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ORIGINAL ARTICLE

Clinical validation of a 13-lead electrocardiogram derived from a self-applicable 3-lead recording for diagnosis of myocardial supply ischaemia and common non-ischaemic electrocardiogram abnormalities at rest

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Aims In this study, we compare the diagnostic accuracy of a standard 12-lead electrocardiogram (ECG) with a novel 13-lead ECG derived from a self-applicable 3-lead ECG recorded with the right exploratory left foot (RELF) device. The 13th lead is a novel age and sex orthonormalized computed ST (ASO-ST) lead to increase the sensitivity for detecting ischaemia during acute coronary artery occlusion.

Methods and results A database of simultaneously recorded 12-lead ECGs and RELF recordings from 110 patients undergoing coronary angioplasty and 30 healthy subjects was used. Five cardiologists scored the learning data set and five other cardiologists scored the validation data set. In addition, the presence of non-ischaemic ECG abnormalities was compared. The accuracy for detection of myocardial supply ischaemia with the derived 12 leads was comparable with that of the standard 12-lead ECG ($P = 0.126$). By adding the ASO-ST lead, the accuracy increased to 77.4% [95% confidence interval (CI): 72.4–82.3; $P < 0.001$], which was attributed to a higher sensitivity of 81.9% (95% CI: 74.8–89.1) for the RELF 13-lead ECG compared with a sensitivity of 76.8% (95% CI: 71.9–81.7; $P < 0.001$) for the 12-lead ECG. There was no significant difference in the diagnosis of non-ischaemic ECG abnormalities, except for Q-waves that were more frequently detected on the standard ECG compared with the derived ECG (25.9 vs. 13.8%; $P < 0.001$).

Conclusion A self-applicable and easy-to-use 3-lead RELF device can compute a 12-lead ECG plus an ischaemia-specific 13th lead that is, compared with the standard 12-lead ECG, more accurate for the visual diagnosis of myocardial supply ischaemia by cardiologists.

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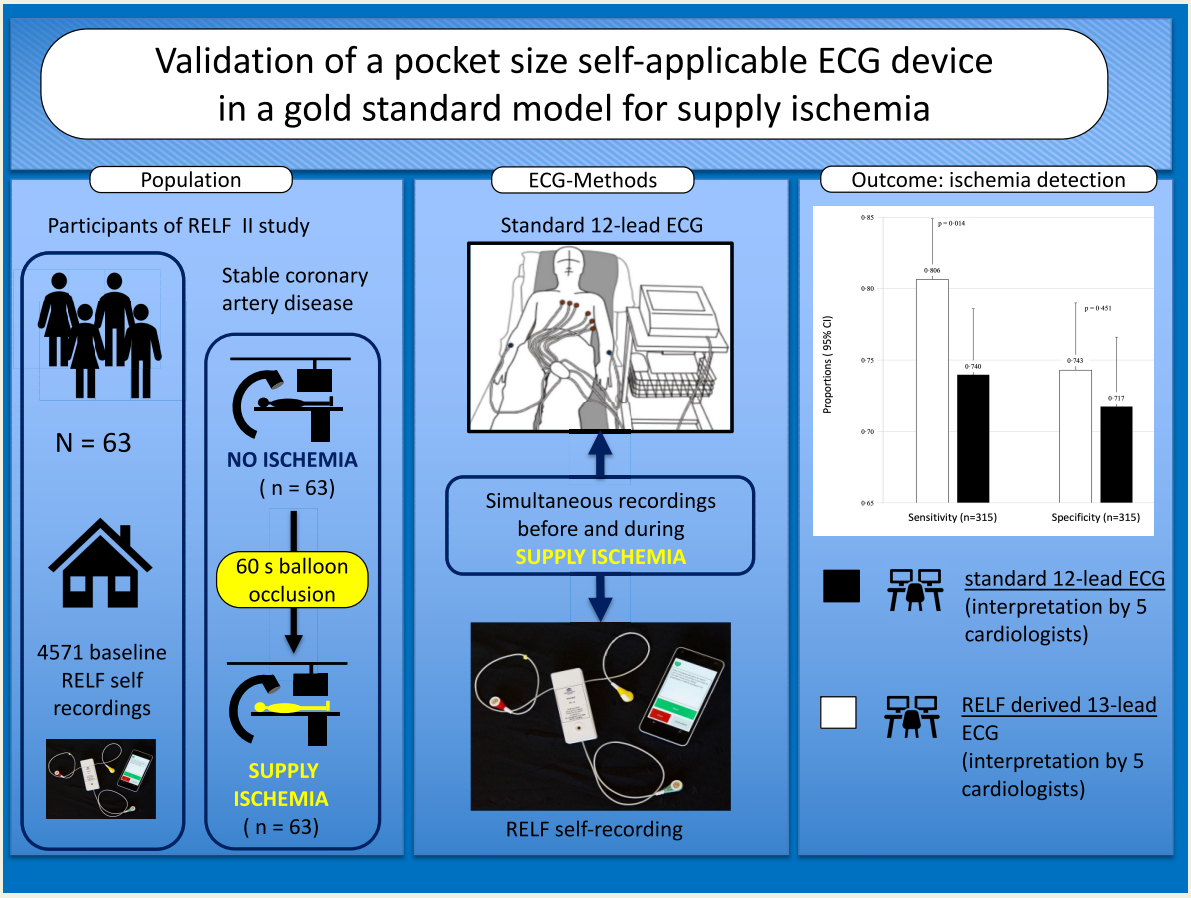
Graphical Abstract



Keywords Acute coronary syndrome • Pre-hospital • Diagnosis • Handheld ECG device • Mobile app • Personalized health

Introduction

Patient delay during myocardial infarction due to acute coronary artery occlusion (ACAO) is associated with out-of-hospital ventricular fibrillation and irreversible myocardial necrosis.[1–3] Detection of ST elevation on the conventional 12-lead electrocardiogram (ECG) is the cornerstone of early diagnosis and treatment of ACAO. To avoid patient delay, a 3-lead right exploratory left foot (RELF) device for self-recording and detection of ACAO has recently been developed and feasibility has been demonstrated for most patients with coronary artery disease (CAD). For detection of the earliest phase of ACAO, the self-applicable RELF device automatically compares the ST segment from a three-dimensional recording with multiple previous RELF recordings of the patient, rendering it faster and more accurate than the visual interpretation of a 12-lead ECG by cardiologists.[4,5] The device is able to detect ST changes in three dimensions, implicating the detection of ST elevations or ST depressions.

