REVIEW ARTICLE

Noninvasive Imaging of Cardiac Excitation: Current Status and Future Perspective

A.W. Maurits van der Graaf, M.D.,* Pranav Bhagirath, M.D.,* Hemanth Ramanna, M.D., Ph.D.,* Vincent J.H.M. van Driel, M.D.,* Jacques de Hooge, M.Sc.,* Natasja M.S. de Groot, M.D., Ph.D.,† and Marco J.W. Götte, M.D., Ph.D.*

*From the *Department of Cardiology, Haga Teaching Hospital, The Hague, The Netherlands and †Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands*

Noninvasive imaging of cardiac excitation using body surface potential mapping (BSPM) data and inverse procedures is an emerging technique that enables estimation of myocardial depolarization and repolarization. Despite numerous reports on the possible advantages of this imaging technique, it has not yet advanced into daily clinical practice. This is mainly due to the time consuming nature of data acquisition and the complexity of the mathematics underlying the used inverse procedures. However, the popularity of this field of research has increased and noninvasive imaging of cardiac electrophysiology is considered a promising tool to complement conventional invasive electrophysiological studies. Furthermore, the use of appropriately designed electrode vests and more advanced computers has greatly reduced the procedural time. This review provides descriptive overview of the research performed thus far and the possible future directions. The general challenges in routine application of BSPM and inverse procedures are discussed. In addition, individual properties of the biophysical models underlying the inverse procedures are illustrated.

Ann Noninvasive Electrocardiol 2014;19(2):105–113

electrocardiography; body surface potential mapping; inverse procedures; noninvasive cardiac activation mapping

Through the years, various noninvasive electrocardiographic imaging techniques have emerged that estimate epicardial potentials or myocardial activation times from potentials recorded on the thorax.[1–8] The recording of potentials from a large number (32–256) of torso electrodes is referred to as body surface potential mapping (BSPM).[9] The BSPM data can later be used in mathematical inverse procedures to calculate local epicardial potentials or myocardial activation times.[10]

Although a vast amount of research illustrates the possible clinical advantages of this noninvasive imaging method, the time consuming nature of BSPM and the complexity of the mathematics underlying the inverse procedures has thus far hampered these techniques to advance into daily clinical practice.

Nevertheless, noninvasive imaging of cardiac excitation is still gaining popularity as a field of research and is considered a promising tool to complement conventional invasive electrophysiological studies.[11] The use of appropriately designed electrode vests and more advanced computers has greatly reduced the procedural time. Recently, a noninvasive imaging technique based on electrocardiographic imaging (ECGI) has been commercialized and has become available for clinical use in Europe.[12] Although ECGI estimates the time course

Address for correspondence: A.W. Maurits van der Graaf, M.D., Department of Cardiology, Haga Teaching Hospital, Leyweg 275, 2545 CH, The Hague, The Netherlands. Fax: 0031 70 210 2224; E-mail: a.vandergraaf@hagaziekenhuis.nl

Body Surface Mapping Reviewed.

Disclosures: our institution has received research grants from St Jude Medical and Medtronic NL. None of the authors report a potential conflict of interest.

DOI:10.1111/anec.12140

of unipolar epicardial electrograms only, several studies have demonstrated that the epicardial potentials and electrograms provide substantial information about intramyocardial activity.[13,14]

This review discusses the general challenges in routine application of BSPM and inverse procedures. Descriptive overview is given to the research performed thus far and the future direction of noninvasive imaging of cardiac excitation. In addition, individual properties of the biophysical models underlying the inverse procedures are illustrated.

BODY SURFACE POTENTIAL MAPPING

Waller was the first to report on the recording of human body surface potentials in 1887.[15] He used a capillary electrometer to systematically investigate the potential distribution associated with the beating heart. Einthoven published the first surface electrocardiogram (ECG) constructed with the string galvanometer in 1903 and later described the method for clinical 12-lead electrocardiography.[16] The use of the 12-lead ECG made it possible to study potential fields over designated areas and to investigate their variations over time.

Although the efficacy of the 12-lead ECG had been widely recognized, several researchers felt that information was lost when the recording of potentials was limited to only nine sites.[17,18] In the following years, alternative configurations using 16–256 torso electrodes were proposed.[19–24] Nevertheless, BSPM has never been incorporated into daily clinical practice because of uncertainty about the clinical utility. In the mean time, much experience had already been gained with the interpretation of the 12-lead ECG and this configuration continues to be the standard of routine clinical practice today.

INVERSE PROCEDURE

The *forward* problem of electrocardiography refers to estimation of body surface potentials from potentials measured on the surface of the heart. Therefore, the effect that different types of body tissue have on the cardiac potentials is simulated.[25] In contrast, the *inverse* problem of electrocardiography describes the opposite (Fig. 1A). Through an inverse procedure, the potentials on the heart surface or activation times of the myocardium are estimated using the recorded body surface potentials as source data.

