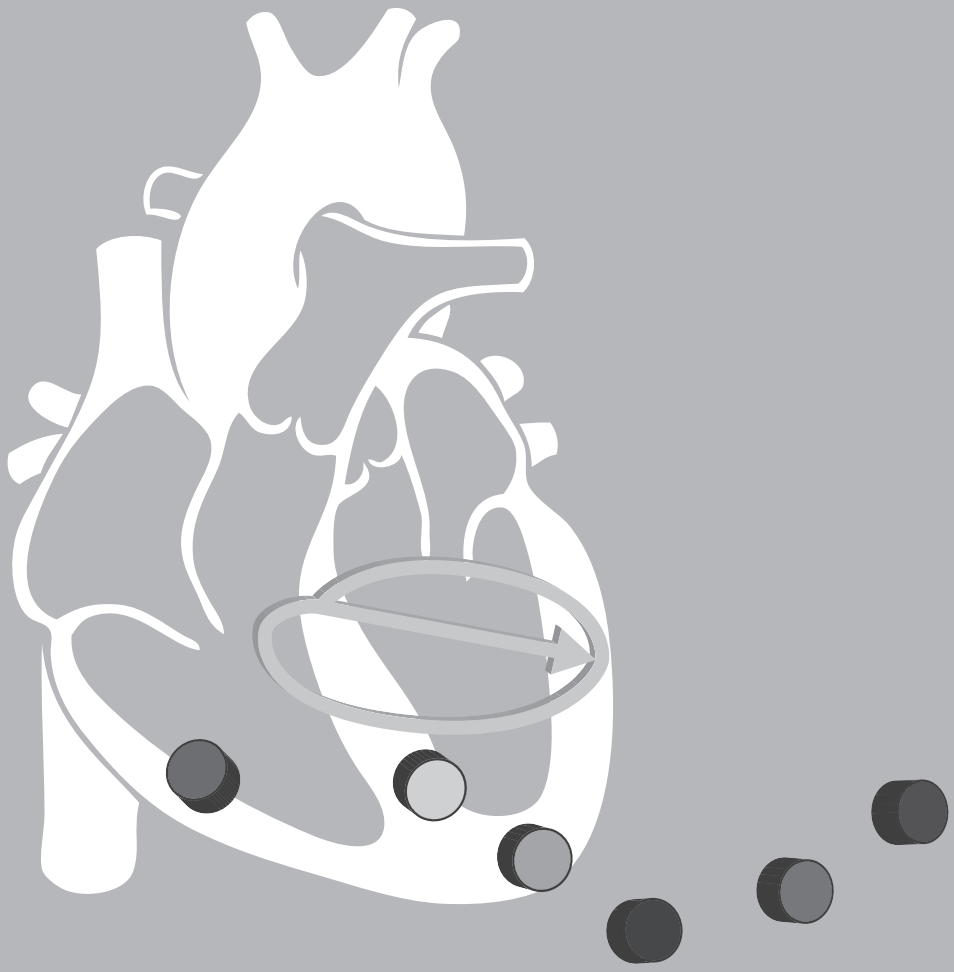

Chapter 7

Influence of the vectorcardiogram synthesis matrix on the power of the electrocardiogram-derived spatial QRS-T angle to predict arrhythmias in patients with ischemic heart disease and systolic left ventricular dysfunction

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Abstract

Background

Several studies have demonstrated that the spatial mean QRS-T angle (SA) predicts cardiac events and mortality. SA is a vectorcardiographic variable. Because in clinical practice 12-lead standard ECGs are recorded rather than vectorcardiograms (VCGs) according to Frank, VCGs are commonly obtained by synthesizing them from 12-lead ECGs, by using a VCG synthesis matrix. Hence, the thus computed SA is an estimate of the real SA measured in the Frank VCG. Recent studies have shown that Kors VCG synthesis matrix yields better estimates of SA than the inverse Dower VCG synthesis matrix. Our current study aims to compare the predictive power of these SA variants for the occurrence of potentially lethal arrhythmias.