In the early phase of the widespread use of the self-applicable and automated device, it is desirable to reconstruct a 12-lead ECG from a 3-lead RELF recording to allow parallel phase validation of a RELF recording by physicians. As a 3-lead recording can be expanded to a 12-lead ECG by universal linear transformation,[6] we developed an algorithm for reconstruction of a 12-lead ECG allowing conventional rule-based diagnosis of myocardial ischaemia at rest (supply ischaemia).

To optimize the use of the three-dimensional ST data, we also constructed the ST vector lead (13th lead) that represents the lead with the highest level of ST change in an orthonormalized space.

In this study, we first tested the hypothesis that a 12-lead ECG derived from a 3-lead RELF recording is non-inferior to the standard 12-lead ECG for detection of myocardial ischaemia at rest and that the novel complementary derived 13th lead increases the sensitivity and accuracy. Subsequently, we tested the hypothesis that the derived 12-lead ECG is as accurate as the standard 12-lead ECG for the diagnosis of sinus rhythm, atrial fibrillation, atrio-ventricular block, Q-waves, bundle branch block, and fascicular block at rest.

Methods

Subjects and data sets

A database of 110 patients and 30 healthy subjects was collected for this study from 2 prior studies (*Table 1* and Supplementary material online,

Figure S1).[4,5] The database was split into a learning and a validation data set. The learning data set included 30 healthy subjects (50% women) with mean age 40 years (SD 11.0) with office recordings (15-lead CardioTek; $n = 767$) during different resting physiological conditions (5 in supine position, 3 in standing position, and 5 in supine position immediately after 10 genuflexions in standing position) and 51 patients with stable angina pectoris (41% women) with mean age 70 (SD 7.0). Each patient had one recording before and one during a 60 s coronary artery occlusion during elective percutaneous coronary intervention (PCI) with a total of 60 effective coronary occlusions (from RELF I study).[4]

The validation data set included 59 other patients (27% women) with stable angina pectoris who performed ambulatory self-recording during daily life conditions ($n = 4571$). Each patient had an additional recording before and during a 60 s coronary artery occlusion during elective PCI with a total of 63 coronary occlusions (RELF II study).[5] Patient characteristics of the RELF I and RELF II studies have been published previously.[4,5] The clinical trial was approved by the central and local ethical committees (Belgium Registration Number: B670201628891). The device was approved for clinical investigation trial by the Federal Agency for Medicines and Health Products (AFMPS/80M0648/). The trial is registered with ClinicalTrials.gov (NCT02983396). All patients provided written informed consent.

Method for deriving a 12-lead electrocardiogram from a 3-lead recording

The matrices to convert a 3-lead recording to a 12-lead ECG were developed within the learning data set consisting of 150 simultaneous recordings of the 3-lead RELF ECG and the standard 12-lead ECG using the CardioTek EP 15-lead system (see Supplementary material online, *Figures S1* and *S2*). The sampling rate was 1 kHz and the samples were gathered for 12 s. From each of the 15 leads, 12 000 points were concatenated to generate an input matrix for men and women, respectively. A linear regression fitting process was used to yield the sex-specific transformation matrices to derive the 12 leads from the recorded 3 RELF leads.[6] The derived 12 leads were printed in a standard ECG format.

Table 1 Clinical and angiographic characteristic of subjects and patients

	RELF I		RELF II
	Healthy subjects	Patients with stable angina	Patients with stable angina
Sex			
Male	15	30	43
Female	15	21	16
Age, years	40.0 (11.0)	70.0 (7.0)	64.4 (9.7)
Weight, kg	74 (12)	78 (13)	82.6 (14.8)
Height, cm	175 (7)	167 (8)	171.1 (14.8)
Body mass index, kg/m^2	24 (3.2)	28 (4.6)	28.2 (5.0)
Stable angina pectoris	0	51	59
Balloon occlusions	—	60	63
Left main artery	—	1	0
Left anterior descending artery	—	27	33
Cirumflex artery	—	10	15
Right artery	—	22	15

Detection of myocardial ischaemia

Ten cardiologists (C1–C10) independently evaluated all the printed, anonymized, and unpaired standard and derived ECGs in random order from the patients with CAD with and without 60 s of coronary artery balloon inflation, based on predefined conventional criteria (see Supplementary material online).[7] Five cardiologists (C1–C5) scored the learning data set and five other cardiologists (C6–C10) scored the validation data set.

The age and sex orthonormalized ST coordinate system

The goal of an orthonormalized ST coordinate system is to perform an orthonormal measurement of the age-adjusted ST vector by deriving three orthogonal unit vectors from the RE, RL, and RF leads of the RELF system.[4] In an orthonormal measurement both of the following requirements are fulfilled: (i) The three measured components of the ST vector are orthogonal in a mathematical sense. (ii) Each of the three components of the ST vector is detected with the same sensitivity; hence, the measurements are normalized. To obtain these three unit vectors (C1, C2, and C3), a group of all available age-adjusted normal ST values from leads RE, RL, and RF from the RELF I and II studies ($n = 5338$, 1758 for women and 3580 for men) were analysed by principal component analysis to find a sex-specific matrix by which the RE, RL, and RF lead vectors are converted to three sex-specific orthogonal unit vectors having the same sensitivity for normal ST vector variations in the defined male and female population (see Supplementary material online, *Figure S2*). The age and sex orthonormalized computed ST (ASO-ST) vector is defined by the ST levels in the sex-specific orthogonal coordinate system (C1, C2, and C3).

The age and sex orthonormalized ST lead as the 13th lead

The ASO-ST lead aims to represent the lead with highest sensitivity for an abnormal ST amplitude caused by ischaemia during balloon occlusion. To obtain the ASO-ST lead along the ASO-ST vector, the values were calculated as a scalar product of the heart dipole $\vec{P}$ and the ASO-ST lead vector $\vec{c}$ according to the formula:

$$\text{Lead value} = \vec{|c|} \cdot \vec{|p|} \cdot \cos\alpha$$

where $\vec{p}$ is the heart dipole in sex-specific coordinate system (C1, C2, and C3), $\vec{c}$ is the ASO-ST lead vector in sex-specific coordinate system (C1, C2, and C3), and α is the angle between the two vectors in the same coordinate system.

The amplitude on the ASO-ST lead (normalized units = nu) is scaled according to the magnitude of the ASO-ST vector (see formula above). As such, the cut-off for normal ST vector magnitude in the ASO-ST coordinate system (3.22 and 2.82 nu for the RELF I and II study population, respectively) is scaled to 1 mm on the ECG. When the ASO-ST level is below the cut-off, meaning that the algorithm does not detect abnormal ST elevation, then the virtual lead is not derived (see Supplementary material online, *Figure S2*).