In order to calculate cardiac activation times from potentials recorded on the body surface, potentials that are generated by the cardiac electrical activity in the torso volume need to be modeled. Unlike the forward problem that can be solved uniquely, the inverse problem in terms of sources is not unique.[26] Many different source configurations in the heart can correspond to the same potentials on the body surface, even for noise-free and error-free data. These different sources are termed equivalent sources because they generate the same potentials on the body surface. Therefore, the inverse problem is said to be "ill conditioned."[27]

In order to cope with this ill conditioned nature, most inverse procedures employ a combination of two types of models: a biophysical source model and a volume conductor model (VCM). In a biophysical source model, the heart is represented as a generator of electrical currents (Fig. 2). The VCM reproduces the influence of different types of tissues in the thorax on the potential waveforms.

In order to reproduce this influence, a detailed anatomical model of the patients' thorax, incorporating the conductivity properties of the main thoracic structures, is a prerequisite. Anatomy is usually provided by a computed tomography (CT) or magnetic resonance imaging (MRI) scan. The conductivity values used for the thorax, ventricular muscle, lungs and blood cavities can be found in literature, for example, 0.2, 0.2, 0.04, and 0.6 S/m, respectively.[28,29] The resulting simulated body surface potentials are then compared to the actual potentials recorded by the torso electrodes. Finally, the activation times and the resulting potential curves are tuned in order to obtain an optimal match between the measured and simulated ECG. Eventually, the most favorable match between simulated and measured thorax potentials is considered to be a true reflection of local cardiac activation.

The inverse problem in terms of potentials is unique; that is, in the absence of noise and errors only one epicardial potential distribution corresponds to a given body surface potential distribution. This inverse problem does not employ a model representation of the source; instead, it uses the actual epicardial potentials as a source.[30]

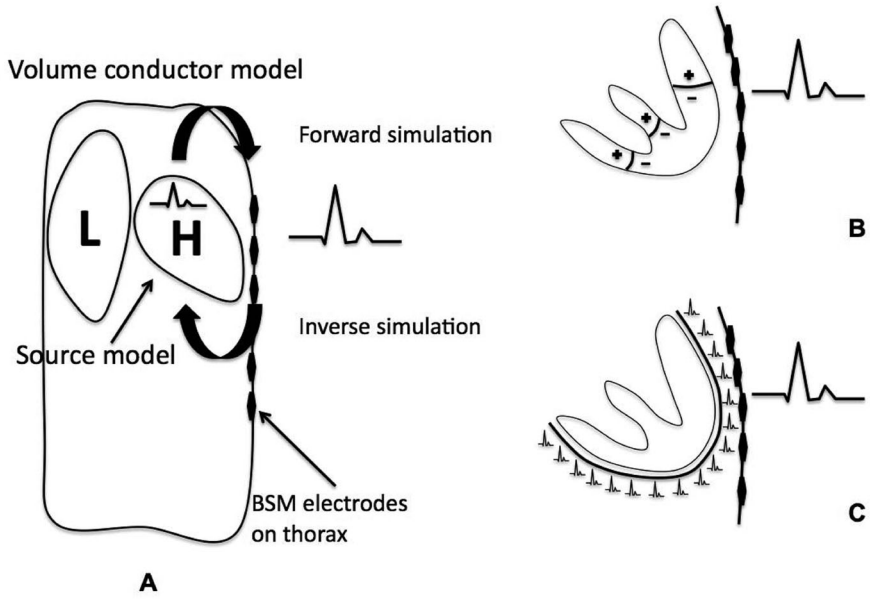

Figure 1. Forward and inverse computation (A) The principle of forward and inverse computation is illustrated in a VCM from a lateral view (H: heart, L: lung). In the EDL source model (B), the wavefront separating resting heart cells in the myocardium from those that have undergone depolarization, is regarded as an activation layer that moves through the heart during the cardiac cycle. In the PPS model (C), a unique relationship exists between the potentials on the body surface and the potentials on the epicardium.

Inverse problems are regarded to have an ill-posed nature, that is, the desired solution is unstable and can vary significantly with the slightest noise or perturbation in the BSPM data. In order to circumvent this issue, investigators have developed several regularization methods that impose constraints to the outcome.[31] The chosen constraints can have a tremendous influence on the outcome and are therefore a subject of constant debate. Nevertheless, regularization is a key issue in contemporary used inverse procedures.[32]

BIOPHYSICAL SOURCE MODELS

A biophysical source model represents the heart as a generator of electrical currents. The first source model to be introduced was the current dipole (CD).

