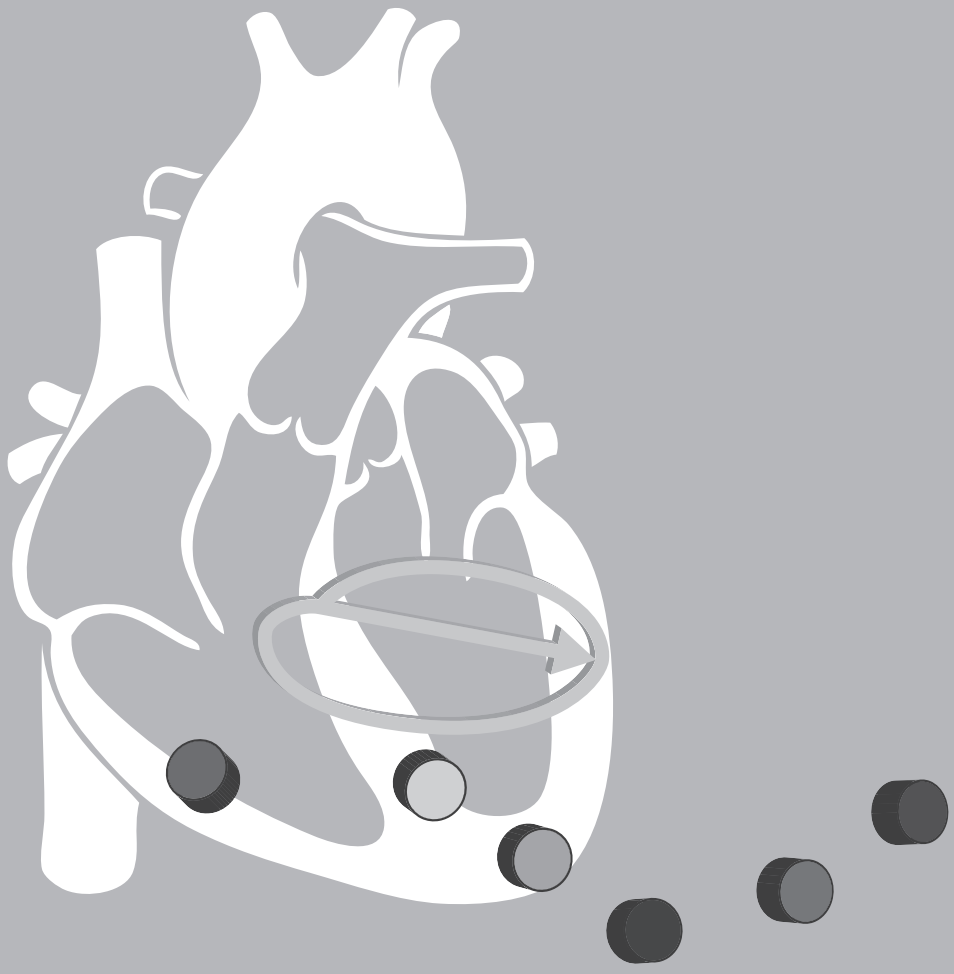

Chapter 13

General discussion and future perspective

General discussion

This thesis consists of a number of studies revolving around the leading research theme, *i.e.*, the derivation of new vectorcardiographic diagnostic & prognostic information from the 12-lead electrocardiogram (ECG). Various research questions have been addressed, but most studies use a similar data processing approach, consisting of initial mathematical synthesis of a vectorcardiogram (VCG) from a standard 12-lead ECG, followed by the measurement of general VCG characteristics like maximal QRS- and T vectors, QRS- and T integrals, the spatial QRS-T angle (SA) and the ventricular gradient (VG). Studies focus on methodological as well as on clinical issues, and are discussed below in the order as they appear in the thesis.