Non-ischaemic electrocardiogram diagnoses

Ten cardiologists (C1–C10) individually received predefined 12-lead ECG criteria (Supplementary material online) to define sinus rhythm,

atrial fibrillation, AV-conduction block, right or left bundle branch block, fascicular block, and pathologic Q-waves. Each cardiologist evaluated independently all the printed, anonymized, and unpaired standard and derived ECGs in random order from patients with and without 60 s of coronary artery balloon inflation. Five cardiologists (C1–C5) scored the learning data set and five other cardiologists (C6–C10) scored the validation data set.

Statistical analysis

Continuous variables are expressed as mean ± SD. Agreement between two raters on the same ECG and between the derived ECG and the standard 12-lead ECG within the same rater were quantified with Kappa statistics. The sex-specific transformation matrices to derive the 12 leads from the known 3 RELF leads were obtained from a linear regression fitting process (SPSS Statistics 27). The McNemar test was used for paired comparison between the dichotomized diagnosis with the derived ECG and the standard 12-lead ECG. *P*-values of <0.05 were considered statistically significant. We conducted the calculations necessary for the forest plot, including weighting of cases according to sample size and variance, using a previously published template.[8] The comparison of accuracy, sensitivity, and specificity is given by proportions and their 95% confidence interval (CI) obtained from bootstrap for paired-samples proportions statistics based on 1000 bootstrap samples (SPSS Statistics 27). For the non-inferiority test of paired-samples proportions (McNemar test), we set the margin for inferiority arbitrarily at −1.0%.

Results

The sex-specific transformation matrices to derive the 12-lead electrocardiogram

The learning data set contained 150 simultaneous 3- and 12-lead ECG recordings. The 12 s segments from each of the 15-lead recordings were concatenated to form an all-embracing sex-specific data set. The sex-specific transformation matrices to derive the 12 leads from the known 3 RELF leads are given in *Figure 1* and Supplementary material online, *Table S1*. The three RELF leads contribute to a different degree in the development of the precordial leads among men and women, which is illustrated in *Figure 2*.

Detection of myocardial ischaemia with the derived and the standard 12-lead electrocardiogram

Five cardiologists (C1–C5) independently scored 236 ECGs of the 60 interventions in the learning data set. Two ECG pairs did not qualify for reading due to noise artefacts in at least one of the pair members. Five other cardiologists (C6–C10) each independently scored 252 ECGs of the 63 interventions in the validation data set.

In the learning data set, the mean accuracy for detection of myocardial supply ischaemia (i.e. 60 s of coronary artery occlusion during elective PCI) with the derived 12 leads was 76.2% (95% CI: 69.1–83.2) which is comparable with 72.9% (95% CI: 66.0–79.8) with the standard 12-lead ECG ($P = 0.118$; *Figure 3*). In the validation data set, the mean accuracy for detection of myocardial supply ischaemia with the derived 12 leads was 74.1% (95% CI: 67.4–80.8) which is comparable with 72.8% (95% CI: 66.1–79.5) with the standard 12-lead ECG ($P = 0.575$). The homogeneity of the accuracy within both sets and between cardiologists is presented in *Figure 3*. The difference of the bootstrapped ($n = 1000$) paired-sampled proportions is +3.2% (95% CI: −0.2–7.3), indicating that the accuracy for detection of myocardial ischaemia with the derived 12-lead ECG is significantly non-inferior to that with the standard 12-lead ECG. When both studies were combined, the accuracy for detection of myocardial supply ischaemia with the derived 12 leads was 75.1% (95% CI: 70.2–80.0) which is comparable with 72.8% (95% CI: 68.0–77.6) with the standard 12-lead ECG ($P = 0.126$).

The sensitivity and specificity of the derived 12 leads for detection of myocardial ischaemia are analysed in analogy and given in Supplementary material online, *Figure S3*.

Detection of myocardial ischaemia with the derived 13 leads

In the validation data set, the diagnostic characteristics of the derived 13-lead ECG were compared by paired analysis with those of a simultaneously recorded standard 12-lead ECG for the detection of myocardial ischaemia at rest (*Figure 4*). The validation group of five cardiologists scored a higher accuracy rate with the derived 13-lead ECG compared with the standard 12-lead ECG (0.775 vs. 0.729; $P = 0.024$) driven by a homogeneously higher sensitivity rate (0.806 vs. 0.740; $P = 0.014$) and an equal specificity (0.743 vs. 0.717; $P = 0.451$). Subanalysis of sensitivity according to coronary vessel is underpowered but indicates that the higher sensitivity is independent of the coronary vessel territory (see Supplementary material online, *Figure S4*).

The incremental diagnostic effect of adding the age and sex orthonormalized ST lead criterion

The 10 participating cardiologists were instructed to additionally diagnose myocardial ischaemia, independently of the ischaemia criteria on the other 12 leads, when an ST level of at least 0.1 mV was observed in the ASO-ST lead. By adding the ASO-ST lead criterion for diagnosis of myocardial supply ischaemia the accuracy of the 13-lead ECG increased to 77.4% (95% CI: 72.4–82.3) compared with the mean accuracy of all (derived and standard) 12-lead ECGs of 74.0% (95% CI: 70.6–77.4; $P < 0.001$; *Figure 5*). The sensitivity increased homogeneously between the 10 experts from 76.8% (95% CI: 71.9–81.7) to 81.9% (95% CI: 74.8–89.1; $P < 0.001$) and the specificity remained unchanged from 70.5% (95% CI: 65.8–75.3) to 72.0% (95% CI: 65.3–78.8; $P = 0.128$; *Figure 5*). An example of the additional sensitivity of the ASO-ST lead criterion is shown in *Figure 6*.

Non-ischaemic electrocardiogram diagnoses with the derived 12 leads

The learning data set contained 118 standard 12-lead ECGs and 118 derived ECGs. Two ECG pairs were not qualified for reading due to noise artefacts in at least one of the pair members. The validation data set contained all 126 standard 12-lead ECGs and all 126 derived ECGs.