Current Dipole

The electrical field generated by the heart was considered equivalent to a single rotating dipole, visualized as a vector of varying strength during the cardiac cycle.[33] Hence, usage of this model is known as vectorcardiography. The effect of an approaching or receding excitation wave can be described using this model. However, multiple excitation wavefronts, spreading simultaneously through the myocardium, and regional electrical activity cannot be discriminated due to the total lack of spatial resolution of this model. Following the introduction of the current dipole, Wilson et al. introduced another source model in 1933; the equivalent double layer (EDL).[34]

Equivalent Double Layer Model

The wavefront separating resting heart cells in the myocardium from those that have undergone depolarization, can be regarded as a surface double layer. This activation layer moves through the heart during the cardiac cycle, reflecting cardiac electrical activity (Fig. 1B). Observed from some distance, this double layer is electrically equivalent to the net effect of the currents generated at the cellular membrane during depolarization with a strength proportional to the local transmembrane potential.[35] However, the validity of the EDL model is disputed; in particular the assumption

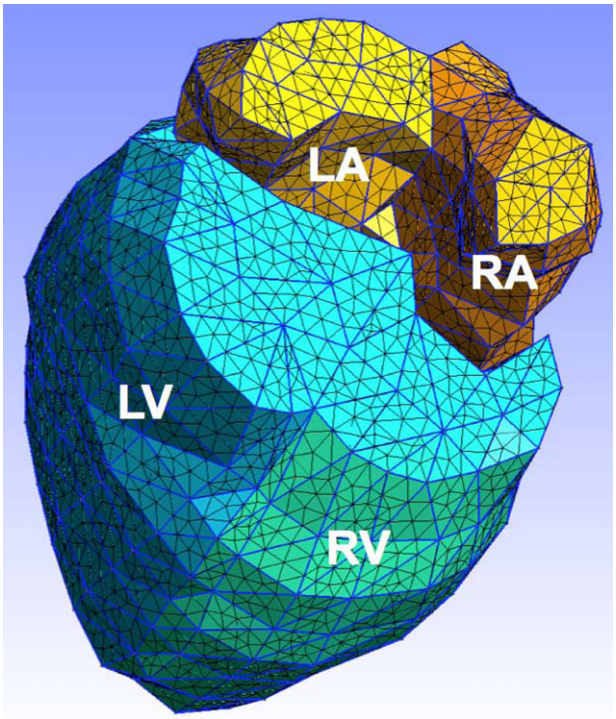

Figure 2. Triangulated mesh of a patient's heart. A triangulated heart model developed and used at our institution. This model can be used for simulations of cardiac activation. After segmentation of the different cardiac compartments on CT or MRI anatomic images, specialized software divides the volumes in triangles of equal size. The nodes and interconnecting spines of the mesh can subsequently be used to calculate probable excitation pathways.

that ventricular cells constitute a homogeneous syncytium. In addition, an equal anisotropy (directional dependence) ratio is assumed, while fiber architecture inside the myocardium is heterogeneous with major regional variations in fiber arrangement.[36]

Pericardial Potential Source Model

Among the biophysical source models, the pericardial potential source (PPS) model has been investigated most extensively.[37,38] In order to inversely compute the pericardial potential distribution from recorded potentials, the PPS model exploits a common physical fact (Fig. 1C). A unique relationship exists between the potentials on the body surface and the potentials on the epicardium, as long as the model descriptions of both surfaces are closed and no other electrical sources are present in between.[39] The entire time course of unipolar epicardial electrograms is estimated. This enables mapping depolarization, repolarization and other electrophysiologic processes that are reflected in the S–T segment. Moreover, it has been demonstrated that the epicardial potentials and electrograms provide substantial information about intramyocardial activity.[40]

Cellular Automaton (CA)

In a cellular automaton (CA) model, the myocardial tissue is considered to be a set of discrete elements (in either active or inactive state) connected to each other. States vary as a function of the preceding state and the state of the neighboring elements. CA are relatively easy to program and allow fast simulations, but have serious limitations when seeking to reproduce the effects of curvature on an activation front.[41] This in turn may results in less accurate estimations on cardiac activation times to be made.

VOLUME CONDUCTOR MODELS

A VCM reproduces the influence of the different types of tissues in the thorax on the potential waveforms. The models most often used are discussed here.

Spherical Element Model

The spherical element model considers the volume-conducting medium to be a symmetrical homogeneous sphere. Therefore, it is not suited for accurate localization of electrical foci, but has proven to be an efficient and fast model in vectorcardiography.[42] The attractiveness of this model relies in the fact that in such a simplistic configuration, the differential equations involved can be solved analytically, rather than by a computer.

Boundary Element Method

The boundary element method (BEM) is a frequently used model that approximates the volume conductor properties of realistic shaped compartments. When using this approach for forward or inverse computation, it is essential to accurately obtain a patient's heart and thorax geometry. The boundaries of the organs involved are of particular interest. The properties of the enclosed tissue (e.g., anisotropy) are purposefully

neglected. Hence, the influence of various types of tissues on the distribution of potentials through a volume cannot be determined. The BEM allows relatively fast calculations as long as only a limited number of boundaries are present.[43]

Finite Element Method

On the contrary, the finite element method (FEM) fully appreciates the volume and architecture of the tissue rather than just its boundaries. Although historically hampered by limited computational resources, this model is used more frequently nowadays. The ability to incorporate the effects of inhomogeneity on the transmission of electrical impulses through the thorax is an important incentive to investigate the FEM. Although its efficiency in localizing epileptic foci in neurological patients has been demonstrated previously,[44] little research has thus far been performed in cardiac patients.

