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Diagnostic accuracy of a novel method for detection of acute transmural myocardial ischemia based upon a self-applicable 3-lead configuration

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Abstract

Background: Delayed medical attendance is a leading cause of death in patients with ST elevation myocardial infarction (STEMI).
Methods: We aimed to introduce, develop, and validate a novel method (RELF method) for detection of transmural ischemia based on a new and easy-to-use 3-lead configuration and orthonormalization of ST reference vectors ($STDV_N$). The study included 60 patients undergoing coronary artery occlusion (CAO) during balloon inflation and 30 healthy subjects.
Results: $STDV_N$ was significantly different and an optimal discriminator between CAO patients and healthy subjects (respectively 8.00 ± 4.50 vs. 1.90 ± 0.86 normalized units, $p < 0.001$). Compared to the 12-lead ECG, the RELF method was sensitive (90 vs. 73%, $p = 0.13$) and more specific (91 vs. 75%, $p < 0.001$).
Conclusions: The RELF method is highly accurate for early detection of acute occlusion related ischemia and it outperforms the conventional 12-lead ECG criteria for STEMI. This method provides a platform for self-detection of CAO with handheld devices or smart phones.

Keywords: Myocardial infarction; Diagnosis; Electrocardiography; Heart arrest

Introduction

Early diagnosis and immediate reperfusion therapy are essential for improving prognosis of patients with symptoms of chest discomfort that are suspected for an acute coronary artery occlusion [1,2]. Despite efforts to improve early diagnosis and reperfusion strategies and to shorten patient's delay by public education campaigns [3,4], a substantial number of patients fail to receive optimal treatment with minimal delay [2].

The first shortcoming for early diagnosis and treatment is the patient's delay to seek medical help, which is influenced by social factors, cognitive processes and emotional reactions, feelings of embarrassment, fear to trouble others, and the consideration that their symptoms are not actually serious [4–6]. This stresses the need for a "carry-on" tool to reliably guide the patient with chest pain toward medical care. Such a tool could theoretically integrate an automated questionnaire and an intra-individual ST elevation detection method to create levels of medical emergency. The second shortcoming is the 12-lead ECG which lacks specificity and sensitivity for acute coronary artery occlusion [7–9]. On the 12-lead ECG, ST elevations can occur in non-ischemic conditions [10,11], whereas transmural ischemia, especially in the postero-lateral area, can occur without ST elevations [12,13]. To overcome these inaccuracies, the current guidelines advise to compare the individual's 12-lead ECG with a previous reference ECG when available, or to use additional leads in order to better detect the postero-lateral transmural ischemia [14–16]. Although intra-individual ST comparisons might be more sensitive and specific to detect transmural ischemia, diagnostic criteria for comparison are lacking.

To tackle both shortcomings, we developed a novel method (RELF method) for intra-individual comparison of ST segments based on an easy-to-use and reproducible lead configuration and orthonormalization of ST reference vectors. This method was validated against the standard 12-lead ECG in healthy subjects and in patients with an acute coronary artery occlusion, and its diagnostic accuracy is reported according to the STARD statements [17].

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Methods

Study subjects

We enrolled patients with a planned one-minute coronary artery occlusion during angioplasty (CAO group) and healthy subjects (control group).

The CAO group comprised 69 angioplasties performed between September 2010 and October 2012 at Ghent University Hospital for elective percutaneous transluminal coronary angioplasty (PTCA). Exclusion criteria for the study were ongoing chest-pain or ST elevation myocardial infarction <48 hours. Nine PTCAs were excluded from further analysis due to the absence of any change in the ST segment or T wave on the 12-lead ECG during one-minute of occlusion. In total, 60 PTCAs from 51 patients were analyzed (Table 1).

The control group comprised 30 healthy subjects (age range 26–56 years) with no history of coronary artery disease. None of the healthy subjects were excluded from further analysis.

The CAO and control groups were each split in half to achieve a learning dataset for development of the method and a validation dataset for testing the method prospectively. The study was approved by the institutional ethics committee and written informed consent was obtained from all study subjects.

ECG acquisition

ECG measurements were recorded using CardioTek EP system (Maastricht, The Netherlands) allowing recording of the standard 12-lead ECG (the 4 standard limb electrodes and the 6 standard precordial electrodes) and simultaneous recording of an additional exploratory unipolar lead (E). Positioning of the standard limb electrodes was according to the Lund configuration with the arm electrodes placed proximal and lateral [18]. The exploratory electrode (E) was positioned 4.5 cm above the fourth left parasternal intercostal space (vertically above V2). Duration of each recording was 12 seconds sampled at 1000 Hz (band-pass filter 0.05–300 Hz, notch filter 50 Hz).

The novel 3-lead configuration

Three bipolar leads defined as the RELF leads were used (RELF stands for the sites on the body on which the leads are connected, Fig. 1, upper left panel): lead 1 measured the voltage difference between the exploratory electrode (E) and the right shoulder (R), lead 2 measured the voltage difference between the left shoulder (L) and the right shoulder, and lead 3 measured the voltage difference between the left iliac crest (F) and the right shoulder. In all leads, the right shoulder was the negative pole.

Table 1
Characteristics of study subjects.

	CAO (n = 51)	Healthy subjects (n = 30)
Male, n (%)	30 (59%)	15 (50%)
Age, y	70 ± 7	40 ± 11
Weight, kg	78 ± 13	74 ± 12
Height, cm	167 ± 8	175 ± 7
BMI, kg/m^2	28 ± 4.6	24 ± 3.2
Baseline ECG		
RBBB, n (%)	5 (10%)	0 (0%)
Incomplete RBBB, n	4 (8%)	2 (7%)
Atrial fibrillation, n	2 (4%)	0 (0%)
LAHB, n	6 (12%)	0 (0%)
Ventricular pacing, n	1 (2%)	0 (0%)

RBBB: right bundle branch block, LAHB: left anterior hemiblock.

