardiac fibrosis in OSA which were associated with increased fibrosis in the left ventricle or left atrium. However, instead of enrolled "purely" OSA patients, these studies focused on hypertrophic obstructive cardiomyopathy, atrial fibrillation patients or community-based cohort of the Multi-Ethnic Study of Atherosclerosis patients. Moreover, the study cohorts were generally older with more comorbidities, such as coronary heart disease, hypertension, diabetes, arrhythmia, and unhealthy living habits. In the present study, our participants were mostly middle-aged men, with no related cardiovascular risk factors or diseases other than hypertension." (See Page 17, Line 342-351)

"This is the first study to analyze LV strain using CMR imaging. Our results showed that OSA patients had lower GCS values than healthy controls, although LVEF was preserved, and comparable findings were found within different OSA groups. LV strain studies remain controversial because of the difficulty in determining the definite effect of OSA on LV mechanics, without potential confounding factors. Some researchers found reduced LV GLS in OSA patients, which gradually decreased with the severity process. Zhou et al. further revealed that the three-layer longitudinal and circumferential LV strains deteriorated in OSA. Wang et al. found that GCS and GRS scores were significantly reduced only in patients with severe OSA. However, some studies failed to show impairment of GCS and GRS values, even in the severe OSA group." (See Page 21-22, Line 436-446)

**Comment 2:** What is the clinical relevance or implication of the findings reported in the study?

**Reply 2:** Thank you very much for the suggestion. It has been the first time to display the myocardial tissue characteristics and explore LV subclinical systolic function changes in patients with OSA with T1 mapping and Feature tracking methods. Our results revealed that patients with OSA had elevated LVMI without focal fibrosis existence. Studies in aortic stenosis have revealed that not only LV cellular mass regresses, but also diffuse fibrosis retreats after aortic valve replacement (2, 3). In respect to OSA, the mostly recommended therapeutic approach is continuous positive airway pressure (CPAP). However, it is very inconvenient and hard to patients to persist on with a mask during sleep. So, our findings will be inspiring and more confident for OSA in clinical treatment and patient compliance with CPAP. We have now modified in our text as advised (see Page 16, Lines 333-335; see Page 19, Lines 391-393).

**Changes in the text:** "In fact, the aforementioned mechanisms could not account for the changes in LV structure and myocardial characteristics as observed in OSA, for the results have not been explored and illustrated previously." (See Page 16, Lines 333-335)

"With respect to OSA, this will stimulate an appropriate and relevant clinical approach for treatment and patient compliance with continuous positive airway pressure therapy." (See Page 19, Lines 391-393)

**Comment 3:** What is the advantage over echo?

**Reply 2:** Thank you very much for the suggestion. There are many differences between CMR and echocardiography study. We have now elaborated in detail in our text as advised (see Page 6, Lines 102-111).

**Changes in the text:** "CMR is the gold standard imaging technique for cardiac structure, volume, and function measurements. In addition to assessing the cardiac morphology, CMR is a unique tool for characterizing myocardial tissue changes. T1 mapping is an emerging noninvasive technique that quantifies T1 relaxation times. Native T1 and extracellular volume (ECV) provide useful information for measuring diffuse myocardial fibrosis. Furthermore, T1 mapping can dichotomize myocardial tissue into cellular and extracellular compartments, which provides a detailed description of cardiac composition. Moreover, the late gadolinium enhancement technique (LGE) not only provides valuable information for the differential diagnosis of cardiomyopathy but also qualifies and quantifies myocardial fibrosis burden." (See Page 6, Lines 102-111)

**Reviewer C:**

Li et al investigated that myocardial structure, function, and tissue characteristic changes of left ventricular (LV) remodeling in patients with obstructive sleep apnea (OSA) by cardiac magnetic resonance (CMR).

The authors found that OSA had higher LV mass index (LVMI) to height than controls. And CMR evaluations revealed that OSA patients' LV remodeling was mainly with cellular hypertrophy but not extracellular volume expansion.

This is a relatively small number study.

I have some questions for the authors.