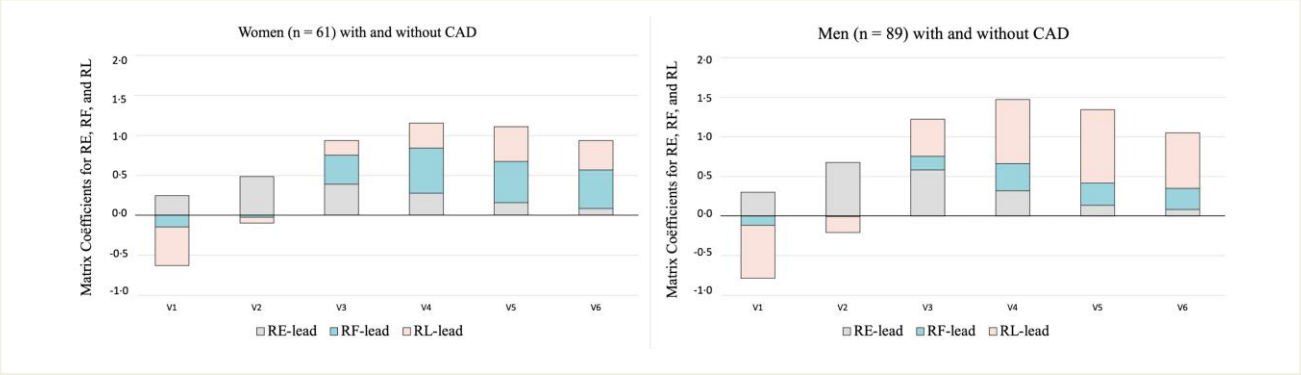


Figure 1 The sex-specific contributions of the three right exploratory left foot leads (RE, RL, and RF) in the derivation of the precordial Leads V1–V6 in women (left panel) and men (right panel) in the learning data set ($n = 150$ paired electrocardiograms from 61 women and 89 men with and without coronary artery disease, including 60 paired electrocardiograms during balloon occlusion).

The clinical validity of the derived 12-lead ECG for diagnosis of non-ischaemic abnormalities is presented in the validation data set in *Table 2*. There was no significant difference between the standard 12-lead ECG and the derived ECG for the diagnosis of sinus rhythm (94.9 vs. 93.7%; $P = 0.791$), atrial fibrillation (5.1 vs. 4.6%; $P = 0.508$), AV-conduction delay (10.3 vs. 11.4%; $P = 0.477$), left bundle branch block (1.3 vs. 1.6%; $P = 0.815$), right bundle branch block (10.3 vs. 10.0%; $P = 0.864$) and fascicular block (13.8 vs. 13.3%; $P = 0.780$). The intra-observer agreement between standard and derived ECG was comparable with the inter-observer agreement on the standard 12-lead ECG and the inter-observer agreements on the derived ECG: sinus rhythm (respectively κ 0.840 vs. 0.845 vs. 0.852), atrial fibrillation (κ 0.864 vs. 0.852 vs. 0.892), AV-conduction delay (κ 0.419 vs. 0.486 vs. 0.471), right bundle branch block (κ 0.704 vs. 0.751 vs. 0.681), and fascicular block (κ 0.649 vs. 0.580 vs. 0.674). However, the standard ECG detected more Q-waves compared with the derived ECG (25.9 vs. 13.8%; $P < 0.001$) and the intra-observer agreements between standard and derived ECG was relatively low for Q-wave detection (κ 0.493) when compared with the inter-observer agreements on the standard 12-lead ECG (κ 0.579) and the derived ECG (κ 0.747). This indicates that the presentation of Q-waves is discordant between standard and derived ECG.

Discussion

In this clinical study, we found that for the detection of myocardial ischaemia, a 12-lead ECG derived from a single 3-lead RELF recording is non-inferior to the standard 12-lead ECG. We focused on the accuracy for the diagnosis of supply ischaemia at rest by using a controlled, temporary coronary occlusion during elective PCI as the 'golden standard'. To our knowledge, this is the first clinical validation of a derived 12-lead ECG by expert clinicians applying rule-based diagnostic criteria for myocardial ischaemia (including ST elevation, ST depression, and T-wave inversion) in this setting.

Additionally, we investigated a novel lead that is automatically derived from the 3-lead RELF recording and could confirm the hypothesis that this lead increases the sensitivity and accuracy for diagnosis of myocardial ischaemia at rest compared with the 12-lead ECG irrespective of the site of coronary occlusion. This ASO-ST lead is derived in the direction of the orthonormalized ST vector and can therefore display a virtual lead with maximum ST elevation also in an area that is blinded in the conventional 12-lead display (see example in *Figure 6*). Leads additional to the standard 12-lead ECG, such as V7–V9[9–12] and the right precordial leads[13] increased the sensitivity for myocardial ischaemia in previous studies. However, these additional leads, that compensate for the presence of 'blind spots' in the standard 12-lead presentation, are not only impractical and therefore underused, but they can also decrease the specificity for the diagnosis. In contrast, the ASO-ST lead remains specific because first, the magnitude of the lead is corrected for age and sex by orthonormalization and second, the cut-off value of the ASO-ST lead is set at the 95th percentile of normal values in a Caucasian target population.[5]

Previous studies on 12-lead ECG derived from EASI-lead system also showed that the diagnostic classifiers for recognizing acute myocardial ischaemia (the sum of absolute ST deviations) are not significantly different in their performance when they are based on ST-segment measurements obtained from EASI-derived 12-lead ECG than when based on measurements from 12-lead ECG.[14] However, it is mandatory for any derived 12-lead ECG to test its clinical validity for the visual interpretation by experts who apply guidelines and use rule-based diagnostic criteria. Although both RELF- and EASI-lead systems measure the heart dipole, we prefer the RELF method as the lead positioning (especially lead RE) was specifically developed and validated to be sensitive for ischaemic ST changes and to be optimally complementary to standard Leads I and II.[4,5] Additionally, the reproducibility of the self-application of the RELF lead system has been validated with focus on the stability of the normal ST vector.[5]

As a second hypothesis, we tested if the derived 12-lead ECG displays non-ischaemic ECG abnormalities equally effective as a standard 12-lead ECG for the rule-based interpretation by experts. The interpretations of right bundle branch block and fascicular block were equal and the intra-observer agreement between standard and derived ECG was comparable with the inter-observer agreement on the standard 12-lead ECG and the inter-observer agreements on the derived ECG. The same applied for diagnosing atrial

