Eighth TRM Forum on Computer Simulation and Experimental Assessment of Cardiac Function: Towards Integration of Cardiac Functions

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Since 1998, the Theo Rossi di Montelera (TRM) forum has brought together researchers working on computer modelling, experimental research, and clinical research, with the objective to facilitate the translation of research findings in computer modelling of the heart into the clinical field. The 8th TRM forum was held at Lugano, Switzerland, on 6–8 December 2015, organized by the TRM foundation and hosted by the Center for Computational Medicine in Cardiology in Lugano. The theme was ‘Towards Integration of Cardiac Functions’. In this forum, cardiac function was addressed from the perspectives of electrical cardiac function, mechanical cardiac function, and circulatory function.

Electrical cardiac function is generally assessed clinically with a body-surface electrocardiogram (ECG). However, the ECG represents an integrative measure of whole heart electrical activity, from which it is sometimes challenging to derive information about local cardiac activity. Computer models can help us to derive better patient-specific knowledge from routine ECG and determine the underlying electrical activation sequence. An example was presented by Cardone-Noott et al.1 with a multi-scale computational study on the role of ventricular endocardial activation sequences on QRS complex variations in both healthy hearts and in the presence of intraventricular block. This study provides physiological insights on ECG biomarkers in terms of QRS morphology and location of early endocardial activation sites. Van Dam et al.2 presented a novel method to localize premature ventricular contractions on the papillary muscles using a 12-lead ECG together with cardiac anatomy and torso geometry derived from magnetic resonance imaging (MRI). The precise localization of the site of origin of premature ventricular contractions could facilitate the planning and execution of an ablation procedure. Saha et al.3 developed a computer model of the atria and torso to study the changes in P wave morphology resulting from pulmonary vein (PV) ablation. Results were compared before and after PV isolation and after PV reconnection, showing that both PV isolation and reconnection induced measurable changes on the 16-lead ECG that might be used to improve patient follow-up after ablation. Another modelling-based study by Loewe et al.4 investigated the influence of atrial activation on P-wave morphology. Simulations showed that the location of earliest activated site in the right atrium and its proximity to functioning inter-atrial connections affects the P-wave terminal force in lead V1 independently of the left atrial size. This should be taken into consideration during the clinical interpretation of electrocardiographic signs of left atrial abnormality. Engels et al.5 investigated electrophysiologic remodelling in patients with left bundle branch block induced by transcatheter aortic valve implantation (TAVI). This was a retrospective study in 107 patients measuring ECG before and after TAVI. Left bundle branch block occurred in approximately one-third of all procedures. The study demonstrated that within 1 month after onset of TAVI-induced left bundle branch block, electrical remodelling developed, mainly expressed as reduction in repolarization variables such as T-wave area. This remodelling was highly variable between patients, despite similar baseline characteristics. One possible mechanism for the observed electrical remodelling might be mechano-electrical coupling.

Therapeutic strategies related to electrical cardiac activation were discussed. Luca et al.6 presented a pacing scheme for atrial fibrillation (AF) developed based on computer modelling studies. The proposed method consists of rapid pacing from a ring electrodes located in the septal area and the translation from computer modelling to experimental testing was discussed. Deng et al.7 used computational modelling to non-invasively predict arrhythmia risk in myocardial infarction patients with preserved left ventricular ejection fraction. Results demonstrate that the personalized virtual heart simulation...
approach may provide a novel risk stratification modality to non-invasively and effectively identify patients with left ventricular ejection fraction > 35% who could benefit from implantable cardioverter defibrillator implantation.

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. An example was given during the forum by Altomare et al. with a novel in vitro model of human stem-cell-derived cardiomyocyte, offering a patient-specific investigational platform in cardiomyocyte physiology. Such models of functional assessment of cardiac ion channels are of great interest to potential applications such as preclinical drug safety screening.

The second cardiac function addressed during the forum was the mechanical cardiac function. It is the electrical activation that triggers the mechanical contraction; however, these two functions are interdependent. Favino et al. presented an electromechanical computer model of the heart and studied the impact of the mechanical deformations on the ECG. Significant differences were observed in simulated ECG between pure electrophysiological and electromechanically coupled models, especially on the T-wave.