Methods

The study group consisted of patients with ischemic heart disease and left ventricular systolic dysfunction who received an ICD for primary prevention. During follow-up, the occurrence of appropriate device therapy (occurrence of ventricular arrhythmia) was noted. Alternative SAs were computed in VCGs synthesized from standard 12-lead ECGs by using either the inverse-Dower matrix (SA-Dower) or the Kors matrix (SA-Kors). Comparison of the predictive power of SA-Dower and SA-Kors was performed by ROC analysis, by Kaplan-Meier analysis and by univariate and multivariate Cox regression analysis, using every 10^{th} percentile of SA as a cut-off value.

Results

The study group consisted of 412 patients (361 men; mean ± SD age 63±11 years), in which 56 patients had appropriate ICD therapy during follow-up. ROC 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=0.043). The discriminative power of SA-Kors for absence/presence of appropriate ICD therapy in patients during follow-up was generally superior to SA-Dower over a wide range of cut-off values in the Kaplan-Meier analysis, and generally yielded stronger hazard-ratios in the univariate and multivariate Cox regression analyses.

Conclusion

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. 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.

Introduction

Increasing evidence underscores the power of the spatial mean QRS-T angle (SA, the planar angle between the mean spatial orientation of the QRS and T axes) to predict cardiac events or mortality in various groups: the general population[1;2], patients admitted with acute ischemic chest pain[3], a clinical population consisting of patients in whom the recording of an ECG was indicated[4], postmenopausal women[5], patients with depressed left-ventricular systolic function on the basis of non-ischemic[6] and ischemic[7] pathology, and patients suspected of coronary artery disease[8]. The concept of the SA emerged several decades[9;10] ago in the setting of vectorcardiography, a form of 3D electrocardiography to which computation of the spatial orientation of the QRS and the T axes is intrinsic. SA characterizes the concordance/discordance of the electrocardiogram (ECG). Similar polarity of the QRS and T waves in most ECG leads usually results in relatively small values of SA, while relatively large values of SA are found when in most ECG leads the QRS complex and T wave have opposite polarity. Hence, a larger SA is associated with discordance, disease, and risk.

When vectorcardiography lost its popularity and the 12-lead ECG became the clinical standard, the SA was no longer routinely computed by commercial software in electrocardiographs and in ECG management systems, and it was considered as relic of the past. However, two decades ago vectorcardiography regained interest and the above cited studies appeared. An essential difference is that modern vectorcardiography uses a vectorcardiogram (VCG) that is synthesized from the 12-lead ECG by multiplying 8 independent ECG leads (2 limb leads and all 6 precordial leads) by a matrix, mostly the inverse Dower matrix[11] or the Kors matrix[12]. The thus computed SA differ from the SA computed in a VCG recorded with the original Frank electrode positions[13]. Recent studies[14;15] demonstrated that the Kors-derived SA (SA-Kors) is a better approach of the Frank-based SA (SA-Frank) than the inverse-Dower-derived SA (SA-Dower). The impact of the VCG synthesis algorithm on the predictive power of SA is still unknown.

The current study aims to compare the predictive power of SA-Dower and SA-Kors. Reasoning in terms of information content, we expect that SA-Kors, being a better approach of SA-Frank than SA-Dower, would perform better than SA-Dower. For this purpose we analyzed the ECGs of the patients described in the recent study

by Borleffs *et al.*[7]. We computed both SA-Dower and SA-Kors, and compared their performance as predictors of the occurrence of life-threatening arrhythmias in this patient group.

Methods

Study Cohort

The study cohort consisted of patients in the Leiden University Medical Center with ischemic heart disease and who received, for reasons of primary prevention, an implantable cardioverter-defibrillator (ICD) or a biventricular pacemaker with defibrillator function (cardiac resynchronization therapy with defibrillation option; CRT-D). Patients were selected according to the international guidelines[16]. Criterion for inclusion was a depressed left ventricular ejection fraction (LVEF<40%) with or without a history of non-sustained ventricular tachycardia. During follow-up, the occurrence of appropriate device therapy was noted. General characteristics of the study group, and of the subgroups with (cases) and without (controls) arrhythmias during follow-up are given in Table 1.