ST level detection algorithm

A custom-made algorithm was developed in Matlab v7.1 (The MathWorks, Natick, MA, USA) to detect the ST-segment in each of the 3 leads. For each beat, the algorithm automatically detects the ST level (defined as the amplitude difference between the PR segment and the beginning of the ST segment) and eliminates invalid QRS complexes due to extrasystoles and noise artifact. This automated algorithm was visually validated (by PG and MEH) prior to the study. Then, the median ST level for all valid beats in a recording (12 seconds) was calculated and denoted as the ST level of the lead (Fig. 1, upper middle and right panels).

ST difference vector (STDV)

The three ST levels (from the three leads) of a recording were used to construct an ST vector (Fig. 1, lower panels). The ST difference vector (STDV) was defined as the difference between the individuals' reference ST vector (RSTV) and the event ST vector (ESTV). The ESTV is the ST vector of a recording during any event of interest.

In the CAO group, the individual's RSTV was calculated as the average of 2 baseline reference measurements recorded within 2–10 minutes prior to the intervention on the catheterization table in supine position. The ESTV was determined from the recording at 60 seconds of balloon inflation or earlier in case of severe symptoms or presence of a large ST deviation during balloon inflation. In total, 120 (2 recordings × 60 PTCA) reference recordings and 60 (1 recording × 60 PTCA) event recordings were analyzed.

In the control group, the individual's RSTV was calculated as the average from 13 consecutive reference recordings: 5 in supine position, 3 in standing position, and 5 in supine position immediately after a mild physical activity (10 genuflexions in standing position). The "event" recordings in the control group (ESTV) were similar to RSTV but were performed at least one week after the RSTVs recordings. In total, 390 (13 recordings × 30 subjects) reference recordings and 390 "event" recordings were analyzed. Median time interval between the reference recording and event recording was 63 days (range: 3–189 days).

Conventional ECG method to assess STEMI criteria

For each recording with the RELF lead system, a simultaneously recorded standard 12-lead ECG was available. The event ECGs (control and CAO, n = 450) were assessed independently by two cardiologists (DV and PG) for the presence of ST elevation criteria according to the third international definition of myocardial infarction criteria [14] including the ST depression criterion for "STEMI equivalent" [19]. In case of mismatch, the assessment of a third cardiologist

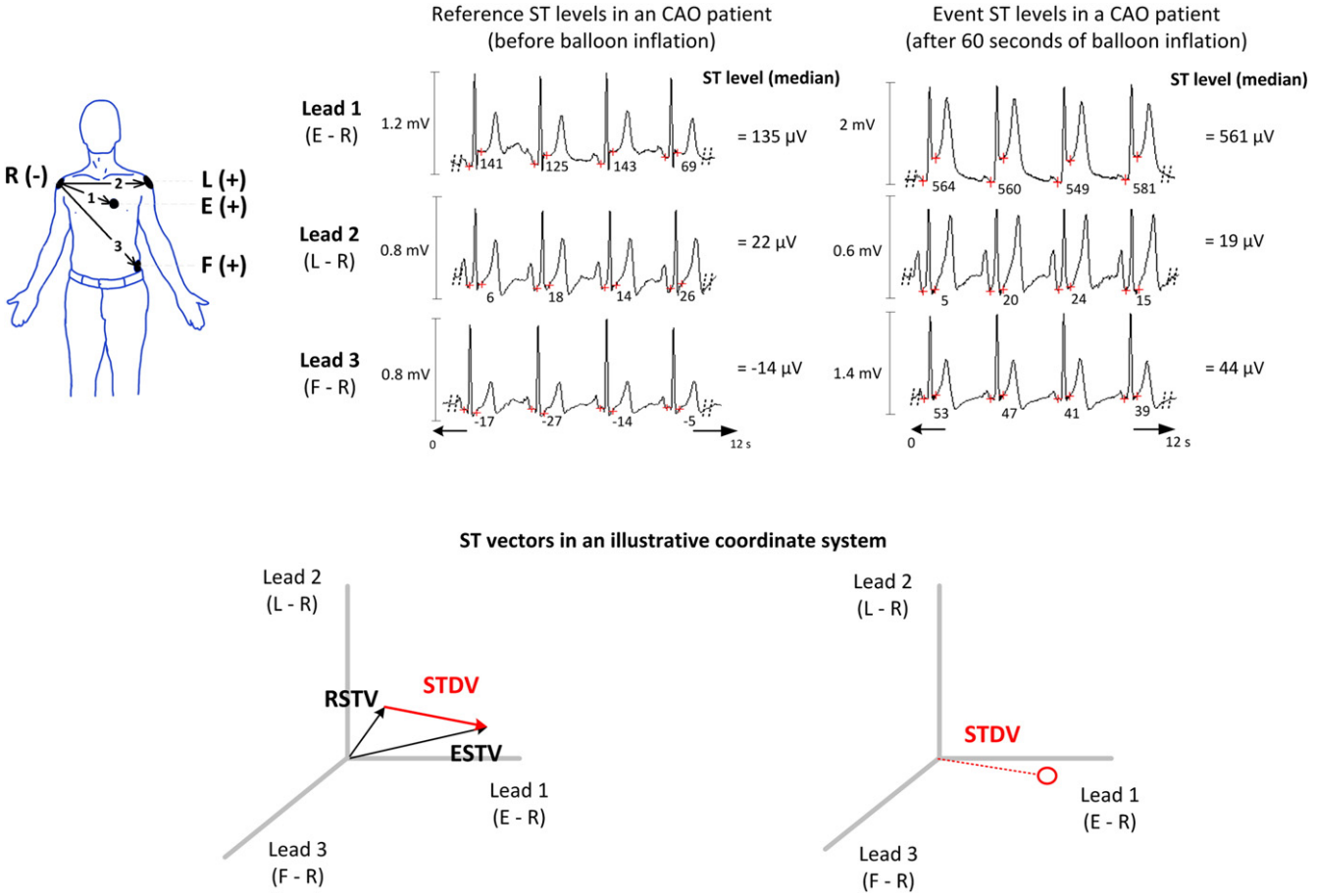


Fig. 1. Upper left panel: the RELF electrodes are positioned at the right shoulder (R), left shoulder (L), 4.5 cm above V2 of the standard 12-lead ECG (E), and left anterior superior iliac spine (F). RELF lead 1 is E minus R, lead 2 is L minus R, and lead 3 is F minus R. Upper right panel: the red crosses indicate the algorithmic markers of PR and ST segments on an RELF recording. Lower panels: ST vectors in an illustrative orthogonal coordinate system. The ST difference vector (STDV) is the event ST vector (ESTV) minus the individuals' reference ST vector (RSTV). Lower panels: presentation of the STDV in an orthogonal system defined by (lead 1, lead 2, and lead 3) to explain the concept of difference vector. The ST difference vector (STDV) is the event ST vector (ESTV) minus the individuals' reference ST vector (RSTV).