Several models of therapeutic strategies linked to the mechanical cardiac function were discussed. Quinn et al. studied the mechanisms of mechanical pacing in Langendorff-perfused rabbit hearts. Mechanical pacing has continued to be of interest for emergency resuscitation as it represents a rapidly available, non-invasive, and generally well tolerated means of pacing the asystolic or bradyarrhythmic heart. However, the benefits of mechanical pacing at higher heart rates are unclear. In this study, it was demonstrated that mechanical pacing achieves lower maximum rates than same-site electrical pacing and that mechanical pacing cannot be sustained for extended periods at rates exceeding normal sinus rhythm. Several models of heart failure including electromechanical coupling were also presented, illustrating how computer modelling can create new insight on the optimization of cardiac resynchronization therapy (CRT) response. Pluijmert et al. developed an electromechanical computational model of both ventricles and investigated the relation between left ventricular pacing site and CRT response. In these model simulations, the best cardiac function was obtained when pacing the mid-basal left ventricular lateral wall, because of fastest recruitment of left ventricular activation. Villoingo et al. investigated whether patient-specific computational models constructed from non-invasive measurements can provide measures of left ventricular dyssynchrony during heart failure. They showed that the indices of dyssynchrony estimated with patient-specific electrophysiology models may predict left ventricular reverse remodelling after CRT as well or better than similar metrics derived from invasive electroanatomic measurements. This type of model could assist clinicians in VV delay optimization. Crozier et al. studied in a patient-specific electromechanical model the optimal pacing location of the left ventricular pacing lead in CRT. They found that pacing in laterobasal regions, optimizing the lead position by minimizing QRS duration, and pacing in regions activated late at sinus rhythm were found to improve acute haemodynamic response to CRT.

The third cardiac function to be addressed during the forum was the circulatory function. Augustin et al. presented a model bidirectionally coupling the three major physics governing a heartbeat: electrophysiology, mechanics, and fluid flow. Today such models are still rare due to their inherent complexity in terms of model formulation, numerical methods, software implementation, and computational cost. They constitute an important and nontrivial step towards fully coupled electro-mechano-fluidic models and show promise as a tool for predicting the response to interventions which affect the conditions of afterload.

All presentations highlighted the importance of patient-specific model of the heart or personalized modelling, taking into account individual variability. Today these models based on clinical imaging and electrophysiological data are becoming a reality. Such models could be used in the future for guiding individual clinical anti-arrhythmic therapies. To achieve such a goal, in addition to integrating the different cardiac functions, these models should take into account tissue structure and cardiac anatomy. One of the challenges in computer modelling lies in the difficulty to access relevant human cardiac electrophysiological data upon which to develop and validate models. Bucciarelli-Ducci et al. presented a review on cardiac MRI as a tool providing accurate data on cardiac function and characterization of fatal arrhythmia substrate. Boyle et al. reviewed the effect of fibrosis on atrial arrhythmia perpetuation and compared several approaches proposed in the field of personalized computational modelling of the fibrotic substrate for atrial arrhythmia. Roney et al. also addressed the challenge of modelling atrial fibrosis. Fibrosis is a major factor associated with AF; however, the optimal methodology for fibrosis modelling remains unknown. Late gadolinium-enhanced MRI data were used to assign different fibrosis models. Simulation results showed that the specific representation of fibrosis has a large effect on AF rotor dynamics and needs to be carefully considered. Mitrofanova et al. investigated the extent of fibrosis and lymphomonomonuclear infiltration based on the studies of postmortem tissue samples from the atria and the ventricles. They found that inflammatory reaction and increased fibrosis extent observed in the atrial myocardium in AF patients is not confined to the atria but is a generalized phenomenon affecting the whole heart. Finally, laizzo et al. presented the Visible Heart® project and the Atlas of Human Cardiac Anatomy free-access website, featuring images of functional and fixed human cardiac anatomies from over 370 human heart specimens. This tool allows researchers a better visualization of anatomical alterations that occur with various pathologies and it provides a unique perspective for observing functional cardiac anatomy.

In the spirit of the TRM forum, the research presented was a combination of computer simulations, experimental work, and clinical observation. Integrating all the cardiac functions in a patient-specific approach is an ambitious task, to which we hope this will contribute.

Conflict of interest: N.V. is a full time employee of Medtronic Europe (Tolochenaz, Switzerland) A.A. Speaker fee, honoraria, consultant; Abbott, Biotronik GmBH, Bristol-Meyers-Squibb, Cordis BDS, DC_Device, EBR Systems, Impulse Dynamics, Medtronic, ResMed, Sorin Group, St. Jude Medical.

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