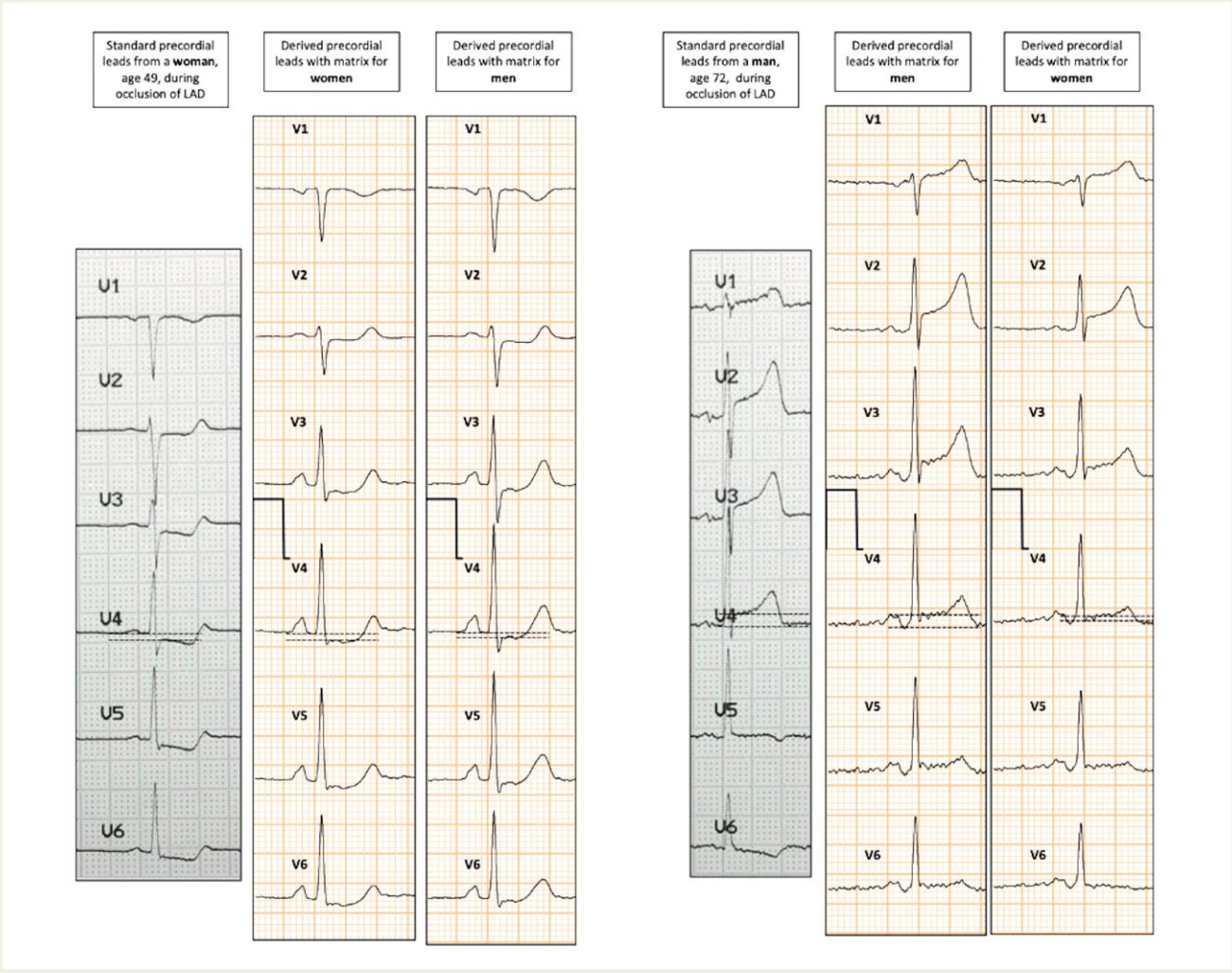


Figure 2 Two examples showing the accuracy of a sex-specific matrix for derivation of the precordial leads during ischaemia. For each example, the standard precordial leads (small panels) are compared with the two sets of derived precordial leads (one for men and one for women). The ST levels, for example, in Lead V4, are more accurate when the sex-specific matrix is derived.

fibrillation and AV-conduction delay. The latter is not unexpected as the diagnosis of atrial fibrillation, AV-conduction delay and many other parameters such as QRS axis, QRS and QT duration, largely depend on the displays of Leads I and II. Leads I and II are intrinsically identical in the derived and standard 12-lead ECG albeit with limited variations in their presentation triggered by different windowing and smoothing algorithms, e.g. for the amplitude of Q-waves. This could explain why we unexpectedly found that pathological Q-waves were less often diagnosed with the derived ECG also in areas that only depend on Leads I and II. Case by case analysis showed (see example in *Figure 6*) that, although Q-waves were indeed present on the derived ECG, their magnitudes differed from the pairwise standard 12-lead ECG and therefore did not reach the standard diagnostic rules that were applied.

Our study further confirms that for the detection of the three-dimensional electrical signals of myocardial ischaemia, not a larger number of recording leads is important, but rather the location of at least three optimally reproducible and spatially complementary leads and the quality of their capturing (unfiltered and high sampling rate). Previous studies confirmed that the information content within 3 of the 12 leads is sufficient for computerized prediction of acute coronary syndromes.[15] The RELF method uses the three extremity electrodes (R, L, and F) and one precordial exploring electrode E, whereas the 12-lead ECG uses six exploring electrodes C1–C6. Hence, we reduced the 9 signal electrodes of the 12-lead ECG (electrode 10 is only for common mode rejection) to the 4 RELF electrodes.

These findings implicate that the fast and easily applicable RELF method can be used in the context where a standard 12-lead ECG is not readily available such as in general practices or in ambulances. In emergency departments, the ease and speed of use may also favour the RELF device over the standard 12-lead ECG. Prospective observational studies in ambulances and emergency departments could compare positive and negative likelihood ratios of both ECG methods for the identification of patients who appear to suffer from ACS and control patients who appear to have a different