(RS) was taken. Assessments were performed blinded to the subjects' group and to the results of the RELF method.

Statistics

Continuous variables are expressed as mean ± SD. Normality of data distribution was tested with Shapiro–Wilk test (SPSS). Boxplots and principal component analysis were performed in SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). Scale numeric data between independent groups were compared using Mann–Whitney U test (2 groups) or Kruskal–Wallis test (3 groups). Receiver operating characteristics (ROC) curves were plotted and analyzed (paired) in SigmaPlot (Systat Inc, San Jose, CA, USA). McNemar test was used for paired comparison between the dichotomized RELF method and the conventional STEMI criteria. P values <0.05 were considered statistically significant.

Results

ST levels in the 3 RELF leads

The inter-individual ranges of ST levels (determined algorithmically) in each of the 3 RELF leads in the learning and validation datasets are presented in the Appendix (see Supplementary data).

ST difference vector (STDV) in the CAO and control groups

In the learning CAO group, we calculated 30 STDV corresponding to occlusion of left anterior descending (LAD, n = 14), left circumflex artery (CX, n = 6), and right coronary artery (RCA, n = 10). In the learning control group (15 subjects), we calculated 195 STDVs corresponding to 75 recordings in supine position, 45 recordings in standing position and 75 recordings in supine position immediately after exercise (flow diagram in Supplementary Fig. 1). All STDVs from the learning dataset (n = 225) are presented in the Frank's orthogonal coordinate system [20,21] in Fig. 2. The STDV of the healthy subjects showed an elliptic variation mainly observed in the frontal view (panel A) and the magnitude of the STDV in the Frank's coordinate system was not an optimal discriminator between CAO and healthy subjects.

The orthonormalized ST difference vector ($STDV_N$) in the CAO and control groups

Principal component analysis (PCA) was applied to orthonormalize the distribution of the STDV in healthy

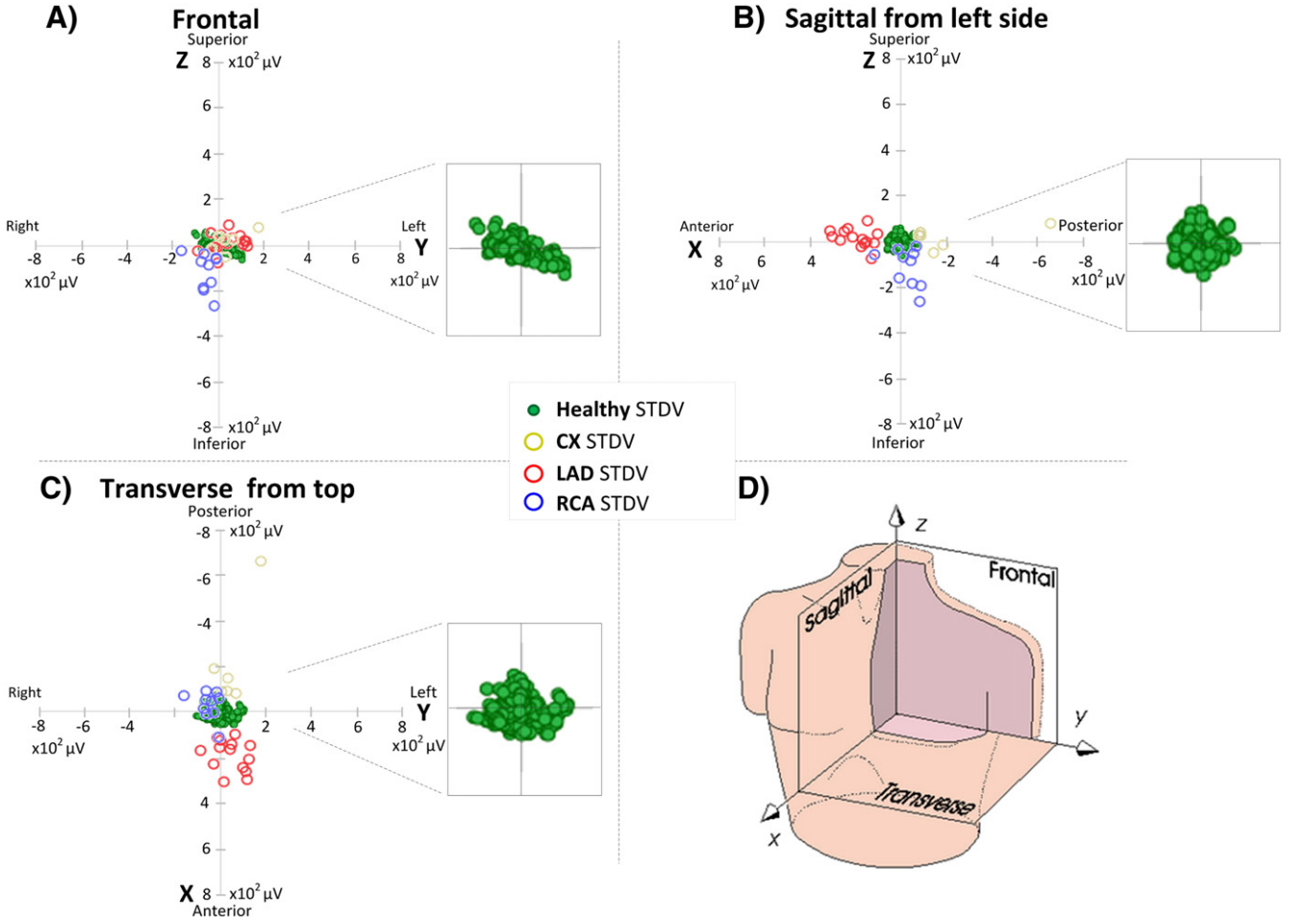


Fig. 2. Presentation of the STDV in the Franks' anatomical coordinate system defined by (X, Y, Z) to present the STDV anatomically in the human torso model [20,21]. Frontal (A), sagittal (B), and transverse (C) views on the STDV of the learning dataset in the Frank's coordinate system. Healthy subjects (green, n = 195) have an elliptic variation of STDV mainly observed in the frontal view and the magnitude of the STDV is not an optimal discriminator between healthy subjects and occlusions in the left anterior descending artery (LAD, red circles, n = 14), right coronary artery (RCA, blue circles, n = 10), and circumflex artery (yellow circles, n = 6).