**Comment 1:** I would like to know if LV hypertrophy could be constructed only by OSA itself, without any interference of hypertension and obesity. If so, the authors should explain or discuss potential mechanisms. The authors tried to explain the mechanisms by dividing many groups (supplemental table). However, such effort makes us more confused. In such a small number study, it must be difficult to lead their definitive conclusions.

**Reply 1:** Thank you very much for this comment. To be honest, although many cardiovascular diseases and related risk factors for cardiovascular system were excluded, some OSA patients still had hypertension. To demonstrate the relationship between OSA and LV structure, multivariable linear regression analyses were performed and OSA was shown to be an independent risk factor for LV structure parameters (e.g. LVMI, LVMVR, iCV). At the same time, multiple grouping methods in supplemental table were also used to demonstrate the impact of OSA on LV structure from the other side (Now, we have deleted two of the grouping methods). The reason for the work we did is that OSA has a complex relationship with cardiac structure and cardiovascular risk factors and the impact of OSA on LV structure has become the focus of controversy in some papers. In this present study, we tend to treat patients with OSA and hypertension or obesity as a whole and to explore the influence of OSA population on LV hypertrophy. **Related reply is also present in the response to "Reviewer A Comment 2".** We have now elaborated the mechanisms of OSA on cardiovascular system in detail in our text as advised (see Page 16, Lines 324-331).

**Changes in the text:** “Intermittent nocturnal hypoxia is believed to be the initial trigger that causes hyperactivity of the sympathetic nervous system, oxidative stress, inflammatory cascade reactions, endothelial dysfunction, and arterial stiffness. These factors work together and eventually increase the cardiac afterload. Moreover, the collapse of the upper airway causes OSA patients to forcibly inhale during sleep, which increases the intrathoracic pressure; consequently, more blood flows in the right heart system, and the ventricular septum shifts to the left during diastole, ultimately leading to a reduction in left ventricle output.” (See Page 16, Lines 324-331)

**Comment 2:** The authors required to explain the status of both decreased ECV and increased iCV without LV delayed enhancement by CMR in OSA patients. How did OSA develop LV into these myocardial histological changes? Why did OSA construct their LV hypertrophy (LV geometry) same as athlete’s?

**Reply 2:** Thank you very much for this comment. The impact of OSA toward cardiac consequence is intricate. Multiple underlying pathophysiological mechanisms account for the impairment of cardiac function and structure in OSA, which are remained uncertain. We observed decreased ECV in OSA, which meant the proportion of extracellular matrix was reduced while cellular compartment expansion (namely iCV). However, the already provided mechanisms in papers couldn’t explain the changes of LV structure and myocardial characteristics as we observed in OSA, for the results have not been explored and illustrated before. Therefore, this phenomenon of OSA make us deduce that in presently the OSA may only suffer short-term stimulation of diseases, which may be beneficial by minimizing wall stress and reducing oxygen consumption. The reasons for us make such speculation are as follow. First, decreased ECV and increased iCV without LV delayed enhancement supported this speculation. Second, in this present study, our subjects were almost middle-aged male gender, with no related cardiovascular risk factors or other disease except for hypertension, which act a relatively gentle effect on cardiac structure and myocardial tissue characteristic changes. Furthermore, the damages on LV caused by OSA will alleviate in the daytime for the collapse of upper airway occurring only during sleep.

In some respects, the LV structure changes demonstrated by CMR in athletes’ heart were similar to the effects of OSA. However, the most basic difference between athlete's heart and OSA subjects is that the former causes LV physiological hypertrophy, while OSA induces disease-related triggers, which causes LV pathological hypertrophy. They are different. We have now modified in our text (see Page 18, Lines 366-377; see Page 17-18, Lines 353-359).

**Changes in the text:** “Many studies have highlighted the negative effects of pathological hypertrophy on cardiovascular diseases. However, it should be noted that LVH is a dynamic course, developing from the compensatory stage in short-term to the maladaptive phase, and ultimately resulting in LV dysfunction. The short-term stimulation of diseases may be beneficial by minimizing wall stress and reducing oxygen consumption. Nevertheless, considering the magnitude and duration of stimulation, long-term detrimental effects can arise. In an animal study even revealed that chronic cardiac overload rats model, animals developed cardiomyocyte hypertrophy without fibrosis after 8 weeks with dobutamine administration, as those running on treadmill did. As the authors mentioned, the features of cardiac overload may essentially be important to LVH, independent of the nature of stimulation.” (See Page 18, Lines 366-377)