ICD Implantation and Follow up

All defibrillator systems were implanted transvenously without thoracotomy. Device follow-up was scheduled every 3 to 6 months. All printouts were carefully checked for appropriate and inappropriate ICD therapy. In the case of any ICD therapy, an electrophysiologist, blinded to QRS-T measurements, determined whether or not the ICD therapy was appropriate. All therapies, either anti-tachycardia pacing (ATP) or shock, were classified as appropriate when they occurred in response to life-threatening arrhythmias (ventricular tachycardia or ventricular fibrillation), and as inappropriate when triggered by sinus tachycardia, supraventricular tachycardia, T-wave oversensing or electrode dysfunction.

ECG analysis

Standard 10s 12-lead resting ECGs of all patients made before implantation were analyzed with our dedicated research-oriented ECG analysis program LEADS (Leiden ECG Analysis and Decomposition Software)[17]. SA-Dower and SA-Kors were calculated from two synthesized VCG variants, obtained by multiplying the 8

independent leads of the 12-lead ECGs by either the inverse Dower matrix or the Kors matrix. The inverse Dower matrix, introduced by Edenbrandt and Pahlm[11] is the pseudoinverse of the matrix proposed by Dower *et al.*[18] originally conceived

TABLE 1. Patient characteristics.

	All patients	Appropriate ICD therapy during follow-up	
		Yes (Cases)	No (Controls)
Patients, n	412	56 (14)	356 (86)
Clinical parameters			
Age (years)	63±11	62±10	63±11
Male	361 (88)	51 (91)	310 (87)
CRT-D	194 (47)	27 (48)	167 (47)
Body mass index (kg/m^2)	27±4	27±3	27±4
LVEF (%)	26±7	23±8	27±4†
NYHA functional class			
I-II	261(63)	35(63)	223(63)
III-IV	151(37)	21(37)	128(37)
History of diabetes mellitus	110 (27)	11 (20)	98 (28)
History of nicotine abuse	190 (46)	30 (55)	154 (45)
Current nicotine abuse	86 (21)	17 (31)	66 (19)
History of atrial fibrillation / flutter	98 (24)	20 (36)	78 (22)*
Atrial fibrillation/flutter at implantation	39(9)	8(14)	31(9)
History of nonsustained VT	81 (20)	16 (20)	65 (18)
Follow up (years)	1.6±1.3	1.0±1.0	1.7±1.4†
Medication			
Beta blocker	317 (77)	33 (59)	245 (69)
ACE inhibitor / AT antagonist	358 (87)	51 (91)	307 (86)
Diuretics for CHF	317 (77)	42 (75)	275 (77)
Statins	349 (85)	47 (84)	302 (85)
Amiodarone	57 (14)	4 (7)	53 (15)
ECG parameters			
Heart rate (bpm)	66±16	67±15	66±16
QRS duration (ms)	130±33	138±32	128±33*
LBBB	64(16)	9(16)	55(15)
RBBB	32(8)	7(13)	25(7)
QTc (ms)	431±51	429±58	432±51
Spatial QRS-T angle Dower (°)	139±32	151±22	138±33†
Spatial QRS-T angle Kors (°)	137±32	150±25	135±33†

Data are presented as n (%) or mean ± SD. ACE indicates angiotensinconverting enzyme; AT, angiotensin; CHF, congestive heart failure; NYHA, New York Heart Association; VT, ventricular tachycardia. *P <.05; †P <.01 compared with patients with appropriate ICD therapy during follow-up.

for the purpose of 12-lead ECG synthesis from a VCG. This matrix is based on the Frank torso model and was created for simultaneous VCG and 12-lead ECG diagnostics in clinical Frank VCG recordings[18]. The matrix proposed by Kors and colleagues[12] is based on a learning set from the CSE multi-lead library and was generated by multiple linear regression, thus minimizing the root-mean-square differences between the synthesized VCG and the simultaneously recorded Frank VCG in a population of patients and normals. The inverse Dower and Kors matrix coefficients are given in Table 2.

TABLE 2. Coefficients of the inverse Dower and Kors ECG-to-VCG conversion matrices.