subjects. The PCA coefficient matrix transformed the STDV into an orthonormal coordinate system. The magnitude of the orthonormalized STDV ($STDV_N$), expressed in normalized units (nu), was an optimal parameter to discriminate the CAO from the healthy subjects. The exact formula to calculate $STDV_N$ is given in Supplementary data. The spatial distribution of the $STDV_N$ for the CAO and control subjects in the learning dataset is presented in Fig. 3. Now, the $STDV_N$ of the control group have a spherical distribution, whereas the $STDV_N$ of the CAO are clustered away from the origin and can be discriminated from the control group by the magnitude of $STDV_N$. Moreover, the orientation of the $STDV_N$ of the CAO group was related to the territory of the occluded vessel (panel D). The view perpendicular on components C2 and C3 coincided with the AHA conventional mid ventricular short axis view of the heart [22]. The $STDV_N$ of the 14 occlusions in the LAD were projected counterclockwise from the C3 axis between 90 and 270 degrees (red circles). In the RCA, 9 out of 10 occlusions were projected clockwise between 180 and 270 degrees (blue circles). In the CX, 6 out of 6 occlusions were projected clockwise between 90 and 180 degrees (yellow circles). Overall, the orientation of the $STDV_N$ specified the territory of the occluded vessel in 29 out of 30 CAO (97%).

The magnitude of $STDV_N$ in the CAO and control groups

The $STDV_N$ in the CAO group were larger than in the control group (8.59 ± 4.93 vs. 1.59 ± 0.68 nu, $p < 0.001$, Fig. 4, upper panel). Even in the subgroup of acute occlusions that did not reach the STEMI criteria on the 12-leads ECG, the $STDV_N$ were still larger compared to the control group (6.05 ± 1.72 nu, $p < 0.001$). In the control group, there were no significant differences among the three physiological conditions (1.55 ± 0.61 vs. 1.70 ± 0.86 vs. 1.56 ± 0.62 nu, $p = 0.77$).

The RELF method showed high diagnostic accuracy to discriminate CAO from healthy subjects in the learning dataset (AUC: 1.000, 95% CI = 1.000–1.000, Fig. 4, lower left panel). With a cutoff at the 97.5 percentile of the control group which corresponded to 3.12 nu, the sensitivity (in CAO patients) was 30/30 (100%) and the specificity (in healthy subjects) was 190/195 (97%).