Part I: Transformations & analysis methods

Chapter 2 addresses the differences between the 12-lead ECGs obtained with the standard electrode positions or with the electrode positions according to Mason-Likar. In the clinic, practical considerations prevail in determining the electrode positions: in monitoring conditions and during exercise the Mason-Likar electrode positions on the thorax are preferred above the standard positions at wrists and ankles. Our study provides evidence that the electrode positions matter when ECG diagnosis is concerned. *E.g.*, in our study group of 180 patients in whom simultaneously standard 12-lead ECGs (STD-ECGs) and Mason-Likar ECGs (ML-ECGs) were recorded, the test set (90 patients) contained 4 patients with an inferior infarction of whom 3 were missed in the ML-ECG. This underscores the need for a reconstruction matrix to restore the STD-ECG from an ML-ECG. We have computed such an ML-ECG-to- STD -ECG reconstruction matrix; after reconstruction of the STD-ECG all missed inferior infarctions were again detected in the test set.

We also investigated what the differences were when vectorcardiograms were synthesized from either STD-ECGs or ML-ECGs. Considerable differences were seen in the maximal QRS- and T vectors, the spatial QRS-T angle and in the ventricular gradient. These differences were strongly reduced when the VCG was synthesized from a reconstructed STD-ECG instead of from the ML-ECG. Hence, our study demonstrates that vectorcardiographic analysis of ML-ECGs is only meaningful if, prior to VCG synthesis, STD-ECGs are reconstructed from ML-ECGs using, *e.g.*, our ML-ECG-to- STD-ECG reconstruction matrix. Up to now, no alternative ML-ECG-to-STD-ECG reconstruction matrices have been published by other groups.

Chapter 3 describes a method to individualize the ECG-to-VCG transformation matrix. Normally, VCG synthesis is achieved by applying a general ("one size fits all") transformation matrix. Transformation matrices are a reflection of the inhomogeneous volume conductor that is constituted by the thorax. When the individual anatomy of a particular subject differs from the model underlying the transformation matrix, the VCG is not faithfully synthesized and information is lost during synthesis procedure. We assumed that such information loss would become apparent after back-transformation from VCG to ECG with the inverse matrix. Hence, the correlation between the original 12-lead ECG and the thus reconstructed 12-lead ECG would indicate how well the generalized transformation matrix fits the individual. We hypothesized that small adaptations (1-10%) in the transformation matrix could maximize the correlation between the original and the reconstructed 12-lead ECG, and would improve the reliability of the (intermediate) VCG. We have successfully worked out this procedure for the inverse Dower matrix and could improve, in a study group of 180 patients, the average original-reconstruction correlation from 0.94 to 0.99. Our concept of an individually optimized VCG synthesis requires further testing, with the Kors matrix instead of the inverse Dower matrix, in a database of simultaneously recorded 12-lead ECGs and Frank ECGs in order to demonstrate that the optimal transformation matrix also yields the best VCG synthesis.

In **Chapter 4**, the BEATS (Beat Editing And Tracking Software) program is described to extract beat-to-beat vectorcardiographic features of the QRS-T complex. Different from 10-s resting ECG analysis programs, that first determine a representative QRS-T wave form and then perform an averaged beat analysis, BEATS is meant to analyze dynamic ECGs, *e.g.*, made during exercise, and can thus be used in T-wave alternans analysis. BEATS produces, for every beat in the recording, the timing of the onset QRS, J point, T apex and end of the T wave. It also produces, for every beat, several vectorcardiographic features like the maximal QRS- and T vectors, the QRS- and T integrals, the QRS-T angle and the ventricular gradient. Development of this software was instrumental for part of the research in this thesis, because no commercial equivalent is available.

Part II: ST injury vector

Chapter 5 describes the vectorcardiographic analysis of the ECGs of 300 patients with acute coronary syndrome (ACS), recorded prior to catheterization. In ACS, ST-segment elevation (STE) is an important ECG criterion for primary percutaneous coronary intervention (PCI). However, several studies showed that in ACS a completely occluded culprit artery can also occur with a non-ST-elevation (NSTE) ECG. Our patients were selected on the basis of a completely occluded culprit artery as evident from the catheterization. It appeared that 214/300 (71%) of the patients had an STE ECG and 86/300 (29%) had a NSTE ECG (228/72 had single/multivessel disease) prior to catheterization. Our study focused on the "injury vector" (vectorcardiographically determined magnitude and spatial orientation of the ST amplitude, computed at the J + 60 ms point). Injury vector elevation and magnitude were larger in STE than in NSTE patients (32° ± 37° vs. 6° ± 39°, and 304 ± 145 μV vs. 134 ± 72 μV, respectively; $P < 0.0001$). We conclude that the STE criteria select certain injury vector directions and larger injury vector magnitudes. Obviously, with the current ECG criteria, several ACS patients with complete culprit artery occlusions requiring primary PCI do not fulfill these ECG criteria. Our study suggests that STE–NSTE-based ACS stratification needs further enhancement.