	Inverse Dower Matrix				Kors Matrix		
	X	Y	Z		X	Y	Z
I	0.16	– 0.23	0.02	I	0.38	– 0.07	0.11
II	– 0.01	0.89	0.10	II	– 0.07	0.93	– 0.23
V_1	– 0.17	0.06	– 0.23	V_1	– 0.13	0.06	– 0.43
V_2	– 0.07	– 0.02	– 0.31	V_2	0.05	– 0.02	– 0.06
V_3	0.12	– 0.11	– 0.25	V_3	– 0.01	– 0.05	– 0.14
V_4	0.23	– 0.02	– 0.06	V_4	0.14	0.06	– 0.20
V_5	0.24	0.04	0.06	V_5	0.06	– 0.17	– 0.11
V_6	0.19	0.05	0.11	V_6	0.54	0.13	0.31

Statistical analysis

Numerical continuous and discrete baseline characteristics of the cases and control patients were compared by a Student's t test for unpaired data, and are expressed in mean ± SD. Categorical nominal and ordinal baseline characteristics were compared by a Chi-square test, and are expressed in numbers and percentages. These analyses were done in PASW Statistics (SPSS) v18.0 (PASW Statistics, SPSS Inc, Chicago, IL, USA).

To compare the predictive power of SA-Dower and SA-Kors independent of a specific cut-off value we constructed receiver-operating characteristics (ROCs). The areas-under-the-curve (AUC) of both the ROC-Dower and ROC-Kors were tested on significance by using the ROC analysis in Prism v5.01 (GraphPad Software Inc., San Diego, CA, USA). The difference between AUC-Dower and AUC-Kors was tested on statistical significance by using the ROC comparison module in MedCalc v11.4.4.0 (MedCalc Software, Mariakerke, Belgium).

We also performed a series of Kaplan-Meier analyses and Cox proportional hazard regression analyses (univariate, as well as adjusted for age, sex, LVEF and QRS duration) for cut-off points chosen at every 10th percentile, ranging from the 10th to the 90th percentile of the SA. These analyses were done in PASW Statistics (SPSS) v18.0 (PASW Statistics, SPSS Inc, Chicago, IL, USA).

Results

Table 1 shows the composition of the study group. Several baseline characteristics differed significantly between cases and control patients: cases had a lower average LVEF (mean ± SD 23±8% vs. 27±4%, P<0.01), more often a history of atrial fibrillation/flutter (36% vs. 22%, P<0.05), a shorter follow-up period (1.0±1.0 vs. 1.7±1.4 years, P<0.01), a longer QRS duration (138±32 ms vs. 128±33 ms, P<0.05) and larger SA's (Dower 151±22° vs. 138±33°, P<0.01; Kors 150±25° vs. 135±33°, P<0.01).

A scatter plot of values of SA-Kors vs. SA-Dower (Figure 1) shows that the largest SA values corresponded better than smaller SA values. This is similar to what we found in a previous study by tertile analysis in a group of 1220 clinical patients[15].

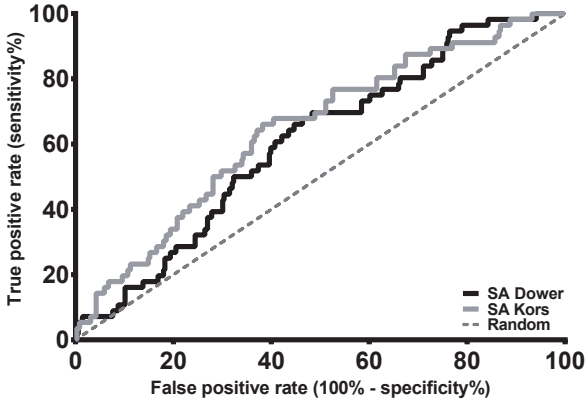

FIGURE 1. Scatter plot of spatial QRS-T angles derived from inverse-Dower-matrix (SA-Dower) *versus* spatial QRS-T angles derived from Kors-matrix synthesized VCGs (SA-Kors).

Figure 2 depicts the ROCs for SA-Dower and for SA-Kors. Both angles performed better than random in predicting appropriate ICD therapy (AUC-Kors = 0.646, P=0.0004; AUC-Dower = 0.607, P=0.010; Table 3). AUC-Kors was significantly larger than AUC-Dower (P=0.043). Visual inspection shows that the performance of

