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DETECTION OF GLOBAL AND LOCAL ISCHEMIC CHANGES IN ELECTRICAL FIELD OF THE HEART

Implications for the concept of electrocardiographic imaging

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Abstract

In this thesis, detailed investigation into the electrical field of the heart is presented in patients with various manifestations of myocardial ischemia. Methods of standard scalar electrocardiography and body surface potential mapping were used through statistical and mathematical analysis in order to compare their diagnostic performance. Body surface mapping proved to be more powerful research and diagnostic tool than standard electrocardiography and also constituted a framework for data entering the computer electrical model of the human heart and torso.

Global and local ischemic changes were the primary objectives of the individual studies of this thesis. Different patient populations were studied including post-myocardial infarction population, patients with variant angina and patients referred for percutaneous coronary angioplasty, and the population of patients suffering from ventricular arrhythmias related mostly to their postinfarction status. Traditional depolarization and repolarization changes were studied together with novel diagnostic parameters such as minimal potential loss within the QRS complex, single-beat cardiac micropotentials, and distribution of the QT interval on the human thorax. Critical appraisal and error performance of so called QT interval dispersion was another important objective.

In summary, however clinical electrocardiography is established and indispensable in clinical practice, and most likely beyond its zenith as a research tool; computerized analysis of electrical heart field keeps opening new areas of interest and valuable insight into the clinical problems. We regard body surface potential mapping as a powerful laboratory research tool and a framework for entering further stage of electrocardiographic analysis using realistic computer electrical model of the human heart and torso. Utilizing such model together with novel 3-dimensional imaging reconstructions might bring new realistic imaging technique into the clinical practice – electrocardiographic imaging.

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Preface and acknowledgement

Electrical field of the heart and electrocardiogram belong to the ultimate wonders of nature, displaying the basic physical driving force of life. Without sparking this genuine electrical fire of life more than 100 thousand times a day that very life would not sustain. Body surface potential mapping is presented as a central tool for sampling this electrical field in this thesis. Although existing for decades, while trying to display the electrical field in its entirety and also to ease the burden of the investigator's abstraction, it has not reached a potential of clinical technology. Perhaps, it still engages too much of that abstraction and distracts the practitioner too far away from the patient. Computer modeling seems to have the ability to change this, and the opportunity to peek into one of the renowned labs employing an advanced electrical heart model brought me to the acknowledgement of technologies that have changed our lives so profoundly. Also, the merit of this thesis could not be conceived without performing as a clinical cardiologist-electrophysiologist. I wish to express greatest thanks to having this opportunity to broaden my views of the surrounding wonders of life.

My special thanks go to my pregraduate medical teachers in cardiology dr. Miloš Stojan and professor František Boudík, to the people from industry ing. Zdeněk Brabec, ing. Pavel Rydlo, and to my closest engineering coworkers ing. Zdeněk Anger and dr. Coen Metting Van Rijn. Also, I am grateful to professor Michael Aschermann, dr. Zdeněk Drška, and my thesis supervisor professor Otomar Kittnar, head of Department of Physiology at Charles University, who have sustained my scientific engagement and brought me to the accomplishment of my postdoctoral studies. This thesis could not be conceived without my best clinical mentor professor Martin Gardner in Halifax, Canada. This gentleman (founder of Cardiac Arrhythmia Service for Queen Elizabeth II Health Sciences Center in Halifax) has substantially broadened my clinical view of arrhythmias. To him and his cardiac EP crew in QEII, including dr. Magdy Basta and dr. John Sapp, I am utmost grateful for being able to start my own cardiac electrophysiology service.

As I said before, without the insight into the computer technology and modeling, this thesis would not be worth of publishing, since it would not bring information matched to this new world of science that has changed so much through the new technologies. Therefore, my great thanks belong to professor Milan Horáček, who made it possible for me to become a visiting scientist at the Department of Physiology & Biophysics at Dalhousie University in Canadian city of Halifax. Through his scientific team (dr. Brian Hoyt, dr. Cindy Penney, dr. Paul McInnis), and students (Clyde Clements, Kim Simelius), I became familiar with technologies that would have otherwise stayed obscure to myself. Also, my stay in Halifax would not be possible without initial funding from the Czech Society of Cardiology.

Acting like clinician and scientist brings many issues in personal and family life, which I am grateful to have fully fledged thanks to my wife Monika. Therefore, this work is also meant to be a faint reward for her patience and my children's Martin and Markéta understanding of their father being too much at work rather than taking care of the challenges of their young lives. To them, for being my closest company, I thank so much wishing for myself to become better father and husband for the rest of my career. Also, to anyone whom I undoubtedly and unwillingly forgot to express my thanks in this text, I apologize for it.

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Petr Šťovíček

List of key publications constituting the thesis

I. Stovicek P, Stojan M, Kasalicky J, Vondracek V, Vojacek J, Linhart A, Anger Z: Analysis of ventricular activation in patients with chronic non-Q wave myocardial infarction: comparison with left ventricular asynergy and myocardial perfusion defects. Physiol Res 1993;42(2):109-17.

II. Stovicek P, Anger Z, Aschermann M, Kasalický J, Kittnar O, Valová O, Vondráček V.: Time and spatial scanning of the QRS complex by statistical departure technique of evaluation of body surface potential maps in old non-Q myocardial infarction. Proceedings XXIInd Internationl Congress on Electrocardiology Nijmegen, The Netherlands, 25-29 June 1995

III. Šťovíček P., Bultas J., Stojan M.: EKG mapování depolarizace komor při reverzibilní ischemii navozené koronárním spasmem. Sborník přednášek mezinárodní konference Cardiag'93, Karlovy Vary, 9.-11.11.1993.

IV. Boudik F, Stojan M, Anger Z, Aschermann M, Vojacek J, Stovicek P: Evaluation of body surface potential mapping changes after successful percutaneous transluminal coronary angioplasty. Can J Cardiol 1996 Aug;12(8):745-9.

V. Stovicek P, Drska Z, Anger Z, Kautzner J., Psenicka M, Tilser P: Singular value decomposition of body surface potential maps and vulnerability to ventricular arrhythmias. HeartWeb, Vol. 2, No 1 November 1996, Article No. 96110009, http://www.heartweb.org/heartweb/1196/ep0006.htm

VI. Stovicek P, Drska Z, Anger Z, Psenicka M, Tilser P, Kautzner J.: Singular value decomposition of body surface potential maps and vulnerability to ventricular arrhythmias. Abstracts, 10th International Congress Cardiostim 96. European Journal of Cardiac Pacing and Electrophysiology, Supplement 5, Vol 6, Number 1, June 1996:p88

VII. Stovicek P, Gardner MJ, Mitchell LB, Burns MA, Sterns LD, Warren JW, Horacek BM: QT dispersion in 120 electrocardiographic leads in patients with structural heart disease. Pacing Clin Electrophysiol 2002 Jan;25(1):20-31.

VIII. Stovicek P, Gardner MJ, Mitchell LB, Burns MA, Sterns LD, Warren JW, Horacek BM: Spatial determinants of QT-dispersion on the body surface. Eur Heart J Suppl, 22:146, Sept 2001

IX. Horacek BM, Warren JW, Stovicek P, Feldman CL: Diagnostic accuracy of derived versus standard 12-lead electrocardiograms. J Electrocardiol 2000;33 Suppl:155-60.

1 Introduction and overview of methods

Electrocardiography has come a long way from its beginnings more than hundred years ago but keeps going as rather a simple clinical tool requiring most of the insight on the side of human imagination and through a set of parameters that are too simple to describe the underlying complexity of the heart electricity. Despite perhaps stagnation or very slow progress, electrocardiography has maintained its principal and indispensable role in clinical practice for decades. Barely any clinical algorithm of diagnosis or treatment of cardiac disorders could stand without electrocardiogram (ECG) as an early simple and noninvasive step undertaken by any physician. Let us think of at least reperfusion therapy of myocardial infarction, detection of exercise induced ischemia, or arrhythmia diagnosis. However elaborate qualitative and quantitative diagnostic criteria clinicians and investigators have ever used to detect various pathological states, most of these are based upon clever and physically sound deduction of early electrocardiographers and later empirical evaluation of vast amount of data from comparative clinical series and trials. [1] Only recent arrhythmia recognition algorithms have been introduced as a product of systematic comparisons of invasively acquired intracardiac electrograms and maps together with more or less synchronous surface ECG tracings. [2,3]

Parallel attempts to analyze electrocardiogram on its physical and mathematical basis have been in place since the beginning of this technique. Early investigators derived their imagination of the electrical field of the heart from the physics of dipole applied to the whole organ of the heart. [4] Later development of body surface potential mapping (BSPM) technique and advances in physiology and biophysics of the heart made clear that the source of the electrical field is a complex structure that undergoes dynamical changes both in time and space throughout the cardiac cycle. [5,6] This level of complexity cannot be appreciated from simple 12-lead scalar tracings of the common ECG. There are several reasons for this. First, the choices of the leads by Einthowen and later Wilson were more or less empirical, based on practical aspects of clinical usefulness and strong belief in the dipolar character of the current source. The ultimate simplification of the problem resulted into the Frank's development of vectorcardiogram (VCG) that has remained in place as rather a didactical accessory of electrocardiography promoted also by Czech scientist Vilém Laufberger [7,8]. Second, the volume conductor surrounding the current source is also rather complex in shape and other physical properties than just a barrel filled with saline water. Third, mutual geometry of the torso and heart surfaces determine the ECG significantly, which relationship is not appreciated in clinical algorithms. In the realm of cartography, physics, and technology, irregularity and complexity is usually approached by mapping and reconstruction techniques. Wilson who later introduced 12-lead ECG perceived well these issues and added irregularly placed chest leads on the torso close to the heart to bring some of the intuitive mapping into the clinical practice. [9] Modern invasive arrhythmology in order to target arrhythmia sources accurately with radiofrequency ablation addresses these complexities carefully. The need to reconstruct accurately the shapes and other properties of arrhythmia circuits and morphological substrates that give a framework for these structures is demonstrated by sophisticated technologies and systems like electroanatomical mapping (CARTO™) [10] and forward solution calculations (EnSite™). [11] These quickly assumed its place in the routine clinical practice together with advanced anatomical reconstructions provided by magnetic resonance imaging (MRI) and computer tomography (CT). [12]

BSPM, so far, has been the only applicable noninvasive technique that approached electrical heart field with respect to its entirety and completeness. Technological complexity and in some circumstances true clumsiness of the method requiring large numbers of electrodes on the body surface precludes its widespread clinical use that is not readily outweighed by the diagnostic gain as compared to the routine ECG. Nevertheless, its informational content is not compromised and therefore is suitable as a research tool. We have used BSPM in our laboratory to evaluate some of the clinical states that can demonstrate the increment of its diagnostic ability over standard ECG in detection of global and local ischemic changes. [Publications I-IX] Since ischemia may translate into the electrical forces in different and often composite ways, we divided the topic with respect to the depolarization and repolarization changes and respective diagnostic criteria, and also conventional and advanced algorithms of analysis. Ultimately, we consider our research and a number of other BSPM studies in the literature to be just a step towards accurate analysis of electrocardiogram that may perhaps reach a level of new diagnostic imaging technique – Electrocardiographic Imaging (ECGI). [13,14] Such technique is not conceivable without using high performance computer technologies and algorithms together with simulation and modeling. Essential steps of building heart model and simulation techniques are so called *inverse* and *forward calculations* (*solutions*). [13,15] Also, the use of advanced imaging techniques like ECG-gated multidetector CT (MDCT) or cardiac MRI may turn a prerequisite for successful clinical solution of these mathematical algorithms. [16]

1.1 Electrophysiological basis and clinical aspects

Impact of ischemia on electrical functions of the cardiac cell and tissue is complex and well described at the level of ionic currents and ultrastructural/metabolic changes. [17,18,19] Since electrical heart field is a direct extension of the cellular electrophysiology, all these changes get reflected in different aspects of ECG. The degree of the ischemic distortion of ECG is a function of severity of ischemia ranging from mild and transient functional impairment to the complete loss of action potential (AP) often but not always signifying the death of the cell. Decrease of the AP upstroke velocity, decrease of the AP amplitude and changes in AP duration (APD) are the notoriously known and well described cellular electrical effects of ischemia. These result into a slower AP propagation or even loss of conduction through the tissue seen as changes of the QRS complex and into the *current of injury* demonstrated by shifts of ST segment (elevation or depression) and T-wave distortions. [20]

