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, ACE inhibitors or β-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 programme, 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.1,2 No other known therapy offers such advantageous characteristics. This even led some researchers to speculate, some 40 years ago, that marathon runners were immune to atherosclerosis.3 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, the late 70s, the number of non-professional runners finishing a marathon has increased 20-fold, and current observational studies are jeopardising the notion of exercise as risk-free. Increased sudden death risk during exercise bouts is well established but extremely rare. An evolving core of evidence supports the hypothesis that regular exercise increases the risk of atrial fibrillation (AF), ventricular arrhythmias or even ischaemic heart disease.3 How do these findings fit with the well-known benefits of exercise? Two papers explore this subject4,5 and provide important insights.

By assessing outcomes such as AF incidence6 and cardiovascular or total mortality,7 both groups elegantly suggest in two large cohorts that exercise intensity and duration are key players in this association. They describe a similar U-shaped or reverse 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 (very) high-intensity and prolonged efforts.

Both groups took previously collected data on exercise performance and correlated them with clinically relevant outcomes. Unfortunately, physical activity had been roughly assessed through self-administered questionnaires, and this is the main drawback of both studies. Drca et al4 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 of misclassification. Moreover, their questionnaire inquired about exercise performance at four discrete lifetime points, while exercise-induced AF risk is probably dependent on lifetime-cumulated amount of exercise. On the other hand, Mons et al7 gathered data on how many days a week ‘strenuous’ physical activity had been performed by participants, but its daily duration or a more accurate estimate of intensity was not collected. Consequentially, both reports have limited ability to reliably assess physical activity. Nevertheless, physical activity questionnaires are commonly used in large registries and, if properly designed, provide fairly good estimates of total exercise.

The results of both reports yield important conclusions and raise interesting additional questions. On the one hand, Drca et al4 profile in the general population the well-known association between exercise and AF. They show that frequent (>5 h/week) intensive exercise in young adults (30 years of age) predicts AF incidence later in life (60 years and older), and does not depend 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.8,9 But how can strenuous exercise during early adulthood cause AF much later in life? Recent findings in an animal model suggest that high-intensity endurance exercise slowly promotes an arrhythmogenic substrate involving atrial fibrosis.9 Atrial fibrosis did not regress after endurance training was stopped. It is conceivable that atrial fibrosis that develops during early and mid life ultimately manifests as increased AF risk at older ages, when exercise-induced fibrosis reaches a certain threshold or other risk factors are subsequently added. Conversely, Drca et al4 show that, in individuals aged 50 or older, more than 5 h/week of high-intensity exercise does not correlate with subsequent AF incidence. These results are consistent with those from the Physicians Health Study, in which frequent endurance exercise only predicted increased AF risk in participants aged less than 50. The explanation for these facts remains unknown, but it might be to do with the way in which ‘high-intensity exercise’ is perceived and affects individuals at different ages. In general, the intensity of exercise performed by 30-year-olds is higher than that performed by 60-year-olds,9 meaning that the same degree of exercise might be reported as moderate at 30 years of age and intense at 60. Accordingly, ‘intense exercise’ at 60 years of age may produce limited haemodynamic disturbance compared with the extreme changes induced by ‘intense exercise’ at 30 years of age. It is also likely that improvements in cardiovascular risk profile overcome the deleterious effects of (very) 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 of Mons et al7 challenge our notion of the benefits of exercise. This study followed for 10 years 1038 patients with ischaemic heart disease who had attended a cardiac rehabilitation programme. 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 who rarely exercised, showed higher event rates. This is apparently contrary to our current knowledge. How should these results be interpreted then? Baseline characteristics and cardiovascular risk of patients included in this cohort do not differ substantially from other registries. Patients in this cohort might have undergone different training protocols from 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 homogeneous groups that could better describe certain subpopulations. For example, the daily-active group comprised only 15% of all patients 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 homogeneous groups found a reverse J-shaped mortality curve.10 Not to be forgotten, a type I error should also be considered as a source of these results.
An increase in all-cause and cardiovascular mortality in the most active groups is the most challenging outcome of the study of Mons et al. Unfortunately, the causes of increased mortality were not assessed. The authors acknowledge the role of increased sudden death during unsupervised exercise. Moreover, it is notable that non-fatal cardiovascular events also increased, although in a weaker relationship. Physical activity aggravating ischaemic heart disease seems counterintuitive, but it is supported by previous small studies. Using calcium score assessment or cardiac MRI, ultra-endurance runners have been suggested to have increased coronary artery disease.

Correlating with exercise duration and intensity, endurance training induces an acute, reversible proinflammatory state, which might mediate atherosclerotic processes if prolonged enough. Patients with a pre-existing cardiovascular condition, such as those studied by Mons et al, develop a significant proinflammatory state at lower exercise doses. A crossover study in patients with ischaemic heart disease demonstrated that daily 60 min intense training promoted an inflammatory state and increased aortic wall stiffness, but opposite effects were found in a shorter, 30 min, daily intensive training regimen.

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. However, huge variability in exercise-induced cardiac remodelling, so-called athlete’s heart, exists among highly trained athletes, and only a minority will suffer exercise-induced cardiovascular harm. Individual genetic backgrounds modulate the features of athletes’ hearts, which also probably has a role in individual susceptibility to exercise-induced harm. Endurance-trained plakoglobin-deficient mice develop greater right ventricle dilation than sedentary wild-type littermates, causing the right ventricle to become arrhythmogenic.

Uncovering genetic predisposition might have important clinical implications. Research aiming at providing a safety threshold that avoids ‘exercise overdose’ and permits maximisation of benefits is warranted. Drca et al and Mons et al identify >5 h/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 individualised mechanistic approach aiming to identify individuals at risk and detect the development of a deleterious substrate might better serve to titrate an optimal individualised dose of exercise.

Overall, the way we conceive physical activity is changing. First, AF was associated with high-intensity exercise. Later, increased risk of right ventricular arrhythmias and ischaemic heart disease was suggested in extremely highly trained athletes. There is a need to communicate these limitations to society. However, 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. The studies reviewed here and future studies will serve to maximise benefits obtained by regular exercise while preventing undesirable effects—just like all other drugs and therapies.

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