Letter to the Editor

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Letter by Rupp and Jux Regarding Article, "Mechanisms of Cardiac Repair and Regeneration"

To the Editor:

The review article "Mechanisms of Cardiac Repair and Regeneration" by Broughton et al[1] overviews several pivotal aspects of biological processes impinging on cardiac maintenance, repair, and regeneration. A main message of the article is that aging is associated with an impairment of cardiac reparative and regenerative potential. As summarized, data of reparative and regenerative capacity in children is sparse, especially on a histological or cellular level. However, clinical courses of several cardiac diseases differ significantly in children compared with adults. In contrast to an inefficient cardiac recovery in adults, a significant recovery of cardiac function is documented in children in several courses. This letter should serve as an extension of the review from Broughton et al, underlining the impressive potential of recovery of young children hearts.

Cardiomyogenesis in the adult mammalian heart remains a rare and inefficient process. This is in contrast to some adult amphibians[2] and young mammals[3] where cardiac regeneration capacity is preserved. In young children, the data about cardiac regeneration are rather limited. Especially, 2 studies are cited in the review article.[4,5] In the study by Bergmann et al,[4] the youngest individual described was 20 years old, cardiac renewal was extrapolated for the younger ones. This might not be reliable as the most cardiac growth occurs in the first months of life as reported from the second study cited and as seen in mammals.[5] In this study, cardiomyocyte mitosis during the first year of life in humans contributed to 0.04% of total cardiomyocytes. In other words, a doubling of cardiomyocytes was detected in this study under physiological conditions in the growing children's heart in the first year of life.

Cardiac recovery potential in children is highlighted in impressive clinical courses that are different compared with adult patient courses.[6] Some children with ALCAPA (anomalous left coronary artery origin from pulmonary artery) present in a poor clinical condition with electrocardiography signs of infarction, elevated troponin, and CK-MB (creatine kinase-muscle/brain) levels indicating significant cardiomyocyte loss. Children surviving after surgical correction show normalization of severely reduced cardiac function.[7] Another example is given by dilated cardiomyopathy, which is a serious disorder in children, and one third of the children die or receive a heart transplant in the first year after diagnosis. In contrast to the poor 1-year prognosis, children surviving beyond this period have a long-term mortality of only 1% per year and have good chances of experiencing recovery of cardiac function.[8] A further example is given by neonatal myocardial infarction. If children survive, significant cardiac recovery up to normalization of ventricular function can be documented.[9] This extraordinary cardiac recovery potential suggests that the regenerative potential of children hearts might be to some extent comparable with experimental observations from animal models. However, especially on a histological or cellular level, data on regenerative capacity in children are sparse. A challenge for the future is to understand and influence the molecular behavior that controls the recovery potential in children and its deregulation in adults.

Besides understanding these processes on a cellular or molecular basis, the recovery potential of young children hearts has already led to new therapeutic approaches. An impressive new approach is, for example, pulmonary artery banding in children with dilated cardiomyopathy.[10] Pulmonary artery banding is leading to right ventricular pressure increase. Pressure increase in the right ventricle is followed by mechanical stabilization of the interventricular septum and the left ventricle. Additionally, mechanical stabilization of the ventricle is eventually followed by some kind of ventricular cross talk leading to cardiac recovery and improved left ventricular function in most of the cases treated so far. This method, which is actually evaluated in a worldwide multicenter study, would probably not work in adult patients where cardiac recovery capacity is severely impaired.

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Disclosures

None.

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References

1. Broughton KM, Wang BJ, Firouzi F, Khalafalla F, Dimmeler S, Fernandez-Aviles F, Sussman MA. Mechanisms of cardiac repair and regeneration. *Circ Res*. 2018;122:1151–1163. doi: 10.1161/CIRCRESAHA.117.312586.
2. Poss KD, Wilson LG, Keating MT. Heart regeneration in zebrafish. *Science*. 2002;298:2188–2190. doi: 10.1126/science.1077857.
3. Porrello ER, Mahmoud AI, Simpson E, Hill JA, Richardson JA, Olson EN, Sadek HA. Transient regenerative potential of the neonatal mouse heart. *Science*. 2011;331:1078–1080. doi: 10.1126/science.1200708.
4. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabé-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, Frisén J. Evidence for cardiomyocyte renewal in humans. *Science*. 2009;324:98–102. doi: 10.1126/science.1164680.
5. Mollova M, Bersell K, Walsh S, Savla J, Das LT, Park SY, Silberstein LE, Dos Remedios CG, Graham D, Colan S, Kuhn B. Cardiomyocyte proliferation contributes to heart growth in young humans. *Proc Natl Acad Sci USA*. 2013;110:1446–1451.
6. Rupp S, Schranz D. Cardiac regeneration in children. *Pediatr Cardiol*. 2015;36:713–718. doi: 10.1007/s00246-015-1120-x.
7. Azakie A, Russell JL, McCrindle BW, Van Arsdell GS, Benson LN, Coles JG, Williams WG. Anatomic repair of anomalous left coronary artery from the pulmonary artery by aortic reimplantation: early survival, patterns of ventricular recovery and late outcome. *Ann Thorac Surg*. 2003;75:1535–1541.
8. Alexander PM, Daubeney PE, Nugent AW, Lee KJ, Turner C, Colan SD, Robertson T, Davis AM, Ramsay J, Justo R, Sholler GF, King I, Weintraub RG; National Australian Childhood Cardiomyopathy

(*Circ Res*. 2018;122:e90-e91. DOI: 10.1161/CIRCRESAHA.118.313291.)

Study. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. *Circulation*. 2013;128:2039–2046. doi: 10.1161/CIRCULATIONAHA.113.002767.

9. Farooqi KM, Sutton N, Weinstein S, Menegus M, Spindola-Franco H, Pass RH. Neonatal myocardial infarction: case report and review of the literature. *Congenit Heart Dis*. 2012;7:E97–102. doi: 10.1111/j.1747-0803.2012.00660.x.
10. Schranz D, Akintuerk H, Bailey L. Pulmonary artery banding for functional regeneration of end-stage dilated cardiomyopathy in young children: world network report. *Circulation*. 2018;137:1410–1412. doi: 10.1161/CIRCULATIONAHA.117.029360.