Myocardium is a complex compound of 3 billions of cells organized into a spatially defined structure; therefore ischemic changes follow the geometry of the myocardial substrate. Even without ischemia, the geometry of myocardium and distribution of electrical connections among cells together with a synchronizing effect of cardiac conduction system dictate the principal features of the electrical field. *Anisotropy* defined as unequal spatial distribution of conduction velocity following the long axis of cardiac myocytes is the most thoroughly studied factor. [21] It is known to have background in the nonuniform distribution of *gap junctions* that are clustered mainly at intercalary discs rather than at the side-to-side intercellular connections where they have been observed scarce. [22] The whole group of cardiac *connexins* that has been recently identified constitutes the structural basis of myocardial electrical conduction and gap junctions and their dysfunction or destruction results in arrhythmias. [23] *Electrotonus* to certain extent follows anisotropy, because of its dependence on electrical intercellular coupling. It is commonly described as modulation of AP by the passive electrical properties of the cell membranes and intercellular coupling causing essentially a sort of damping of the individual AP by the surrounding and prevailing

cellular mass. This is a very important feature underlying electrical stability and cohesion of myocardium and disorders at the level of the cellular coupling may lead to uncontrolled firing of the individual cells or groups of cells causing arrhythmias. [24] Cellular mechanisms of *abnormal automaticity, early* and *late afterdepolarizations* (together called *triggered activity*) have been thoroughly studied in the cellular and tissue preparations same as *reentry* as a tissue-related mechanism. [25] All these mechanisms and features play significant role in modulation of ECG and in arrhythmias in the setting of cardiac ischemia. Scalar ECG is incapable of demonstrating anisotropy, whereas body surface maps of the QRS complex display trajectories of potential extrema related to the ventricular fiber orientation. [26] Some of the indirect features (arrhythmia onset and offset, heart rate related features) may hint to the specific arrhythmia mechanisms in the scalar tracing of ECG, but they are often too unreliable. On the other hand, macroscopic reentry can be easily distinguished from focal arrhythmias (mostly caused by automaticity or triggered activity) by clinical endocardial mapping (CARTO™, EnSite™). [27,28] If ECGI could similarly reconstruct at least the major features of arrhythmias at the level of the anatomically defined heart surfaces, this could be another significant progress due to BSPM as a precursor of ECGI. Also, spatial resolution of BSPM was studied in detail by systematic pace-mapping of the endocardial surface of all four chambers of the heart leading to atlases of maps identifying the location of focal activations. [29,30,31] The resolution of 3.3±1.4 cm² (LV endocardial pacing) and 6.7±2.9 cm² (RV pacing) could not be matched by standard ECG. [32]

Factors governing ischemic injury are known to take place that have to be taken in consideration for mathematically and physically correct analysis. Cardiac ischemia is usually more pronounced in subendocardium than in subepicardium and this gradient of changes depends on the severity of blood supply diminution and the location of the atherosclerotic stenotic lesions or obstructions within coronary arteries. The location of these lesions determines the topography of the ischemic current source. Therefore, knowledge of the anatomy of the coronary artery tree significantly improves understanding of ischemia on ECG. Also, most of ischemic attacks affect left ventricular (LV) myocardium rather than right ventricle (RV) or atria but it does not spare the latter ones. Often a number of ischemic loci coincide within a single heart, leading to a combined effect that is in terms of electrical field a vectorial addition (see below). The loci may undergo disparate developmental changes that is a consequence of their sometimes differing age; one infarction may be remote, other recent. [20]

Loss of AP, conduction slowing or block of propagation cause changes in vector representation and constitute newly established balance of the depolarization forces leading to the changes of QRS complex. These are widely recognized as infarction Q-waves, changes in QRS duration (QRSD), and other less specific QRS changes. [20] We studied the less specific changes (minor potential losses) in a population after remote *non-Q myocardial infarction* (NQMI), because they represented a group where diagnostic increment of BSPM in comparison with standard ECG could be demonstrated clearly at the level of clinical data (minimal or no changes within QRS complex of 12-lead ECG). We approached the problem with statistical analysis of the body surface maps and also by computerized time and spatial scanning throughout the whole QRS complex in order to find criteria that best identified regions of abnormal depolarization. We related those regions to the presence of wall motion abnormalities defined on echocardiography or ventriculography and to the perfusion defects detected by nuclear imaging. [Publications I-II] Also, we studied a small group of patients with vasospastic angina in order to detect depolarization changes that might be a correlate of transient severe conduction changes opposing a common clinical perception of Q-waves being

an exclusive marker of irreversible ischemic destruction of the myocardial cells. [Publication III] Also, necrosis, scarring, and survival of cardiac cells often combine into a mosaic structure within the infarction lesion causing disparate and slow conduction through the surviving strands of muscle. These are known to mediate reentrant ventricular arrhythmias that are the most dangerous with regard to prognosis and sudden cardiac death of patients with coronary artery disease. [33] The electrical activity of surviving bundles have been successfully and reproducibly extracted from surface ECG by a technique called *signal averaging*, that was originally designed as a general algorithm for effective noise reduction. [34] They were also successfully matched with synchronized intracardiac recording of the diastolic potentials taken directly from endocardial spots displaying features of scarring. [35] These recordings represented attempts to use clinically cardiac *micropotentials* (in order of microvolts) in the form of so called *late potentials*. Therefore, other group of patients that we studied was a postinfarction population regardless of presence or absence of pathological Q-wave that we addressed with BSPM with respect to the prevalence of depolarization micropotentials. We compared conventional late potentials extracted by the technique of signal-averaged ECG (SAECG) with one mathematical approach called singular value decomposition (SVD) that we applied to the body surface maps to extract *single-beat late potentials*. [Publication V and VI]

Myocardial ischemia has been always described as an acute and rapidly evolving event, ranging from dynamic *coronary insufficiency* to the development of irreversible acute myocardial infarction. Later, clinicians and investigators described chronic long-term oxygen starvation of the myocardium frequently termed *hibernation* specifically when viewed as a chronic mechanical dysfunction of the ventricular myocardium. [36] Only in the late decades, with the advent of revascularization surgery and percutaneous techniques of mechanical dilatation of the atherosclerotic vessel narrowing or obstruction (percutaneous transluminal coronary angioplasty, PTCA), were the proofs laid of the contractile function recovery after such successful procedures. [37,38,39] Spontaneous Q-wave recovery had been recognized clinically even before that, [40] and BSPM studies of the remote Q-wave infarctions quantified and described accurately these ECG changes. [41] We studied a group of patients who underwent PTCA of a single or multiple significantly stenosed coronary arteries mostly causing chronic angina in order to identify eventual sequential potential changes in the several-month course after the PTCA. [Publication IV]

APD can be either shortened or prolonged in ischemia, leading to the respective QT interval changes and T-wave distortions. Both short and long QT is known to be arrhythmogenic especially if disparate, leading to a condition commonly termed *dispersion of repolarization*. [42,43] Some authors tried to implicate dispersion of repolarization as an underlying cause of dispersion of QT interval (*QT dispersion*, QTD) a simple ECG parameter readily available for clinical practice. [44] We analyzed QTD in one predominantly postinfarction population in several ECG lead systems starting from Frank orthogonal XYZ leads to a complete BSPM lead set in order to characterize its nature, error performance, and dependence on the method of measurement. [Publications VII and VIII] The QTD has been refuted repeatedly by other authors as substantially erratic [45] which aspect we could also address with our study.

None of the cellular and pathophysiological mechanisms gets translated into the ECG tracing directly. For example, the spatial extent or size of ischemic regions leading to a distinct geometry of the ischemic current source determines the resulting changes of the electrical field. All of the aspects mentioned above are known to interplay and create a composite effect on ECG modulated substantially by biophysical factors (see below). It is, therefore, hard to

conceive that simple scalar tracings of ECG can readily yield all this intermingled and often confusing information. Standard electrocardiogram represents only time course of potential sampled at selected points of the electrical field. The vast and redundant number of criteria accumulated in the history of electrocardiography as a diagnostic technique for clinical practice is a consequence of such complex nature of the electrical heart field. Many of them due to inaccuracy and lack of sensitivity or specificity like voltage criteria for left ventricular hypertrophy get gradually discarded with the advent of other diagnostic modalities. Imaging techniques like echocardiography, X-ray angiography or later computer aided technologies of CT or MRI or nuclear imaging have much better diagnostic ability to detect morphological abnormalities thus contributing significantly to the demise of ECG in this field. This fact may lead to a perception of electrocardiography as a technique that has already reached its zenith and with little chance for further improvements. Nevertheless, the situation may not be necessarily such an impasse. The advanced computer technology opens the door for further development of electrocardiography, possibly giving a chance for new electrophysiological imaging technique that could marry for example recent morphological imaging with advanced bioelectrical field analysis techniques like inverse and forward solutions. [13]

1.2 Biophysical factors

Factors of biophysics play critical role in the genesis of the electrical heart field and ECG. They can be divided into the biophysics of the current source and of the surrounding volume conductor.

In early days of electrocardiography, the idea of potential origin and distribution was of a simple dipolar or moving dipole character. [4] Exclusive *vectorial physics* of the field, however physically and mathematically correct, lead to the idea of vectorcardiography based on reduction or lumping of all content of the field into a single representative moving vector detected entirely by orthogonal 3-lead or modified ECG lead system. [7,8] The only biophysical irregularity that this technique has acknowledged was eccentricity of the current source within the torso, and some VCG lead systems have provided electrical correction for it. BSPM on the contrary first demonstrated patterns compatible with rather a complex structure underlying the measured distributions. [5,6] By covering the chest surface with more or less complete electrode array it has been capable to reconstruct shapes of the electrical field projected on the outer surface of the volume conductor. Moreover, as an exclusively computerized technique from the beginning, it has offered variety of options for data display, compression, processing, and potential for further development, esp. in binding to the more extensive computer analysis. Nevertheless, the effects of *electrical shunting* or *short-circuiting* coming from the surrounding conductive media leading to the loss of information was clearly recognized, further supporting the stance of dipolar content and its sufficient reflection by limited ECG or VCG systems. Furthermore, vectorial concept also identified and rationalized obvious *cancellation* of opposite electrical forces possibly leading to a complete loss of some potentials, that could be otherwise measured only invasively. [46,47] Other basic biophysical principles as *solid angle theorem* or potential decay (voltage) along the measuring axis (*lead field theory*) have helped substantially to understand the resulting measured potentials with regard to the suspected processes within the current source. [48] Many experiments with elementary or more complex sources in a homogenous and controlled heterogeneous *volume conductor* supported the view of complex structures determining the surface potential patterns. [21] However, only recent experimental works on the complex and physically scalable model of electrical heart field coming from laboratories employing a beating heart immersed in a human torso phantom confirmed applicability of these

fundamental theories. Also, by virtue of simulation and modeling, these experiments demonstrated that substantial part of electrical information stays conserved in the body surface potential distributions and can be recovered towards real anatomical structures of the heart. Carefully steered experimental trials also separated the issues of torso conductivity inhomogeneities from the influence of mutual geometrical relationships between the body surface and cardiac surfaces (equivalent current sources) showing that the geometry and cardiac conduction anisotropy influence the ECG signal more then the diverse conductivity of the volume conductor. [49,50,51,52] These are the most convincing results supporting a potential role of BSPM as a step toward clinically applicable ECG imaging.

ECG or BSPM alone cannot separate factors originating at the level of source from the effects of surrounding conductor. On the top of that, the conductor is not a simple homogenous media but a spatially curved volume conductor that is complex and heterogeneous. However, BSPM already possesses at least a capability to relate e.g. some spatial distributions of interest (regions) towards the heart more readily than simple ECG tracings. Also, by covering the entire chest, BSPM can logically capture some information that could be inadvertently and irrecoverably lost by limited lead systems. [53, 54] In our series, we could demonstrate diagnostic gain by detecting e.g. missed infarction Q-waves that have been well known to clinicians as Q-waves detected in additional ECG leads (V2R-V6R, back-torso leads). [55,56] We could also relate the regions of minor loss of potential spatially to the perfusion defects or to the wall motion abnormalities. [Publication I]

Only advanced computerized discretization techniques of reconstruction of morphological data with the electrical information parameterized by and superimposed on the real anatomy can attribute all the above mentioned factors to the real structures. The techniques of MDCT or MRI can for example reconstruct real boundaries of various components of the passive volume conductor, and, at the same time, yield the framework for equivalent current sources in terms of cardiac surfaces. The most advanced techniques of MRI, so called *diffusion weighted images (DWI)*, can already disclose some of the structural details of myocardium such as ventricular fiber architecture that, in turn, could serve as a framework for computations of the heart model reflecting real individual cardiac anisotropy. [57] Reconstructed endocardial surfaces might at the same time already serve as a target structures for the specialized clinician – for example cardiac electrophysiologist.

1.3 ECG lead systems, transform calculations

BSPM is by far cumbersome technique with respect to the level of diagnostic gain it has provided to the clinicians so far. The number of leads used in various recording matrices in the research laboratories has ranged from 32 to 384. [49,58,59] Research into the number of independent signals and consequently number of independent leads necessary to faithfully reconstruct the body surface part of the entire electrical field narrows it down to around 60. [60,61] These numbers reflect mathematical interpretation of BSPM without knowledge of the underlying current sources and volume conductor. At the same time, studies show that lead system actually can be reduced drastically without significant loss of critical features of the potential maps and scalar ECG deflections in the same individual. [58] However, these data cannot be simply transferred to an independent subject and across different underlying pathological states, since it is known that these variables significantly influence the computations. Therefore, effort should be undertaken to elucidate factors that must be respected and perhaps investigated in each individual when trying to reduce the lead system into a clinically useful diagnostic tool. Our study demonstrated feasibility of one transform

calculation within postinfarction population. [Publication IX] This was conducted in an effort to find transform coefficients that could constitute a framework for a simplified and small regular grid of electrodes (EASI lead system) applied to the patient chest with the aim of mathematically reconstructing 12-lead ECG without loss of diagnostic postinfarction features like pathological Q-wave.

