The Journal of Physiology

PERSPECTIVES

And the beat goes on

Jack R. T. Darby and Janna L. Morrison
Early Origins of Adult Health Research Group, School of Pharmacy & Medical Sciences, University of South Australia, Adelaide, SA, Australia, 5001
Email: janna.morrison@unisa.edu.au

Edited by: Harold Schultz & Laura Bennet

Each year over 17 million people die from cardiovascular disease and both cardiac dysfunction and progression of cardiovascular disease correlate strongly with ageing. This is of concern given that at least in the developed world, populations are ageing, and the elderly population is growing, with the proportion of people aged over 65 having almost doubled since 2000.

A study by Kuo *et al.* (2018) in this issue of *The Journal of Physiology* utilized cardiac magnetic resonance imaging (CMRI) to assess biventricular cardiac function in a baboon (*Papio* spp.) model across the life course (Kuo *et al.* 2018). Whilst life course cardiovascular studies have been performed in humans, the findings have been challenged by limitations in the ability to control the confounding features of the human environment. As ethical concerns limit the use of great apes in medical research, the non-human primate baboons appear to share the closest cardiovascular and metabolic physiology to humans.

Importantly, the authors assessed life course cardiovascular function at four different ages (adolescence, young adulthood, mid adulthood and elderly) in both male and female baboons. Understanding sex-specific cardiovascular function with age is specifically important given the emergence of cardiovascular disease some 7–10 years later in females than males in the human population. Male baboons had higher normalized myocardial mass than females, and myocardial mass declined with age, with the slope only reaching significance in females. Sexually dimorphic differences were observed in relation to left ventricular (LV) volume and time spent in systole. Elderly male baboons exhibited increased LV volume and increased duration of the cardiac cycle spent in systole in comparison to adolescence. In contrast, elderly female baboons had decreased LV volume and a significant increase in cardiac diastole over systole ratio. Although absolute values for stroke volume (SV), cardiac output (CO), average ejection rate (AER) and average filling rate (AFR) were increased in males over females and decreased significantly in both sexes with age, when appropriately normalized to body surface area, no sex-specific differences were observed. Furthermore, LV systolic functional parameters, such as normalized ejection fraction, stroke volume and cardiac index, decreased across age without sex-specific differences. Similar functional declines were observed in the right ventricle with absent sex effects. Whilst it is important to assess longitudinal cardiovascular physiology in both sexes, the results in the present article suggest that these sex differences may be subtle.

Despite the strengths of this study, the same baboons were not used in each age group, and more informative findings could be obtained in the future by performing serial across age cardiovascular magnetic resonance imaging (CMRI) sessions in the adolescent baboons of the present study. Moreover, the authors have successfully highlighted the feasibility of CMRI longitudinal baboon studies. The authors suggest that a limitation of the study was the necessity for anaesthesia, which may suppress cardiac function; however, the anaesthesia is required for the ethical treatment of the baboons. In addition, assessment of cardiac function was only in a normative resting state rather than under stress, which could be achieved with adenosine or dobutamine treatment. Future work could include serial CMRI sessions across the life course in a population that is already predisposed to the onset of cardiovascular disease.

Studies using serial CMRI will make a strong contribution to understanding the early life mechanisms of the cardiovascular disease. For example, the developmental origins of adult health and disease hypothesis describes the mechanisms by which suboptimal *in utero* conditions programme offspring for the development of adult-onset disease, including cardiovascular disease (CVD). The authors have previously utilized a moderate 30% maternal nutrient restriction to induce intrauterine growth restriction (IUGR) in baboons to assess the consequences on both left (Kuo *et al.* 2017*b*) and right (Kuo *et al.* 2017*a*) ventricle CMRI-derived cardiac function. In these partner studies, left and right cardiac function and remodelling in young adult baboons born with IUGR (human equivalent ∼25 years) was shown to exhibit a phenotype similar to an aged geriatric group, with the authors speculating that IUGR hearts may exhibit accelerated ageing. There is evidence that IUGR induced cardiac remodelling and altered contractility may start as early as fetal life. For example, a severe 50% maternal nutrient restriction in late gestation increased myocardial fibrosis and altered the phosphorylation state of key contractile proteins in the fetal sheep right ventricle (Darby *et al.* 2018). CMRI has recently been employed to study the fetal heart (Duan *et al.* 2017) and thus CMRI studies could be employed across the life course, beginning as early as fetal life, to identify changes in cardiac function in populations at increased risk of cardiovascular disease prior to the development of dysfunction.

Overall, the cardiac functional and remodelling consequences of ageing from adolescence onwards have been comprehensively characterized in a clinically relevant baboon model. Insights from longitudinal studies may provide a greater understanding of the normative cardiac ageing phenotype. Further studies are anticipated assessing life course cardiac function in baboons that were born with IUGR in an effort to understand their predisposition to adult-onset CVD.

References

Darby JRT, McMillen IC & Morrison JL (2018). Maternal undernutrition in late gestation increases IGF2 signalling molecules and collagen deposition in the right ventricle of the fetal sheep heart. *J Physiol* **596**, 2345–2358.

Duan AQ, Lock MC, Perumal SR, Darby JR, Soo JY, Selvanayagam JB, Macgowan CK, Seed M & Morrison JL (2017). Feasibility of detecting myocardial infarction in the sheep fetus using late gadolinium enhancement CMR imaging. *J Cardiovasc Magn Reson* **19**, 69.

Kuo AH, Li C, Huber HF, Nathanielsz PW & Clarke GD (2018). Ageing changes in biventricular cardiac function in male and female baboons (*Papio* spp.). *J Physiol* **596**, 5083–5098.

DOI: 10.1113/JP277026

Kuo AH, Li C, Huber HF, Schwab M, Nathanielsz PW & Clarke GD (2017*a*). Maternal nutrient restriction during pregnancy and lactation leads to impaired right ventricular function in young adult baboons. *J Physiol* **595**, 4245–4260.

Kuo AH, Li C, Li J, Huber HF, Nathanielsz PW & Clarke GD (2017*b*). Cardiac remodelling in a baboon model of intrauterine growth restriction mimics accelerated ageing. *J Physiol* **595**, 1093–1110.

Additional information

Competing interests

The authors have no conflict of interest.

Author contributions

Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

J.L.M. holds an Australian Research Council Future Fellowship (Level 3; FT170100431).