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EDITORIAL COMMENT

Slicing Into Human Translational Cardiovascular Biology*

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The heart failure literature is filled with a growing body of research that has identified an array of signaling pathways, transcription factors, noncoding ribonucleic acids (micro- and long noncoding ribonucleic acids), and genetic variants that are associated with either the presence and/or severity of heart failure. Although these findings often constitute important and seminal observations, such studies are limited in that they are essentially hypothesis-generating and do not establish causal relationships. Moreover, it remains challenging to dissect the mechanistic elements that ultimately govern how a particular molecule exerts its effects on the human myocardium. Most investigators have turned to rodent models to address these issues; however, it has become apparent that vast differences exist between human and model organisms (1,2).

In an effort to overcome these limitations, numerous investigators have attempted to establish primary human ventricular cardiomyocyte preparations that are suitable for cell culture and in vitro studies (3). Unfortunately, these systems are hindered by poor cardiomyocyte viability, inability to culture cells for a prolonged period of time, limited transfection efficiency, and a wide range of experimental variability (4). More recently, substantial attention has focused on the development of cardiomyocyte systems derived from human embryonic stem cells and induced pluripotent stem cells. These types of cardiomyocytes can be cultured for indefinite periods of time and seem to constitute a promising approach to understand the functional impact of genetic variants; these approaches are limited, however, by the realization that these cells are immature and most closely resemble embryonic cardiomyocytes (5,6). Moreover, each of these cell culture-based systems is confounded by the notion that cultured cardiomyocytes are being studied out of their native context. Specifically, these systems ignore important contributions from extracellular matrix elements and supporting cells such as fibroblasts, endothelial cells, and resident immune cells.

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The limitation of adequate experimental approaches has imposed an enormous challenge on investigators engaged in human translational cardiovascular biology: how can one establish causal links and define relevant molecular mechanisms in human systems? In this issue of *JACC: Basic to Translational Science*, Thomas et al. (7) offer an innovative and promising solution. Using a slice culture base system, they show that 250-μm slices of human ventricular myocardium can be readily obtained from patients with heart failure and remain viable in culture for at least 3 days. To highlight the versatility of this system, the investigators present evidence that human myocardial slice preparations are suitable for cell signaling, mechanical transduction, and viral transfection experiments. As proof of principle, they reveal for the first time that the alpha$_1$-adrenergic signaling pathway is functional in

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the human adult myocardium and in this context serves as a positive regulator of muscle contraction.

This paper (7) builds on a body of research that has used slice culture systems for the study of human brain, liver, and kidney physiology and pathology. Within these contexts, slice culture preparations have served as invaluable resources to investigate tissue responses to infection, pharmaceutical agents, environmental toxins, and molecular pathways that govern tissue fibrosis (8,9). A central advantage of tissue slices is that they elegantly preserve many aspects of tissue architecture, including cellular orientation, intercellular connections, and extracellular matrix elements. Moreover, these systems not only allow interrogation of signaling events within cells but also the ability to identify signaling events that mediate interactions between diverse tissue-resident cell types.

Although the findings of Thomas et al. (7) have provided a potentially exciting avenue to approach human translational cardiovascular biology with a more mechanistic mindset, it is likely that substantial research remains to better refine human heart slice culture systems and more adequately define their limitations. Future studies will ultimately be required to decipher the optimal conditions for slice preparation, determine the duration that slices can be cultured, and define the range of variability seen within and between specimens. To date, there are few reports of human heart slice culture (10–12). One group used septal myectomy specimens and a different slicing apparatus (10). Intriguingly, they reported that slices could survive for up to 4 weeks in culture, albeit with altered tissue morphology. As more investigators adopt slice culture systems, the strengths, weaknesses, and optimal uses of these preparations will be better defined, including adaptation of culture conditions that most closely resemble endogenous myocardial tissue.

Most importantly, the continued development of experimental systems to study human cardiac biology will ultimately provide the missing link necessary to establish the requisite causal relationships and molecular mechanisms that underlie the pathogenesis of human cardiac disease. Such insights will be essential to efficiently and successfully develop novel therapies that could ultimately be translated into clinical practice.

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