NONINVASIVE ELECTROCARDIOGRAPHIC IMAGING TECHNIQUES

Through the years, various methods using different combinations of BSPM and inverse procedures (source and volume conductor model) have been proposed. Numerous experiments were performed to determine a technique's localization accuracy. Validation studies in humans with various pathologies are an ongoing effort that should continue. The mean resolution of currently used noninvasive electrocardiographic imaging techniques is approximately 1–2 cm, though some have obtained better results.[45–50]

Electrocardiographic Imaging

Electrocardiographic Imaging (ECGI) uses 250 torso electrodes and combines the PPS and BEM.[51] Recently, this technique has been commercialized by CardioInsight (CardioInsight Technologies Inc., Cleveland, OH, USA). The clinical applicability of ECGI is currently being investigated in a multicenter trial and the first reports have been published. ECGI effectively predicted which patients would respond to cardiac resynchronization therapy (CRT), based on differences between estimated left ventricular (LV) and right ventricular (RV) mean activation times. A greater difference was associated with clinical CRT response and appeared to be a more powerful predictor than 12-lead ECG parameters.[52] The feasibility of CRT optimization by using ECGI had been reported earlier.[53]

Another study demonstrated the clinical utility in mapping simple and complex atrial tachycardias (AT).[54] The overall diagnostic accuracy of the noninvasive system compared to invasive EP diagnosis, as the gold standard, was 92% (100% in patients with de novo ablations and 83% in patients with previous AF ablations).

The ability of ECGI to map atrial fibrillation (AF) was investigated in several studies.[55,56] Body surface signals generated by AF are typically of low amplitude and the volume conductor smoothes the potential distribution. Because ventricular signals are typically of much greater magnitude than the atrial signals, it might be necessary in some patients with normal atrioventricular (AV) conduction to remove the ventricular signals. This can be achieved by using QRS(T) subtraction algorithms or by the administration of AV blocking agents. Hence, it can be challenging to acquire long continuous recordings of atrial signals of adequate quality.

In 2011, Wang et al. reported on the application of ECGI in a series of 25 patients undergoing catheter ablation procedures for various types of VT (Fig. 3).[57] BSPM were recorded during episodes of sustained VT in nine patients. The remaining patients were imaged during premature ventricular contractions (PVC). The sites of origin as determined by ECGI were in agreement with the invasive electrophysiological study (EPS) in 10 of 11 RV sites (91%) and in 11 of 12 LV sites (92%). ECGI correctly categorized both focal and reentrant mechanisms of VT, but was not able to differentiate between focal activity and microreentry.

Electrical remodeling due to right ventricular pacing was investigated in nine patients with an implanted dual-chamber pacemaker system.[58] This remodeling resulted in action potential prolongation near the site of abnormal activation and a marked dispersion of repolarization. This dispersion of repolarization is potentially arrhythmogenic and was less evident during continuous RV pacing.

When recording the atria, the ventricular signal is a problem when the ventricular rate is rapid. Analysis requires that a few cycles do not conduct to the ventricles. AT with 2:1 conduction to the ventricles pose an analytic challenge in the absence