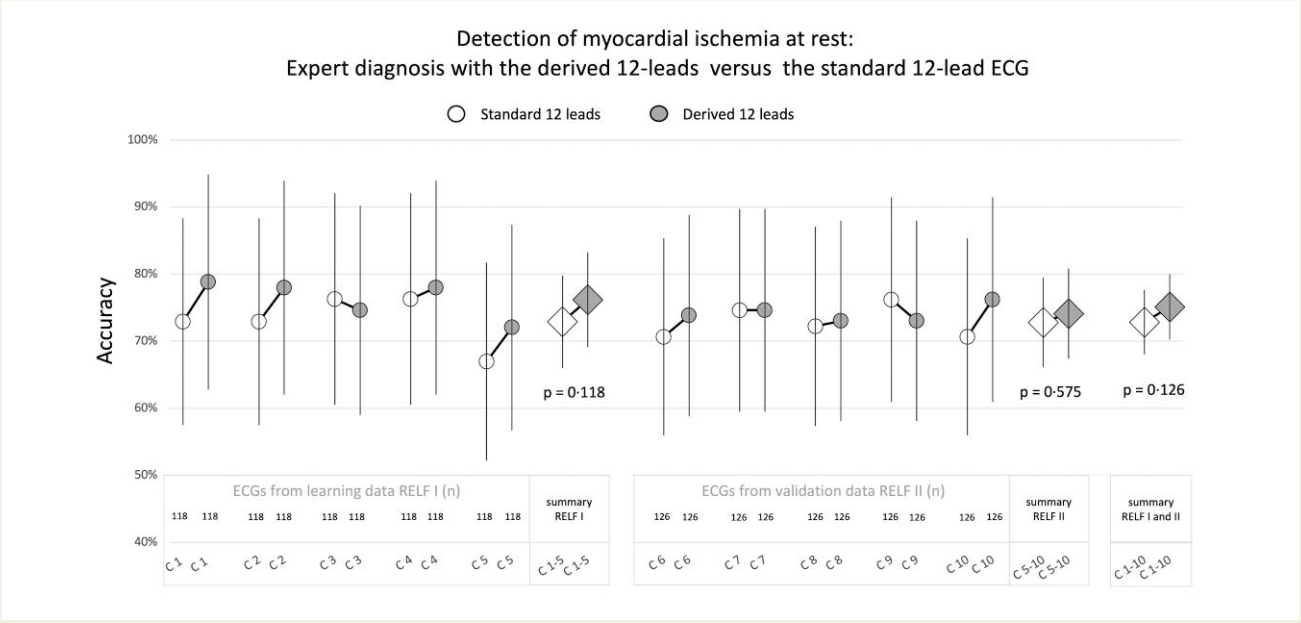


Figure 3 The accuracy of the derived 12-lead electrocardiogram compared with the standard 12-lead electrocardiogram for detection of myocardial supply ischaemia. Five cardiologists (C1–C5) each evaluated 236 electrocardiograms from the matrix learning data set (left panel). Five other cardiologists (C6–C10) each evaluated 252 electrocardiograms from the matrix validation data set (right panel).

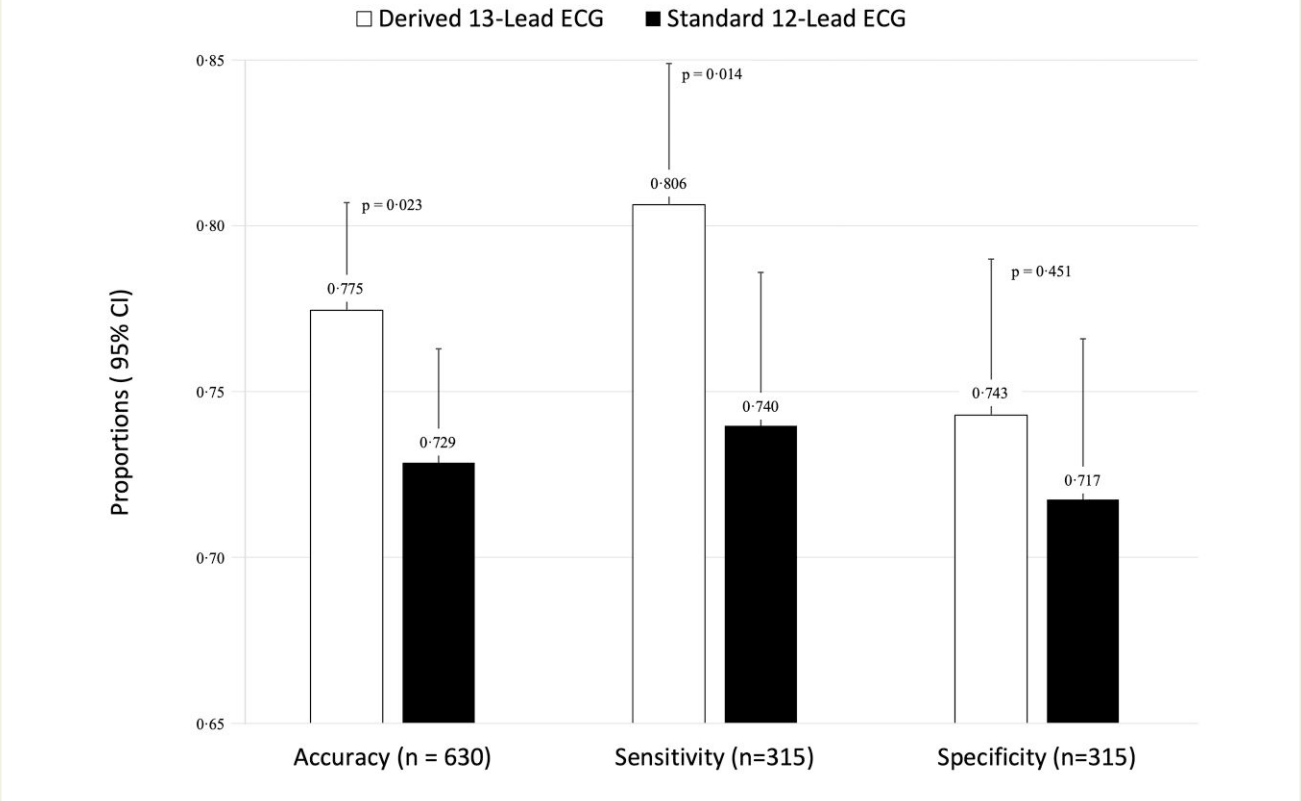


Figure 4 Detection of myocardial supply ischaemia (i.e. 60 s of coronary artery balloon occlusion during elective PCI) by five cardiologists (C6–C10). Paired comparison of the diagnostic characteristics of the standard 12-lead electrocardiogram vs. the derived 13-lead electrocardiogram in the validation data set.

