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Response to Letter to the Editor Analysis of Novel Cardiovascular Biomarkers in Patients With Pulmonary Hypertension (PH)

To the Editor

Hereby, we would like to submit our response to the Letter to the Editor concerning our manuscript entitled ''Analysis of novel cardiovascular biomarkers in patients with pulmonary hypertension (PH)" [1]. We will discuss the comments by the readers below:

We want to thank the readers for their thoughtful comments and the interest in our research. As they point out, sST2 could be associated with a broad range of diseases in previous studies, including inflammatory conditions, coronary artery disease and heart failure [2–5]. The reason for this ''lack of tissue specificity" most likely originates from the underlying pathophysiologic processes. Current knowledge suggests that interleukin 33 (IL33), the ligand for ST2L, the membrane-bound isoform of sST2, acts as a danger signal for immunological cells in response to tissue damage by exposure to pathogens, injury or necrosis. sST2, in turn, acts as a ''decoy-receptor" and attenuates the effects of IL33/ST2L signalling. In fact, the main source of circulating sST2 in humans remains elusive and the complex pathophysiologic mechanisms involved are still not fully understood [6–8].

Pulmonary hypertension (PH) is a haemodynamic state that can be the result of various underlying pathophysiologic processes [9,10]. Because of the versatility of diseases that can lead to an elevation of resting mean pulmonary artery pressure (mPAP), patients with PH comprise a very heterogeneous cohort *per se*. Therefore, the presence of comorbidities is a frequent finding in patients with PH.

Because of the diverse causes of PH, and the lack of tissue specificity of sST2, we certainly cannot exclude an impact of certain concomitant conditions, such as endothelial dysfunction or impaired glucose tolerance on the plasma levels of sST2. However, since previous trials found a significant association of sST2 with mechanical strain, e.g. chronic and acute heart failure [5,11] or patients undergoing transcatheter aortic valve implantation (TAVI) [12], we believe that the increase in sST2 in patients with PH from our cohort is a result of the mechanical strain that is caused by the elevation of pulmonary artery pressure (PAP).

To exclude the effect of endothelial dysfunction or impaired glucose tolerance, further investigative trials are warranted. Nevertheless, as we point out in the discussion section of our manuscript, biomarker concentrations should always be interpreted within the clinical context they are used. Since the main pathophysiologic finding in PH is a significant elevation of PAP, and sST2 could be associated with mechanical strain previously, it is only plausible that its increase is a result thereof.

Declaration of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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