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EDITORIAL FOCUS

Cardiac Excitation and Contraction

Postnatal development of human atrial cardiomyocytes: linking atrial gene expression profiles and atrial electrophysiology

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During postnatal development, the mammalian heart undergoes extensive changes in association with metabolic, structural, and biophysical maturation of cardiomyocytes (1–3). The neonatal heart at the time of birth is ~10% of the size of the adult heart. Initially, cardiac growth occurs through hyperplasia as cardiomyocytes proliferate and divide. Later in development, the heart size increases through cardiac hypertrophy as cardiomyocytes increase in size without a change in cell number. This progression from hyperplasia to hypertrophy is a characteristic feature of cardiomyocyte maturation that importantly facilitates the ability of cardiomyocytes to adapt to changing hemodynamic and metabolic demands (1).

As cardiomyocytes grow during the developmental process, they undergo structural changes to adapt the cells to their changing physiological conditions. These structural changes include the organization of the sarcomeres, development of the T-tubules and sarcoplasmic reticulum, and assembly of intercalated disks (1–4). Ion channel expression and regulation also undergo spatiotemporal changes during development (3). As a result of these processes, cardiomyocytes experience a maturation of electrophysiological, Ca^{2+} handling, and contractile properties. These processes occur with some similarities as well as some differences in different chambers of the heart (e.g., atrial vs. ventricular cardiomyocytes), due at least in part to developmental changes in gene expression (1).

Although it is clear that cardiomyocytes undergo extensive adaptations during the maturation process to ensure cardiac function can sustain life in the perinatal period and through development, our current understanding of human cardiomyocyte properties and function during distinct phases of maturation is limited. This is due in part to the scarcity of human heart tissue for research purposes. Moreover, these deficiencies in knowledge have important implications. For example, more than 1 million babies are born with congenital heart disease each year and many of these require heart surgery in the first years of life (5). Age at the time of surgery is an important risk factor for adverse outcomes, including cardiac arrhythmias, suggesting that postoperative recovery from cardiothoracic surgery can be influenced by the development stage (6, 7). Improving our understanding of cardiomyocyte maturation, including in the context of cardiomyocyte electrophysiology, during development could help improve surgical outcomes in these individuals.

In this journal, Salameh et al. (8) have conducted important and elegant studies to address these issues and improve our understanding of the temporal changes in cardiomyocyte maturation. The authors were able to collect a substantial number of atrial tissue samples (117 samples in total) from male and female patients with congenital heart disease who ranged in age from 5 days to 32 yr. This enabled the authors to divide the samples into five developmental stages (neonatal, infant, toddler/preschool, school aged, and adolescent/young adult) and consider sex differences, which represent the major strengths of the study. The authors extensively assessed age-dependent adaptations in atrial gene expression and then used computational approaches to apply these gene expression data to the assessment of ionic current conductances, action potential morphology, and Ca^{2+} transient morphology using an established human atrial computational model (Fig. 1).

Analysis of differentially expressed genes revealed several changes, including in cardiac ion channels and Ca^{2+} handling genes (Fig. 1). The computational studies indicate that changes in Na^{+}-Ca^{2+} exchanger current (I_{NCX}) and inwardly rectifying K^{+} current (I_{K1}) were most strongly associated with an age-dependent reduction in the action potential plateau potential and action potential triangulation, respectively. The study also identified changes in repolarization reserve that occurred in association with age-dependent change in KCNH2 (I_{Kr}) expression. Intriguingly, the authors were also able to use their novel data to conduct simulations to predict patient arrhythmias.

The gene expression data generated in the study are extensive and thus represent a wealth of information that can be further utilized in future studies. There is still much to learn

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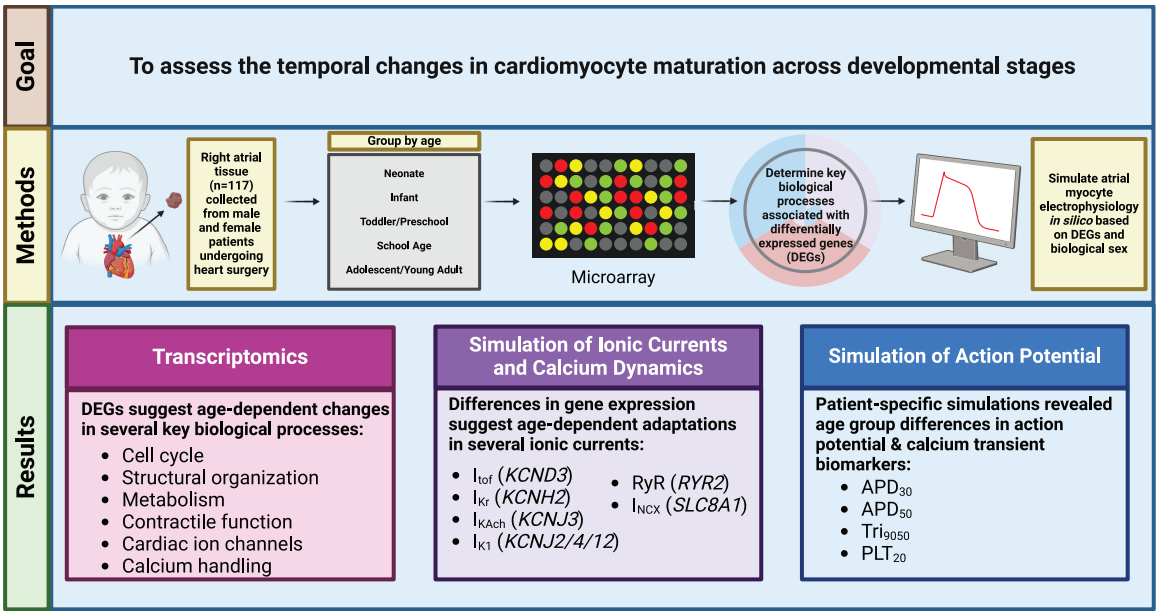