“Similar CMR results were reported for cardiac parameters in athletes, wherein lower native T1 and ECV values were noted than in untrained controls; the values were particularly lower in athletes with high

performance. The difference between an athletic and OSA patient is that the former represents physiological stresses that cause LV physiological hypertrophy, while OSA induces disease-related triggers which lead to LV pathological hypertrophy." (See Page 17-18, Lines 353-359)

**Comment 3:** Once the authors investigated the effect of high blood pressure or dyslipidemia on LV hypertrophy, they should show information of participant's medications such as ACEI/ARB, Ca antagonist, be-ta blocker and diuretics. We have already known these medications affect LV hypertrophy.
**Reply 3:** Thank you for this suggestion. According to your suggestion, we have already added medications information of OSA coexisted hypertension patients.
**Changes in the text:** we added some data in Table 1.

**Comment 4:** By using CMR evaluation, the authors tried to give us another aspect of LV hypertrophy in patients with OSA. The authors require to explain their histological or functional differences in myocardial structure by CMR compared to another modalities. And the authors should emphasize its clinical implications of CMR evaluation in patients with OSA. Is this specific myocardial change going to lead OSA patient worse prognosis?
**Reply 4:** Thank you very much for this suggestion. Since the pathophysiological mechanisms of OSA are intricate, which are remained uncertain, it is really a bit hard to elucidate the impairment of cardiac function and structure caused by OSA. Meanwhile, the LV structure changes and myocardial compositions we observed have never been discussed before. Thus, this phenomenon of OSA make us deduce that in our study the OSA may only suffer short-term stimulation of diseases, which may be beneficial in cardiac performance at present and deteriorative in the long-run with the stimulation magnitude and duration going on. **Related reply is also present in the response to "Reviewer B Comment 2".** OSA causes hyperactivity of the sympathetic nervous system, endothelial dysfunction, and arterial stiffness, which is analogous to hypertension in some respects through increasing cardiac afterload. Hypertension persists throughout the day, however, the damages on LV caused by OSA will alleviate in the daytime for the collapse of upper airway occurring only during sleep. Therefore, the enrolled subjects per se and the OSA specific pathogenic mechanism may explain the negative T1 mapping results as contrary to higher native T1 and ECV values observed in hypertension (4). We have now modified in our text as advised (see Page 18, Lines 359-366; see Page 19, Lines 389-393).
**Changes in the text:** "The specific stimulation of the cardiovascular system by OSA is analogous to hypertension in some respects by increasing cardiac afterload. Hypertension persists throughout the day; however, the damage to the LV caused by OSA is alleviated during the daytime because the collapse of the upper airway occurs only during sleep. Therefore, the enrolled patients and the OSA-specific pathogenic mechanism may explain the negative T1 mapping results, in contrast to eccentric or concentric left ventricular hypertrophy (LVH) with higher native T1 and ECV values observed in hypertensive patients." (See Page 18, Lines 359-366.)
"Studies have revealed that not only LV cellular mass regresses but also diffuse fibrosis retreats after aortic valve replacement in aortic stenosis. With respect to OSA, this will stimulate an appropriate and relevant clinical approach for treatment and patient compliance with continuous positive airway pressure therapy." (See Page 19, Lines 389-393)

References:

1. Yang Y, Yin G, Jiang Y, et al. Quantification of left atrial function in patients with non-obstructive hypertrophic cardiomyopathy by cardiovascular magnetic resonance feature tracking imaging: a feasibility and reproducibility study. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2020;22:1.

2. Bing R, Cavalcante JL, Everett RJ, et al. Imaging and Impact of Myocardial Fibrosis in Aortic Stenosis. JACC Cardiovasc Imaging 2019;12:283-96.

3. Treibel TA, Kozor R, Schofield R, et al. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. Journal of the American College of Cardiology 2018;71:860-71.

4. Rodrigues JCL, Amadu AM, Dastidar AG, et al. Comprehensive characterisation of hypertensive heart disease left ventricular phenotypes. Heart (British Cardiac Society) 2016;102:1671-9.