9th Theo Rossi di Montelera forum on computer simulation and experimental assessment of cardiac function

ESC European Society of Cardiology
Europace (2018) **20**, iii1–iii2
doi:10.1093/europace/euy256

EDITORIAL

9th Theo Rossi di Montelera forum on computer simulation and experimental assessment of cardiac function: from model to clinical outcome

Nathalie Virag[1]*, Vincent Jacquemet[2], Lukas Kappenberger[3], Rolf Krause[4], Frits Prinzen[5], and Angelo Auricchio[4]

[1]TRM Foundation, Lausanne Switzerland and Medtronic Europe, Tolochenaz, Switzerland; [2]Université de Montréal and Hôpital du Sacré-Cœur de Montréal, Montréal, QC, Canada; [3]TRM Foundation, Lausanne, Switzerland; [4]Center for Computational Medicine in Cardiology, Università della Svizzera Italiana, Lugano, Switzerland; and [5]Department of Physiology, Maastricht University, Maastricht, the Netherlands

The Theo Rossi di Montelera (TRM) Forum was created in 1998 by Nathalie Virag and Lukas Kappenberger with the objective to bring together engineers, mathematicians, and clinicians working in computer modelling, experimental, and clinical cardiovascular research in order to facilitate the translation of cardiac simulation results into clinical understanding and applications. The 9th TRM Forum was held in Lugano, Switzerland, on 4–5 December 2017, organized and supported by the TRM foundation and hosted by the Center for Computational Medicine in Cardiology in Lugano (CCMC). The theme was 'From Model to Clinical Outcome'. The focus was on the translation of observations and concepts developed within computer models into clinical outcome. *In silico* medicine refers to the use of computer simulations for the development of clinical interventions.

The first day of the forum was dedicated to the atria and to cardiac conduction. The first session focused on atrial modelling and experimental data. Roney *et al.*[1] investigated in a bilayer computer model of atrial fibrillation (AF) the interplay between rotors, wavelets, and focal sources during fibrillation. They were able to identify preferential sites for wavefront initiation and rotational activity, showing that computer simulations can predict that only a small number of connections sites are functionally important in sustaining AF.

Computer models can help us to understand the mechanisms underlying clinical observations such as changes in the P-wave morphology. The effect of epicardial–endocardial activation delay in the atria on P-wave morphology was studied in a computer model by Irakoze *et al.*[2] The results presented suggest that such a delay modifies the P-wave amplitude and area, notably on leads V2–V4, even when the P-wave duration and activation map remain the same. Another study of the P-wave morphology in a computer model of AF by Pezzuto *et al.*[3] revealed that P-wave variability in patients with paroxysmal AF could be explained by a variability in sinoatrial node exit location in combination with slow conducting regions. Andlauer *et al.*[4] investigated the influence of left atrial size on the P-wave morphology, paying attention to differential effects of dilation and hypertrophy. Starting with atrial geometries determined from Magnetic Resonance Imaging images from four subjects, they changed the geometry and calculated the electrocardiogram (ECG) using a model that included conduction in the thorax. This computational modelling study suggests that anatomical left atrial enlargement is not distinctly reflected in the P-wave and that increased P-wave terminal force is more indicative of left atrial hypertrophy.

The second session focused on translating atrial models into clinical practice for AF. Hakim *et al.*[5] showed in patient-specific computational models that post-ablation AF can be perpetuated by emergent re-entrant drivers, or by macro-reentrant circuits that form around lesions. These findings will be integrated in efforts to create custom-tailored ablation procedures for persistent AF. Another potential strategy for persistent AF ablation was presented by Roney *et al.*[6] They simulated in a virtual patient cohort the ablation of the interatrial connections to isolate the atria, predicting that this type of ablation is effective in returning the right atrium to sinus rhythm for many cases. Patient-specific modelling approaches have the potential to stratify patients prior to ablation by predicting if drivers are located in the left or the right atria. Finally, Gharaviri *et al.*[7] simulated various pharmacological interventions during AF. The atrial model explained the loss of efficacy of sodium channel blockade in terminating AF in the presence of severe structural remodelling observed experimentally and clinically. In all these examples, the use of an *in silico* approach overcame the limitation of a clinical evaluation and gave insight into patient-specific treatment of AF.