1.4 Concepts of data acquisition and body surface potential mapping

We described the BSPM recording systems in detail in individual studies that are presented in this thesis. Basically, two different hardware and software solutions have been used depending on the lab where the author conducted or participated in the studies. Both offer fully computerized and synchronous recordings from tenths to hundreds of electrodes, signal sampling, and various types of display of scalar signals, vectors and maps depending on the custom software. They differ mainly with respect to the electrode matrix covering the chest and some features of the electronic circuitry of amplifiers, digitizing electronics, computer resources, and interpolation techniques used for map display. The Dalhousie University laboratory at the Department of Physiology & Biophysics employs 120-lead matrix covering larger percentage of the human torso then the 80-lead system at the Charles University, Department of Medicine II. (Fig 1, Fig 3) The main difference, however, is that the Dalhousie matrix is firmly incorporated as an input for ECG data for entering the *Heart & Torso* computer *model*. (Fig 2) The torso (Fig 3) is represented as a tessellated surface, discretized into 700 triangles (triangularized surface) and thus constitutes a certain type of *standard torso*. The electrode positions are at firmly defined points that are located at the vertices of the triangles. Interpolation technique for map construction utilizes 3-dimensional properties of the torso [62] and was also the basis of the lead transformation study [Publication IX] and for 3D representation of maps in this thesis. The Heart & Torso model represents the connection between BSPM and the computer modeling and simulations that are mentioned throughout this text. The model for example allows for immediate calculation of epicardial potential maps from the BSPM by means of inverse solution based on *finite element method*. [15,16] In this thesis, the Dalhousie system helped in studying the QT dispersion on the body surface.

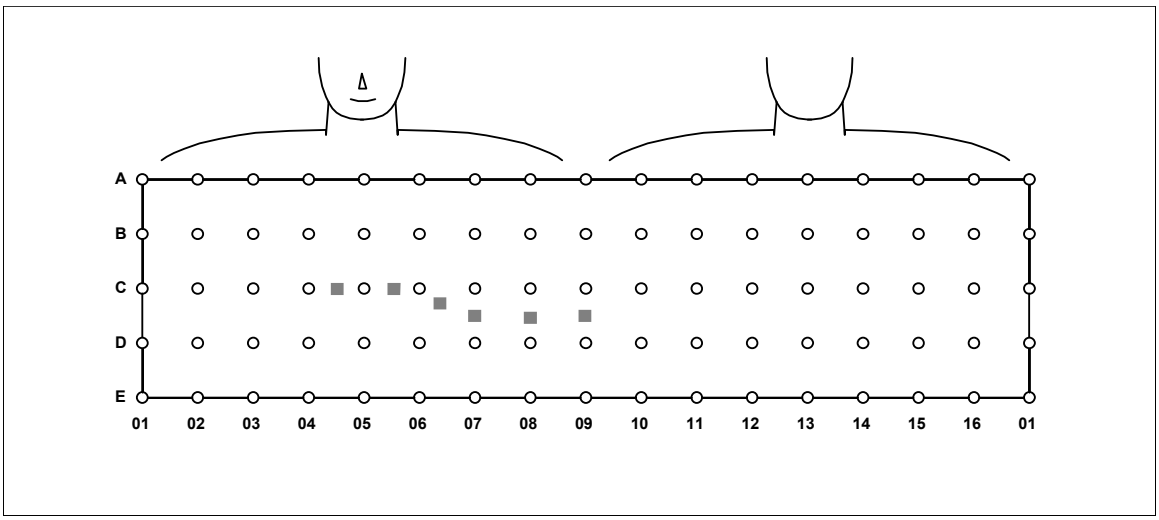

Fig 1 Regular 80-lead BSPM matrix as used at the Department of Medicine II, Charles University. Circles represent the lead points, squares denote standard precordial leads points V1-6 that are measured through dedicated electrodes. Details of the map interpolation and display are available in individual publications.

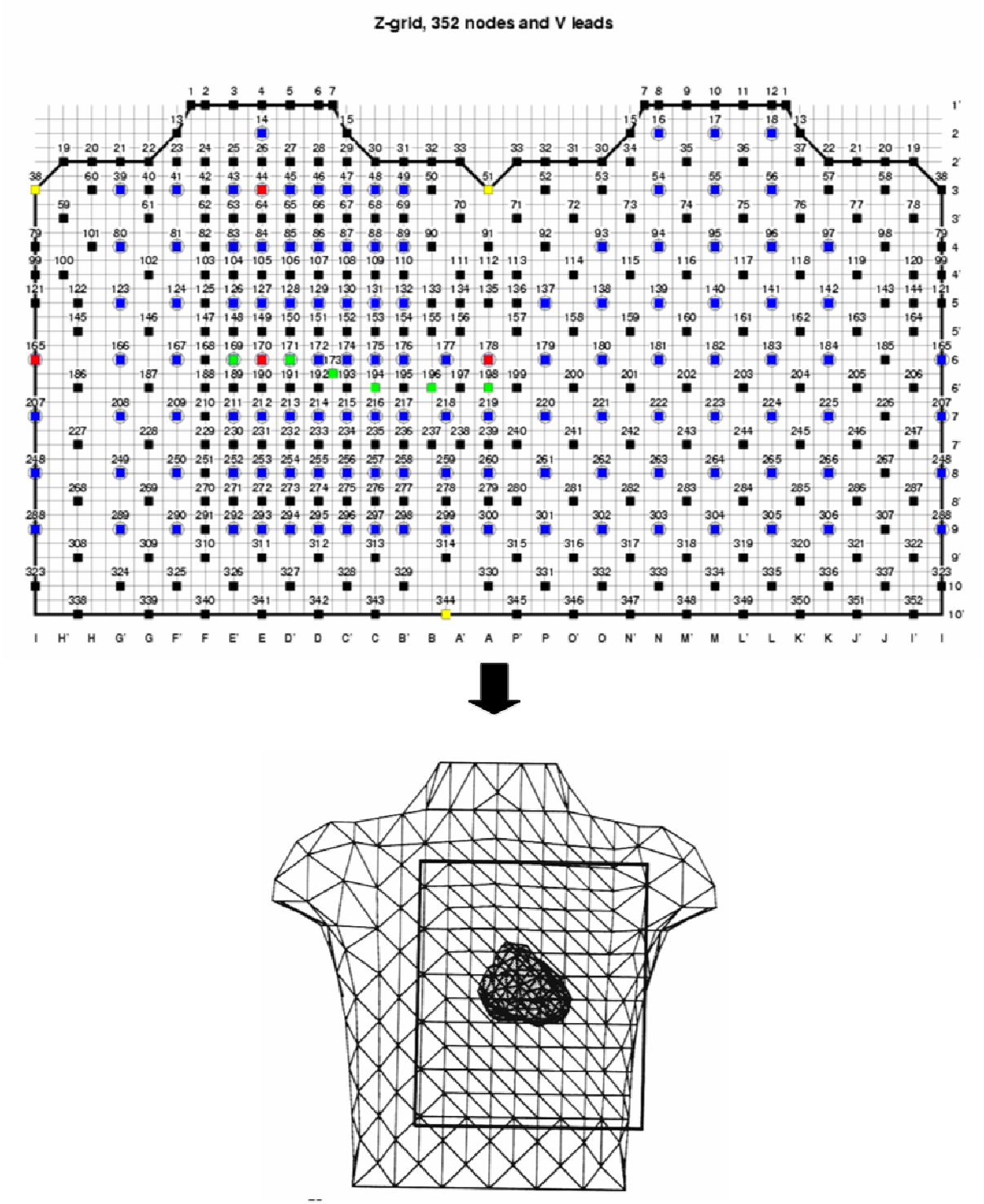

Fig 2 Dalhousie BSPM matrix (upper panel, left half – front, right half – back) features lead points (circles) together with the 352 nodes of the standard torso (all numbered squares correspond to the vertices of the triangles of the standard torso, lower panel). Encircled blue, green, and red squares represent measured BSPM lead points where data acquisition is performed. Green squares correspond to the precordial leads (V3-6 are not measured but interpolated), red and yellow to the EASI lead system (see text and Publication IX on lead transformation). Of notice is the higher density of sampling in the precordium. The Dalhousie Heart & Torso model where the torso and ventricular epicardium are represented as tessellated triangluarized surfaces provides also interpolation of the body-surface and epicardial maps and features inverse calculation and allows for lead transformation algorithms.

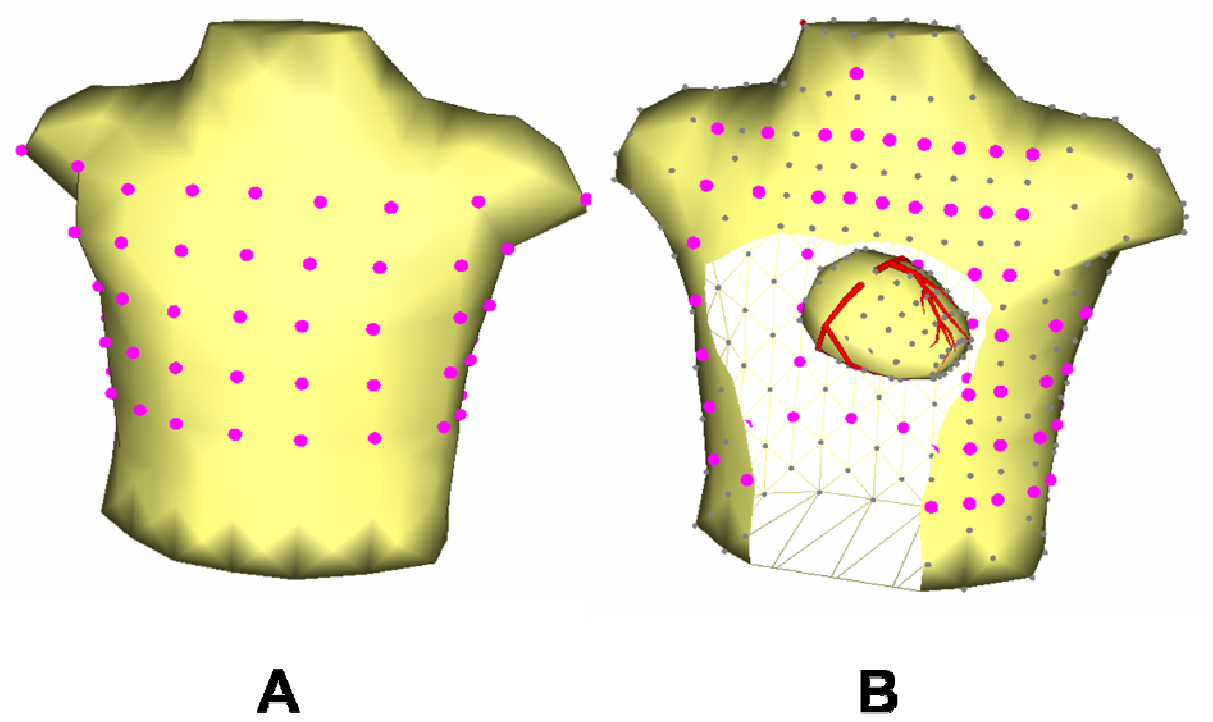

Fig 3 Anatomical/geometrical features of the Dalhousie Heart&Torso as displayed by map3d software from University of Utah [140] represents an example of compact solution for computer modeling and simulation, exploration of the lead systems and - by connecting electrical and anatomical information – one possible tool for electrocardiographic imaging (see text). Tessellated anatomical surfaces can be fitted or superimposed with physiological data such as electrical potential or other scalar data. Data from Charles University BSPM lead system (panel A, lead points colored in magenta) that covers smaller percentage of the torso surface can thus be displayed in 3D space. Data from Dalhousie lead system (panel B) as an integral part of the model (see Fig 2) allow for the whole torso-surface and epicardial interpolation and display of the BSPM. Coronary arteries (red-colored symbols) can be displayed as landmarks on the epicardial surface to allow e.g. for spatial analysis of inverse-calculation computed ischemia-induced electrical changes. [63]

1.5 Data analysis

1.5.1 Pattern recognition

Generally, the simplest way of analyzing measured data is by exploring visible qualities through pattern recognition of the maps, similarly as we do with the scalar ECG waveforms. The advantage of BSPM is its dominant capability to display spatial features of the electrical field in terms of shapes of isopotential, isointegral/isointerval lines, locations of extreme values and their trajectories throughout the cardiac cycle. These features represent the means of increased sensitivity for detection of ischemic or postinfarction changes. [54,64,65,66,67,68,69,70,71,72] We used qualitative pattern description in small series of patients with vasospastic angina. We recorded changes of repolarization and depolarization in the maps in patients during provocation of ischemic anginal pain, and found them better pronounced in the maps than in standard scalar 12-lead ECG in accordance with studies that demonstrated these changes during PTCA. [63,73,74,75,76] [Publication III, Fig 4]