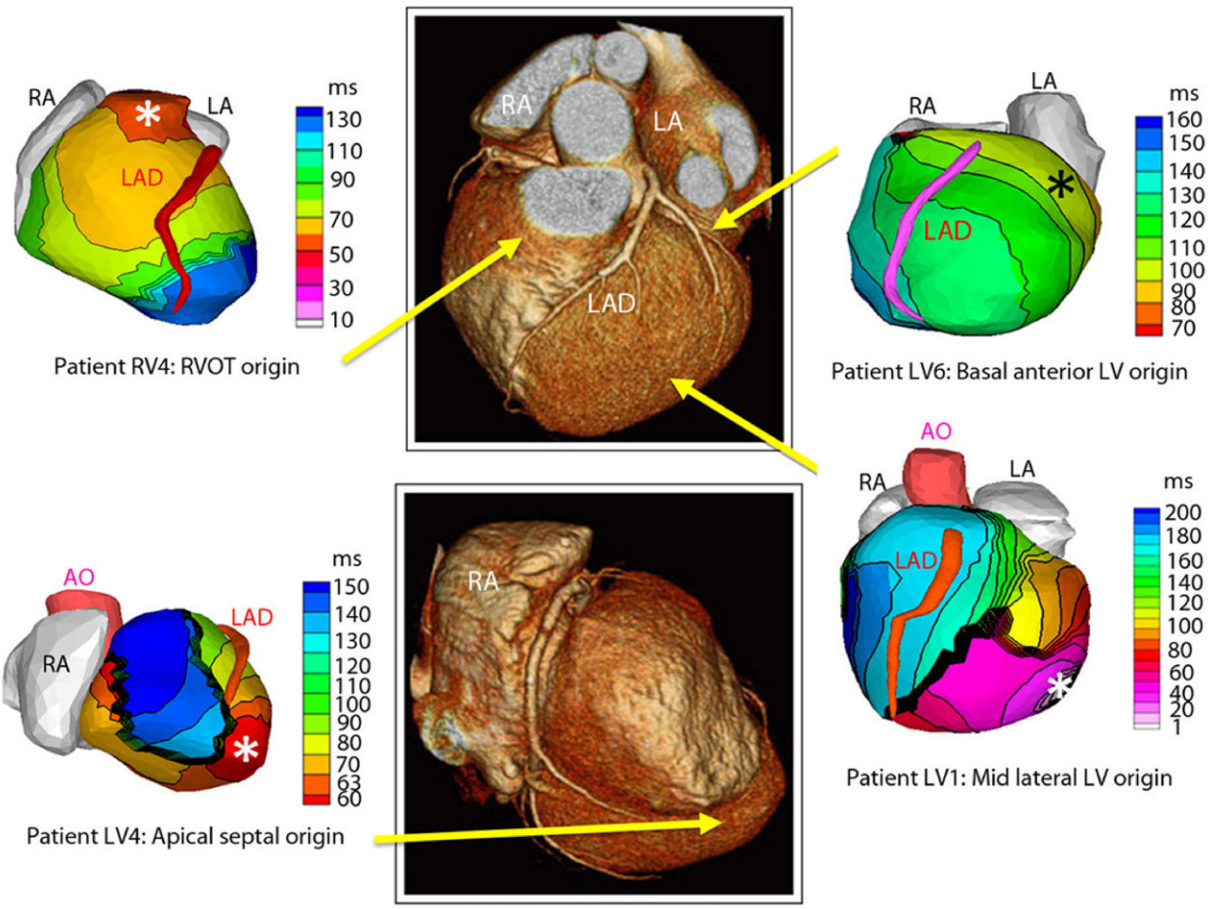

Figure 3. Noninvasive ECGI isochrone maps for localization of VT site of origin. Epicardial isochrone maps are shown for four patients, with earliest epicardial activation marked with an asterisk. EP-study-determined sites of origin are indicated under the ECGI maps. Yellow arrows point to VT origin on a representative CT scan. RA = right atrium; LA = left atrium; AO = aorta; LAD = left anterior descending coronary artery; LV = left ventricle; RVOT = right ventricular outflow tract. Reprinted with permission from Cuculich et al.[55]

of reliable QRST subtraction software program. It can be difficult to estimate signals around the mitral annulus, which can be problematic for perimitral atrial flutter. In most studies, a CT scan was performed that includes the abdomen in order to register the location of all BSPM electrodes on the image. The inclusion of the abdominal region is associated with substantially higher patient radiation doses.[59]

Noninvasive Imaging of Cardiac Electrophysiology

Noninvasive imaging of cardiac electrophysiology (NICE) employs 64 electrodes, the EDL and BEM.[60] NICE has been performed in seven patients with WPW syndrome undergoing catheter ablation of the accessory pathway.[61] All ventricular accessory pathway insertion sites were identified with an accuracy of 18.7 ± 5.8 mm. In CRT and control patients, endocardial and epicardial ventricular activation were visualized noninvasively.[62]

However, the atria cannot be analyzed using the NICE technique and the model does not account for ventricular repolarization. The small number of study subjects in which NICE was applied makes it difficult to fully appreciate the quality of this system. Studies on functional electrocardiographic imaging are generally limited by the small number of study subjects owing to the complexity of data acquisition and image segmentation procedures for reconstruction of patient-specific anatomical models.

AMYCARD

AMYCARD uses 83 electrodes, PPS, and BEM.[63] It has been commercialized by AMYCARD LLC (AMYCARD LLC, Moscow, Russia). Since AMYCARD has only recently been installed in several Russian research centers, no data on the accuracy of this technique is yet available.

Current Density Reconstruction (CDR)

Another method developed by He et al. uses current density reconstruction (CDR) to estimate the current density distribution on the endocardial surface of the LV from measured body surface potentials.[64] The dipole source model and BEM are used in combination with 90 torso electrodes. The first report on in vivo validation has recently been published by Lai et al.[65] BSPM was performed in six patients with monomorphic PVC. Compared with the successful ablation site, the mean localization error of the CDR approach was 13.8 ± 1.3 mm.

Future perspective

Noninvasive imaging of cardiac excitation has been the focus of several investigators, but it has not yet evolved into a clinical technology that is usable in daily clinical practice. This is mainly due to technical challenges in the recording, processing, and interpretation of the data. To enter the clinical arena, the physical validity of the simulations and robustness of the method must be undisputed. As far as validation is a key issue, there is a need for continued validation in humans. In addition, practical aspects of handling a great number of electrodes must be considered. Until now several multielectrode vests have been developed, but it remains unclear to what extent these vests allow routine clinical application of BSPM.

