JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 2, NO. 5, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2016.07.007

EDITORIAL COMMENT

Chatty Cells

Not Cardiac Regeneration, But Segregation for Rhythm Preservation?*

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Communication between cells is at the very essence of optimal cardiac function. One mechanism of cellular communication is via so-called gap junctions (1). These junctions represent intercellular channels, which are established by docking of connexin hemichannels from neighboring cardiomyocytes. This network of channels allows multidirectional transfer of electric and chemical signals across the myocardium. Although such gap junctional (GJ) communication contributes to optimal cardiac function in the healthy condition, it also allows adaptation of cardiac function in case of injury, as in ischemia, acidosis, and cell death. Here, GJ communication is reduced, which may dampen the spread of injury signals and thereby decrease further damage (2). However, this may also lead to further impairment of electric impulse generation and propagation, which is known to increase proarrhythmic risk (3).

One pathological condition that comes with impaired GJ communication is myocardial infarction (MI). This involves the replacement of spatially well-organized, excitable, electrically coupled and beating cardiomyocytes by an accumulation of inexcitable, relatively poorly coupled and non-beating (myo)fibroblasts. Such fibrosis resulting from infarction leads to both structural and functional heterogeneity on a regional level but may affect cardiac function on a global level, as with arrhythmias. Although early reperfusion therapy could result in smaller infarct sizes, some myocardial damage is inevitable and, even if small, will be permanent. In addition, although a smaller scar size by early reperfusion seems favorable in terms of pump function, it was shown that such scars come with more surviving myocardium throughout the scarred region (4). In fact, such strings of surviving myocardium are also found in chronic MI without reperfusion, but here they are located in the border zone between the normal and fibrotic (i.e., infarcted) myocardium (3). These surviving but isolated areas of myocardium result in heterogeneous scarring after MI and are associated with increased proarrhythmic risk (5). Indeed, these areas may not only produce the substrate for conduction slowing and block, ectopic activity and wave break, but also act as a pathway for re-entrant conduction (6).

One, yet ambitious, way to deal with this structural and functional heterogeneity would be to actually regenerate the infarcted region by repopulating the scar with new cardiomyocytes, while meeting all the needs in terms of spatial integration, maturity, and electric and contractile behavior (7,8). Instead of replacing scar tissue with myocardial tissue, one may also aim to modify the electrophysiological properties of the resident scar cells by genetic modification. Although this may not achieve regeneration in the true sense of the word, it may "regenerate" the electrophysiological properties by allowing the scar cells to become excitable and/or better coupled (9,10), thereby potentially still lowering proarrhythmic risk. Even more ambitious would be to reprogram the (myo)fibroblasts directly into new cardiomyocytes, while taking into account the same requirements (11). Although a detailed discussion of these approaches would reach beyond the word count and scope of this comment, it seems clear that many hurdles are yet to be taken before such cellular regeneration or genetic

*Editorials published in *JACC: Clinical Electrophysiology* reflect the views of the authors and do not necessarily represent the views of *JACC: Clinical Electrophysiology* or the American College of Cardiology.

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JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 2, NO. 5, 2016
OCTOBER 2016:583–6

modification of the myocardial scar could be investigated in the clinical setting. The opposite approach, however, which does not aim to expand the size of the surviving areas of myocardium but instead to ablate them, is yet a clinical reality and seems effective.

Such so-called scar homogenization (or scar dechanneling) aims to create a scarred area with uniform characteristics, especially regarding the electrophysiological properties throughout the scar (12–14). This would allow the ablation of aberrant pathways of conduction facilitating re-entry. Also, interaction between surviving cardiomyocytes and scar-occupying (myo)fibroblasts would now only occur at the smoother circumference, thereby potentially reducing the likelihood and/or magnitude of so-called course-sink mismatch-related abnormalities in impulse generation and propagation (6). Effectively, such an approach should result in myocardial scar segregation, which seems counterintuitive, at least from a biological point of view (i.e., irreversible ablation of terminally differentiated cardiomyocytes). Nevertheless, studies have shown that this approach, when achieved through catheter ablation, can be effective in treating ventricular arrhythmias. More experimental, but with promising results, is a pharmacological approach to myocardial scar homogenization. Here either the extracellular matrix within the scar is targeted by bioenzymatic ablation (15) or GJ communication is improved by drugs increasing the intercellular conductance of these cells (16,17). Studies relying on the latter intervention showed that rotigaptide (previously known as ZP123), a peptide analog that increases GJ conductance, significantly attenuated GJ closure upon acidosis, compared with control. This effect was associated with higher conduction velocity and less dispersion in action potential duration, which was indeed associated with reduced proarrhythmic risk (16–18). Although naturally GJs tend to close upon hostile conditions such as acidosis and infarction, here the opposite (enhanced GJ communication), by rotigaptide administration, seems to be beneficial in terms of arrhythmia management. These intriguing findings of creating chatty cells to deal with ventricular arrhythmias so to speak, may provide a new strategy to counteract cardiac arrhythmias.