Part III: Spatial QRS-T angle and ventricular gradient

Since the determination of normal limits[1] of the spatial angle between QRS- and T axes (SA) and the ventricular gradient (VG), many studies using the SA and VG has been done. The spatial QRS-T angle (SA) is defined in an earlier study as a predictor of sudden cardiac death, therefore it is important how this angle should be computed in an ECG recording. Mostly, this is done in a synthesized VCG, either by multiplying the ECG by the model-based inverse Dower matrix or the statistically optimized Kors matrix. However, gold standard VCGs are those recorded with VCG equipment and by using the Frank electrode positions. However, with the commonly available 12-lead ECG, VCGs must be synthesized by matrix multiplication (inverse Dower matrix/Kors matrix). Alternatively, Rautaharju proposed a method to calculate SA directly from the 12-lead ECG. Neither spatial angles computed by using the inverse Dower matrix (SA-D) nor by using the Kors matrix (SA-K) or by using Rautaharju's method (SA-R) have been validated with regard to the spatial angles as directly measured in the Frank VCG (SA-F). **Chapter 6** aimed to perform this essential validation. We analyzed SAs in 1220 simultaneously recorded 12-lead

ECGs and Frank VCGs, and found that the Kors-synthesized VCG yielded SA values that resembled most the "real" Frank-based SA values. Our study hence underscores the superiority of the Kors transformation matrix in synthesizing VCGs. In general, when there is no specific reason either to synthesize VCGs with the inverse Dower matrix or to calculate the spatial QRS-T angle with Rautaharju's method, it seems prudent to use the Kors matrix.

Chapter 7 compares the predictive value of SA calculated in either the inverse-Dower-synthesized or the Kors-synthesized VCG for the occurrence of serious ventricular arrhythmias in a study group of 412 patients with ischemic heart disease and left ventricular systolic dysfunction who received an implantable cardioverter-defibrillator (ICD) for primary prevention. During follow-up, the occurrence of appropriate device therapy (occurrence of ventricular arrhythmia) was noted. Receiver operating characteristic analysis revealed that the area under the curve of SA-Kors was significantly larger than area under the curve of SA-Dower (0.646 vs 0.607, P = .043). The discriminative power of SA-Kors for the absence/presence of appropriate ICD therapy in patients during follow-up was generally superior to SA-Dower over a wide range of cutoff values in the Kaplan-Meier analysis and generally yielded stronger hazard ratios in the univariate and multivariate Cox regression analyses. We concluded that if there is no specific reason to use the inverse Dower matrix, VCG synthesis from standard 12-lead ECGs should preferably be done by using the Kors matrix, and that it is likely to assume that already published studies in which the predictive value of SA-Dower was demonstrated would yield stronger results if the SA-Dower angles were substituted by SA-Kors angles.

Chapter 8 addresses the problem of the electrocardiographic diagnosis of left ventricular hypertrophy (LVH). The current ECG criteria have a low diagnostic accuracy, and in the guidelines the addition of demographic or anthropomorphic data is suggested as a potential improvement. As hypertrophy affects action potential morphology and intraventricular conduction, QRS prolongation and T-wave morphology may occur and become manifest in the vectorcardiographic variables spatial QRS-T angle (SA) and spatial ventricular gradient. In this study, we attempted to improve the diagnostic accuracy for LVH by using a combination of demographic, anthropomorphic, ECG, and vectorcardiographic variables. We

studied 196 patients who had, on one hand, echocardiographically diagnosed LVH or a normal echocardiogram and, on the other hand, with any of the conventional ECG signs for LVH, or with normal ECGs. We found a discriminant model for LVH diagnosis $D = 5.130 \times BSA - 0.014 \times SA - 8.74$ (BSA = body surface area), wherein D greater than or equal to 0 predicts a normal echocardiogram and D less than 0 predicts LVH. The diagnostic accuracy (79%) was better than the diagnostic accuracy of conventional ECG criteria for LVH (57%). A potential clinical application of this finding is that all ECGs who get either the conventional ECG interpretation "normal" of "LVH" are subjected to the here presented algorithm to detect LVH on the basis of SA and BSA.