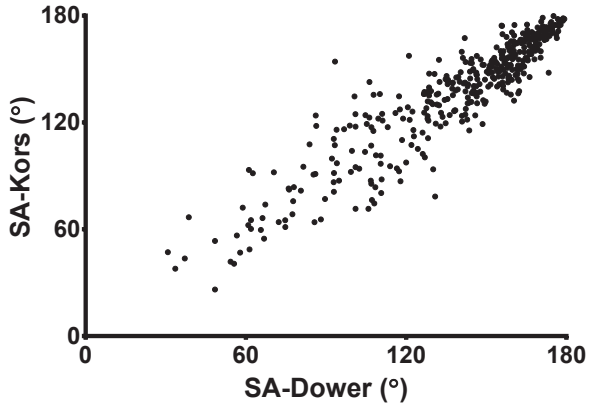

FIGURE 2. ROCs of the predictive power of either SA-Dower or SA-Kors on the presence/absence of appropriate ICD therapy in the study population.

TABLE 3. Receiver operating characteristic analysis results.

	AUC	95% confidence interval		P
		Lower	Upper	
SA-Dower	0.607	0.534	0.680	0.0097
SA-Kors	0.646	0.571	0.721	0.0004
Difference	0.039	0.001	0.077	0.043

SA-Kors was better over the full range of the curve, which corresponds to a shift of the cut-off point from small angles (upper right corner of the ROC) to the largest angles (lower left corner of the ROC).

Tables 4 and 5 give the Kaplan-Meier and Cox regression analyses results. Over a wide range of SAs, SA-Kors discriminated better in the Kaplan-Meier analysis (Table 4) than the SA-Dower. A similar result could be observed for both the univariate and multivariate Cox regression results (Table 5): for cut-off values above the 20th percentile, the SA-Kors had stronger predictive power (as reflected through the hazard ratios) than the SA-Dower.

Discussion

In this study we compared the prognostic value of two alternatively computed values of SA for the occurrence of potentially lethal arrhythmias in patients with left ventricular systolic dysfunction on the basis of ischemic heart disease who were treated, for primary prevention, with an ICD or CRT-D. The alternative SA values were computed in VCGs synthesized from standard 10-second 12-lead ECGs

TABLE 4. Kaplan-Meier analysis for appropriate ICD therapy sampled every 10th percentile of the spatial QRS-T angle as a cut-off value.

Cut-off percentile	SA-Dower						SA-Kors					
	Cut off (°)	≤cut off		>cut off		P	Cut off (°)	≤cut off		>cut off		P
		No. of total	No. of cases	No. of total	No. of cases			No. of total	No. of cases	No. of total	No. of cases	
10th	92	41	1	371	55	0.031	87	41	1	371	55	0.038
20th	111	82	3	330	53	0.003	116	82	5	330	51	0.025
30th	130	123	11	289	45	0.052	128	123	7	289	49	0.001
40th	142	165	17	247	39	0.080	138	165	13	247	43	0.002
50th	149	206	18	206	38	0.004	145	206	18	206	38	0.005
60th	156	247	26	165	30	0.034	152	247	21	165	35	0.001
70th	161	289	34	123	22	0.115	158	289	31	123	25	0.010
80th	166	330	42	82	14	0.365	165	330	39	82	17	0.030
90th	171	371	50	41	6	0.872	171	371	46	41	10	0.083

by using the inverse Dower matrix and the Kors matrix, respectively. On the basis of ROC analysis, SA-Kors performed significantly better than random and performed also significantly better than SA-Dower (AUC = 0.646 vs. 0.607, P = 0.043; Table 3). Similar results were found for the Kaplan-Meier, univariate and multivariate Cox regression analyses, using every 10th percentile of the SA as a cut-off value. SA-Kors discriminated in a wider range of cut-off values between presence/absence of appropriate ICD therapy in our study population than SA-Dower (Table 4), whereas hazard ratios were generally better and confidence intervals were generally narrower for SA-Kors (Table 5).

Figure 1 illustrates that in this study group, individual values of SA-Dower and SA-Kors can differ considerably. It also demonstrates that the differences are largest for smaller angles. As the smaller angles are more associated with normality, the increased scatter for those smaller angles is not necessarily detrimental to the discriminative power of SA in separating health and disease. However, scatter continues to occur also for the larger angles, and this is where discrimination between cases and controls occurs, and where differences in performance of SA-Dower and SA-Kors arise.

The difference in the discriminative performance of SA-Dower and SA-Kors was not spectacular, but large enough to demonstrate that SA-Kors was overall superior to

TABLE 5. Cox regression analysis for appropriate ICD therapy sampled every 10th percentile of the spatial QRS-T angle as a cut-off value.

