Published in final edited form as:

Circ Res. 2015 August 14; 117(5): 390–391. doi:10.1161/CIRCRESAHA.115.307064.

Genetically encoded voltage indicators: Mapping cardiac electrical activity under a new light

Mario Delmar, MD, PhD and Gregory E Morley, PhD

The Leon H Charney Division of Cardiology. New York University School of Medicine. NY

Since the days of Einthoven, graphical representations of cardiac electrical activity have greatly advanced our understanding of arrhythmias and their mechanisms. Throughout the 20th century, technological advances led to improvements in the temporal and spatial resolution with which electrical signals were detected. Optical mapping of electrical activity was made possible by the discovery of voltage sensitive dyes that report changes in light emission as a function of transmembrane potential.¹ A major breakthrough came with the use of high-speed cameras that can simultaneously detect the optical signal from thousands of neighboring sites, adding orders of magnitude to the spatial resolution.² As in many other fields of science, visualizing what before had only been imagined led to a rapid advance in the understanding of function. Optical mapping continues to progress and with the work of Liao et al, published in this issue of Circulation Research,³ the field takes a new leap forward. Instead of using voltage-sensitive dyes, the authors have recorded cardiac electrical activity using a genetically encoded voltage indicator (GEVI) with no apparent toxicity and a good signal-to-noise ratio. The data show that the emitter is a reliable reporter of activation and that it has the potential for use in minimally invasive in vivo recordings in the presence of normal blood perfusion. The results also show that the time response of the indicator is adequate to follow relatively slow events, such as the action potential morphology of human adult cardiac myocytes and human embryonic stem cell-derived cardiac myocytes. Altogether, the authors convincingly show that GEVIs can be effectively used to detect cardiac electrical activity, thus adding a very important new tool to the toolbox of the cardiac electrophysiologist, and heralding a future of novel studies (well discussed in the paper) that were not practical in the past.

The breakthrough work of Liao et al³ represents an addition to, and not a replacement for, other methods. And like any new technology, it carries new limitations. Perhaps the most important is the slow “off time” of the fluorophore. The authors show that the decay of signal fluorescence is best described by a single exponential with a time constant of over 30 milliseconds. This magnitude is similar to that of the entire action potential duration at 90% repolarization (APD90) of the mouse ventricle paced at a cycle length of 300 ms.⁴ The authors do demonstrate that an empirical linear correction can adequately predict the APD90 of the cells based on the “optical APD50.” However, it is possible that genetic or drug-induced changes in APD will disrupt this relation, making this new system still not the

Address correspondence to: Mario Delmar MD PhD, The Leon H Charney Division of Cardiology, New York University School of Medicine, 522 First Avenue, Smilow 805, New York NY 10016, Phone: (212)263-9492, Mario.delmar@nyumc.org.

Disclosures: The authors have no conflicts of interest.

model of choice for studies where accurate determinations of APD are a priority. Furthermore, the slow kinetics of the emitter may impede an accurate spatial representation of activation waves at fast rates, such as those seen in the mouse ventricle during atrial or ventricular tachycardia. This is not to reduce the importance of the present paper; only to emphasize that this new approach is a major step forward that remains complementary of others. Just like the first camera-based optical mapping study opened a huge door of investigation even if constrained by technical limitations of its time,² this study has set a major cornerstone from where to build ahead. Faster GEVIs are already being used in the neuroscience field (e.g.,⁵) and are likely to be followed by others. The new approach described by Liao et al³ opens numerous new paths of investigation, such as the possibility of developing GEVIs that, by use of specific promoters, report from individual elements of the cardiac conduction system or even from non-myocyte cells populating the neighborhood of surviving tissue after injury.⁶ There is much to be known that remains veiled by technical constraints now lifted through the use of GEVIs. Exciting times are ahead, illuminated from within the very genome of the cardiac cells.

Acknowledgments

Supported by grants RO1-HL106632 and RO1 GM057691 (MD) and RO1 HL076751 (GM).

LITERATURE CITED

1. Salama G, Morad M. Merocyanine 540 as an optical probe of transmembrane electrical activity in the heart. *Science*. 1976; 191(4226):485–487. [PubMed: 1082169]
2. Davidenko JM, Pertsov AV, Salomonsz R, Baxter W, Jalife J. Stationary and drifting spiral waves of excitation in isolated cardiac muscle. *Nature*. 1992; 355(6358):349–351. [PubMed: 1731248]
3. Chang Liao ML, de Boer T, Mutoh H, Raad NS, Richter C, Wagner E, Downie BR, Unsold B, Arooj I, Streckfuss-Bomeke K, Doker S, Luther S, Guan K, Wagner S, Lehnart SE, Maier LS, Stuhmer W, Wettwer E, van Veen TA, Morlock MM, Knopfel T, Zimmermann WH. Sensing Cardiac Electrical Activity With a Cardiac Myocyte Targeted Optogenetic Voltage Indicator. *Circ Res*. 2015
4. Anumonwo JM, Tallini YN, Vetter FJ, Jalife J. Action potential characteristics and arrhythmogenic properties of the cardiac conduction system of the murine heart. *Circ Res*. 2001; 89(4):329–335. [PubMed: 11509449]
5. St-Pierre F, Marshall JD, Yang Y, Gong Y, Schnitzer MJ, Lin MZ. High-fidelity optical reporting of neuronal electrical activity with an ultrafast fluorescent voltage sensor. *Nature neuroscience*. 2014; 17(6):884–889. [PubMed: 24755780]
6. Vasquez C, Mohandas P, Louie KL, Benamer N, Bapat AC, Morley GE. Enhanced fibroblast-myocyte interactions in response to cardiac injury. *Circ Res*. 2010; 107(8):1011–1020. [PubMed: 20705922]