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Effects of exercise training on endothelial and diastolic age-related dysfunctions: a new view of an old problem

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Ageing has significant impacts on human health. Biological ageing (or senescence) results in a gradual functional deterioration of multiple cells and tissues, which may occur regardless of comorbidities, environmental exposure and lifestyle. However, most elderly subjects have one or more associated diseases, which can further aggravate this functional decline (Meschiari *et al.* 2017). Therefore, determining whether age-related biological dysfunctions are due to senescence *per se* or arise from concomitant pathological conditions may prove challenging.

Development of diastolic dysfunction is one such case. Diastolic dysfunction is characterized by impaired left ventricular relaxation and compliance, which causes a reduction in left ventricular filling volume, as well as in stroke volume, contributing to exercise intolerance (Meschiari *et al.* 2017). In a large European cross-sectional survey study involving people aged 25–75 years, echocardiographic evidence of diastolic abnormalities, defined as a low ratio of early diastolic velocity to peak velocity with atrial contraction (E/A) or a high isovolumic relaxation time (IVRT), was found in 11% of the study sample. However, when stratified according to age, the prevalence of diastolic abnormalities ranged from 2.8% in individuals younger than 35 years to 15.8% among those older than 65 years (Fischer *et al.* 2003). Even though most patients presenting with echocardiographic evidence of diastolic abnormalities remain asymptomatic, progression to clinical diastolic dysfunction may occur and has become a major public health concern, as up to 50% of patients admitted to hospitals for heart failure present diastolic dysfunction.

Ageing, therefore, has been recognized as a major risk factor for diastolic dysfunction, but so are obesity, hypertension, diabetes, and coronary artery disease, all highly prevalent in the elderly (Meschiari *et al.* 2017). Conversely, exercise training has been found to improve diastolic function by mechanisms not yet fully understood. Thus, clinical studies looking into the pathogenesis of diastolic dysfunction must resort to statistical methods to account for such confounding variables. In this regard, experimental animal studies pose some advantages over clinical research. First of all, they allow separate analysis of the impact of each factor on a given outcome. Second, they enable specific organ and tissue analysis that would be unfeasible in human subjects.

In previous animal studies, ageing has been shown to cause progressive myocardial degeneration and fibrosis. The papillary muscles and their attachment sites on the left ventricle wall are the most frequent involved areas, but interventricular septum and areas adjacent to the coronary arteries may be affected as well. Moreover, age-related alterations in aortic structure and function have been demonstrated by depressed contractility, increased aortic stiffness, aortic medial thickening, and alterations in elastin/collagen composition (Walker *et al.* 2006). Taken together, these cardiac and aortic structural and functional alterations are believed to provide the pathophysiological basis for diastolic dysfunction, but many questions remain. What are the triggers for this degenerative process? Can it be prevented? Once the process has started, can it be reversed?

Having said that, we read with great interest the study of Hotta *et al.* (2017). They recently published in *The Journal of Physiology* a carefully conducted experimental study aimed at investigating the relationship between ageing, exercise training and development of diastolic dysfunction in rats. Briefly, young (3–4 months) and old (20–21 months) healthy rats were assigned to either an exercise training programme or cage confinement with no exercise for 10 weeks. Resting echocardiographic measurements of diastolic function were taken at baseline and at the end of the study intervention in all four groups. Also, at the end of the 10 week period, coronary blood flow was analysed during and 30 min after treadmill exercise using radiolabelled microsphere infusion. Following this experiment, rats were killed and coronary vasodilatory response was assessed *ex vivo*.

The authors found that old rats had lower E/A ratio, and higher IVRT, myocardial performance index (MPI) and aortic stiffness compared to young rats at baseline. Moreover, exercise training was able to increase E/A, and reduce IVRT, MPI and aortic stiffness in old rats, reaching levels similar to the ones found in their young counterparts. In addition, resting exercise coronary blood flow to the right and left ventricles decreased with age, but the training programme was able to normalize this reduction in exercise blood flow in old rats. Finally, ageing decreased responsiveness and sensitivity to endothelium-dependent vasodilatation mediated by bradykinin, both of which were increased in trained old rats (Hotta *et al.* 2017).

As acknowledged by the authors, this study cannot be said to have established causality between ageing and diastolic dysfunction, since rats were not prospectively evaluated from young to older age. However, it does bring fresh evidence that ageing *per se*, regardless of age-related comorbidities, can negatively impact diastolic function. Furthermore, the authors succeeded in showing that exercise training was able to reverse diastolic dysfunction in old rats as previously demonstrated (Brenner *et al.* 2001). Brenner *et al.* (2001) demonstrated that exercise training was able to reverse the age-associated impairment in early diastolic filling in old rats and hypothesized that the increased rate and degree of ischaemia-induced diastolic impairment may reflect deconditioning rather than inevitable consequences of ageing (Brenner *et al.* 2001). That being said, an important contribution of the present study lies in the fact that the authors investigated further the potential biological mechanisms involved in the development of diastolic dysfunction and its improvement with exercise. In this sense, the present study was able to demonstrate an association between ageing and reduced coronary blood flow, as well as between age and endothelium-dependent vasodilatory function, both of which were reversed by exercise training.

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Overall, the core results presented by Hotta *et al.* (2017) regarding the effects of exercise seem to be in line with previous clinical studies. In humans, exercise training has been shown to improve endothelial function, promote cardiac remodelling, and reduce left ventricle diastolic stiffness. Moreover, exercise programmes have been found to improve exercise capacity and diastolic dysfunction in healthy elderly as well as in patients with heart failure with preserved ejection fraction, with a positive impact on quality of life. There is also some evidence that exercise training enhances endothelium function in young healthy individuals, but, interestingly, the current study failed to demonstrate an endothelium-dependent response to bradykinin in young rats. It should be noted, though, that the two groups were submitted to exercise programmes of considerably different intensities. While young rats trained at only 50–60% of their maximum exercise capacity, old rats trained at 70–80% of their maximum exercise capacity. In humans, for example, training at 50–60% of maximal exercise capacity did improve, but was unable to completely reverse, diastolic dysfunction in elderly men. Therefore, despite acknowledging that both exercise intensities fall within the clinically recommended range for cardio-pulmonary rehabilitation, we cannot rule out the possibility that the apparent lack of benefit of physical training in young rats was due to the lower exercise intensity in this group.

In conclusion, the study of Hotta *et al.* (2017) sheds new light in the pathogenesis of diastolic dysfunction, stressing the importance of the sedentary lifestyle, rather than age, as a major determinant of diastolic function. Overall, current evidence seems to be leading to significant changes in our understanding of diastolic dysfunction, with implications for medical care and public health. Diastolic dysfunction, therefore, can no longer be considered an inexorable consequence of ageing, but rather a preventable disease, largely dependent on lifestyle and level of physical activity. Future studies in humans should focus on establishing whether lifelong training has similar effects to lifelong training on diastolic function and determining the ideal exercise intensity required to achieve maximal improvement of age-related diastolic dysfunction. In addition, potential mechanisms that mediate the exercise-induced improvement of coronary endothelial function need further investigation, such as increased shear stress, decreased sympathetic activity, inflammation, and oxidative stress. Notably, elucidating such mechanisms may contribute to the development of alternative treatment options for endothelium and diastolic dysfunction at a large population scale.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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