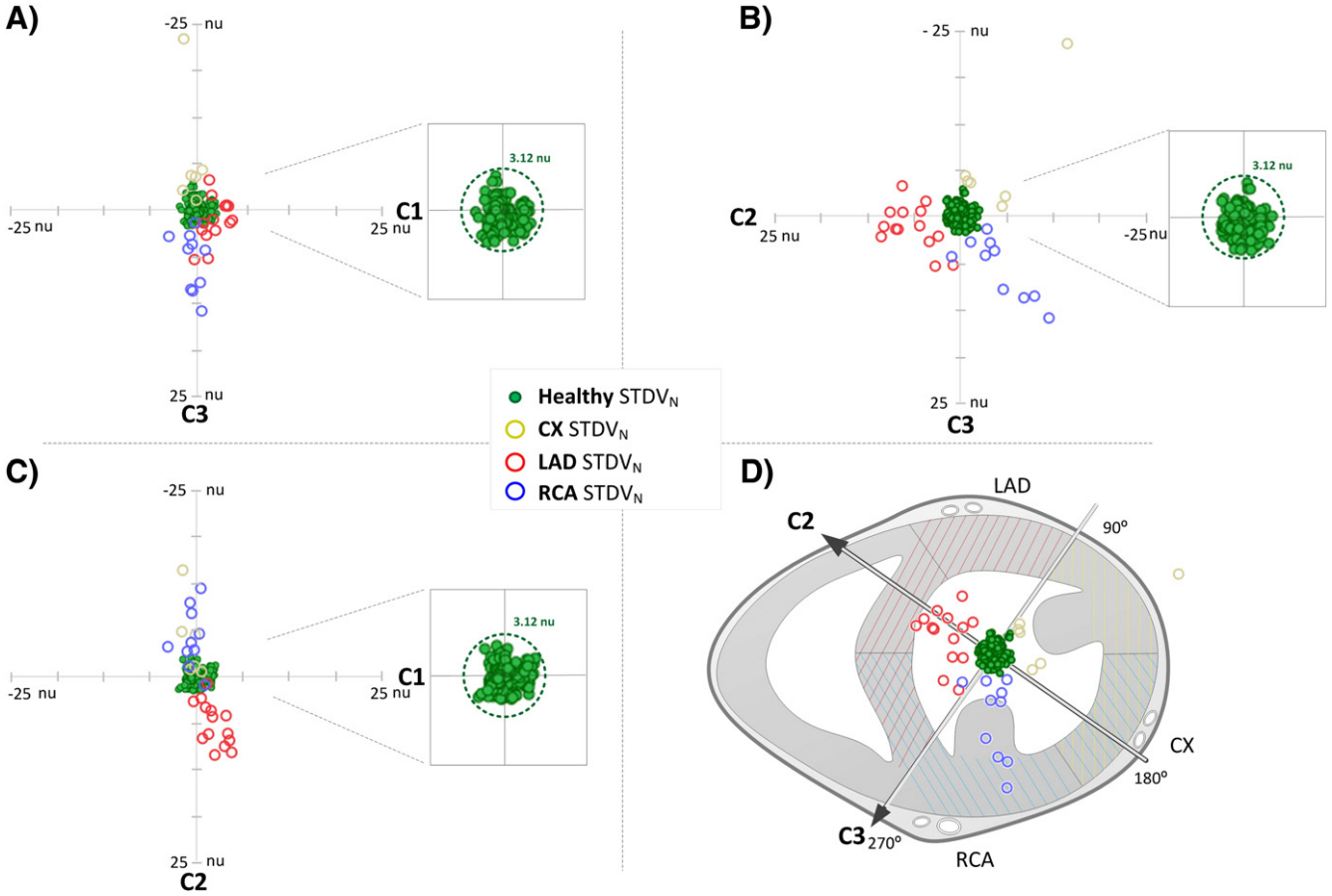


Fig. 3. Panels A, B, and C: presentation of the STDV of the learning dataset in an orthonormalized coordinate system (C1, C2, and C3) to discriminate optimally between the CAO and controls using the $STDV_N$ magnitude. The calculations of C1, C2 and C3 are given in Supplementary data. The distribution of $STDV_N$ in healthy subjects is spherical and the magnitude of the $STDV_N$ is an optimal discriminator between healthy subjects (green dots, n = 195) and occlusions in the left anterior descending artery (LAD, red circles, n = 14), right coronary artery (RCA, blue circles, n = 10), and circumflex artery (CX, yellow circles, n = 6). The dashed circle at 3.12 normalized units (nu) represents the 97.5 percentile of the magnitude of the $STDV_N$ of healthy subjects. Panel D: the view perpendicular on axes C2 and C3 fits with the AHA conventional mid ventricular short axis view of the heart, on which the three coronary vessels territories are delineated [22]. In this view, the $STDV_N$ of occlusions are oriented toward the corresponding territory.

Prospective validation of the RELF method

Prospective validation confirmed the results from the learning phase. The $STDV_N$ in the CAO group were significantly larger than in the control group (8.00 ± 4.50 vs. 1.90 ± 0.86 nu, $p < 0.001$, Fig. 4). In the subgroups of acute occlusions that did not reach the STEMI criteria on the 12-lead ECG, the $STDV_N$ were still larger compared to the control group (4.35 ± 1.92 nu, $p < 0.001$). Again, there were no significant differences among the three physiological conditions in healthy subject (1.72 ± 0.67 vs. 2.10 ± 0. 91 vs. 1.96 ± 0.97 nu, p = NS).

The RELF method showed high diagnostic accuracy to discriminate CAO from healthy subjects also in the validation dataset (AUC: 0.962, 95% CI = 0.930–0.995, Fig. 4). Applying the cutoff value of 3.12 (from the learning dataset), the sensitivity (in CAO patients) of the RELF method was 27/30 (90%) and the specificity (in healthy subjects) was 175/193 (91%). Additionally, after correct detection of CAO, the RELF method prospectively identified the region of the occluded vessel by the orientation of the $STDV_N$ in 26/27 (96 %). However, the magnitude of the $STDV_N$ was not associated with the region of the occluded vessel or with the location of the occlusion (data not shown).

The $STDV_N$ versus STDV

Paired comparison of the ROC curves of the magnitude of $STDV_N$ (RELF coordinate system) and the magnitude of STDV (Frank's coordinate system) is given in Fig. 4 (lower panels). In both learning and validation datasets, $STDV_N$ had better diagnostic accuracy than STDV (AUC in validation dataset: 0.962, 95% CI: 0.930–0.995 vs. 0.938, 95% CI: 0.895–0.981, p = 0.035).

RELF method versus conventional 12-lead ECG

The diagnostic accuracy of the RELF method was compared to the guidelines-STEMI criteria on the conventional 12-lead ECG (Fig. 5). In an illustrative case with a one-minute occluded circumflex artery, the RELF method (upper left panel) shows an $STDV_N$ magnitude (4.53 nu) greater than the cutoff value of 3.12 nu (green circle), indicating transmural ischemia. On the contrary, the corresponding 12-lead ECG (upper right panel) shows no