Cut-off percentile	SA-Dower							SA-Kors						
	Cut off (°)	Crude HR	95% CI		Adjusted HR*	95% CI		Cut off (°)	Crude HR	95% CI		Adjusted HR*	95% CI	
			Lower	Upper		Lower	Upper			Lower	Upper		Lower	Upper
10th	92	6.57	0.91	47.52	4.72	0.65	34.52	87	6.24	0.86	45.07	4.42	0.60	32.38
20th	111	4.99	1.56	15.97	3.77	1.16	12.28	116	2.73	1.09	6.85	2.02	0.79	5.20
30th	130	1.90	0.98	3.67	1.51	0.77	2.98	128	3.50	1.59	7.74	2.83	1.26	6.37
40th	142	1.66	0.94	2.93	1.28	0.71	2.32	138	2.54	1.36	4.72	2.09	1.09	4.00
50th	149	2.24	1.28	3.92	1.71	0.94	3.11	145	2.18	1.24	3.82	1.77	0.99	3.17
60th	156	1.75	1.04	2.97	1.33	0.76	2.33	152	2.49	1.47	4.34	2.02	1.14	3.60
70th	161	1.54	0.90	2.63	1.18	0.67	2.07	158	1.97	1.17	3.34	1.57	0.90	2.76
80th	166	1.32	0.72	2.42	1.14	0.62	2.10	165	1.86	1.05	3.29	1.47	0.81	2.67
90th	171	1.07	0.46	2.50	0.87	0.37	2.05	171	1.81	0.92	3.60	1.51	0.75	3.04

CI indicates confidence interval. *Hazard ratio (HR) was adjusted for age, sex, LVEF and QRS duration.

SA-Dower in discriminating cases and control patients. Exception was a small part of the ROC near the upper-right corner, where SA-Dower discriminated better than SA-Kors (Figure 2). The cut-off value of SA is here ≈100°, a value within the normal range of SA-Dower (80±24° for male subjects; 66± 23° for female subjects;[19]) but not within normal range of SA-Kors (43±21° for male and female subjects;[20]). The shape of both ROCs is not really smooth, which suggests that the size of the database may have been too small to precisely measure the discriminatory performances of SA-Dower and SA-Kors. Especially, the number of cases is small (N=56). On the other hand there are no good reasons to believe or hope that an increase in the number of cases would dramatically alter the general impression that our current study yielded.

On the contrary to some studies about SA[2;4], our study group included many patients who have a prolonged QRS duration, *e.g.* 16% of the patients have a left bundle branch block (Table 1), which received a CRT-D according to the guidelines[16]. As shown in Table 1, case patients have a significant longer QRS duration than control patients, however, there was no significant difference between the percentages of left bundle branch block (LBBB) or right bundle branch block (RBBB) in case and control patients. The difference in QRS duration in case and control patients may be explained by intraventricular conduction disturbances that occur in patients which cannot be addressed as LBBB or RBBB. Consequently,

in the univariate regression analysis the present of LBBB or RBBB did not contribute to the differentiation of case and control patients, while QRS duration did. Therefore, QRS duration was added in the multivariate regression analyses to adjust for its contribution to differentiate between case and control patients.

Limitations

Obviously, the here presented results are based on one specific study group. This is a relevant study group, however, because the decision to implant a defibrillator for reasons of primary prevention is a difficult one, and much research is being done to find extra, preferably noninvasive, predictors of life-threatening arrhythmias, more investigation is needed in other patient groups wherein patients with prolonged QRS duration are included.

Conclusions

In our study population, SA-Dower was inferior to SA-Kors in discriminating cases (patients with arrhythmias during follow-up) and controls (patients without arrhythmias during follow-up). We attribute the superior discriminative power of SA-Kors to the fact that SAs computed from VCGs synthesized by using the Kors transformation matrix are closer to SA-Frank than SAs computed by using the inverse Dower transformation matrix[14;15]. 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. Because of the superior estimation of SA-Frank by SA-Kors, it is likely that already published studies, in which the predictive value of SA-Dower was demonstrated, would yield even better results if the SA-Dower angles were substituted by SA-Kors angles.

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