In this issue of *JACC: Clinical Electrophysiology*, Ng et al. (19) further explore the potential of rotigaptide to manage cardiac arrhythmias in the context of chronic MI. Here, the investigators hypothesized that enhanced GJ communication during acute MI could lead to more homogenous infarct scar and thereby reduce proarrhythmic risk in the chronic phase of MI. To study this, a bolus of rotigaptide (2.5 nmol/kg) was injected subcutaneously just before permanent left anterior descending coronary artery ligation in adult Sprague-Dawley rats, followed by rotigaptide administration using intraperitoneal osmotic minipumps (0.11 nmol/kg/min) for the next 7 days.

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Another 3 weeks later (4 weeks post-MI), the hearts were excised and studied for their electrophysiological and histological properties by optical voltage mapping and tissue staining, respectively. The results from this study indicate that such rotigaptide treatment during the acute and subsequent phases of MI could indeed result in more homogenous infarct border-zone scarring and in higher conduction velocity across this border zone and reduce arrhythmia susceptibility as assessed by programmed electric stimulation. Ng et al. (19) propose that such enhanced GJ communication may boost the exchange of signaling molecules involved in cell death and survival between healthy and dying cells in the border zone, thereby resulting in a more homogenous pattern of salvaged and infarcted myocardial tissue. With these results, the investigators provide important new insight into myocardial scar modification through temporary enhancement of GJ communication by revealing the effects on scar morphology and arrhythmogenesis beyond the acute phases. Besides further extending and refining the concept of scar homogenization as antiarrhythmic approach, this study also suggests that such a pharmacological approach may come with clinical potential. However, both from a conceptual and translational point of view, a number of aspects warrant further attention and investigation. Besides the intrinsic advantages and disadvantages that come with each and every model and technique, the following 4 aspects seem of special interest. First of all, with the current guidelines and modern infrastructure and technology, patients with acute MI are treated in such a way that the infarcted regions stay relatively small, but also with significant strands of surviving myocardium throughout the scar (4). It is therefore important to study the effects of rotigaptide, or other agents that increase GJ conductance, for this clinically more relevant scenario. Also, when dealing with larger hearts, it should be studied whether and how the optimal conditions can be achieved regarding dose, initial scar size and composition, and exposure to the drug via perfusion and diffusion.

Second, a more technical point of attention would be the detailed assessment of the causal relationship between scar heterogeneity and electrophysiological

abnormalities, especially on a more microscopic level beyond conventional mapping techniques (20). Such assessment may further refine the balance between the desired and adverse effects, including potentially increased proarrhythmic risk (6). Now a so-called arrhythmia inducibility score and a dispersion of interface complexity ratio are used to correlate scar heterogeneity with proarrhythmic risk, which remains rather descriptive and provides modest mechanistic insight.

The third aspect of this study that deserves attention is the pre-treatment with rotigaptide by bolus injection prior to induction of MI. It does not become clear how important this bolus is in producing the effects observed at 4 weeks post-MI. Would there be a significantly different outcome if rotigaptide would be administrated a few hours after induction? For a proof-of-concept study this seems less relevant, but for clinical translation it might have profound implications in terms of timing, patient selection, and adverse effects of long-term GJ modulation. Indeed, the heart is not the only organ that expresses GJs; many other organs rely on these channels for communication, such as the brain, kidneys, and reproductive organs (21).

This fourth aspect concerns the potential adverse effects of systemic administration of rotigaptide. As with any pharmacological intervention, this drug could affect GJ communication throughout the whole body. In their paper, Ng et al. (19) do not describe any adverse effects. Maybe the dose of rotigaptide was sufficient to affect cardiac (electric) function, while GJ communication in other organs was only mildly affected. In addition, longer follow-up, with or without additional challenges such as exercise and/or subsequent disease, may be needed before such adverse effects could manifest themselves. These are only a few possible explanations, but here additional research is certainly required.

In conclusion, Ng et al. (19) provide novel insight into pharmacological homogenization of myocardial scar by showing beneficial effects of enhanced GJ communication during the acute and early phases of MI on cardiac electrophysiology and rhythm. Thereby, the investigators significantly expand on previous work on this topic, but such progress also poses new questions and challenges. Still, even with this notion in mind, investigation of such new means to modify scar tissue are certainly worth the effort given the limited number of approaches currently available to modify the properties of the myocardial scar from within. In addition, although cardiac regeneration might still hold great promise to actually cure the heart from infarction, for now, scar segregation has already proved its potential in the clinical setting and deserves further investigation.

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KEY WORDS antiarrhythmic, cardiac arrhythmias, drugs, gap junctions, myocardial infarction, scar homogenization