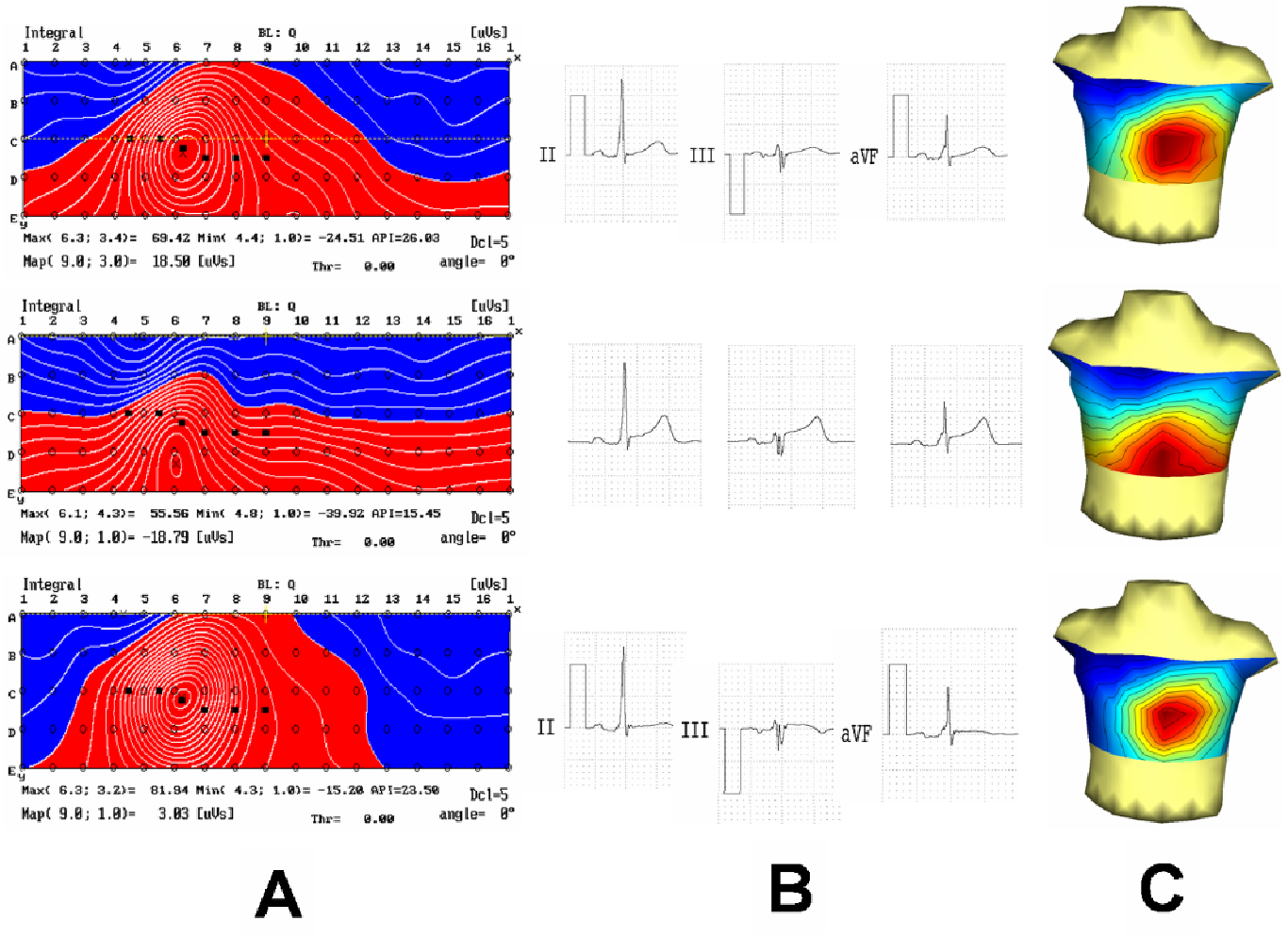

Fig 4 T-wave isointegral body surface maps (panel A and C) recorded before (top), during (middle) and after (bottom) provoked episode of anginal pain caused by spasm of right coronary artery (RCA) in the patient with dynamic narrowing of RCA (superimposed on mild to moderate atherosclerotic stenosis – a common manifestation of Prinzmetal angina) relieved after sublingual nitroglycerin. In panel A, positive voltage is in red and negative in blue colors. While there is a clear global change of maps during ischemia, the 12 lead ECG changes represented by inferior leads are not very dramatic (panel B). In panel C, map3d representation of the maps gives spatial and anatomical body-surface appreciation of the global ischemic changes. Potential distribution is rather color-graded and the interpolation is limited to the range of the electrode array since the 80-lead system is not mathematically incorporated into the Dalhousie model.

Also, we evaluated global features of maps in the post MI patients and in the individual QT interval maps in the QT dispersion data set similarly as others in the literature. [77,78,79,80,81,82] [Publications VII and VIII].

1.5.2 Statistical analysis

Statistical analysis has been employed in many studies and was applied in this thesis to directly visualize areas of potential values differing significantly (outside 2SD interval) from the mean values of control group of patients. Namely, areas of potential loss too small to cause infarction Q waves and Q-waves outside the scope of 12 lead ECG were the target of this kind of analysis. [53,54,67,83] At the same time, these areas could be easily attributed to the underlying pathology due to their spatial distribution using imaging techniques (echocardiography, contrast ventriculography, nuclear perfusion imaging) as a reference. [Publications I and II] Also, we evaluated the diagnostic robustness of potential losses in terms of sensitivity and specificity by calculation of receiver operator characteristics (ROC) [84] with regard to the extent of time integration of potentials. Various incremental time intervals within QRS complex starting from isopotentials (discrete instant of time) until the entire QRS isointegral values were inspected systematically for the presence of respective areas of potential losses and their diagnostic values. We called this technique Time and Spatial Scanning of the QRS complex. [Publication II]

In the QTD study, we computed mean QT interval maps and correlation coefficients between maps in an attempt to explore potential role of underlying pathological processes (presence of previous MI, [85] location of MI, presence of ventricular arrhythmias) in shaping the distribution of the QT interval on the body surface. [Publication VIII]

1.5.3 Mathematical methods

BSPM is inherently well suited for mathematical analysis of the ECG signal. ECG is a compound of various signals differing in amplitude, frequency and spatial complexity. In the literature, the concepts of Fourier transform, wavelet analysis, principal component analysis or similar eigenvector analyses were used to extract components of higher order from ECG or BSPM. In BSPM, again, the main difference is that these higher-order signals represent vectorially and spatially distinct components rather than those from scalar ECG that are defined solely on the basis of frequency and amplitude. [86,87,88,89,90] Techniques like eigenvector analysis, principal component analysis or singular value decomposition (SVD) work mathematically with the entire matrix of potentials. We used the SVD of the BSPM matrix in order to detect low-amplitude and high-frequency signals in the patients after MI similarly as SAECG did for extraction of late potentials. [34,91,92] At the end, root mean square (RMS) signal from the entire set of BSPM leads represented the amplitude of these components at the same frequency range as late potentials. [Publication V and VI]

1.5.4 QT dispersion error performance

Introduction of new parameters in electrocardiography rarely underwent critical evaluation for error of measurement. This has been mostly due to an easy appreciation of the ECG intervals or potential measurements like voltage criteria for hypertrophy or a presence of the infarction Q-wave or ST elevations. Also more robust voltage-time integrals have been used in attempts to increase the diagnostic performance of ECG even though these require rather computer assisted techniques. [93,94] Unlike traditional parameters, QT interval dispersion (QTD) has

rightfully been critically evaluated in the literature. [45] Many investigators made unsubstantiated assumption that QT dispersion measurement is a direct extension of measurement of QT interval, which it is not. [45,95,96] QT interval measurements are usually well reproducible with an acceptable level of accuracy. Unlike QT interval, QTD defined as a difference between the longest and shortest QT within a particular lead system is a relatively small number often about ten times smaller than QT interval with equal or larger absolute error of measurement. Therefore the relative error of QTD measurement is too high [97] and by some authors interpreted even as a source of this erratic variable. [98] The underlying mechanisms of QTD have been discussed and different pathophysiology and biophysics of this phenomena have been suggested. [96,98,99,100,101] We evaluated QTD in various lead systems and also the distribution of QT interval on the body surface in order to assess the relationships between the lead systems, error performance of QTD depending on the lead system, and possibly the underlying mechanisms of QTD. However, the QT interval maps allowed only hypothesizing about the source of QT dispersion. Also, the heart rate correction of QTD was evaluated as a concept previously addressed by authors who found QTD actually independent on the heart rate. [102] [Publications VII and VIII]

1.6 Patient populations involved

We studied different clinically and electrocardiographically defined groups of patients. Details of the control group of normal healthy individuals, patients with variant (Prinzmetal) angina, [Publication III] patients referred to PTCA, [Publication IV] postinfarction patients (post Q-MI and non-Q MI patients) [Publications I, II, V, VI, VII, VIII, IX] and ventricular tachyarrhythmia patients [Publications V, VI, VII, VIII and IX] were published in the individual studies.

2 Overview of results and discussion

Most of the results were published in detail in individual papers and presentations [Publications I-IX]. Brief summary review of the results and heretofore unpublished data are presented in this text.

2.1 Body surface potential mapping - pattern recognition

By visual inspection, we could confirm patterns of relatively homogenous potential distribution during depolarization and repolarization in our data set of normal subjects. The maps displayed generally dipolar or nearly dipolar character with well preserved trajectories of extrema during the QRS complex and relatively stable potential maxima and minima during the T wave. [5,6,103, 104,105,106,107] Right epicardial breakthrough patterns were more or less discernible in the first half of QRS complex in the normal subjects as a previously well described disturbance of the dipolar distribution of potentials [108] and as a clear example of otherwise undetectable information content of electrocardiogram. [64] (Fig 5) Nevertheless, normal findings that have been repeatedly addressed in the literature were not principally sought in the studies of this thesis and therefore were not published in detail. We considered group of normal subjects as rather a validation data set for our mapping technology at Charles University and also for creating a control data set in our studies.

2.1.1 Variant angina

In the study of variant (Prinzmetal) angina, ECG changes due to transient symptomatic ischemia were clearly translated into the repolarization body surface maps. Anginal episodes were provoked in 8 study subjects by cold immersion of hands and face and hyperventilation and subsequently resolved with sublingual nitroglycerin. Repolarization changes on the body surface maps reflected differential changes of scalar waveforms and were observed as displacement of the repolarization maxima towards the leads displaying ST elevation even in the cases that based on scalar readings would conventionally be seen as mild changes (Fig 4). On top of that, depolarization/QRS changes were specifically sought and showed transient widening of the negative areas corresponding to the enlargement of the Q-waves or emergence of new Q waves, often outside conventional ECG leads. These findings were in accordance with severe Prinzmetal angina cases with transient Q waves in 12-lead ECG in the literature. [20] Similarly, areas with baseline rS waveforms often turned into QS. (Fig 6) All of these changes were fully reversible after disappearance of symptoms. We consider the depolarization changes to be a consequence of slowing of activation or even complete local transient loss of action potential and conduction changes at the sites of maximum ischemia similarly to the PTCA-induced ischemia. [Publication III] [109]

2.1.2 Post MI patterns

We could observe principal depolarization and repolarization patterns in the maps of post myocardial infarction patients described in the literature. [77,78,80,81,110,111,112] Areas of loss of potential translated into pathological initial QRS negative depolarization potentials were reliably present in post Q-MI patients. These changes were truly global in the sense of easily discernible displacement of minima and maxima on the initial QRS isopotential and isointegral maps. Generally, areas of pathological negativity copied the location and

occurrence of pathological Q-waves in the scalar tracings, (Fig 7) but also additional extreme potential values could be identified, often outside the scope of 12-lead ECG. Majority of Q-MI patterns included also gross repolarization changes with displacement of ST-T extreme values (maxima and minima). Q-MI patterns were not primarily evaluated in our studies; nevertheless, they represented substantial part of data in Publications V-IX and served for mapping technology validation purposes.

On the contrary, in the non-Q MI patients, the distortions of the electrical field were often less clear and also difficult to interpret in terms of diagnostic patterns. Areas of minor potential losses [83] or Q-waves outside the scope of 12 lead ECG were the principal target of analysis that proved to be optimally treated statistically (see below). This held true especially for posterior and lateral remote non-Q infarctions, where Q-waves were often not generated by infarction at all. In anterior infarctions, "missed" Q-waves could often be seen outside the 12 lead ECG which patterns were obvious on the native potential and integral maps as areas of pronounced and well demarcated areas of initial QRS negative potentials. These areas often just edge into some of the leads of the 12-lead ECG (typically right precordial or apical leads) producing borderline or rudimentary Q-waves, traditionally seen as non diagnostic, since they do not fill the clinically accepted criteria of pathological Q-waves. (Fig 8) Additional leads (V2R, étage leads – i.e. leads placed one intercostal space above or below standard precordial leads) familiar to the knowledgeable clinical cardiologists may reveal these missed Q waves. [Publications I and II]

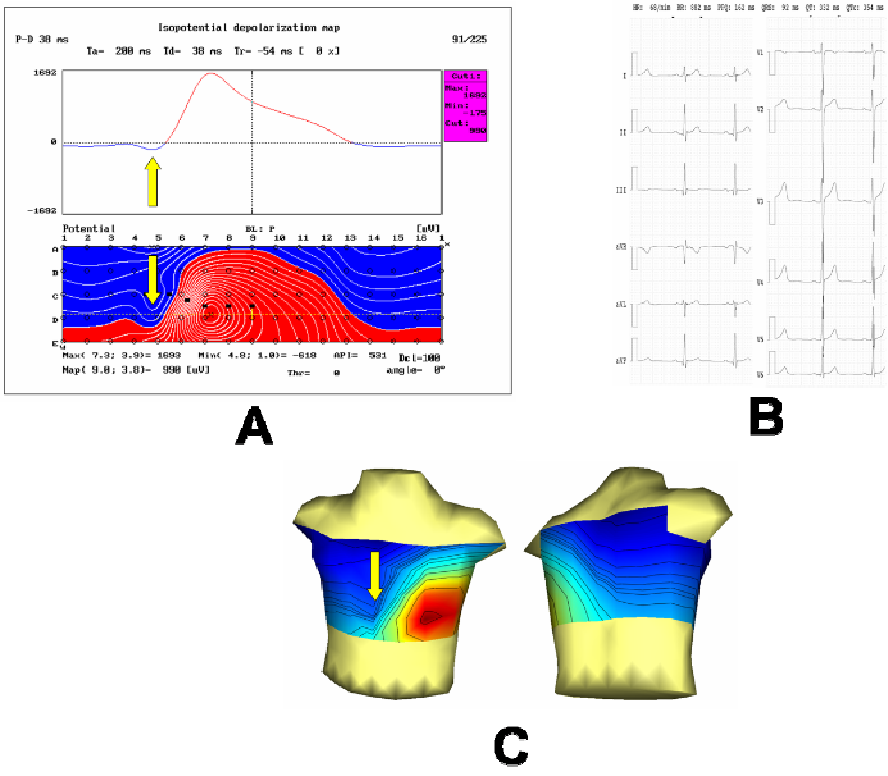

Fig 5 Example of the instantaneous (38. ms) isopotential map of the QRS complex in 22 years old healthy male. A niche of potential (yellow arrow, panel A and C) impinges acutely onto the positive area and actually represents additional current sink that is recognized in comparative studies in the literature as *right epicardial breakthrough* and reflects the instant when the depolarization wavefront reaches the epicardium of the right ventricle near the interventricular septum and also close to the chest surface. [108]This feature is not discernible on the 12-lead ECG (panel B). Otherwise smooth countours and overall near-dipolar distribution is characteristic of normal healthy individuals.