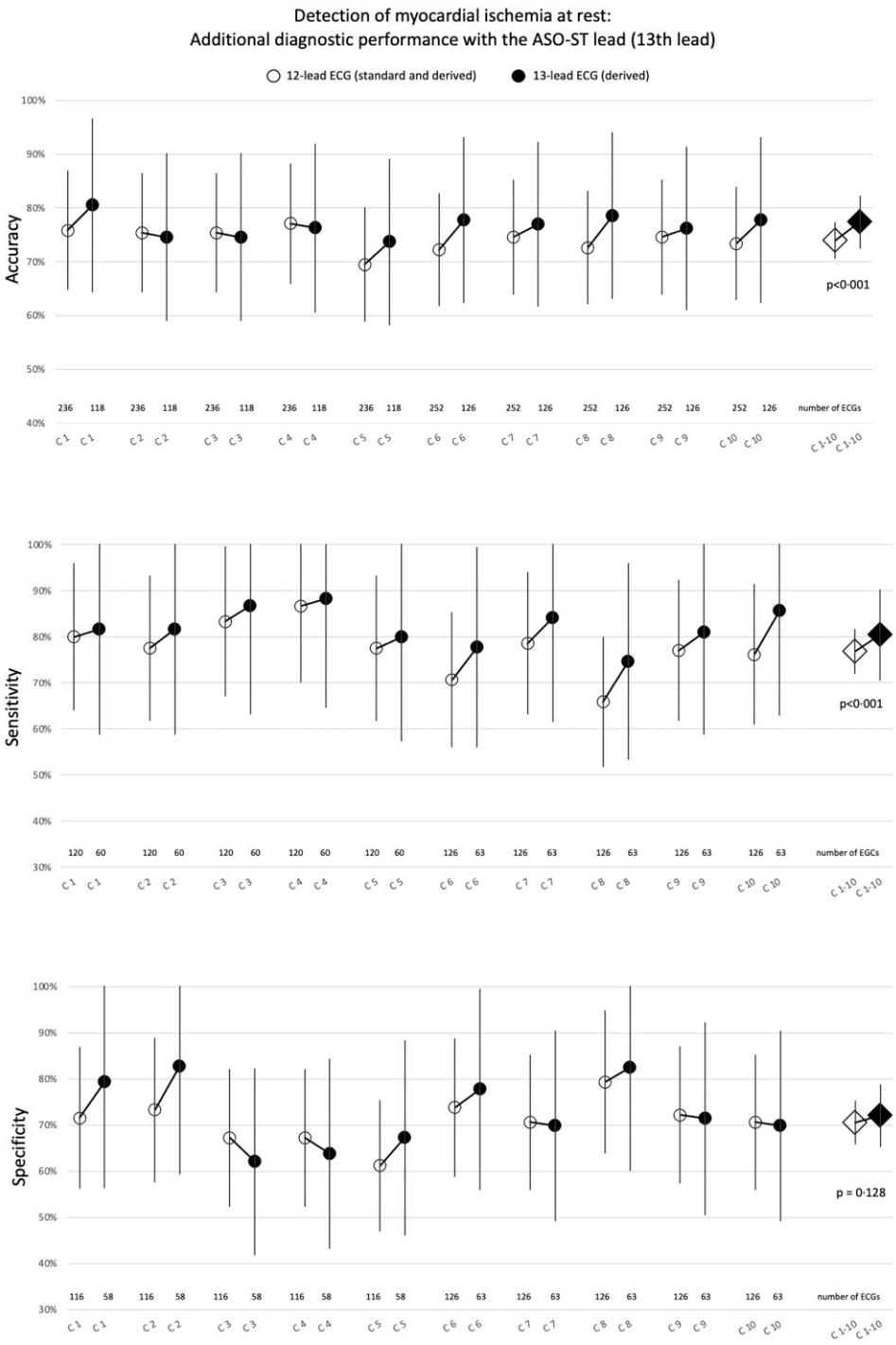


Figure 5 The incremental diagnostic effect of adding the age and sex orthonormalized ST lead criterion to the 12-lead electrocardiogram criteria for detection of myocardial supply ischaemia (i.e. 60 s of coronary artery balloon occlusion during elective PCI) by 10 cardiologists (C1–C10). The three panels show respectively the additional accuracy, sensitivity and specificity by adding the age and sex orthonormalized ST lead (1 mm elevation criterion) to the rule-based diagnostic criteria for 12-lead electrocardiogram.

diagnosis after hospital evaluation. The RELF ECG-deriving algorithm can, in absence of an individual RELF reference recording, instantaneously generate a 13-lead ECG with immediate and optimal display of the ST segment allowing visual diagnosis by expert ECG readers. Its additional 13th lead may even uncover ischaemia resulting from areas for which the standard 12-lead ECG is blinded.

Despite the feasibility of wireless transmission of ECG data, one essential, yet time consuming step remains the time to conventional

