Manuscript Draft

Manuscript Number:

Title: Noninvasive electrophysiology in risk assessment and screening

Article Type: * Editorial Commentary (EDC)

Corresponding Author: Professor Marek Malik, MD, PhD

Corresponding Author's Institution: St Paul's

First Author: Marek Malik, MD, PhD

Order of Authors: Marek Malik, MD, PhD; Alfred E Buxton, MD; Heikki Huikuri, MD; Federico Lombardi, MD; Georg Schmidt, MD; Markus Zabel, MD

Manuscript Region of Origin: UNITED KINGDOM

CONFLICT OF INTEREST STATEMENT - HeartRhythm (First and Corresponding Author(s) Must Sign)

Thank you for your submission to the Heart*Rhythm* journal. CONFLICTS OF INTEREST FOR ALL AUTHORS MUST BE STATED ON THE TITLE PAGE. Please have the first and corresponding author(s) sign and upload with your manuscript submission. Its purpose is to inform all interested parties of any significant affiliations or relationships you may have with any commercial enterprise or any other potential conflicts of interest. This is a standard form required by most leading journals.

1.	Were you loaned any equipment, materials or medication for this study? Yes No _✓ Explain
2.	Were you given any equipment, materials or medication for this study? Yes No _✓ Explain
3.	Did you receive any funding to support your research for this article? Yes No Explain _ Properly acknowledged in the manuscript
4.	Were you provided with any honoraria, payment or other compensation for your work on this study? Yes No _✓ Explain
5.	Did you receive any stock options, stock ownership or other valuable materials in conjunction with this study from any source whatsoever? Yes No ✓ Explain
6.	Did you receive any outside financial support for travel or lectures to present the information covered in this study? Yes No Explain
7.	Do you have any financial relationship with any entity that may closely compete with the medications, materials or instruments covered by your study? Yes No Explain
8.	Do you own or have you applied for any patents in conjunction with the instruments, medications or materials discussed in this study? Yes No Explain
9.]	Do you receive any compensation for any therapy discussed in your article? Yes No _✓ Explain
10.	. Does anyone in your immediate family have a conflict of interest that would be covered by any of the above questions? (This would include closely held family trusts, limited liability corporations, etc.) Yes No _✓ Explain
If y	you have any doubts about the nature of your conflict, please contact Peng-Sheng Chen, MD, Editor-in-Chief.
Ma	anuscript Number or Title: Noninvasive electrophysiology in risk assessment and screening
Sig	gned:/Date 31st January 2018
Pr	int Name: Marek Malik

Imperial College London

National Heart and Lung Institute

Peng-Sheng Chen, MD, Editor-in-Chief Heart Rhythm

31st January 2018

Dear Dr Chen,

Thank you for your invitation to write an editorial comment to accompany the manuscript JHRM-D-17-01370R2 "Prognostic Significance of Ventricular Late Potentials in Patients with Pulmonary Sarcoidosis" by Yodogawa et al.

My co-authors and I very much hope that the text which we are submitting will satisfy your expectations and that it will be of interest to the readers of the Journal.

In anticipation, many thanks for considering our submission.

With all best wishes, Yours sincerely,

Marek Malik

Noninvasive electrophysiology in risk assessment and screening

by

Marek Malik, PhD, MD¹, Alfred E Buxton, MD², Heikki Huikuri, MD³, Federico Lombardi, MD⁴, Georg Schmidt, MD⁵, Markus Zabel, MD⁶ on behalf of e-Rhythm Study Group of EHRA

¹Imperial College, London, England, ²Harvard Medical School, Boston, USA, ³University of Oulu, Oulu, Finland, ⁴Policlinico, University of Milan, Milan, Italy, ⁵Technische Universität München, München, Germany, ⁶University of Göttingen, Göttingen, Germany

Short title

Noninvasive electrophysiology

No conflict of interest

Correspondence:

Marek Malik, PhD, MD, NHLI, Imperial College, London SW3 6LY, England

marek.malik@btinternet.com

Invasive electrophysiology has substantially advanced over previous years. Procedures such as defibrillator implantations or pulmonary vein isolation that have previously been an exclusive domain of major centers are presently available from many small clinics. This somewhat contrasts with general perception of noninvasive electrophysiology. Whilst substantial noninvasive research advances have been reported, their wide utility in clinical practice is not forthcoming. Some teaching centers even believe that noninvasive electrophysiology including electrocardiography is not worth teaching and that standard electrocardiographic diagnoses can rely on computerized diagnoses by modern equipment.

At the same time, existing research suggests that noninvasive electrophysiology can address a wide spectrum of unmet clinical needs. In addition to the distinction between patients benefitting and not benefiting from defibrillator implantation[1] and diagnosis of channelopathies[2], advanced electrocardiography was reported to aid stratification of patients with both cardiovascular and non-cardiovascular diagnoses, including kidney disease[3], diabetes[4], endocrinopathies[5], and others[6].