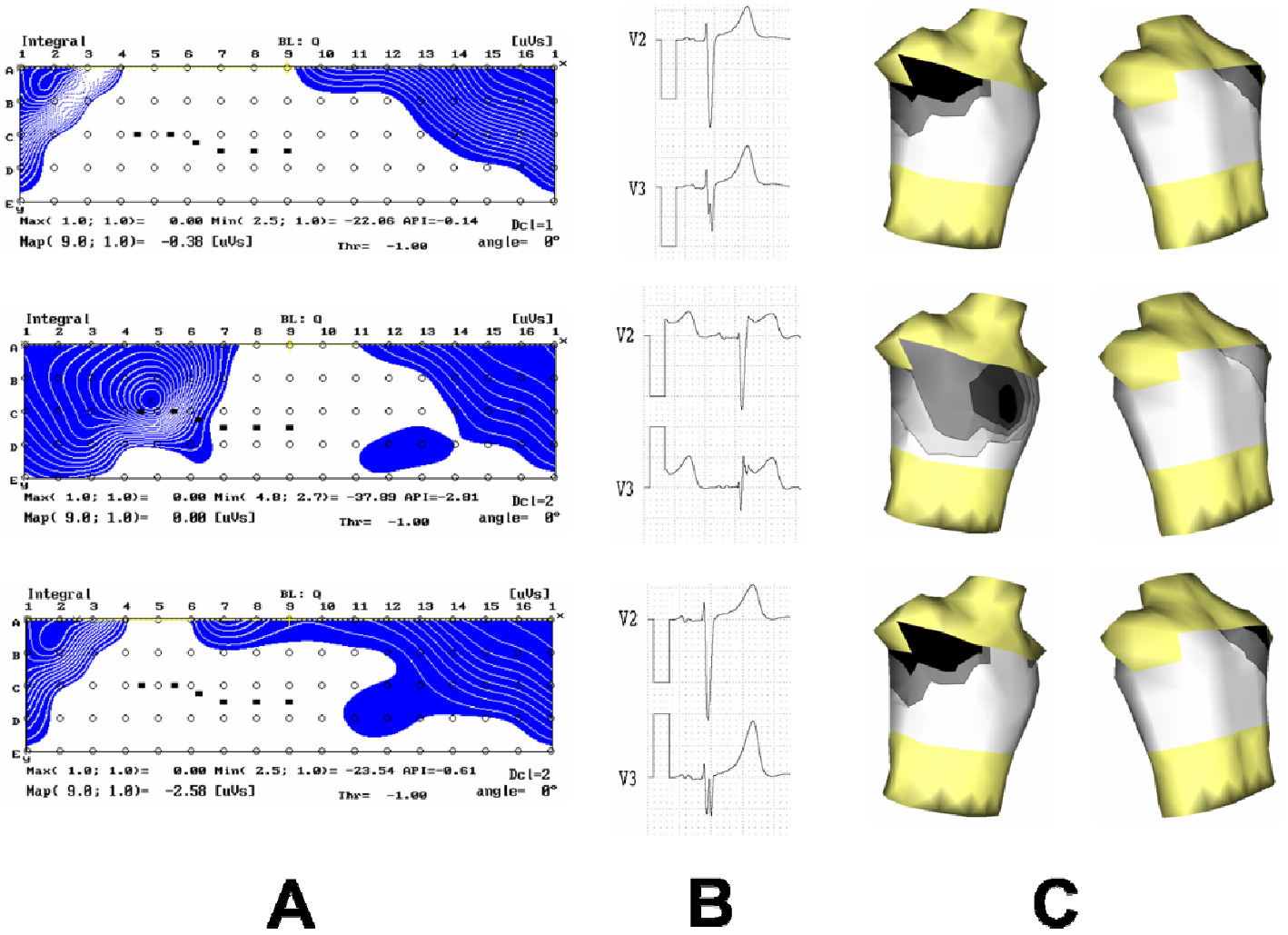

Fig 6 Distribution of the Q-wave integrals on the body surface (Q-wave maps, panel A) before (top), during (middle) and after (bottom) coronary spasm of the left anterior descending artery. Only negative potentials are plotted in blue color on the monochromatic maps. Dynamic nature and reversibility of the Q-wave (see the scalar leads V2,3, panel B) during ischemic episode with transient anterior ST elevations is of note, demonstrating that not only necrosis or loss of myocardial tissue is the underlying cause of the pathological Q-wave. Map3d representations of the same maps (panel C) show the Q-waves in shades of gray and black colors.

2.1.3 QT interval distribution patterns

QT interval represents the entire electrical activation and recovery of the ventricles. It has come to attention of researchers many times in relation to malignant ventricular arrhythmias. The last attempt to find a readily available marker of ventricular arrhythmia risk was that of QT interval dispersion. [44] We sought the distribution of the QT interval on the body surface in order to figure out some principal patterns or possibly the likely underlying mechanisms of QT distribution and dispersion. We studied the QT maps in different predominantly post MI groups of patients with and without ventricular arrhythmias. The QT maps provided fairly chaotic and random, and the patterns did not follow any intra- or inter-group features as expressed by correlation analysis by presence and location of remote MI and ventricular arrhythmia occurrence. [Publication VIII] At the end, averaging inside and across all study groups ended in nearly identical mean distribution patterns showing the longest QT intervals in the precordium. This corresponds to the finding that the longest QT interval was found in lead V2 in one study. [113] Also, the method of T-wave offset detection significantly influenced the QT distribution patterns. Therefore, we think of substantial part of QT interval dispersion as being determined either by extracardiac or simple dipolar (representative vector) principles, which view would be supported by VCG studies (vector loop features) and one BSPM study. [99,100,114] The rest (the random part) of the QT dispersion is most likely due to high error of measurement that was analyzed in the other QTD study and also supported by other studies (see below – error performance). [Publication VII]

2.2 Statistical analysis

2.2.1 Post non-Q MI patients

BSPM is a method very much suitable for statistical analysis. In contrast to the empirical and irregular sampling of the electrical field by 12-lead ECG, BSPM by covering most of the torso provides the opportunity to compare and evaluate statistically electrical information from site to site without or at least minimizing the error of displacement of the leads. By computation of the average maps and subsequent subtraction of individual potential values, we could evaluate point by point and extract areas of abnormally diminished or increased potentials. This technique was not new at the time of our study and was called *departure technique* [83,110,112,115,116,117,118,119,120] and by plotting *departure index (DI)* maps it effectively represented a sort of *statistical imaging*. We found the areas of small potential losses outside the 2SD (standard deviation) limit to correspond quite well spatially to the perfusion defects (sestaMIBI perfusion scans) and local myocardial contraction asynergy as displayed by echocardiography or contrast ventriculography (angiography). Occurrence and significance of these regions of abnormal potentials also depend on their size expressed in number of electrodes and on the amount of integration of potential along the time axis of the scalar electrocardiogram. (Fig 7 and Fig 8) Therefore, we used ROC analysis to elucidate the diagnostic performance of these areas depending on the degree of integration. This technique effectively performed time and spatial scanning of the entire QRS complex for areas with abnormal potential. The ROC analysis (Fig 9) showed 16-ms integrals as the optimum window for evaluation of abnormally decreased potentials within the QRS complex. Instantaneous maps tended to overdiagnose potential deviations, whereas larger time integrals, although more specific, were suppressive toward small potential losses. Such 16-ms window of integration is impossible to conceive with standard analysis of scalar ECG waveforms since it represents 0.25-0.5 mm using usual paper speed and losses of potentials that are not easy to appreciate by visual inspection of the tracing. (Fig 8) Also, in clinical setting, the

accurate electrode placement is hardly secured, therefore, voltage readings that are prerequisite for such analysis and significantly depend on the location on the body surface cannot be performed reproducibly. [Publications I-II] This approach of time and spatial scanning tackled well the statistical and multifactorial nature of postinfarction depolarization changes where experimentally and empirically predicted Q-waves and other postinfarction changes (loss of potential, activation slowing) were a result of the size, location and penetration of infarct lesion into the ventricular wall and resulting/preexisting conduction patterns. [121,122,123] To address the location of the potential loss in relation to the activation we plotted diagnostic performance (sensitivity and specificity) of 2-ms (instantaneous) DI maps against time instant throughout the QRS. (Fig 10) Finally, we combined the 16-ms integrals with spatial information into a set of 6 parameters and predicted the normal/non-q group membership with discriminant function analysis. In an extended data set from Publications I and II, such combined parameters detected the minor loss of potential relevant to the findings from imaging techniques (echocardiography, ventriculography, sestaMIBI nuclear scans) with sensitivity and specificity of up to 70% and 80% respectively.

2.2.2 PTCA patients

In this group of patients (11 male, 5 female, 42-58 yrs) with predominantly single-vessel coronary artery disease (12 pts with left anterior descending, 2 pts with right coronary artery, 1 pt with left circumflex, 1 pt with right coronary artery plus left circumflex), the analysis was aimed at the repolarization (T-wave) changes. Serial BSPMs (13 recordings) were aquired in each individual during 6-month follow-up with subsequent repeat angiography. The principal hypothesis was that gradual restitution of altered repolarization would be detectable over weeks or months after PTCA. [120] We calculated difference ST-T maps between individual pre- and post-PTCA and average normal maps. The resulting area of negativity was then quantified as a sum of potentials and graphically represented as a time course (trend) over the follow-up period. The difference between initial and final sum of negative potentials (delta U) as a simple measure of this trend was then compared between subgroups of patients (t-test). In patients with recurrent angina despite successful PTCA, this value was significantly smaller than in those without angina reflecting impaired restitution of repolarization. Interestingly, there were no significant differences among other subgroups (restenosis vs. no restenosis, MI vs. no-MI, Q MI vs. non-Q MI). However, these results should be regarded with caution because of the small sample of patients and substantial variance in potentials. (Fig 12)

As of now, it is difficult to ascribe these changes to reflect long-term processes of recovery from ischemia or hibernation reported in the literature, since invasive *electroanatomical* data are inconclusive on the side of electrical changes. [38,39] However, since the entire 80-lead matrix was successively reevaluated at the follow-up intervals, higher degree of reliability of signal readings from site to site than in standard clinical 12-lead ECG was obtained and therefore should reflect meaningful changes in the quantified geometry of potential distributions. The level of reproducibility of lead locations in the successive data acquisitions was important also for 12-lead ECGs that were subset readings of maps and served for comparison and approximation of the clinical evaluation. [Publication IV] This is in contrast to the clinical settings where the leads are often placed inaccurately which fact can impair reproducibility of the readings and potentially suppress important changes or produce false positive findings.