Part IV: T-wave alternans

Chapter 9 describes the relevance of T-wave feature selection for T-wave alternans (TWA) analysis. To this purpose we compared the alternans in two vectorcardiographic variables: maximal T-loop vector (MaxT) and the T-loop vector integral (Ti). We analyzed TWA in the 72 standard 12-lead ECGs comprised in the Physionet TWA Challenge Database with our research ECG/VCG processing program LEADS[2]. We computed TWA by taking the absolute differences of the even and odd averaged beat values of Ti and MaxT (MaxT-TWA and Ti-TWA); also percentual alternans (%MaxT-TWA and %Ti-TWA) was computed. Finally, we computed both the Pearson and Kendall tau-b correlation coefficients between the MaxT-TWA and Ti-TWA, and between %MaxT-TWA and %Ti-TWA. All correlation coefficients differed significantly ($P<0.01$) from zero, but were relatively low ($R=0.333$-0.663). We conclude that T-wave features contain only in part common information; the selection of the T-wave feature in which TWA is computed deserves more attention.

A low left ventricular ejection fraction is a major criterion for cardioverter-defibrillator implantation for the primary prevention of serious ventricular arrhythmias in heart failure patients. Because this criterion lacks specificity, other risk indicators for electrical instability are investigated, amongst others T-wave alternans (TWA). Our specific interest was to investigate TWA in vectorcardiographic features of the ECG. At the same time, we tested another parameter of electrical instability, namely the exercise-recovery hysteresis in the ventricular gradient (VG). In **Chapter 10**, the performance of TWA amplitude (TWAA) during a complete exercise test and of the exercise-recovery hysteresis in the ventricular

gradient (VG) are evaluated as predictors for lethal arrhythmias in a small group of 34 heart failure patients with cardioverter-defibrillators (ICDs) implanted for primary prevention, half of whom (cases) had and half of whom (controls) had no ventricular arrhythmia during follow-up. We computed, in electrocardiograms recorded during exercise tests, TWAA (maximum over the complete test) and the exercise-recovery hysteresis in the VG. Receiver operating characteristics (ROC) analysis showed that VG hysteresis discriminated cases and controls with 94.1% sensitivity and 41.2% specificity; hazard ratio was 3.34 (1.17-9.55). ROC analysis of TWAA discriminated cases and controls with 93.8% sensitivity and 23.5% specificity; hazard ratio was 2.07 (0.54-7.91). Hence, ventricular gradient hysteresis bears predictive potential for arrhythmias in heart failure patients with an ICD for primary prevention, whereas TWA analysis seems to have lesser predictive value in our pilot group. The ventricular gradient hysteresis is relatively robust for noise, and, as it rests on different electrophysiologic properties than TWA, it may convey additional information. Hence, joint analysis of TWA and SVGH may, possibly, improve the noninvasive identification of high-risk patients. Further research, in a large group of patients, is required.

Because ejection fraction and T-wave alternans (TWA) lack specificity to predict sudden cardiac death in heart failure (HF) we addresses in **Chapter 11** the predictive value of resting ECG variables (QRS duration, lead-dependent T-amplitudes) and exercise-ECG-derived TWA variables (amplitude in the 12 leads, in the orthogonal X,Y,Z leads and in the vector magnitude) of 56 HF patients with an implanted cardioverter-defibrillator: cases and matched controls with/without device-induced antiarrhythmic therapy for serious ventricular arrhythmias during follow up. Linear discriminant models, using resting and exercise ECG variables, were built in half of the study group, and were tested on the other half. QRS duration and TWA in lead Z discriminated best in the resting and exercise ECG, respectively, and had comparable diagnostic accuracy for serious ventricular arrhythmias prediction. This study indicates that the resting ECG has also predictive value for arrhythmias.