In this issue of the Journal, Yodogawa et al[7] add another piece to this mosaic showing possible advantages offered by high-resolution electrocardiography to early diagnosis of cardiac sarcoidosis. Using simple assessment of late potentials previously designed to detect large proarrhythmic ischemic scars, they predicted the risk of sarcoidosis-related cardiovascular events, albeit merging rhythm disturbances and hemodynamic dysfunction. The mechanistic link between positive late potentials and the nature of events described by Yodogawa et al is not easy to see. The finding thus likely means nonspecific identification of cardiac sarcoidosis which might cause variety of abnormalities. Regretfully, Yodogawa et al have also not employed any of the more advanced methods for the signal analysis reported to detect not only late depolarization abnormalities but also deformities well within the QRS complex [8,9]. We can only speculate that if these more powerful methods were used, the success reported by Yodogawa et al would have been stronger. Still, even with the simpler signal analyses, the report broadens the applicability of noninvasive methods.

Naturally, not all previous attempts of clinical outcome improvements by noninvasive electrophysiology have been successful[10]. Nevertheless, considering the disparity between research results and day-to-day clinical application, we share the opinion that noninvasive electrophysiology methods do not presently receive due attention in studies that define evidence-based care. The simplicity of obtaining high quality digital electrocardiographic

signals and their low costs make noninvasive electrophysiology suitable to be included not only in large clinical studies but also in new population screening programs. For example, evidence suggests that noninvasive electrophysiology can meaningfully contribute to the identification of patients in whom sudden cardiac death is the first manifestation of ischemic heart disease[11,12,13], as well as to the detection of impending atrial fibrillation[14], which are both major challenges of present preventive cardiology.

To connect the clinical day-to-day practice with reported research results, new large prospective investigations are needed. Their successful conduct will depend not only on the understanding of the potential of noninvasive methods by funding bodies but also on the industrial support and on the acceptance by clinical community. The manufacturers of noninvasive equipment should facilitate the collection of high quality electrocardiographic signals well above the standard 10-second recordings and the storage of digital signals in easily accessible formats. The clinical community involved in future studies should appreciate the potential value of high quality signal collection. Far too frequently are electrocardiographic recordings obtained in ongoing studies stored only as paper prints which precludes their advanced analyses. The designers of future prospective studies can only gain from involving specialists in noninvasive electrophysiology.

Acknowledgment

Supported in part by the British Heart Foundation (NH/16/2/32499), and by the European Community's Seventh Framework Programme (FP7-HEALTH-2013-INNOVATION-1 #602299)

References

- 1 Rizas KD, McNitt S, Hamm W, Massberg S, Kääb S, Zareba W, Couderc JP, Bauer A. Prediction of sudden and non-sudden cardiac death in post-infarction patients with reduced left ventricular ejection fraction by periodic repolarization dynamics: MADIT-II substudy. Eur Heart J 2017;38:2110-8.
- 2 Fowler SJ, Priori SG. Clinical spectrum of patients with a Brugada ECG. Curr Opin Cardiol 2009;24:74-81.
- Waks JW, Tereshchenko LG, Parekh RS. Electrocardiographic predictors of mortality and sudden cardiac death in patients with end stage renal disease on hemodialysis. J Electrocardiol 2016;49:848-54.
- A Nagaya T, Yoshida H, Takahashi H, Kawai M. Heart rate-corrected QT interval in resting ECG predicts the risk for development of type-2 diabetes mellitus. Eur J Epidemiol 2010;25:195-202.
- Wald DA. ECG manifestations of selected metabolic and endocrine disorders. Emerg Med Clin North Am 2006;24:145-57.
- Piper C, Butz T, Farr M, Faber L, Oldenburg O, Horstkotte D. How to diagnose cardiac amyloidosis early: impact of ECG, tissue Doppler echocardiography, and myocardial biopsy. Amyloid 2010;17:1-9.
- 7 Yodogawa K, Seino Y, Ohara T, Iwasaki Y, Hayashi M, Miyauchi Y, Azuma A, Shimizu W. Prognostic significance of ventricular late potentials in patients with pulmonary sarcoidosis. Heart Rhythm 2018;??:??-??.
- 8 Kelen GJ, Henkin R, Starr AM, Caref EB, Bloomfield D, el-Sherif N. Spectral turbulence analysis of the signal-averaged electrocardiogram and its predictive accuracy for inducible sustained monomorphic ventricular tachycardia. Am J Cardiol 1991;67:965-75.
- 9 Englund A, Hnatkova K, Kulakowski P, Elliott PM, McKenna WJ, Malik M. Wavelet decomposition analysis of the signal averaged electrocardiogram used for risk stratification of patients with hypertrophic cardiomyopathy. Eur Heart J 1998;19:1383-90.
- 10 Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM. Telemonitoring in patients with heart failure. NEJM 2010;363:2301-9.
- 11 Wellens HJ, Schwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J 2014;35:1642-51.

- 12 Kenttä TV, Nearing BD, Porthan K, et al. Prediction of sudden cardiac death with automated high-throughput analysis of heterogeneity in standard resting 12-lead electrocardiograms. Heart Rhythm 2016;13:713-20.
- 13 Waks JW, Sitlani CM, Soliman EZ, et al. Global Electric Heterogeneity Risk Score for Prediction of Sudden Cardiac Death in the General Population: The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. Circulation 2016;133:2222-34.
- 14 Gang Y, Hnatkova K, Mandal K, Ghuran A, Malik M. Preoperative electrocardiographic risk assessment of atrial fibrillation after coronary artery bypass grafting. J Cardiovasc Electrophysiol 2004;15:1379-86.