The second day of the forum was dedicated to the ventricles and the whole heart. The first session focused on ventricular modelling

* Corresponding author. Tel: +41 21 802 73 35. *E-mail address*: nathalie.virag@medtronic.com

and experimental data. Nguyen *et al.*[8] investigated the influence of the ventricular activation sequence on voltage amplitudes of local electrograms. In patients and patient-specific computer models without scars, lower unipolar voltage amplitudes in the septum were exclusively associated with a left bundle branch block activation sequence. Furthermore, ventricular pacing substantially impacted voltage amplitudes with average changes of half the intrinsic value, both in the patients and the computer models. The message of this work is that care should be taken to interpret low voltages during cardiac mapping as scar.

The second session focused on translating ventricular models into clinical practice for arrhythmia and cardiac resynchronization therapy (CRT). Cardiac resynchronization therapy does not improve cardiac function in all patients despite application of guideline criteria. This issue was addressed by Dupuis *et al.*[9] These investigators coupled a novel module of sarcomere contraction to the well-known CIrcAdapt model. The results of this multiscale modelling study suggest that septal rebound stretch predicts healthy mechanical function in cardiac tissue and positive response to CRT. Decreased cross-bridge cycling rates in the myocardium resulted in the loss of septal rebound stretch. Celilnik *et al.*[10] presented a simulation framework that has an application in ventricular tachycardia (VT) ablation procedures planning. It could be used to guide electrophysiology explorations and even predict ablation targets pre-operatively. This could reduce intervention duration and improve success rate. High performance computing simulations were conducted by Lyon *et al.*[11] to dissect key features explaining the ECG phenotypes with increased hypertrophic cardiomyopathy. They concluded that two of the ECG phenotypes may be explained by two distinct mechanisms, with potential relevance to patient management: apico-basal repolarization gradients, also associated with higher sudden cardiac death risk score, and abnormal Purkinje-myocardium coupling. Finally, Hermans *et al.*[12] investigated the added value of T-wave morphology markers in the diagnosis of long QT syndrome (LQTS). A support vector machine with T-wave morphology markers resulted in a major rise in sensitivity and specificity compared to a similar model without these markers, concluding that T-wave morphology markers have an added value in diagnosing LQTS.

While most of the work presented during the forum was done at the organ or tissue level, a clear understanding of the arrhythmogenic processes is also required at the cellular and molecular level. Rog-Zielinska *et al.*[13] studied the differences in the mouth of the T-tubules in ventricular myocardium from different species. T-tubular mouth topology may contribute to differences in experimental model behaviour, underscoring the importance of an appropriate model selection for research into cell and tissue function. Montnach *et al.*[14] studied the implication of gene mutations on arrhythmogenic right ventricular cardiomyopathy. The analysis suggests that the molecular cascades initiated by the seemingly unrelated genetic mutations converge downstream into a common pathway. This could explain the clinical manifestation of arrhythmogenic right ventricular cardiomyopathy in humans.

In the spirit of the TRM forum, the research presented in this Supplement is a combination of computer simulations, experimental work, and clinical observation with a focus on translational research and clinical outcome. The authors think that these articles reflect the trend of increasing influence of mathematical modelling and computational methods in cardiology. Two decades after its foundation, we proudly notice that the TRM Forum has reached its scope of being a stimulating environment for the development and use of new computational approaches and tools to extend our understanding of cardiac pathophysiology, improve diagnosis, and predict treatment efficacy.

Conflict of interest: N.V. is a full-time employee of Medtronic Europe (Tolochenaz Switzerland). V.J., L.K., and R.K. have no conflict of interest to disclose. F.P. received research grants from Medtronic, Abbott, Microport, Biotronik, Biosense Webster, and EBR Systems. A.A. is a consultant to Abbott, Biosense Webster, Daiichi-Sankyo, Boston Scientific, Medtronic, Microport-CRM, and received speaker fee from Daiichi-Sankyo, Boston Scientific, Medtronic, Microport-CRM.