More reliable simulations of greater physical validity are aspired in the near future. In order to achieve this, high-resolution imaging techniques and improved inverse algorithms need to be developed and integrated. For example, the integration of patient specific MRI data on cardiac fiber orientation into biophysical models (FEM) poses new challenges.[66] The selection of an appropriate source and volume conductor model may prove to be of utmost importance to construct highly accurate, patient-specific three dimensional simulation models for clinical use. Therefore, substantial knowledge on the general challenges regarding the use of inverse procedures seems imperative.

Despite these challenges, noninvasive imaging of cardiac electrophysiology is considered a promising tool to complement conventional EPS. For example, in patients suffering from arrhythmias, ectopic foci may be localized noninvasively prior to entering the catheterization suite. Reducing the duration of an invasive procedure and to decrease the associated exposure to radiation could be an important advantage of this application.

With regard to optimization of pacing therapy, detailed simulation studies may be performed using patient-specific three dimensional computer models prior to implantation of a cardiac pacing device. By incorporating knowledge on anatomy, location of scar tissue and the site of latest mechanical activation, optimal sites for lead placement may be determined noninvasively.

In case of AF, these techniques may offer new insights in the extent of structural and functional remodeling of the atria. Especially, when incorporating information on the extent and location of atrial fibrosis in patients undergoing pulmonary vein antrum isolation (PVAI). Through follow-up investigations, therapeutic effects or progression of substrate remodeling can be assessed and monitored carefully.

CONCLUSION

The development of robust inverse procedures has kindled renewed interest in BSPM. The combined use of inverse procedures and BSPM, referred to as noninvasive imaging of cardiac electrophysiology, is considered a promising tool to complement conventional EP studies. To enter the clinical arena, the physical validity of the simulations and robustness of individual methods must be undisputed. The selection of appropriate biophysical models may prove to be of utmost importance to construct highly accurate, patient-specific three dimensional simulation models for clinical use.

REFERENCES

1. Liu C, He B. Noninvasive estimation of the cardiac activation sequence using the extended Kalman Filter. IEEE Trans Biomed Eng 2011;58:541–549.