T-wave alternans (TWA), an electrophysiological phenomenon associated with serious ventricular arrhythmias, is usually detected from selected ECG leads. **Chapter**

12 refers to the investigation about the comparison of TWA amplitude measured in the 12-standard and the 3-orthogonal (vectorcardiographic) leads to identify which lead system yields a more adequate detection of TWA as a noninvasive marker for cardiac vulnerability to ventricular arrhythmias. An adaptive match filter (AMF) technique was applied to the exercise ECG tracings from 58 patients with an implanted cardioverter-defibrillator, 29 of which had ventricular tachycardia or fibrillation during follow-up (cases), while the remaining 29 were used as controls. Two kinds of TWA indexes were considered, the single-lead indexes, defined as the mean TWA amplitude over each lead (MTWAA), and lead-system indexes, defined as the mean and the maximum MTWAA values over the standard leads and over the orthogonal leads. Significantly ($P < 0.05$) higher TWA in the cases versus controls was identified only occasionally by the single-lead indexes (odds ratio: 1.0–9.9, sensitivity: 24–76%, specificity: 76–86%), and consistently by the lead-system indexes (odds ratio: 4.5–8.3, sensitivity: 57–72%, specificity: 76%). The latter indexes also showed a significant correlation (0.65–0.83) between standard and orthogonal leads. Hence, when using the AMF, TWA should be detected in all leads of a system to compute the lead-system indexes, which provide a more reliable TWA identification than single-lead indexes, and a better discrimination of patients at increased risk of cardiac instability. The standard and the orthogonal leads can be considered equivalent for TWA identification, so that TWA analysis can be limited to one-lead system.

Future perspectives

The studies presented in this thesis demonstrate how transformation techniques and vectorcardiographic analysis of the standard 12-lead ECG can improve diagnosis and risk assessment/stratification. Also, other recent studies done in our department have demonstrated the usefulness of vectorcardiographic analysis of electrocardiograms, *e.g.*, in the setting of ischemia detection[3-5], pulmonary hypertension[6], ventricular arrhythmia risk assessment[7], and as a technical ECG recording quality index[8] to detect limb electrode interchanges.

It would be a positive step forward if the software in commercial electrocardiographs would be extended by vectorcardiographic analysis, *e.g.*, in the form of an optional extra page on which the scalar X, Y and Z average beats and their 2D and

3D vector loops like in Figure 5 of the Introduction of this thesis, and extended by a P-wave vector loop and a list of the measured values of general vectorcardiographic features like maximal QRS- and T vectors, mean QRS- and T vectors, spatial QRS- and T integrals, spatial QRS-T angle and ventricular gradient. This would greatly facilitate clinical research that is currently hampered by lacking vectorcardiographic analysis facilities. The need for software that calculates these general VCG features is likely larger than the need for additional vectorcardiographic diagnosis, because the diagnostic performance of automated ECG diagnosis and automated VCG diagnosis is nearly the same[9;10].

General, vectorcardiographic, ECG features that describe overall properties of the QRS complex, the T wave or the total QRS-T complex are well suited for individual trend analysis, to monitor possible detrimental functional or structural changes in the heart. Analogous to monitoring of QRS duration in patients with tetralogy of Fallot to determine the point in time where pulmonary valve replacement is indicated[11], it is conceivable that tracking the spatial QRS-T angle, a risk indicator for ventricular arrhythmias in heart failure patients[7], could be useful to monitor patients after acute myocardial infarction. In several routine clinical protocols, a periodic follow-up of patients after acute myocardial infarction includes periodic electrocardiography and trend analysis in such ECGs could be done almost without extra cost or effort, provided that the software for such serial analysis is available. Similar monitoring efforts could be done by analyzing the ventricular gradient[6] in patients at risk for pulmonary hypertension (*e.g.*, patients with scleroderma and patients after pulmonary embolism). Several other chronic conditions can be monitored in this way. The main goal of such monitoring would be the early detection of deterioration in heart function and possible early intervention.

Whereas, in the past decades, multiple modalities for the measurement of several aspects of cardiac function have been developed and are under development, *e.g.*, intra-vascular ultrasound (IVUS), cardiac magnetic resonance imaging (cMRI), computerized tomography (CT) and echocardiography, the electrocardiogram remains unbeaten as non-invasive measurement modality to assess electrical heart function. As it is apparent that the electrocardiogram contains more information than we currently can derive from it, further research, in the footsteps of Waller and Einthoven who started electrocardiography more than a century ago, is mandatory.

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