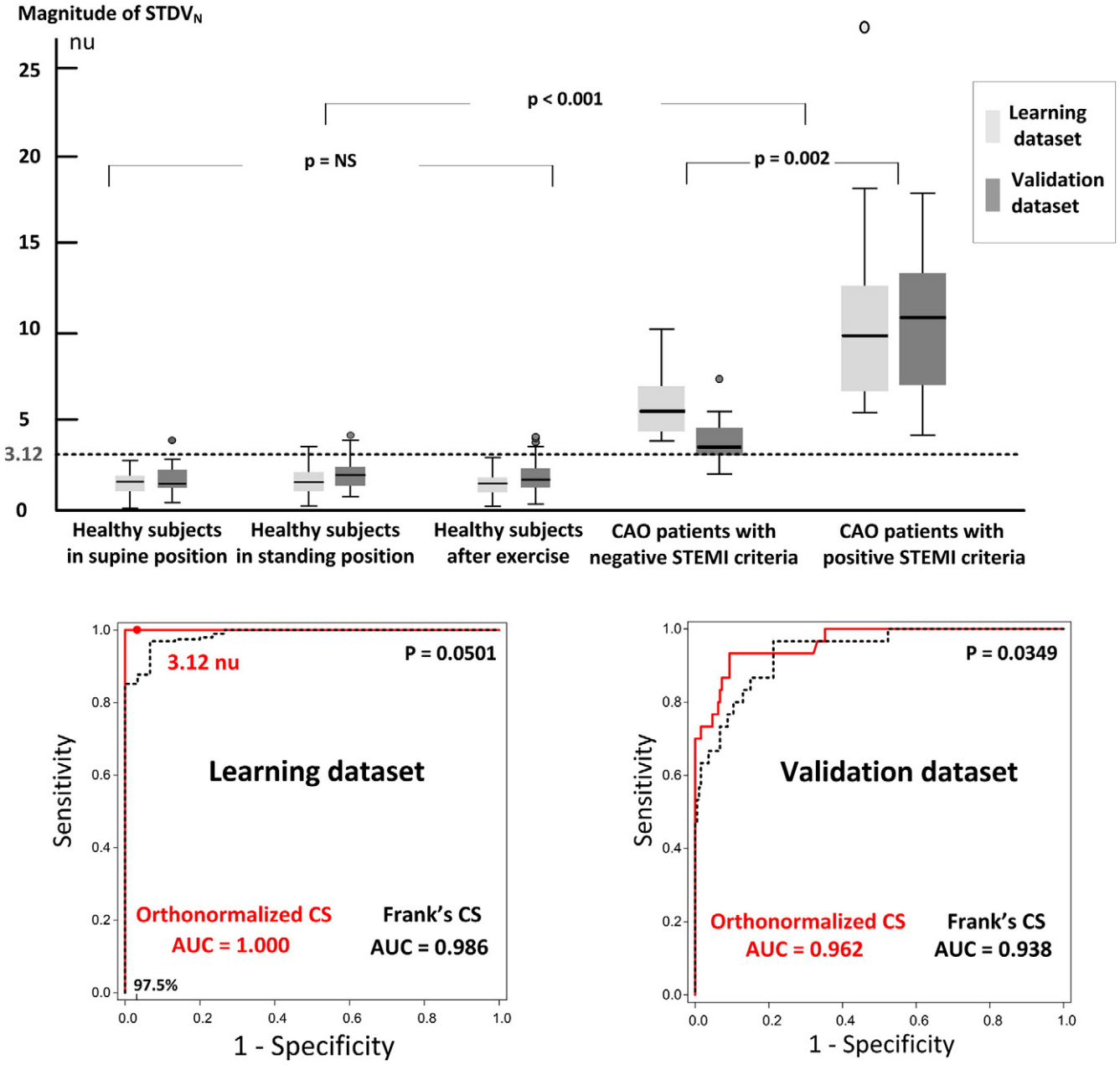


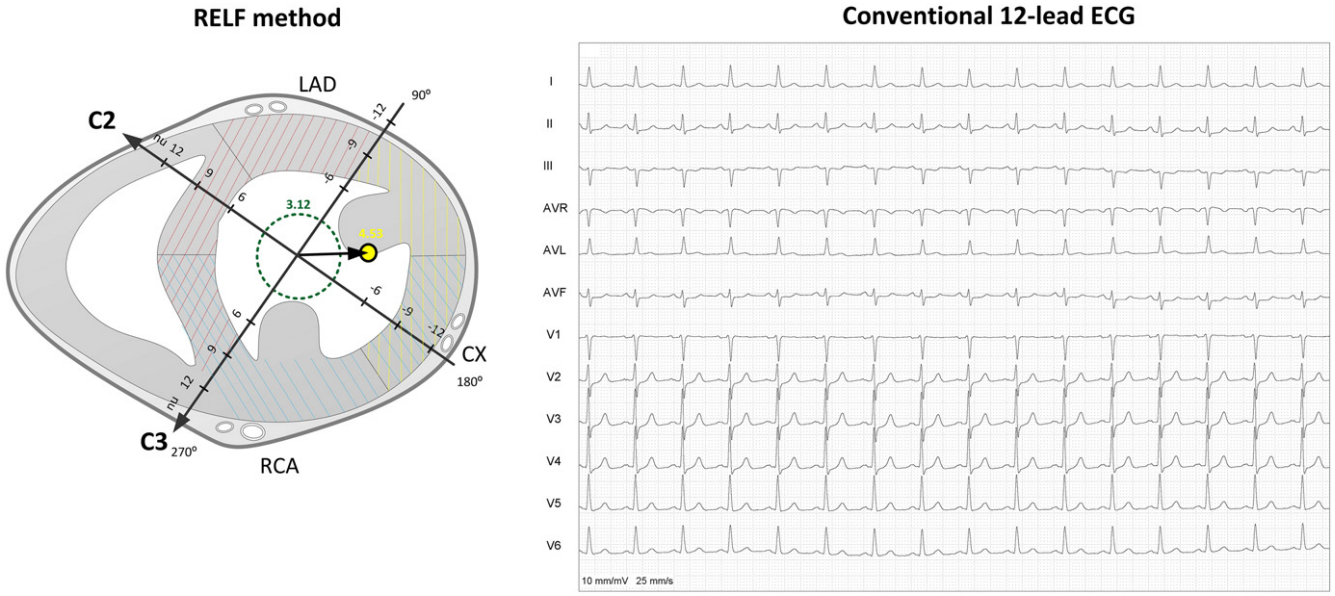
Fig. 4. Upper panel: distributions of the magnitude of the orthonormalized ST difference vector ($STDV_N$) in the healthy and coronary artery occlusion (CAO) subgroups. The dashed line at 3.12 normalized units (nu) represents the 97.5 percentile of the magnitude of $STDV_N$ of healthy subjects. The $STDV_N$ of CAO patients with negative and positive STEMI criteria are distributed above 3.12 nu. Lower panels: receiver operating characteristics curves of STDV in Frank's coordinate system and $STDV_N$ in the orthonormalized coordinate system. In the learning dataset the magnitude of the $STDV_N$ is a better discriminator compared to the magnitude of STDV in Frank's coordinate system. The enhanced value of using an orthonormalized coordinate system was confirmed in the independent validation dataset.

ST elevation but ST depression of more than 0.05 mV in leads V2–V4, fulfilling the STEMI criteria. In the validation dataset, the sensitivity of the RELF method versus the 12-lead ECG was respectively 90 vs. 73% ($p = 0.13$) and the specificity was 91 vs. 75% ($p < 0.001$, paired comparison McNemar tests, Fig. 5 lower panel). Overall, combining the learning and validation dataset, the RELF method was more sensitive (95 vs. 65%, $p < 0.001$) and more specific (94 vs. 85%, $p < 0.001$). Also when taking into account the coronary territory, the sensitivity of the RELF method was significantly higher than that of the 12-lead ECG (for LAD occlusions 27/27 vs. 19/27, $p = 0.008$, for RCA occlusions 20/22 vs. 15/22, $p = 0.13$, and for CX occlusions 9/10 vs. 5/10, $p = 0.13$, Supplementary Table 1).

