Reply to 'Exercise intolerance in heart failure

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LETTERS TO THE EDITOR

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Reply to 'Exercise intolerance in heart failure: beyond mitochondrial dysfunction'. Letter regarding the article 'Exercise: a molecular tool to boost muscle growth and mitochondrial performance in heart failure?'

Kambic *et al.* address important points not fully covered in our article 'Exercise: a molecular tool to boost muscle growth and

mitochondrial performance in heart failure?'.[1] In our review article we focus on the beneficial effects of physiological exercise on the cardiovascular system in heart failure (HF), which may serve to improve exercise performance. We are thankful for the additional input by Kambic *et al.* highlighting two exercise-limiting factors which are common in HF.

Firstly, the authors discuss iron deficiency as an exercise-limiting factor in HF. We acknowledge that iron deficiency may aggravate exercise intolerance in HF and that treatment of iron deficiency can improve exercise performance.[2,3] It should be borne in mind, however, that our review was directed at the potential therapeutic effect of physiological exercise in the context of HF, and we were therefore unable to take the confounding effects of the entire spectrum of possible comorbidities into account. Nevertheless, we agree with the authors that from a broader perspective, assessing iron levels and treating iron deficiency should be implemented alongside the advice to adhere to an exercise regimen. While we advise to combine novel molecular therapies with exercise; this should also go for established therapies such as for iron deficiency treatment.

Secondly, (hyper)activity of the autonomic nervous system during aerobic and resistance training as mentioned by Kambic *et al.* may serve as an exercise-limiting factor in HF patients.[4] Similar to other possible therapies, exercise training may also impose beneficial effects in this context. As hypothesized by the authors, exercise may be able to attenuate vascular dysfunction and damage, inflammation, tissue necrosis and muscle wasting. To some extent, these mechanisms overlap with physiological muscle growth and mitochondrial performance enhancement, which can be induced by both aerobic and resistance exercise. A combined exercise regimen of resistance and aerobic exercise could therefore be even more beneficial for HF patients. In our review, we do not advise a specific type of exercise, because we believe that future studies should focus on developing the optimal exercise modality personalized for the individual patient.

Taken together, we thank Kambic *et al.* for communicating their perspectives and expertise on our paper and we agree that a description of iron deficiency and (hyper)reactivity of the autonomic nervous system could have enriched our paper. Nevertheless, the comments by Kambic *et al.* further emphasize our main conclusion that the development of novel molecular therapies to boost physiological mechanisms in HF patients, should be combined with the advice to perform some form of exercise training.

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