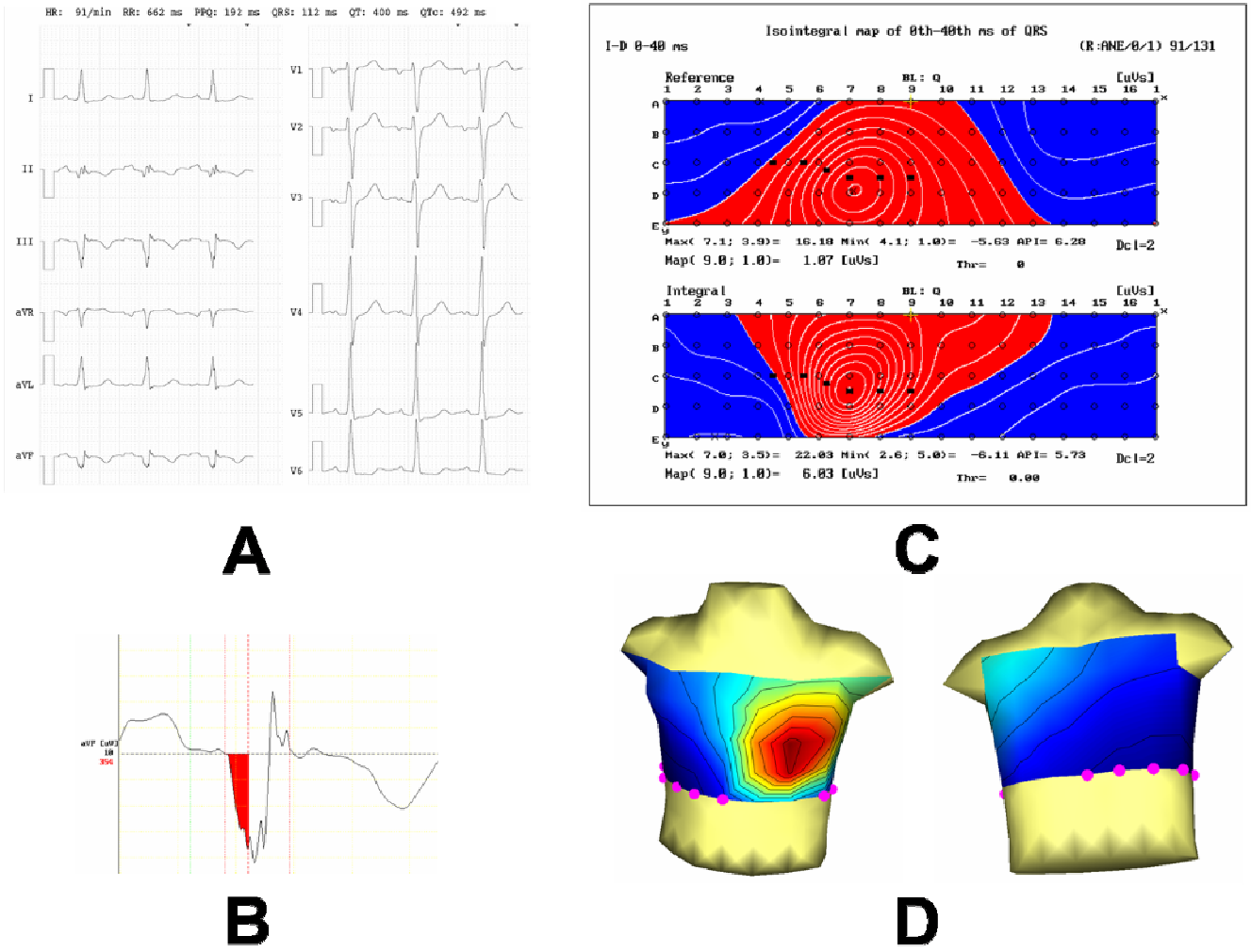

Fig 7 Pathological inferior postinfarction Q-wave clearly visible in the 12-lead ECG (panel A) and zoomed lead aVF (panel B, initial 40 ms integral in red color) in the patient after remote inferior MI. Initial 40-ms individual patient integral map (bottom map in panel C) demonstrate negative potentials (blue) that concentrate on the inferior part of the torso as opposed to the average normal map (top, panel C). The negative potentials translate into the significant loss of potential displayed in the departure index map (here represented in magenta-colored map leads that are beyond -2SD in panel D, see definition in text and Publications I and II). Maps in this patient represent gross depolarization alteration of potentials after Q-MI.

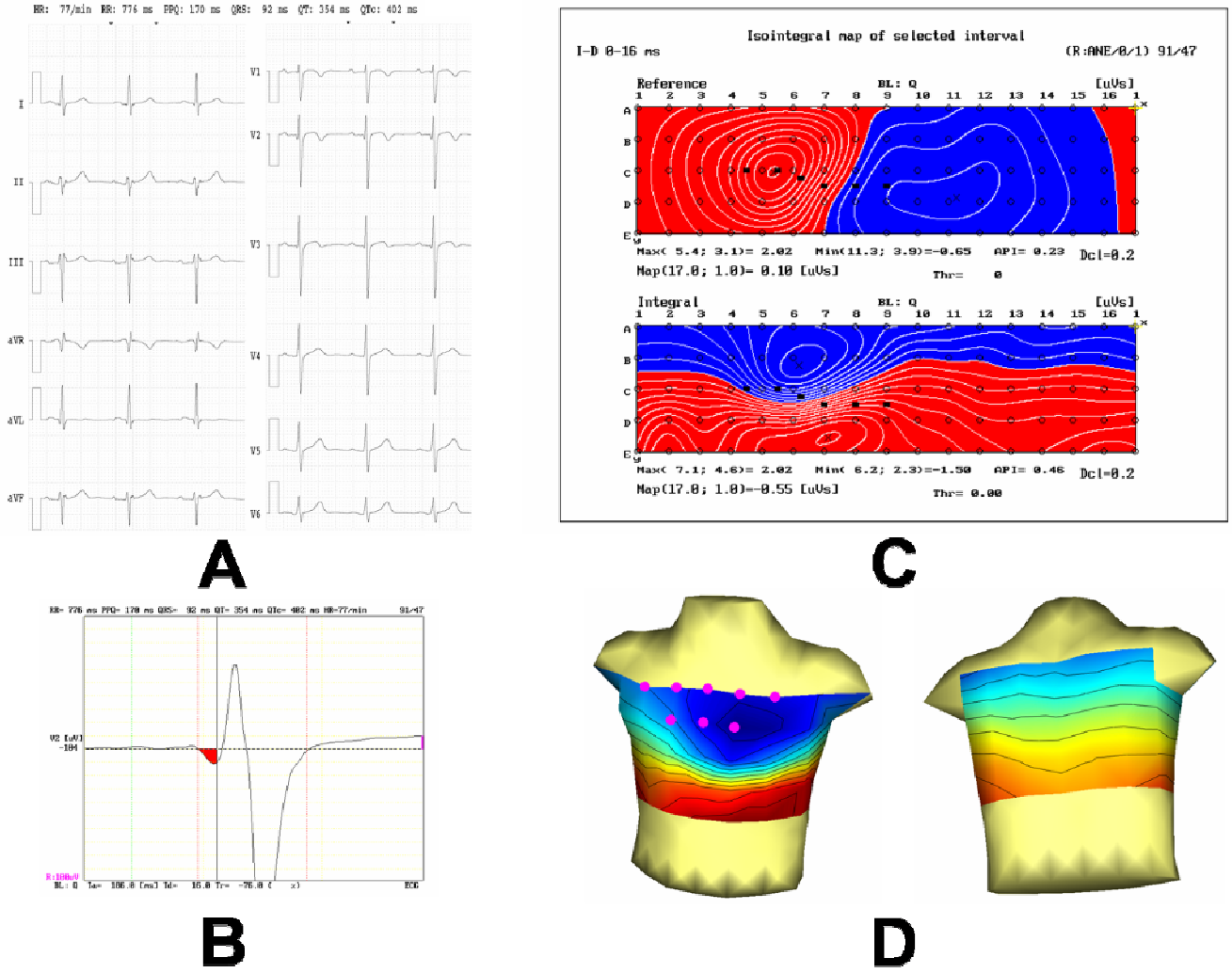

Fig 8 Example of the rudimentary and perhaps largely "missed" (see text) anterior q-wave that could be easily overlooked in the 12-lead ECG reading (panel A) and therefore routinely interpreted as non-Q MI case in this patient after remote anterior MI. The lead V2 is zoomed in the panel B with initial 16-msec integral filled with red color. In panel C, dominant negative anterior chest area (blue in the 16-msec integral maps) in the individual patient map (bottom) is displaced toward positive (red) area when compared to the average normal map (top). Departure index map (panel D, map3d representation) indicates the area significantly abnormal anterior loss of potential (magenta leads). When initial 40 ms were integrated in the same patient, the integral map turned normal, the significant loss of potential disappeared, and the departure index map turned empty.

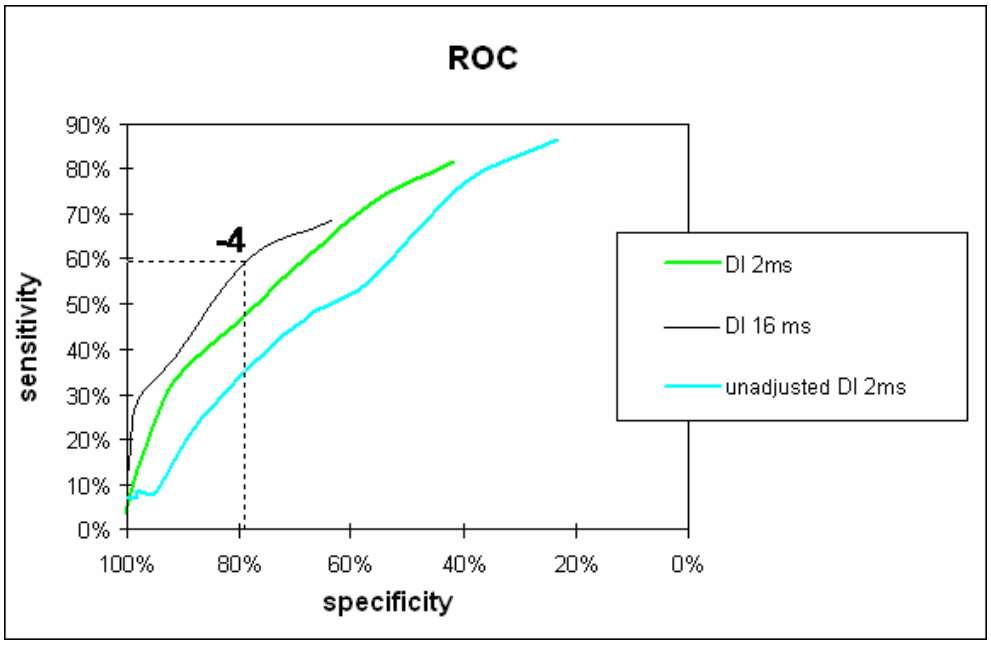

Fig 9 Receiver operator characteristic (ROC) analysis of different integration intervals when using departure index (DI, see text) technique for detection of areas of minimal potential loss within the QRS complex. Best performance was obtained when integrating over 16-msec interval within the QRS. The ROC curves are a result of manipulating the sum of DI (∑DI) over the DI area (reflecting the number of leads recording potentials beyond -2SD in Fig 7 and Fig 8) constituting in fact a threshold value. The best sensitivity (60%) and specificity (78%) was obtained for the ∑DI = -4 (i.e. area covering thorax surface spanned by 4 adjacent electrodes). Intervals were adjusted to the QRS duration, whereby unadjusted DI (blue curve) performed worse than adjusted (green).

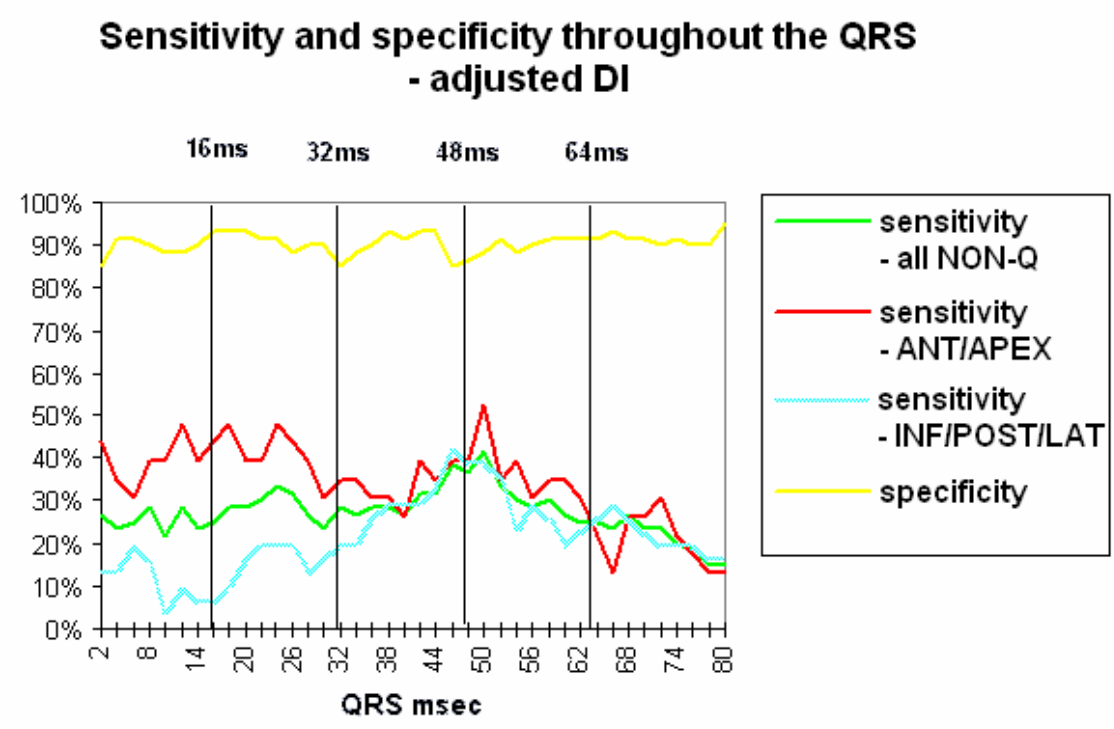

Fig 10 Diagnostic performance of instantaneous DI maps in relation to the location of the morphological postinfarction lesions (see text, ANT/APEX = anterior/apical, INF/POST/LAT = inferior/posterior/lateral) throughout the entire QRS complex. As expected, anterior/apical lesions were best detected during the first half whereas inferion/posterior/lateral within the later phase of the QRS.

Parameter	Interval of integration	Area of interest
Par 1	0-16 msec	A2-A12, B2-10, C2-C8
Par 2	16-32 msec	D1-D5, E1-E15
Par 3	16-32 msec	A5-A7, B5-B7, C4-C6
Par 4	32-48 msec	C13-C16, D13-D16, E13-E16
Par 5	48-64 msec	C9-C14, E9-E14
Par 6	48-64 msec	D2-D5, E2-E5

Fig 11 Definition of six compound diagnostic parameters that combine the time interval within QRS (aspect of activation sequence) and location (expressed as area of interest defined by electrode positions, according to the electrode matrix in Fig 1). When used in discriminant function, higher sensitivity and specificity was obtained in detection of local postinfarction loss of potential.