A flow diagram of the study design and results of the RELF method in the learning and validation dataset are given in Supplementary Fig. 2.

Discussion

There is a need for an easily applicable and more accurate ECG method to detect transmural ischemia. The accuracy of the initial 12-lead ECG for diagnosing transmural ischemia is relatively poor with reported sensitivities between 30 and 75% and specificities between 81 and 97% depending on the definitions of 'significant' ST elevation and on the coronary



			LEARNING DATASET				VALIDATION DATASET				COMBINED			
			RELF method		Total	p	RELF method		Total	p	RELF method		Total	p
			+	-			+	-			+	-		
CAO	STEMI criteria	+	13	0	30	<0.001	21	1	30	0.13	38	1	60	<0.001
		-	17	0			6	2			19	2		
Healthy subjects	STEMI criteria	+	0	11	195	0.21	8	41	193	<0.001	8	52	388	<0.001
		-	5	179			10	134			15	313		
Sensitivity	57 %		100 %				73 %	90 %			65 %	95 %		
Specificity	94 %		97 %				75 %	91 %			85 %	94 %		

Fig. 5. Upper panels: illustrative case during acute occlusion of the left circumflex coronary artery with magnitude of $STDV_N$ above the cutoff (green circle), whereas the simultaneous 12-lead ECG shows no ST elevation but ST depression of more than 0.05 mV in leads V2–V4 fulfilling the "STEMI equivalent" criterion indicative for occlusion of the LCx [19]. Lower panels: comparison between RELF method and STEMI criteria (including the criteria for STEMI equivalent) in the learning and validation datasets.

territory involved [7,8,23]. The sensitivity for the left ascending coronary artery was reported between 72 and 85%, for the right coronary artery between 71 and 77%, and only between 48 and 50% for the left circumflex coronary artery [9,13]. Lead systems that included the posterior chest leads V7 through V9 showed a notable increase in sensitivity to detect posterior ischemia [15,16]. The current guidelines additionally, suggest to compare the 12-lead ECG to a previous ECG when available, although there are no quantitative criteria for comparison to identify 'significant' ST changes that are related to transmural ischemia [14].

In the current study, we introduced and developed a novel method (RELF) for detection of transmural ischemia. The RELF method is easily applicable (3 reproducible leads) and it is significantly more sensitive and specific than the 12-lead ECG to detect transmural ischemia. The larger sensitivity of the RELF method over the conventional STEMI criteria is inherent to the methodology of quantitative intra-individual comparison of ST levels by using the principles of vectorcardiography as was demonstrated by others [24–29]. In these studies, the magnitude of the ST difference vector (STDV) was the most sensitive variable to detect acute transmural ischemia. ter Haar et al. found a sensitivity of 80% after 3 minutes of coronary occlusion compared to 55% with the 12-lead ECG [24]. Our method showed a sensitivity of 95% after only 1 minute of occlusion. Moreover, in these vectorcardiographic studies, the specificity in healthy subjects is not well documented. A low specificity has been reported by Nørgaard et al. in 21 healthy subjects, as one third had an STDV magnitude above the ischemic cutoff [30]. The RELF method obtained an overall specificity of 94% in 30 healthy subjects.

Although in this study the RELF method was not compared to other vectorcardiographic methods, three novel elements in the RELF method can explain why the sensitivity and specificity were higher than those reported with standard vectorcardiographic methods. First, we introduced a novel lead (lead 1) measuring the voltage difference between the right shoulder and third intercostal space at parasternal level, 4.5 cm above the standard V2 of a 12-lead ECG. The area above V2 is sensitive for detection of CAO related to the circumflex and right coronary artery [31–33]. Second, prior studies on STDV in healthy subjects recorded the reference ST vector in solely supine position [27], whereas we used an average of the ST vectors in standing position, supine position, and after mild exercise.

Third, our data showed that the magnitude of the STDV in the Frank's coordinate system was not an optimal discriminator due to the elliptic distribution of the STDV of healthy subjects. The orthonormalization of the STDV in the RELF method converted the magnitude of the orthonormalized STDV ($STDV_N$) to an optimal discriminator.

Clinical applications

Currently, multiple systems construct a 12-lead ECG from a reduced number of leads (usually from the EASI lead system) [34–36]. These methods have at best the accuracy of a 12-lead ECG for detection of CAO. Compared to the standard 12-lead ECG, the RELF method is more accurate for early diagnosis of transmural ischemia and requires only 3 leads which can be easily positioned and reproduced by untrained personnel. Moreover, the algorithm to determine the discriminatory vector variable ($STDV_N$) can be incorporated into small handheld devices. Therefore, when applied during chest pain or discomfort, an objective personal alarm for STEMI can be obtained rapidly and precipitate medical attendance. By simultaneously integrating a validated automated questionnaire for life-threatening symptoms, such a carry-on tool could reliably guide the patient to seek medical care according to, for example, three levels of medical urgency. The first level (code RED) could be for patients with ongoing chest pain associated with ST elevation. This is the highest risk group for primary ventricular fibrillation and sudden cardiac death [37]. The fact that the device has measured a validated abnormality in these patients could decrease their feelings of embarrassment, the fear to trouble others, and their consideration that their symptoms are not actually serious [4–6] and therefore could shorten their delay to seek urgent medical help. The second level (code ORANGE) is for patients with ongoing chest pain and no detectable changes of ST level. These patients could be advised by the algorithm to make consecutive repeat measurements and to answers questions that can exclude immediate life-threatening conditions. This category could have the advice to seek medical attention within the next two hours of ongoing chest pain. The third category (code GREEN) is for patients with short episode(s) of chest pain (<20 min) not accompanied by change in ST level. These patients could also be advised by the algorithm to make consecutive repeat measurements and to answers questions that can exclude immediate life-threatening conditions. This category could be advised to seek medical help, for example within the first 12 hours. The method however works on the condition that RELF reference measurements of the individual are available. In further application of the method in handheld devices, the algorithm should immediately indicate code RED if a patient with ongoing chest pain cannot perform — by circumstances — an accurate recording. Patients who might benefit from such a carry-on tool are those at risk for acute coronary occlusion, according to their cardiovascular risk profile or clinical history. Also patients with aspecific complaints, such as those suggestive for Prinzmetal angina are candidates for this ambulatory diagnostic tool.

