

## Exercise and the heart: Unmasking Mr. Hyde

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As physicians, we often face patients with cardiovascular risk factors or different kinds of heart disease. We prescribe statins, ACEi or beta-blockers, but also (should) encourage our patients to engage in regular physical activity to reduce cardiovascular-disease burden. Physical exercise, as a part of cardiac rehabilitation or a primary prevention program, is seemingly one of a kind. *“For most health outcomes, additional benefits occur as the amount of physical activity increases through higher intensity, greater frequency, and/or longer duration”* [1]. No other known therapy offers such advantageous characteristics. This even led some researchers to speculate, some forty years ago, that marathon-runners were immune to atherosclerosis [2]. Running a marathon was quite unusual at that time, and cardiovascular adaptation to such a high load of exercise had been scarcely explored. Since then, in late 70's, the number of non-professional individuals finishing a marathon has increased by 20-fold, and current observational studies are jeopardizing the notion of exercise as risk-free. Increased sudden death risk during exercise-bouts is well established but extremely infrequent. An evolving core of evidence supports that regular exercise increases the risk of atrial fibrillation (AF), ventricular arrhythmias or even ischemic heart disease [3]. How do these findings fit into well-known benefits of exercise? Two papers in this issue of Heart explore this subject [4 5] and provide important insights.

Through assessing outcomes like AF incidence [4] and cardiovascular or total mortality [5], both groups elegantly suggest in two large cohorts that exercise intensity and duration are key players in this association. They describe a similar U- or reversed-J-shaped pattern for the dose-response effect of exercise: maximum cardiovascular benefits are obtained if performed at moderate doses, while these benefits are lost with high-intensity and prolonged efforts.

Both groups took profit of previously collected data on exercise performance and correlated them to clinically relevant outcomes. Unfortunately, physical activity had been loosely assessed through self-administered questionnaires, and this is the main drawback of both studies. Drca et al. [4] did not obtain direct information on intensity, but roughly classified physical activity during transportation as light/moderate and leisure-time exercise as intensive. This poses a risk for misclassification. Moreover, their questionnaire inquired about exercise performance at 4 discrete lifetime-points, while exercise-induced AF-risk is likely dependent on the lifetime-cumulated amount of exercise. On the other hand, Mons et al. [5] gathered data on how many days per week *“strenuous”* physical activity had been performed by participants, but its daily duration or a more

accurate estimate of intensity was not collected. Consequently both reports show limited ability to reliably assess physical activity. Nevertheless, physical activity questionnaires are commonly used in large registries and, if properly designed, provide fairly good total-exercise estimates.

The results of both reports yield important conclusions and raise interesting additional questions. On one side, Drca et al. [4] shape in the general population the well-known association between exercise and AF. They show that frequent (>5 hours per week) intensive exercise in young adults (30 years-old) predicts AF-incidence in the elderly (beyond 60 years-old), not depending on whether regular training is continued. This fact is consistent with data from small studies suggesting a long latency between engaging in high-intensity exercise and a rise in AF-risk [6]. But how can strenuous exercise during early adulthood cause atrial fibrillation much later in life? Recent findings in an animal model suggest that high-intensity endurance exercise slowly promotes an arrhythmogenic substrate involving atrial fibrosis. Atrial fibrosis did not regress after ceasing endurance training [7]. It is conceivable that atrial fibrosis developing during early- and mid-life ultimately unveils as increased AF-risk at older ages, when exercise-induced fibrosis reaches a certain threshold or other risk factors subsequently add. Conversely, Drca et al. show that in individuals aged 50 or older, more than 5 hours/week of high-intensity exercise does not correlate to subsequent AF-incidence. These results are consistent with those from the Physicians Health Study [8], in which frequent endurance exercise only predicted increased AF-risk in participants aged less than 50. The explanation for these facts remains unknown, but the way in which “*high-intensity exercise*” is perceived and affects individuals at different ages might be involved. In general, the intensity of exercise performed by 30 year-old individuals is higher than 60 year-old ones [9], this meaning that the same degree of exercise might be reported as moderate at 30 years old and intense at 60. Accordingly, “intense exercise” at 60 years old might produce limited hemodynamic disturbances in comparison to extreme changes induced by “intense exercise” at 30 years. It is also likely that improvements in cardiovascular risk profile overcome the deleterious effects of intensive-exercise at 50 years old, but not at 30. Should this be taken into account for exercise-counselling at different ages? Further studies are clearly needed.