2. Berger T, Hintringer F, Fischer G. Noninvasive imaging of cardiac electrophysiology. Indian Pacing Electrophysiol J 2007;1;7(3):160–165.
3. Huiskamp G, Greensite F. A new method for myocardial activation imaging. IEEE Trans Biomed Eng 1997;44(6):433–446.
4. Varma N. Variegated left ventricular electrical activation in response to a novel quadripolar electrode: Visualization by non-invasive electrocardiographic imaging. J Electrocardiol 2014;47(1):66-74.
5. Bokeriia LA, Revishvili ASH, Kalinin AV, et al. Hardware-software system for noninvasive electrocardiographic examination of heart based on inverse problem of electrocardiography. Med Tekh 2008;6:1–7.
6. SippensGroenewegen A, Hauer RN, van Hemel NM, et al. Atlas of paced body surface QRS integral maps for localization of the site of origin of postinfarction ventricular tachycardia. J Electrocardiol l994;27(Suppl 1):IO5–1I2.
7. Cakulev I, Sahadevan J, Arruda M, et al. Confirmation of novel noninvasive high density electrocardiographic mapping with electrophysiology study: implications for therapy. Circ Arrhythm Electrophysiol 2013;6(1):68–75.
8. Van Dam PM, Oosterdorp TF, Linnenbank AC, et al. Noninvasive imaging of cardiac activation and recovery. Ann Biomed Eng 2009;37(9):1739–1756.
9. Taccardi B, Punske BB, Lux RL, et al. Useful lessons from body surface mapping. J Cardiovasc Electrophysiol 1998;9(7):773–786.
10. Hoekema R, Uijen GJ, van Oosterom A. On selecting a body surface mapping procedure. J Electrocardiol 1999;32(2):93–101.
11. Sapp JL, Dawoud F, Clements JC, et al. Inverse solution mapping of epicardial potentials: quantitative comparison with epicardial contact mapping. Circ Arrhythm Electrophysiol 2012;5(5):1001–1009.
12. Rudy Y. Noninvasive electrocardiographic imaging of arrhythmogenic substrates in humans. Circ Res 2013;112(5):863–874.
13. Oster HS, Taccardi B, Lux RL, et al. Electrocardiographic imaging: noninvasive characterization of intramural myocardial activation from inverse-reconstructed epicardial potentials and electrograms. Circulation 1998;97(15):1496–1507.
14. Hutchinson MD, Gerstenfeld EP, Desjardins B, et al. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 2011;4(1):49–55.
15. Waller AD. A demonstration on man of electromotive changes accompanying the heart's beat. J Physiol (Lond) 1887;8:227–234.
16. Einthoven W. Die galvanometrische Registerung des menschlichen Elektrokardiogram: Zugleich eine Beurtheilung der Anwendung des Capillar-Elektrometers in der Physiologie. Pflügers Arch ges Physiol 1903;99:472–480.
17. Horan LG, Hand RC, Flowers NC, et al. The influence of electrode placement in the reconstruction and analysis of body surface potential maps from limited thoracic arrays. J Electrocardiol 1980;13(4):311–21.
18. Evans JW, Erb BD, Brody DA. Comparative proximity and remoteness characteristics of conventional electrocardiographic leads. Am Heart J 1961;61:615–621.
19. Donnelly MP, Finlay DD, Nugent CD, et al. Lead selection: old and new methods for locating the most electrocardiogram information. J Electrocardiol 2008;41(3):257–263.
20. Barr RC, Spach MS, Herman-Giddens S. Selection of the number and position of measuring locations for electrocardiography. IEEE Trans Biomed Eng 1971;18(2):125–138.
21. Lux RL, Burgess MJ, Wyatt RF, et al. Clinically practical lead systems for improved electrocardiography: comparison with precordial grids and conventional lead systems. Circulation 1979;59(2):256–263.
22. Kornreich F, Montague TJ, Rautaharju PM, et al. Identification of best electrocardiographic leads for diagnosing anterior and inferior myocardial infarction by statistical analysis of body surface potential maps. Am J Cardiol 1986;58(10):863–871.
23. Van Oosterom A. The equivalent surface source model in its application to the T wave. J Electrocardiol 2002;527–535.
24. Lux RL, Smith CR, Wyatt RF, et al. Limited lead selection for estimation of body surface potential maps in electrocardiography. IEEE Trans Biomed Eng 1978;25(3):270–276.
25. Gulrajani RM. The forward and inverse problems of electrocardiography. IEEE Eng Med Biol Mag 1998;17(5):84–101.
26. Van Oosterom A. Source models in inverse electrocardiography. Int J Bioelectromag 2003;5(1):211–214.
27. Van Oosterom A. The inverse problem of bioelectricity: an evaluation. Med Biol Eng Comput 2012;50(9):891–902.
28. Roth BJ. Electrical conductivity values used with the bidomain model of cardiac tissue. IEEE Trans Biomed Eng 1997;44(4):326–328.
29. Geddes LA, Baker LE. The specific resistance of biological material: a compendium of data for the biomedical engineer and physiologist. IEEE Trans Biomed Eng 1967;5:271–293.
30. Martin RO, Pilkington TC. Unconstrained inverse electrocardiography: epicardial potentials. IEEE Trans Biomed Eng 1972;19(4):276–285.
31. Shou G, Jiang M, Xia L, et al. A comparison of different choices for the regularization parameter in inverse electrocardiography models. Conf Proc IEEE Eng Med Biol Soc 2006;1:3903–3906.
32. Cluitmans MJ, Karel JM, Bonizzi P, et al. Wavelet-sparsity based regularization over time in the inverse problem of electrocardiography. Conf Proc IEEE Eng Med Biol Soc 2013;2013:3781–3784.
33. Burger HC, van Milaan JB. Heart vector and leads. Br Heart J 1946;8:157–161.
34. Wilson FN, Macleod AG, Barker PS. The distribution of action currents produced by the heart muscle and other excitable tissues immersed in conducting media. J Gen Physiol 1933;16:423–456.
35. van Dam PM, Tung R, Shivkumar K, et al. Quantitative localization of premature ventricular contractions using myocardial activation ECGI from the standard 12-lead electrocardiogram. J Electrocardiol 2013;46(6):574–579.
36. Streeter DD, Ramon C. Muscle pathway geometry in the heart wall. J Biomech Eng 1983;105(4):367–373.
37. Spach MS, Barr RC, Lanning CF, et al. Origin of body surface QRS and T wave potentials from epicardial potential distributions in the intact chimpanzee. Circulation 1977;55(2):268–268.
38. Franzone PC, Taccardi B, Viganotti C. An approach to inverse calculation of epicardial potentials from body surface maps. Adv Cardiol 1978;21:50–54.
39. Ramanathan C, Jia P, Ghanem R, et al. Noninvasive electrocardiographic imaging (ECGI): application of the generalized minimal residual (GMRes) method. Ann Biomed Eng. 2003;31(8):981–994.
40. Burnes JE, Taccardi B, Ershler PR, et al. Noninvasive electrocardiogram imaging of substrate and intramural ventricular tachycardia in infarcted hearts. J Am Coll Cardiol 2001;38(7):2071–2078.

