Early exercise for lifelong benefit: Sustained cardiac programming in rats and the potential translation to humans

It is well established that the intrauterine environment has the potential to determine the lifelong health of an organism. For example, prenatal stress can reduce gestational length and have negative downstream effects on endocrine and metabolic outcomes, which propagate across subsequent generations. Recent advances in research have identified the developmental period (postnatal to adulthood) to have a similar potential for ‘programming’ that can have both positive and negative consequences for long-term health. Subsequently, this early stage of life has emerged as a fruitful area of investigation, as programming in response to physical activity has been shown to produce numerous lifelong benefits for both the heart (Wadley et al., 2016) and the brain.

A recent article in the *Journal of Physiology* by Asif et al. (2018) has shed new light on how the heart adapts in response to exercise training and detraining during different stages of development in male Wistar Kyoto rats. The rats were assigned to four treatment groups: sedentary, juvenile exercise (trained from 5-9 weeks of age), adolescent exercise (trained from 11-15 weeks of age) and adult exercise (trained from 20-24 weeks of age). All exercise groups completed the same exercise training programme, and remained sedentary throughout the remainder of the study period. Training involved treadmill running 5 days per week for 4 weeks, progressively increasing exercise duration to one hour. An extensive range of techniques including echocardiography, microscopy, genetic and molecular assessment were utilised for analysis. These techniques were applied in a subset of sedentary and juvenile rats at 9 weeks of age, and all four experimental groups at 24 weeks of age. The results indicate that exercise training in juvenile rats led to cardiac remodelling that persisted into adulthood, despite a prolonged period of sedentary behaviour. Most notably, hypertrophy (increased longitudinal area of binucleated cardiomyocytes), hyperplasia (cardiomyocyte population) and an increased proportion of mononucleated to binucleated cardiomyocytes were evident in adulthood when exercise was performed at a young age, but these adaptations were absent when exercise training was initiated after adolescence. In line with the aforementioned cellular adaptations, echocardiography revealed an increased left ventricular (LV) mass and wall thickening in the juvenile trained group, which remained elevated at adulthood when compared with sedentary counterparts. This landmark study provides evidence for exercise-induced cardiac programming during infancy, regardless of subsequent sedentary activity.

Until recently, it was thought that the mammalian heart remodelled to exercise only via hypertrophy of existing cardiomyocytes. The findings from Asif et al. (2018) indicate that hyperplasia provides a substantial contribution to cardiac remodelling in juvenile rats, as dictated by the greater number and proportion of proliferative, mononucleate cardiomyocytes. This process diminishes with age and is absent by adulthood, possibly due to the increased binucleation of cardiomyocytes and transition to a terminally differentiated state (at which point they can no longer proliferate). It appears that exercise during the juvenile period encourages cardiomyocyte proliferation; Asif et al. (2018) found a 40% increase in cardiomyocyte number in the juvenile exercise group compared to sedentary rats. This increase was sustained into adulthood, with a 36% difference to their sedentary counterparts, suggesting that when exercise is performed during developmental years, it has lasting benefits to the cardiomyocyte population.

In adult humans, endurance training elicits a bi-phasic pattern of cardiac remodelling characterised by an initial increase in chamber size, likely due to plasma volume expansion, which is then followed by an increase in wall thicknesses reflecting adaptive cellular hypertrophy (Weiner et al., 2015). Whether children also experience cardiac remodelling in the same phasic nature is yet to be determined. Obert et al. (2001) found that children who trained for 13-weeks had increased chamber volumes, but not
wall thicknesses, similar to the acute phase of training with adults. This programme was followed by an eight-week detraining period, during which all measures returned to baseline. Therefore, a 13-week endurance programme is likely insufficient to induce cardiac remodelling via hyperplasia in 10 to 11-year olds (Obert et al., 2001). In comparative terms, the 4-week training programme adopted by Asif et al. (2018) translates to approximately 2.5 human years. Although relatively shorter-term training programmes in humans provide a basis to study adaptations to exercise, cardiac programming appears to require longer-term physical activity. An extended training period of eight months, for example, resulted in significant increases in LV posterior wall thickness and LV mass in a younger cohort of children (Geenen et al., 1982). As such, wall thickness and LV mass may provide an appropriate surrogate for information regarding cardiac programming in vivo. This has important implications for the design of interventions aiming to improve cardiovascular health in children, as prolonged exposure to physical activity may be required to induce sustained cardiac programming via hyperplasia.

**The Rat to Human Translation**

Animal models have an important role in pre-clinical trials, providing pertinent information about principal mechanisms by utilising intrusive methodologies that cannot be obtained from in vivo human studies. In this regard, Asif et al. (2018) should be commended for their extensive mechanistic investigation. However, there is substantial inter-species variation in the length of gestation, timing of binucleation, and proportion of mononucleated to binucleated cardiomyocytes. Therefore, further studies in humans should be encouraged in this burgeoning area of research to substantiate the findings from animal models.

The existence of exercise-induced cardiac programming in humans is yet to be ascertained. However, the findings from Asif et al. (2018) could provide an insight as to how this might translate from a rodent model. The most pronounced adaptations were induced during the ‘juvenile’ period, which is the equivalent of childhood or adolescence in humans. Therefore, if cardiac programming exists in humans, a focus should be placed upon sustained physical activity and active play throughout the developmental stage of life. It is also important to identify whether the cardiovascular system is more or less sensitive to programming during specific periods of development, as key ‘windows of opportunity’ may occur that should be targeted by school-based interventions.

**Protection from Cardiovascular Disease**

Preservation of cardiomyocyte number could potentially fortify the heart against stress later in life by providing a greater functional reserve. The fascinating results of the research conducted by Asif et al. (2018), regarding sustained increases in cardiomyocyte number, reveals the lifelong benefits that exercise-induced cardiac programming may provide. A 36% increase in cardiomyocyte number in adulthood, equating to an additional 20 million cardiomyocytes, could render the hearts better equipped to cope with healthy ageing or disease progression later in life. For example, following myocardial infarction or cardiotoxicity from cancer treatment, the absolute number of functional cardiomyocytes may be higher due to a greater initial cardiomyocyte population. To determine this cardioprotective capability, further investigation could incorporate disease models at adulthood using the study design of Asif et al. (2018) as a template.

**Future Directions**

If the findings from this landmark paper by Asif et al. (2018) translate to humans, it is imperative that the life-long benefits of exercise are instilled early in life. Beyond this period of developmental plasticity, it is likely that the opportunity for such remarkable adaptations will have been missed,
highlighting this phenomenon as a crucial area of research. Further investigation of this complex process should identify (i) the window of opportunity and volume of physical activity necessary to induce cardiac programming in humans, and (ii) whether or not sustained cardiac programming provides fortification against cardiovascular disease. The outcomes of such research could lead to global changes in guidelines or policies, prioritising childhood physical activity, improving health outcomes across the lifespan and reducing the financial burden placed on healthcare services.

**References**


**Additional Information**

**Competing Interests**

None declared.

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