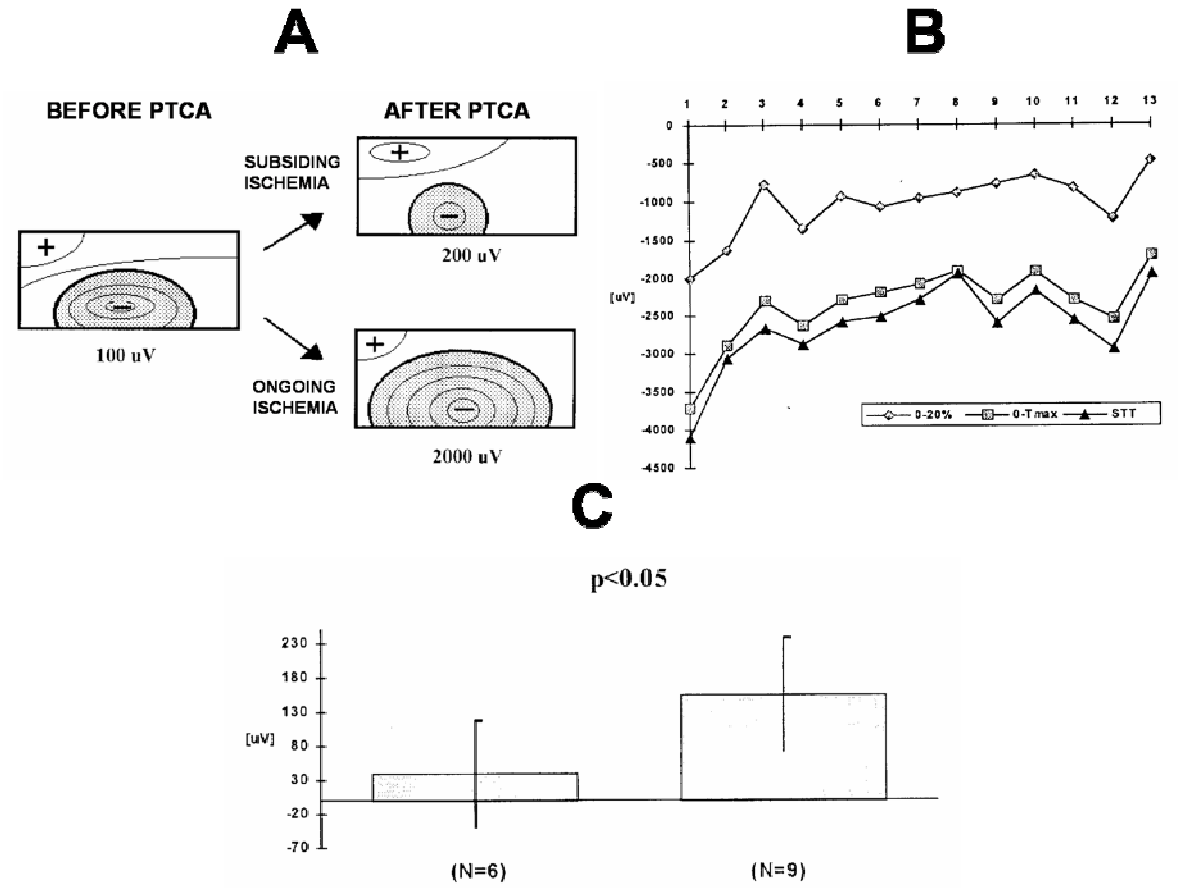

Fig 12 Analysis of the long-term restitution of repolarization after PTCA. Panel A shows the hypothesis that the electrical magnitude of negative difference of ST-T potentials between individual pre- and post-PTCA maps and average normal map should diminish after successful PTCA. Example time course of the sum of negative difference potentials (the three curves represent various portions of ST-T) during the follow-up period (see text) in a patient with successful PTCA of left anterior descending coronary artery and no recurrent angina/restenosis is in the panel B. Panel C shows statistically significant difference in delta U (see text) between the subgroups with recurrent angina (left column) and no angina (right column).

2.3 Mathematical techniques

The techniques of detection of low-amplitude *non-dipolar* content of ECG/BSPM have been for years in focus of investigators dealing with arrhythmias esp. malignant ventricular tachycardia/fibrillation. Native maps in patients prone to these arrhythmias have displayed often multipolar distributions of repolarization or QRST integral maps. [124,125,126] As opposed to the QT dispersion (see below), these fractionated patterns of electrical field that reflect true dispersion of repolarization are sensible, nevertheless requiring sophisticated evaluation and quantification techniques. Among number of mathematical methods suitable for ECG and BSPM analysis (see above), we chose Singular Value Decomposition (SVD) originally suggested in literature for data reduction and noise suppression purposes. [127] At the end, we could process the output of SVD in the form similar to the late potential analysis. In 80-lead matrix, the SVD similarly to other orthogonal expansion techniques (e.g. Karhunen-Loewe, [87] principal component/factor analysis [88, 128] by analyzing the entire matrix of BSPM yielded a spectrum of 80 ECG waveforms (components) per lead with increasing frequency and decreasing voltage. A single tracing of root mean square (RMS) value of the first 20 of 80 signals from all the leads was presented and filtered similarly to the SAECG. The results of late potential analysis were then used to predict the risk for induction of ventricular arrhythmia in the EP laboratory. The results were quite comparable to the SAECG in ability to discriminate between patients with and without a risk for inducible ventricular tachycardia VT and showed the information content of BSPM being at least comparable to the conventional methods. We see the diagnostic value of BSPM-derived micropotentials in capability to map the distribution of these components on the body surface similarly as was shown in the literature. [Publications V and VI] [87,91,92] The maps of late potentials have not been utilized as yet in clinical practice. However XYZ-derived late potentials in the large clinical trial (CABG-PATCH) lacked indication of SAECG of being capable to predict a preventive effect of preoperatively implanted defibrillators, [129] preoperative absence of these potentials was predictive of postoperative improvement of LV ejection fraction after coronary bypass surgery. [130] Therefore, we are convinced that the techniques of fine analysis of individual components of ECG signal remain to be evaluated more thoroughly, perhaps by ECG imaging, in order to relate them as accurately as possible to the anatomical substrates.

2.4 QT dispersion error performance

We evaluated QTD measurements carefully at the level of measurement accuracy. The reason was the ongoing unsettled clinical significance of QTD, disparate results of studies that have reached more than thousand papers published. Some studies already indicated that the error of measurement is unacceptable for routine use. [45] The interest in the QTD is logical since it offers incentive for a simple measurement that can be performed in just about any clinician's office equipped with an ECG machine and at the same time having a power of prediction for severe events like malignant VT or even sudden cardiac death. We found clear dependence of the magnitude of QTD (and also of its relative error computed from 2 independent readings by 2 human operators) on the lead system used for the measurement. At the same time, BSPM matrix proved to have the least error of measurement, and therefore, was also used to elucidate the nature of QT interval distribution on the body surface. At the level of 12-lead ECG or XYZ (Frank) leads that have been used in studies most frequently, the relative error reached 30-50% of the entire QTD; therefore, we think that this parameter should not be used for clinical practice. The erratic behavior of QTD also explains the contradicting results of studies. Also, we found the heart-rate correction of QTD unsubstantiated and misleading since

this parameter did not correlate with heart rate which finding was in agreement with the literature. [102] In our study, QTD was also not predictive of ventricular arrhythmia events, however this was analyzed retrospectively. The author regards the error performance analysis to be most important message of this study, proving BSPM to be a very accurate and versatile measurement tool. [Publication VII]

2.5 Transformation of the lead systems

The redundant nature of BSPM matrix for routine clinical use has been mentioned and is widely held by clinical community as an argument against it. Reports dealing with transformation of the lead systems have been in place almost since the beginning of era of BSPM. Some studies show feasibility of the limited lead systems for the reconstruction of the whole electrical heart field. [58,131] So far, however, none of them has substituted the entire BSPM matrix in experimental work neither the 12-lead ECG in clinical practice. Mathematical trials extracted about 60 independent individual components in body surface maps necessitating rather extensive BSPM leadsets to display the maps correctly. [61]
Also, when body surface maps produced by identical current source in a physical model (electrolytic tank with beating immersed heart) were compared among various leadsets, significant drop of correlation between maps was observed when approaching about 50-lead array. [132] These results were obtained using 3D interpolation technique employed in Dalhousie and Utah torso models. [62]

In clinical medicine, one important aspect of electrocardiography is simplicity and ease of electrode placement, therefore limited lead systems are an advantage weighed against diagnostic performance. Certain current ECG bed-side monitoring systems employ mathematical transform to reconstruct 12-lead ECG from the limited monitoring lead set. We tested one such lead set called EASI (Hewlett-Packard) using the Dalhousie BSPM matrix as means for calculation the transformation coefficients that would allow to compute 12-lead ECG from EASI leads. These calculations engaged the Dalhousie Heart-torso model as an example of practical application of electrocardiographic modeling. In the setting of patients after Q-wave MI, the calculations proved accurate enough to preserve the mean diagnostic features such as infarction Q-waves. These calculations provide insight into the nature of electrical field that allows sampling with practical and limited set of electrodes (leads) without significant loss of important diagnostic content. We do not know whether these computations are transferable from our data set to other patient populations with other pathological states. [Publication IX]

3 General and clinical implications – Electrocardiographic Imaging

Detection of global and local ischemic changes of the electrical heart field is of paramount importance. Standard 12-lead ECG has proved its indispensable role in clinical practice yet for almost a century since it first time displayed changes due to myocardial ischemia and infarction. Nowadays, many clinical algorithms (reperfusion therapy, arrhythmia management) could not be conceived without ECG as a necessary diagnostic step. In this thesis, the author summarizes his view of electrocardiographic mapping (BSPM) not only as a research tool for validation of certain clinically derived algorithms for detection of ischemia (infarction or ischemic Q-waves, infarct-related loss of potential, chronic ischemia/hibernation changes, cardiac micropotentials, QT dispersion) but also as a step toward a potentially new and more physically and physiologically sound diagnostic technique – ECGI (Electrocardiographic Imaging). [13] For example, just about any body surface map in this thesis could undergo transformation into an epicardial map via Dalhousie inverse solution and Heart&Torso model as can be seen in Fig 13 with original Dalhousie data. Since there was no validation technique available to verify the correctness of such calculations at the time of conduction of the studies, ECG modeling was not used with exception of lead transformation study that validated the measured against projected (calculated) electrocardiograms. In author's opinion, however, similar studies ought to be performed in the nearest future using a realistic anatomical framework and standards acquired from 3D imaging techniques. The role for invasive electroanatomic imaging or mapping has been firmly established in the clinical practice in the field of cardiac electrophysiology (CARTO™, EnSite™). This is regarded by author as a driver for developing noninvasive counterpart to such imaging techniques that could facilitate clinical algorithms and push forward technologies employing image integration and possibly catheter navigation (e.g. magnetic navigation driven by 3D anatomical surfaces) and therapeutic procedures using such tools as it was already demonstrated for catheter ablation of arrhythmias. [133, 134] However, prerequisite of such integration of ECGI into clinical algorithms is its feasibility and light-weightiness. ECGI would be inherently less accurate in comparison with invasive techniques; (see Biophysical factors) nevertheless, it could still be of significant help if it proves fast, correct, and easy to apply nearly the same as other standard noninvasive methods. On the side of computing speed the unceasing technology advancements give comfort in foreseeing even complex calculations like segmentation algorithms, inverse/forward calculation, and detailed detection and display of complex structures feasible. The detail of structural information necessary to have in advance for successful solution of inverse and forward problems of electrocardiography will be rather substantial otherwise some inherent issues of these computations would preclude meaningful outcomes. [135] Nevertheless, just about any successful software engine (sophisticated computer games, tools in aviation, astronomy, and space technology, mapping and forecast engines) underwent a process of dramatic improvement of performance and acceleration when built into compact hardware-software solutions (graphic and specialized cards, specialized hardware chips/accelerators). Therefore it is not difficult to imagine the heart and torso electrocardiographic model to be manufactured as a specialized hardware/software solution or chip if it is feasible and correct. Lead transformation should be seen as another necessary step toward such feasibility and clinical applicability, and the results of our and other studies are encouraging in the sense of accurate transformation from one lead system to the other without loss of significant diagnostic features.

The validation role of BSPM for the selected empirical criteria (Q-waves, potential losses, QT dispersion etc.) proved useful. In all aspects of clinical detection of global and local ischemic changes under investigation, BSPM displayed better sensitivity in order of percents, and if properly adjusted (see Time and Spatial Scanning of QRS complex), this was reached without sacrificing specificity. Therefore, imaging or reconstruction of electrical heart field might bring further insight into the pathological processes in cardiology or lead to a development of better diagnostic or treatment algorithms. However, in the clinical settings, such algorithms cannot employ impractical BSPM as it has been performed to this date in the research laboratories including ours. In this regard, BSPM is a research tool and a framework for development and further refinement of the mathematical space for modeling, simulation and realistic imaging. From the practical point of view, it is also difficult to conceive even advanced computerized technology of ECGI to be used in other fields than highly specialized cardiovascular medicine.