The results by Mons et al. [5] challenge our notion of the benefits of exercise. One thousand thirty-eight patients with ischemic heart disease who had attended a cardiac rehabilitation program were followed for 10 years. They found that patients exercising strenuously for 2-4 days/week were at the lowest risk of death and cardiovascular events while patients exercising daily, as well as those rarely exercising, showed higher event-rates. This is apparently contrary to our current knowledge. How these results should be interpreted, then? Baseline characteristics and cardiovascular risk of patients included in this cohort do not remarkably differ from other registries. Patients in this cohort might have undergone different training protocols than those in previous registries, but this information was not collected. We feel that a different study design might partially account for these differences. Most registries split the whole population into tertiles or quartiles. Mons et al. alternatively split their population into smaller, more homogenous groups that could better describe certain subpopulations. For example, the daily-active group comprised only 15% of all patients [5] and might better reflect the consequences of exercise in a small group of very highly trained individuals. Remarkably, other studies that also distributed the whole population into smaller and more homogenous groups found a reverse J-shaped mortality curve [10]. Not to be forgotten, a type I error should also be considered a source for these results.

An increase in all-cause and cardiovascular mortality in the most active groups is the most challenging outcome of Mons et al. [5] study. Unfortunately, the causes for increased mortality were not assessed. The authors acknowledge on the role of increased sudden death during unsupervised exercise. Moreover, it is notable that non-fatal cardiovascular events were also increased, although in a weaker relationship. Physical activity aggravating ischemic heart disease seems counterintuitive, but it is supported by previous small studies. By mean of calcium score assessment or cardiac magnetic resonance, ultra-endurance runners have been suggested to suffer from increased coronary artery disease [10]. Correlating to exercise duration and intensity, endurance training induces an acute, reversible pro-inflammatory state [11], which might mediate atherosclerotic processes if prolonged enough. Patients with a pre-existing cardiovascular condition, such as those studied by Mons et al. [5], develop a significant pro-inflammatory state at lower exercise doses. A crossover study in patients with ischemic heart disease demonstrated that daily 60 minutes intense-training promoted an inflammatory status and increased aortic wall stiffness, but opposite effects were found in a shorter 30 minutes daily intensive-training [12].

It remains unknown why some individuals develop deleterious effects when engaged in regular training while others remain unaffected. Exercise intensity, as well as the type of exercise, is clearly a major determinant [3 4 5 6 13]. Notwithstanding, a huge variability in exercise-induced cardiac remodelling, so-called athlete's heart, exists amongst highly trained athletes [14], and only a minority will develop exercise-induced cardiovascular harm. Individual genetic background modulates athlete's heart features, likely also playing a role in individual susceptibility to exercise-induced harm. Endurance-trained plakoglobin-deficient mice develop larger RV dilation than sedentary wild-type littermates, and turn the RV arrhythmogenic [15].

Uncovering genetic predisposition might have important clinical implications. Research efforts aiming at providing a safety threshold that avoids "exercise overdose" and permits maximization of benefits are warranted. Both papers in this issue of Heart journal [4 5] identify >5hours/week and daily intense exercise as thresholds for increased AF incidence and cardiovascular-events, respectively. These values should be considered solely as vague guidelines and might have little value in exercise counselling. In the clinical setting, an individualized mechanistic approach aiming at identifying individuals at risk and detecting the development of a deleterious substrate might better serve to titrate an optimal individualized dose of exercise.

Overall, we are experiencing a change in the way we conceive physical activity. First, AF was associated to high-intensity exercise [6]. Later, increased risk for right ventricular arrhythmias and ischemic heart disease has been suggested in extremely trained athletes [3]. There is a need to communicate these limitations to the society. Nevertheless, a thin line separates accurate information and unnecessary alarmism leading to inactivity and consequent heart disease. The beneficial effects of exercise are definitely not to be questioned; on the contrary they should be reinforced. These [4 5] and future studies will serve to maximize benefits obtained of regular exercise while preventing undesirable effects. Just like all other drugs and therapies.

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