Figure 1. Summary of study design and experimental approaches used to assess atrial myocyte maturation in pediatric patients with congenital heart disease. Figure created with BioRender.

about cardiomyocyte development, not only in the context of cardiac electrophysiology and Ca^{2+} homeostasis but in numerous other contexts as well. It is anticipated that the gene expression data will yield additional targets that could be investigated in detail to determine their impacts on cardiomyocyte development and their implications for patients with congenital heart disease. Similarly, the computational modeling aspects of the study suggest developmental changes in atrial action potential morphology that could have very significant implications for understanding arrhythmogenesis in patients with congenital heart disease at different developmental stages. Validating these computational results in human patients or other experimental models will be necessary in future studies. This is particularly important because changes in gene expression may not always correlate with changes in protein levels. In addition, extrapolating the results of the study beyond the patients with congenital heart disease from whom the samples were obtained should be done with caution. Future studies could also consider chamber-specific differences in cardiomyocyte maturation. Continued efforts to build on the arrhythmia risk simulations developed in the present study and to improve their predictive power should be pursued, as this could have profound implications for patient care.

In summary, Salameh et al. have generated a very important dataset and conducted elegant studies that provide much-needed new insight into the temporal changes that atrial cardiomyocytes undergo during postnatal development and maturation (8). Their study is one of the most thorough and extensive studies conducted to date due to their ability to obtain a large number of atrial tissue samples and to couple their transcriptomic studies with in silico modeling approaches. Continued work in this important area will lead to further advances in our understanding of the maturation processes that affect cardiomyocytes through different developmental stages, which has important implications for patient care.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

E.R., A.D., and R.A.R. conceived and designed research; E.R. and R.A.R. prepared figures; R.A.R. drafted manuscript; E.R., A.D., and R.A.R. edited and revised manuscript; E.R., A.D., and R.A.R. approved final version of manuscript.

REFERENCES

1. **Salameh S**, **Ogueri V**, **Posnack NG.** Adapting to a new environment: postnatal maturation of the human cardiomyocyte. *J Physiol* 601: 2593–2619, 2023. doi:10.1113/JP283792.
2. **Singh BN**, **Yucel D**, **Garay BI**, **Tolkacheva EG**, **Kyba M**, **Perlingeiro RCR**, **van Berlo JH**, **Ogle BM.** Proliferation and maturation: Janus and the art of cardiac tissue engineering. *Circ Res* 132: 519–540, 2023. doi:10.1161/CIRCRESAHA.122.321770.
3. **Guo Y**, **Pu WT.** Cardiomyocyte maturation: new phase in development. *Circ Res* 126: 1086–1106, 2020. doi:10.1161/CIRCRESAHA.119.315862.
4. **Manfra O**, **Frisk M**, **Louch WE.** Regulation of cardiomyocyte T-tubular structure: opportunities for therapy. *Curr Heart Fail Rep* 14: 167–178, 2017. doi:10.1007/s11897-017-0329-9.
5. **Wu W**, **He J**, **Shao X.** Incidence and mortality trend of congenital heart disease at the global, regional, and national level,

1990–2017. *Medicine (Baltimore)* 99: e20593, 2020. doi:10.1097/MD.0000000000020593.

6. **Delaney JW**, **Moltedo JM**, **Dziura JD**, **Kopf GS**, **Snyder CS.** Early postoperative arrhythmias after pediatric cardiac surgery. *J Thorac Cardiovasc Surg* 131: 1296–1300, 2006. doi:10.1016/j.jtcvs.2006.02.010.
7. **Imura H**, **Caputo M**, **Parry A**, **Pawade A**, **Angelini GD**, **Suleiman MS.** Age-dependent and hypoxia-related differences in myocardial protection during pediatric open heart surgery. *Circulation* 103: 1551–1556, 2001. doi:10.1161/01.cir.103.11.1551.
8. **Salameh S**, **Guerrelli D**, **Miller JA**, **Desai M**, **Moise N**, **Yerebakan C**, **Bruce A**, **Sinha P**, **d'Udekem Y**, **Weinberg SH**, **Posnack NG.** Connecting transcriptomics with computational modeling to reveal developmental adaptations in pediatric human atrial tissue. *Am J Physiol Heart Circ Physiol* 327: H1413–H1430, 2024. doi:10.1152/ajpheart.00474.2024.