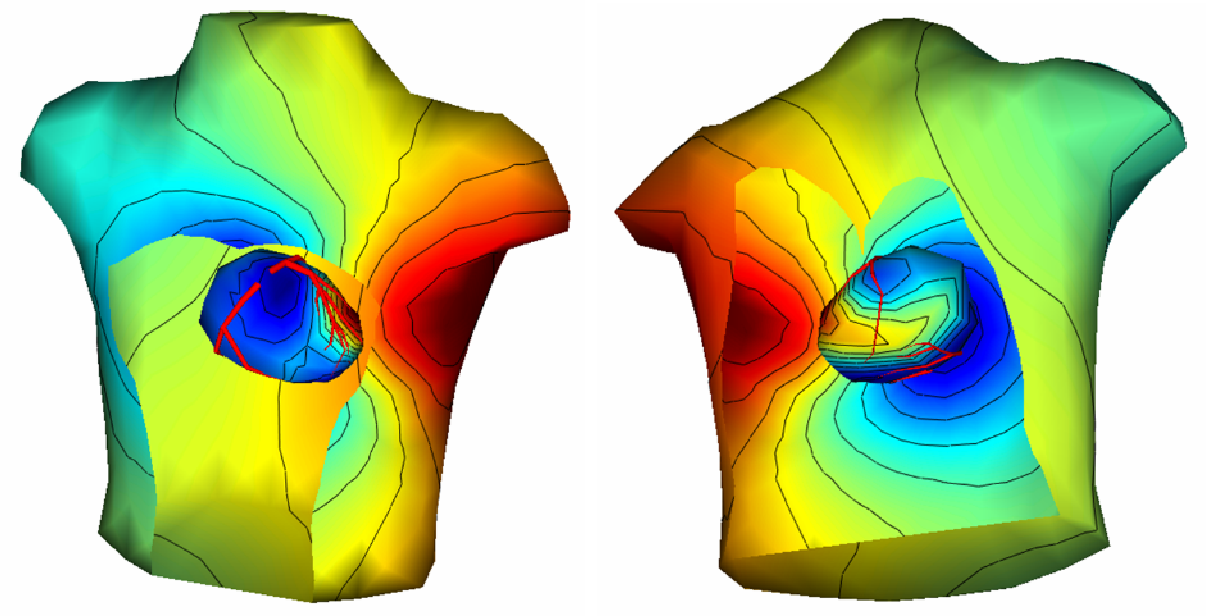

Fig 13 Dalhousie Heart&Torso model with parts of the torso surface clipped off to reveal epicardial ventricular surface with example of the whole-torso interpolation and display of body surface potential data acquired with Dalhousie mapping system. Also, inverse-solution calculated epicardial potentials are displayed in this sample that might be seen as a step toward electrocardiographic imaging since the epicardial data are related to the target anatomical structure and facilitate physiologically sound interpretation.

4 The role of computer processing, imaging, simulation and modeling

Computer technology has been a centerpiece of all algorithms throughout this thesis. Starting with data acquisition down to the display of the maps and statistical analysis; none of these steps is conceivable without computerized workspace. Realistic imaging and integration of modalities through technologies of *image segmentation* and *registration* are also driven purely by digital processing and highly automated algorithms. [136,137] Yet these techniques can still be managed through use of custom soft- and hardware solutions as it has been done successfully in the past in most of the research laboratories. Also, industrial leaders often use custom high-end solutions for marketing purposes and keeping prices up to pay-off high research and development expenditures. However, this approach seems exhausted and ineffective, mostly due to platform and algorithm related incompatibilities. These factors slow down the scientific progress in the field of cardiac modeling and simulation. Therefore, emergence of open-source technologies such as *computational steering* and visualization engines that constitute a relatively universal *problem solving environment* (PSE) is invited and highly appreciated. One such PSE comes from Scientific Computing and Imaging Institute from University of Utah called SCIRun and BioPSE. [138,139] For example the BioPSE software offers algorithms of image segmentation and also forward and inverse calculation as an integral part of the open-source package. (Fig 14) The software also incorporates import of external 3D models (e.g. CT/MRI-based) and allows seamless integration of different imaging modalities including simulated electrical fields. Similarly, scientific open-source software like *map3d* allows for 3-dimensional display of data as it was graphically presented throughout this thesis. All the torso representations of maps in this thesis come from map3d software that allows in fact any 3D surface to be manipulated, displayed, and connected with scalar data that most often come from heart or brain research. [140] Clinicians and scientists are clearly in need of the tools that allow for fast interchange of products of visualized experiments to be able to publish their results of clinical trials without spending too much effort and time on programming the tools that are available and effective in the public scientific domain. In author's opinion, software tools like SCIRun and map3d are the current perspective for successful solution of problems with high degree of complexity such as cardiac modeling.

Computerized workspace has already assumed rein in many aspects of patient care in the most developed health care facilities and systems. Hospital information systems contain patient electronic medical records (EMR) that already provide seamless connection between various text-based data and medical imagery. One such industry standard Picture Archiving Communication System (PACS) is widely used in radiology and telemedicine and recently effort is spent to integrate such systems with complete EMR. [141] Also, medical imaging has already reached a point where boundaries between functional and anatomical data become rather symbolic and actually more than stimulate attempts to cross them and create new hybrid or functional imaging modalities. Such example is a complex cardiac imaging like CT/PET and various MRI-based methods like DWI. [57] It is most likely that a substantial level of structural detail will be necessary for building organ models to secure acceptable accuracy for their function and provision of clinically meaningful data. [135] CT and MRI push themselves forward into a standard and commonplace in noninvasive digital angiography, both for coronary or peripheral artery disease imaging and surgery planning. 3D cardiac imaging is already taking place as a routine clinical aid in catheter navigation e.g. in complex procedures like catheter ablation of atrial fibrillation (CARTO Merge™). [142] In

such advanced environment, it is not too difficult to conceive having not only images or animated data available but also entire functional computer organ models as an integral part of patient EMR and sort of ongoing workspace for facilitating individual diagnostic and therapeutic workups. Successive reevaluations (follow up) of temporal and spatial changes in organ functions would be much enhanced in such environment. Patient's repetitive follow-up ECG analysis could become an example of technique that might change from highly abstract and often expert guesswork to the realistic imaging technique working finally with tangible structures rather than elusive tracings allowing often too much speculative approach.

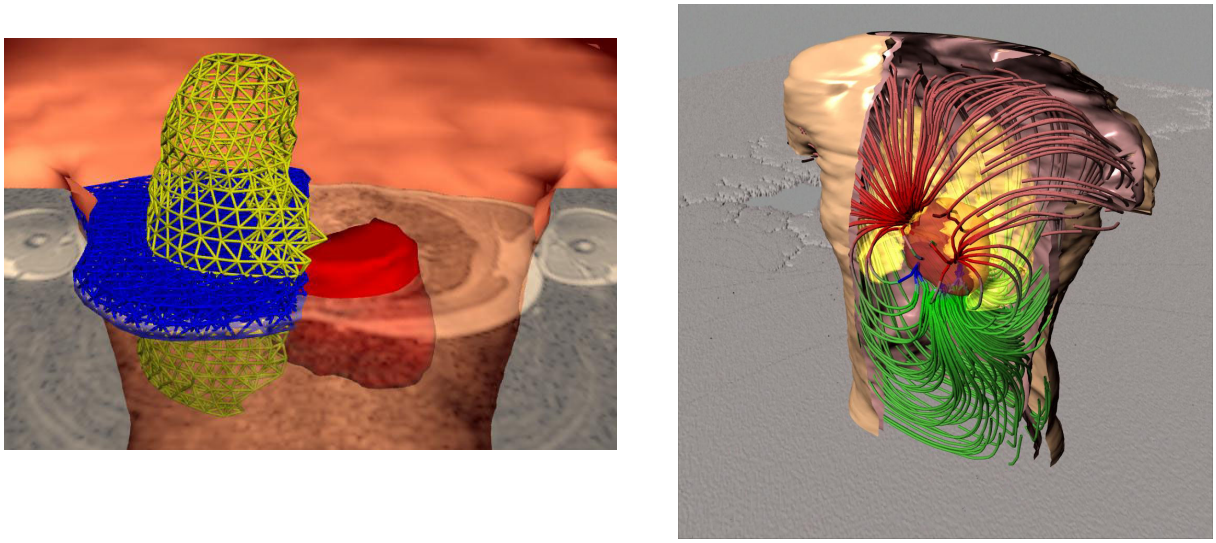

Fig 14 Example snapshots from the SCIRun image gallery at Scientific Computing and Imaging Institute at University of Utah (http://www.sci.utah.edu/cgi-bin/sci_gallery.pl). The picture on the left symbolizes the process of image segmentation from MRI and subsequent computerized creation of discretized 3D surfaces and organ models. On the right, the heart and torso model incorporating important segmented surfaces and anatomical structures with visualized electrical current streamlines resulting from modeling of cardiac electrical activity.

5 Author's contribution to the studies

The completion of the studies that constitute this thesis was by all means a result of teamwork and close collaboration of investigators from both laboratories in Prague, Czech Republic and Halifax, Canada. It was a privilege for the author to perform studies in the host Department of Physiology and Biophysics in Halifax since 1998 until 2001. The author had the opportunity to design, perform and publish the QT dispersion study using the 257-patient data set coming from the VT study at University of Calgary. [143] The BSPM recordings were acquired by Dalhousie researchers mostly in Calgary and partly in Halifax. The author performed an independent computerized reading of more than 30 thousands of signal-averaged QT intervals independently and in succession to one of the co-authors of the QTD study (Dr. Mark Burns, Publications VII and VIII). The analysis of QT interval maps was presented at the Annual Conference of European Society of Cardiology in Stockholm at 2001. In the lead transformation study, the author contributed in a collaborative and consultative clinical role, since the design, heart modeling and transformation calculations, and publication of results has been fully under direction of professor Milan Horáček at Dalhousie University. [Publication IX] In the studies from Prague (non-Q MI, variant angina), the author designed the data sets, recruited the patients and performed the studies starting from data acquisition until publication of data at conferences and preparation of the final paper. In the case of non-Q-MI study, this was in collaboration with the Department of Nuclear Medicine in IKEM (Institute of Clinical and Experimental Medicine, Prague) where the perfusion scans were performed. [Publications I-III] The pre- and post-PTCA serial BSPM recordings were designed and patients recruited by professor Michael Aschermann. The data were published at Czech and Slovak national conferences by author of this thesis who also performed the data processing and contributed to the evaluation of ischemic changes in the maps. [Publication IV] In the study employing SVD for detection of cardiac micropotentials, the author recruited the post-MI patient population and worked under the principal investigator dr. Zdeněk Drška, who designed the method of application and computation of SVD and SVD-derived cardiac late potentials. The author then presented the study at the European conference for pacing and electrophysiology Cardiostim 96 in Nice, France and prepared the manuscript for Internet-based periodical Heartweb. [Publications V and VI]

Summary of key publications

[Publication I]

In this study, we identified regions of potential loss within the QRS complex due to a remote non-Q MI using statistical departure technique of BSPM. We analyzed surface maps in 30 patients undergoing coronary angiography and compared them with the results of nuclear perfusion scans, echocardiography and ventriculography. We found the areas of potential loss outside 2SD to correlate well spatially with the perfusion defects and segmental contractile dysfunction.

[Publication II]

The study was an extension of the previous one in the sense of more detailed analysis of the QRS non-Q potential losses performed in extended data set of 60 patients. We integrated QRS potentials incrementally along the time axis in order to find the best diagnostic performance. We found a 16-ms window of integration of potentials to have the best sensitivity and specificity for detection of potential losses that correlated with the perfusion defects and segmental contractile dysfunction. Less integration (toward the instantaneous/isopotential maps) increased sensitivity while sacrificing specificity, whereas integration toward larger portions of QRS complex lead to loss of sensitivity but yielded more specific findings.

[Publication III]

In this study, we used vasospastic angina as a model of transient ischemia and we studied its impact on QRS complex potentials. We found the symptomatic ischemia (anginal episodes with ST-segment shift provoked by hyperventilation and/or cold immersion) to cause reversible changes of depolarization maps. These changes (Q-area extension) were compatible with transient Q-waves occasionally described in the literature in the 12-lead ECG of Prinzmetal angina patients.

[Publication IV]

In patients referred to PTCA, we compared their pre- and postprocedural maps and time course of repolarization BSPM patterns up to 6 months after PTCA. We could observe long-term changes compatible with hypothesis of recovery after PTCA.

[Publications V and VI]

This study was inspired by SAECG recordings in patients with ventricular arrhythmias. We used the complete BSPM matrix to extract cardiac micropotentials alternative way using a technique of SVD of the single cardiac beat, thus avoiding extensive signal averaging. We used the set of 80 ECG components with decreasing amplitude and increasing frequency and calculated RMS values in order to find late potentials analogical to SAECG. These SVD-derived components performed similar to SAECG-derived late potentials in comparison with other clinical variables (ejection fraction and others) in the data set of patients with ventricular arrhythmias mostly after MI.

[Publications VII and VIII]

In publication VII, we evaluated the QT dispersion measurement accuracy, diagnostic and error performance. We used a data set of BSPM recordings of patients with ventricular arrhythmias mostly with underlying cardiac structural disease. Patients after myocardial infarction without arrhythmias constituted a control group. QTD proved poor diagnostic performance and erratic nature. We compared measurement errors depending on the lead set used for evaluation and found limited lead sets (12-lead ECG, Frank XYZ leads) to be flawed with high relative error. We also studied QT interval distribution [Publication VIII] in relation to various clinically defined subgroups and found no correlation between these groups and body surface maps of QT interval which maps displayed fairly chaotic patterns. On the contrary, spatial averaging of the QT maps revealed stable patterns of maximal QT interval located in the precordium regardless of the individual maps or subgroups entering the averaging process. Therefore, we considered the spatial features of the QT interval rather random in nature and possibly reflecting the high and significant error content computed in the publication VII.

[Publication IX]

In this study, we designed and evaluated a lead transformation derived on the basis of the Dalhousie Heart and Torso model. The study demonstrated feasibility of such transform aimed at lead reduction or expansion (from 12-lead standard ECG to 7-lead EASI system and vice versa). It demonstrated that through limited ECG recordings (monitoring EASI leads) it was possible to conserve important diagnostic information (e.g. post MI pathological Q-waves) and also to reconstruct 12-lead ECG with clinically acceptable accuracy.

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