Future perspectives

A large group of subjects including subgroups of patients and control subjects will be studied by custom-built 3 lead handheld devices that can easily apply the RELF method (in preparation).

The RELF method opens perspective for further simplification by converting the simultaneous 3 lead measurements into a series of 3 consecutive measurements by a single lead device. As the method uses one common negative pole located at the right shoulder — which is electrically equal to the right hand [38] it enhances the self-applicability to detect transmural ischemia via a completely cordless system depicted as 'RELF-self' method (Fig. 6). The RELF-self method uses the right hand as the negative pole R(−) in each measurement.

Study limitations

The universal definition of MI criteria was defined to be applied on patients with prolonged chest pain. Therefore, the true sensitivity of the 12-lead ECG might be underestimated with only one minute of occlusion. With occlusions longer than one minute, we expect an increase in ST elevation and consequently, an increase in the sensitivity of both the 12-lead ECG and the RELF method.

The RELF event recordings in the CAO were performed while the patients were supine during balloon inflation. However, our data from healthy subjects indicated that the position of the subject does not significantly change the discriminatory variable. Therefore we expect that sitting or standing will not significantly affect the length of the $STDV_N$ during acute coronary occlusion, although this still needs to be validated.

The orthonormalization of ST vectors was based on 30 healthy subjects during different physiological conditions. A more representative sample of the healthy population might improve the orthonormalization parameters.

The validity of the RELF method in subgroups of healthy subjects such as in very obese or elderly subjects, needs to be further explored. The validity of the method has also to be confirmed in patients with occlusion of left main, in acute occlusions on top of chronic occlusions, in patients with conduction and rhythm disturbances, and in patients with variants of QRST morphology such as left ventricular hypertrophy, early repolarization, Brugada syndrome, hyperkalemia and hypothermia. Nevertheless, the current validation included 15 patients with conduction abnormalities (right bundle branch block or left anterior hemiblock) and two patients with chronic atrial fibrillation.

The RELF method relies on the positioning of the precordial electrode (E). Although we did not explore the position boundaries of electrode E, prior literature showed that variations within a radius of 2 cm from this specific position do not affect the intra-individual ST segment changes [39].

The absence association between the magnitude of $STDV_N$ and the region of the occluded vessel or with the location of the occlusion might be due to the low number of patients.

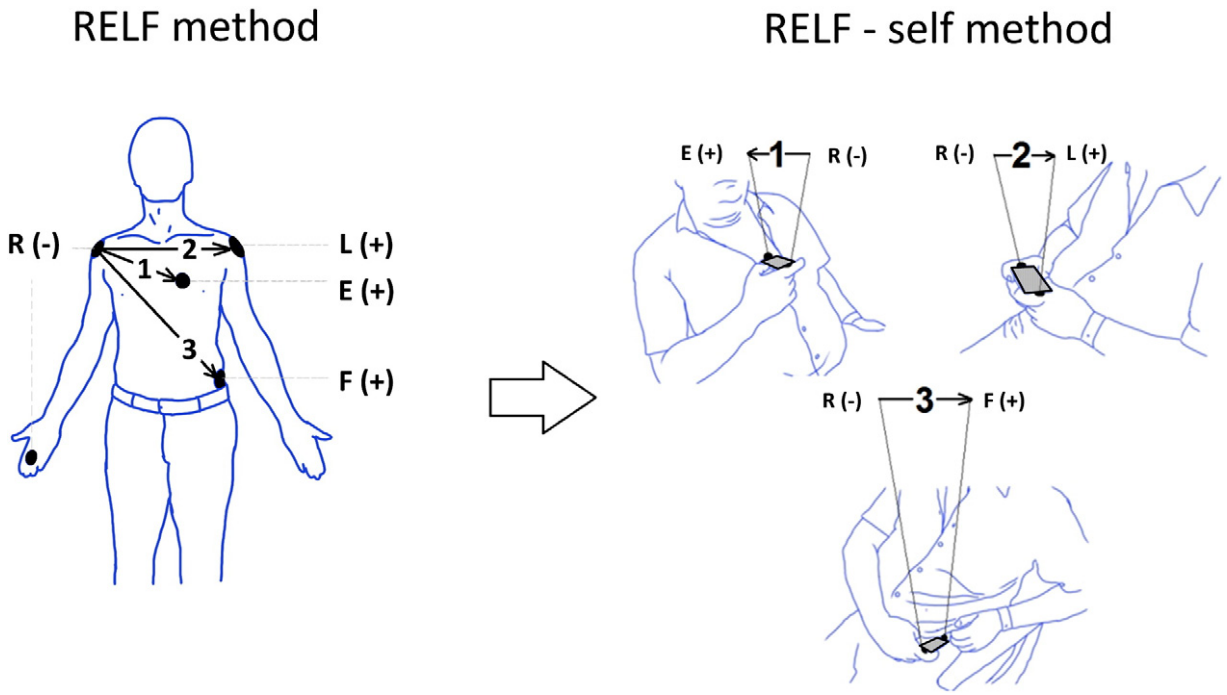


Fig. 6. RELF method (left panel) as a methodological basis for handheld devices without the use of wired electrodes (RELF-self, right panel). The voltage on the right hand and the right shoulder curvature is the same [38].

Conclusions

We introduced and validated a highly accurate method (RELF method) to detect acute occlusion related ischemia. The diagnostic accuracy of this method is superior to the 12-lead ECG criteria for STEMI due to three methodological improvements for the intra-individual comparison of ST vectors. Although further evaluation in specific subgroups is mandatory, the RELF method is the first validated method for self-detection of transmural ischemia that can be applied by 3-lead handheld devices. This method should be further validated with single lead devices or smart phones using sequential recordings of the different RELF leads.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jelectrocard.2015.11.007.

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