41. Dossel O, Bauer W, Farina D, et al. Imaging of bioelectric sources in the heart using a cellular automaton model. Conf Proc IEEE Eng Med Biol Soc 2005;2:1067–1070.
42. Holmes JR, Alps BJ. Studies into equine electrocardiography and vectorcardiography: I. Cardiac electric forces and the dipole vector theory. Can J Comp Med Vet Sci 1967;31(4):92–102.
43. Jamison C, Navarro C, Turner C, et al. The inverse problem utilizing the boundary element method for a nonstandard female torso. IEEE Trans Biomed Eng. 2011;58(4):876–883.
44. Fuchs M, Wagner M, Kastner J. Development of volume conductor and source models to localize epileptic foci. J Clin Neurophysiol 2007;24(2):101–119.
45. Lee K, Lv W, Ter-Ovanesyan E, et al. Cardiac ablation catheter guidance by means of a single equivalent moving dipole inverse algorithm. Pacing Clin Electrophysiol 2013;36(7):811–822.
46. Lai D, Sun J, Li Y, et al. Usefulness of ventricular endocardial electric reconstruction from body surface potential maps to noninvasively localize ventricular ectopic activity in patients. Phys Med Biol 2013;58(11):3897–3909.
47. Ghosh S, Rudy Y. Accuracy of quadratic versus linear interpolation in noninvasive Electrocardiographic Imaging (ECGI). Ann Biomed Eng 2005;33(9):1187–1201.
48. Shannon HJ, Navarro CO, Smith BA, et al. Activation patterns during selective pacing of the left ventricle can be characterized using noninvasive electrocardiographic imaging. J Electrocardiol 2007;40(6 Suppl):S111–S117.
49. Han C, Pogwizd SM, Killingsworth CR, et al. Noninvasive cardiac activation imaging of ventricular arrhythmias during drug-induced QT prolongation in the rabbit heart. Heart Rhythm 2013;10(10):1509–15.
50. Barr RC, Spach MS. Inverse calculation of QRS-T epicardial potentials from body surface potential distributions for normal and ectopic beats in the intact dog. Circ Res 1978;42(5):661–675.
51. Ramanathan C, Ghanem RN, Jia P, et al. Noninvasive electrocardiographic imaging for cardiac electrophysiology and arrhythmia. Nat Med 2004;10(4):422–428.
52. Ploux S, Lumens J, Whinnett Z, et al. Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: beyond QRS duration and left bundle-branch block morphology. J Am Coll Cardiol 2013;61(24):2435–2443.
53. Varma N, Jia P, Rudy Y. Electrocardiographic imaging of patients with heart failure with left bundle branch block and response to cardiac resynchronization therapy. J Electrocardiol 2007;40(6 Suppl):S174–8.
54. Shah AJ, Hocini M, Xhaet O, et al. Validation of novel 3-dimensional electrocardiographic mapping of atrial tachycardias by invasive mapping and ablation: a multicenter study. J Am Coll Cardiol. 2013;62(10):889–897.
55. Cuculich PS, Wang Y, Lindsay BD, et al. Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. Circulation 2010;122:1364–1372.
56. Haissaguerre M, Hocini M, Shah AJ, et al. Noninvasive panoramic mapping of human atrial fibrillation mechanisms: a feasibility report. J Cardiovasc Electrophysiol 2013;24(6):711–717.
57. Wang Y, Cuculich PS, Zhang J, et al. Noninvasive electroanatomic mapping of human ventricular arrhythmias with electrocardiographic imaging. Sci Transl Med 2011;3(98):98ra84.
58. Marrus SB, Andrews CM, Cooper DH, et al. Repolarization changes underlying long-term cardiac memory due to right ventricular pacing: noninvasive mapping with electrocardiographic imaging. Circ Arrhythm Electrophysiol 2012;5(4):773–781.
59. Mettler FA Jr, Huda W, Yoshizumi TT, et al. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 2008;248(1):254–263.
60. Pfeifer B, Hanser F, Seger M, et al. Patient-specific volume conductor modeling for non-invasive imaging of cardiac electrophysiology. Open Med Inform J 2008;2:32–41.
61. Berger T, Fischer G, Pfeifer B, et al. Single-beat noninvasive imaging of cardiac electrophysiology of ventricular pre-excitation. J Am Coll Cardiol 2006;48:2045–2052.
62. Berger T, Pfeifer B, Hanser FF, et al. Single-beat noninvasive imaging of ventricular endocardial and epicardial activation in patients undergoing CRT. PLoS One 2011;6(1):e16255.
63. Denisov AM, Zakharov EV, Kalinin AV, et al. Numerical methods for some inverse problems of heart electrophysiology. Differential Equations 2009;45(7):1034–1043.
64. Lai D, Liu C, Eggen MD, et al. Localization of endocardial ectopic activity by means of noninvasive endocardial surface current density reconstruction. Phys Med Biol 2011;56(13):4161–4176.
65. Lai D, Sun J, Li Y, et al. Usefulness of ventricular endocardial electric reconstruction from body surface potential maps to noninvasively localize ventricular ectopic activity in patients. Phys Med Biol 2013;58(11):3897–3909.
66. Toussaint N, Stoeck CT, Schaeffter T, et al. In vivo human cardiac fibre architecture estimation using shape-based diffusion tensor processing. Med Image Anal 2013;17(8):1243–1255.