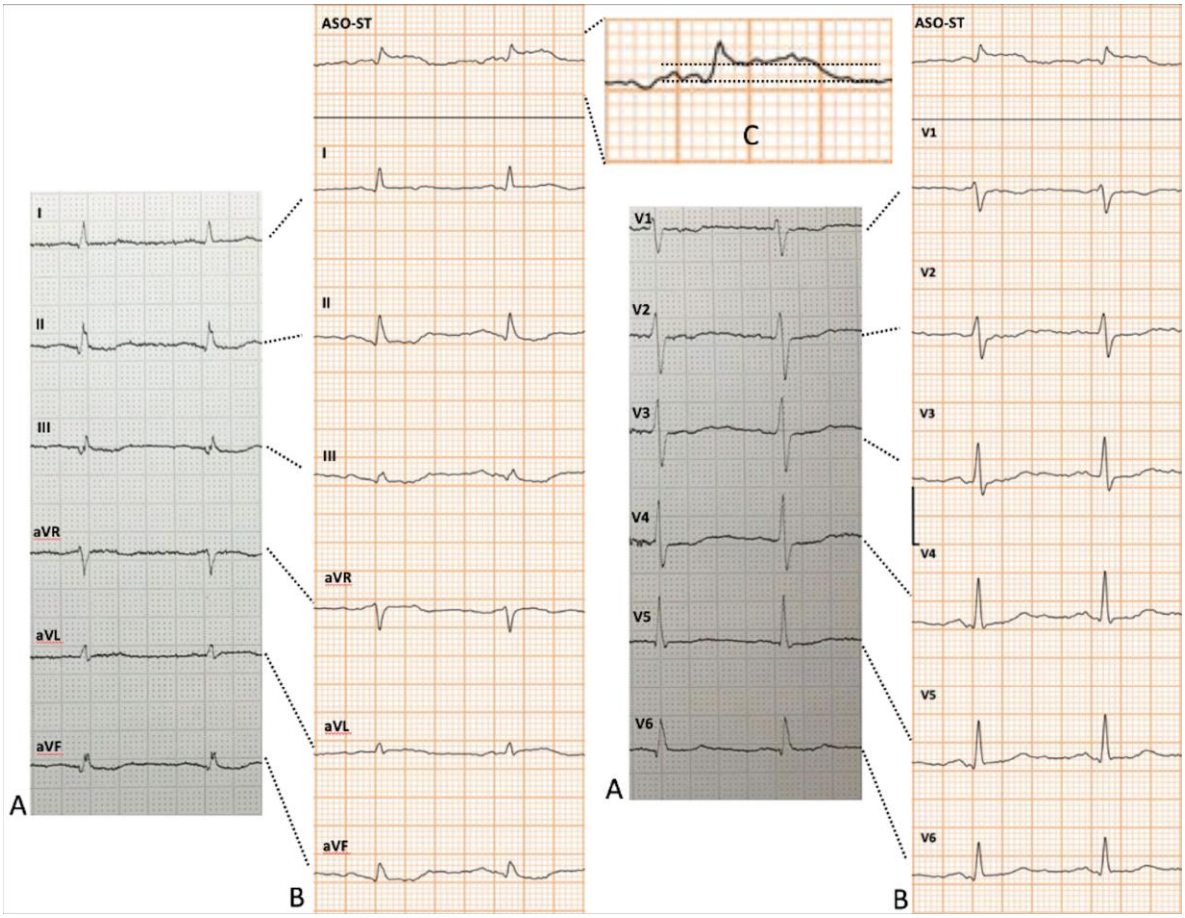


Figure 6 Example of standard 12-lead electrocardiogram (*A*) and simultaneous derived 13-lead electrocardiogram (*B*) with a magnification window (*C*) of the age and sex orthonormalized ST lead during supply ischaemia (60 s of circumflex artery occlusion during elective PCI).

expert ECG interpretation. In this context, artificial intelligence-enabled algorithms have received much attention for automated, instant and reliable ECG interpretations.[16,17] Despite many advances, studies reporting on artificial intelligence-enabled ECG diagnosis of myocardial ischaemia are currently still limited. A self-applicable device capturing three-dimensional ECG data like RELF can increase the availability of large valid ECG data sets covering both inter- and intra-individual data. If self-recordings are coupled with validated event labels, then these data sets provide the means necessary for training artificial intelligence-enabled ECG algorithms that could obtain even greater and faster diagnostic performance compared with the conventional methods. It has been shown that a deep learning-based algorithm can reliably detect myocardial ischaemia using a 6-lead ECG, suggesting feasible application to wearable devices.[18] Despite showing significant promise and many potential applications, artificial intelligence-enabled ECG interpretation requires further improvement, prospective validation, and standardized frameworks for acceptable transparency of these applications.[19] However, further enhancement of the RELF method to identify both high- and low-risk patients through artificial intelligence could allow refined utilization of resources, could promote individualized care[20] and enable effective human–AI interaction.

Limitations

This validation of the RELF device is limited to a population of men and woman with age 67.0 years (SD 9.0) and body mass index (BMI) 28.1 (SD 4.8). Therefore, the use is currently limited to adults with a BMI between 17 and 36 kg/m^2.

The normal values for the ASO-ST vector in our population ($n = 5338$) are set for daily life resting conditions such as in the supine position, standing position, or immediately after (but not during) a mild physical activity. These normal values are set to detect supply ischaemia at rest and are not applicable during physical activity such as during stress tests. These normal values might also not be applicable to non-Caucasian races that could have population-specific variations of their ST levels.[21] In order to apply the ASO-ST lead to non-Caucasian populations, the race ASO-ST vector (RASO-ST vector) should be developed and could overcome the well-documented problem of >20% false-positive ST deviations in specific populations when applying universal rule-based criteria.[15]

The 60 s of balloon occlusion is a limitation as it induces short-term supply ischaemia and does not represent long-term ongoing supply ischaemia. However, it is expected that longer periods of ongoing supply ischaemia will be associated with more pronounced ST deviations and will increase the sensitivity of both the standard

Table 2 Paired analysis of non-ischaemic diagnosis with respectively standard 12-lead electrocardiogram and derived 12-lead electrocardiogram in the validation data set scored by five independent cardiologists

Validation data set	Standard 12-lead	Derived 13-lead	*P*-value for paired comparison	Agreement between two raters on the same ECG (Kappa)		Agreement between standard 12-lead and DERIVED 13-lead within the same rater (Kappa)
Number of ECGs	126	126		Standard 12-lead	Derived 13-lead	
Number of ratings	630	630	630 paired	1260 paired	1260 paired	630 paired
Sinus rhythm (%)	94.9	93.7	0.791	0.845	0.852	0.840
Atrial fibrillation (%)	5.1	4.6	0.508	0.852	0.892	0.864
AV block (Grade > 0) (%)	10.3	11.4	0.477	0.486	0.471	0.419
Right bundle branch block (%)	10.3	10.0	0.864	0.751	0.681	0.704
Fascicular block (%)	13.8	13.3	0.780	0.580	0.674	0.649
Q-wave (%)	25.9	13.8	0.000	0.579	0.747	0.493

The prevalence of left bundle branch block (1.3%) did not allow further analysis.

12-lead ECG and the 13-lead RELF ECG. Therefore, it is not excluded that the superior sensitivity of the 13-lead RELF ECG is limited to the very early phase of supply ischaemia.

As a final limitation, we note that we used an electrode configuration that is close to the Lund configuration for the standard 12-lead ECG (see Supplementary material online, *Figure S2*). We noticed no higher incidence of right axis deviation, which is associated with the Mason–Likar configuration.

Conclusion

For Caucasians, the easy-to-use 3-lead RELF method can display a 13-lead ECG that is clinically valid and more accurate compared with the 12-lead ECG for the visual diagnosis of myocardial supply ischaemia at rest. The novel ASO-ST lead that is based on the ASO-ST vector decreased the blind spots inherent to a 12-lead ECG display. This solution could be further generalized with the RASO-ST vector and RASO-ST lead for universal display of the 13-lead ECG derived from a 3-lead RELF recording in the context where a standard 12-lead ECG is not readily available.

Lead author biography

Dr Frederic Van Heuverswyn is a cardiologist at Ghent University Hospital in Belgium since 2006. He trained both in interventional cardiology and in cardiac electrophysiology. With experience in both fields, Dr Van Heuverswyn joined the research group of Prof. Peter Gheeraert in the field of primary ventricular fibrillation in myocardial infarction. He developed the studies that led to the clinical validation of the RELF device and will aggregate the knowledge in his PhD thesis.

Supplementary material

Supplementary material is available at *European Heart Journal – Digital Health*.

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Conflict of interest: P.G. and M.E.H. declare the patents EP3003140A1 (European Patent Office), CA2912476C (Canada), WO2014187998A1 (WIPO [PCT]), US9867577B2 (USA). All other authors declare no competing interests.

Data availability

All data collected for the study are available upon request. Data available are de-identified participant data and the data dictionary. Data will be made available on request by contacting the primary author at frederic.vanheuverswyn@uzgent.be or the lead investigator at peter.gheeraert@uzgent.be.

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