References

1. Roney CH, Ng FS, Debney MT, Eichhorn C, Nachiappan A, Chowdhury RA *et al.* Determinant of new wavefront locations in cholinergic atrial fibrillation. *Europace* 2018;**20**(Suppl 3):iii3–15.
2. Irakoze E, Jacquemet V. Simulated P wave morphology in the presence of endo-epicardial activation delay. *Europace* 2018;**20**(Suppl 3):iii16–25.
3. Pezzuto S, Gharaviri A, Schotten U, Potse M, Conte G, Caputo ML *et al.* Beat-to-beat P-wave morphological variability in patients with paroxysmal AF: an *in silico* study. *Europace* 2018;**20**(Suppl 3):iii26–35.
4. Andlauer R, Seemann S, Baron L, Dössel O, Kohl P, Platonov P *et al.* Influence of left atrial size on P-wave morphology: differential effects of dilation and hypertrophy. *Europace* 2018;**20**(Suppl 3):iii36–44.
5. Hakim JB, Murphy MJ, Trayanova NA, Boyle PM. Arrhythmia dynamics in computational models of the atria following virtual ablation of re-entrant drivers. *Europace* 2018;**20**(Suppl 3):iii45–54.
6. Roney CH, Willimans SE, Cochet H, Mukherjee RK, O'Neil L, Sim I *et al.* Patient-specific simulations predict efficacy of ablation of interatrial connections for treatment of persistent atrial fibrillation. *Europace* 2018;**20**(Suppl 3):iii55–68.
7. Gharaviri A, Verheule S, Eckstein J, Potse M, Krause R, Auricchio A *et al.* Effect of Na^+-channel blockade on the three-dimensional substrate of AF in a model of endo-epicardial dissociation and transmural conduction. *Europace* 2018;**20**(Suppl 3):iii69–76.
8. Nguyen UC, Potse M, Vernooy K, Masi-Rad M, Heijman J, Caputo ML *et al.* A left bundle branch block activation sequence and ventricular pacing influences voltage amplitudes: an *in vivo* and *in silico* study. *Europace* 2018;**20**(Suppl 3):iii77–86.
9. Dupuis LJ, Arts T, Prinzen FW, Delhaas T, Lumens J. Linking cross-bridge cycling kinetics to cardiac resynchronization therapy: a multiscale modelling study. *Europace* 2018;**20**(Suppl 3):iii87–93.
10. Cedilnik N, Duchateau J, Dubois R, Sacher F, Jais J, Cochet H *et al.* Fast personalized electrophysiological models from CTI images for ventricular tachycardia ablation planning. *Europace* 2018;**20**(Suppl 3):iii94–101.
11. Lyon A, Bueno-Orovio A, Zacur E, Ariga E, Grau V, Neubauer S *et al.* ECG phenotypes in hypertrophic cardiomyopathy caused by distinct mechanisms: apico-basal repolarization gradients versus Purkinje-myocardial coupling abnormalities. Insights from a high performance simulation study informed by cardiac magnetic resonance. *Europace* 2018;**20**(Suppl 3):iii102–12.
12. Hermans BJM, Stoks S, Bennis FC, Vink AS, Garde A, Wilde AAM *et al.* Support vector machine-based assessment of the T-wave morphology improves LQTS diagnosis. *Europace* 2018;**20**(Suppl 3):iii113–9.
13. Rog-Zielinska EA, Kong CHT, Zgierski-Johnston CM, Verkade P, Mantell J, Cannell MB *et al.* Species differences in morphology of T-tubule openings in ventricular cardiomyocytes. *Europace* 2018;**20**(Suppl 3):iii20–4.
14. Montnach J, Agullo-Pascual E, Tadros R, Bezzina CR, Delmar M. Bio-informatic analysis of PKP2-dependent transcription network: implications for the mechanisms of arrhythmogenic right ventricular cardiomyopathy in humans and in boxer doges. *Europace* 2018;**20**(Suppl 3):iii125–32.