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An initial exploration of subtraction electrocardiography to detect myocardial ischemia in the prehospital setting

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Abstract

Background: In the prehospital triage of patients presenting with symptoms suggestive of acute myocardial ischemia, reliable myocardial ischemia detection in the electrocardiogram (ECG) is pivotal. Due to large interindividual variability and overlap between ischemic and nonischemic ECG-patterns, incorporation of a previous elective (reference) ECG may improve accuracy. The aim of the current study was to explore the potential value of serial ECG analysis using subtraction electrocardiography.

Methods: SUBTRACT is a multicenter retrospective observational study, including patients who were prehospitally evaluated for acute myocardial ischemia. For each patient, an elective previously recorded reference ECG was subtracted from the ambulance ECG. Patients were classified as myocardial ischemia cases or controls, based on the in-hospital diagnosis. The diagnostic performance of subtraction electrocardiography was tested using logistic regression of 28 variables describing the differences between the reference and ambulance ECGs. The Uni-G ECG Analysis Program was used for state-of-the-art single-ECG interpretation of the ambulance ECG.

Results: In 1,229 patients, the mean area-under-the-curve of subtraction electrocardiography was 0.80 (95%CI: 0.77–0.82). The performance of our new method was comparable to single-ECG analysis using the Uni-G algorithm: sensitivities were 66% versus 67% (p-value > .05), respectively; specificities were 80% versus 81% (p-value > .05), respectively.

Conclusions: In our initial exploration, the diagnostic performance of subtraction electrocardiography for the detection of acute myocardial ischemia proved equal

to that of state-of-the-art automated single-ECG analysis by the Uni-G algorithm. Possibly, refinement of both algorithms, or even integration of the two, could surpass current electrocardiographic myocardial ischemia detection.

KEYWORDS
acute myocardial ischemia, serial electrocardiography, subtraction electrocardiography, vectorcardiogram

1 | INTRODUCTION

Accurate prehospital triage of patients presenting with symptoms suggestive of acute myocardial ischemia is crucial. Any diagnosis involving myocardial ischemia necessitates rapid transport to a hospital for treatment of the underlying cause in order to salvage as much myocardium as possible (Ibanez et al., 2017; O'Gara et al., 2013). In contrast, inaccurate triage could result in flooding of emergency/cardiology departments, performing unnecessary urgent catheterization and/or and administering potentially hazardous thrombolytics, while false-negative cases would miss important treatment. Prehospital clinical decision-making requires reliable myocardial ischemia detection. Although biomarkers, e.g., troponins, are widely used to assess myocardial ischemia, biomarkers are not always reliable in this early stage of ischemia and take time to process. In contrast, the electrocardiogram (ECG) is easily acquirable and directly interpretable and is therefore considered the key objective prehospital diagnostic tool for myocardial ischemia detection.

Usually, and according to the guidelines (Ibanez et al., 2017; O'Gara et al., 2013), the ECG is evaluated for signs of ST-elevation or depression measured at the J-point. Although J-amplitude deviations often accompany myocardial ischemia, ischemia-induced myocardial action potential changes create injury currents during all phases of the cardiac cycle (Downar, Janse, & Durrer, 1977) leading to ECG changes throughout the QRST-complex (ter Haar, Maan, Warren, et al., 2013; Surawicz, Orr, Hermiller, Bell, & Pinto, 1997; Wagner et al., 1988). J-point restricted electrocardiographic criteria could therefore gravely affect diagnostic accuracy, even in patients with completely acutely occluded coronary arteries (Koyama, Hansen, Hanratty, Nelson, & Rasmussen, 2002; Man et al., 2014; ter Haar, Maan, Schalij, & Swenne, 2013). Non-J-point related variables could also be of use since sometimes no J-point deviations can be observed at all.

Unfortunately, signs of ischemia in the QRS-complex and in the T wave cannot readily be detected due to the wide ranges of normal values which can overlap with ischemic changes (Macfarlane et al., 2014; Rijnbeek et al., 2014). Additionally, nonacute pathology, e.g., left ventricular aneurysm, can severely alter the ECG. Indeed, considerable overlap of even J-point amplitudes exists between ischemic and nonischemic ECGs (Deshpande & Birnbaum, 2014). Consequently, ischemia detection in the entire QRST-complex, including the J-point, without knowing the pre-existing ECG of the patient can be incorrect. A serial approach, e.g., comparing the current ECG to a previously acquired ECG, corrects for interindividual variability thus revealing the actual intra-individual ischemic changes, and is, indeed, recommended by the guidelines (Ibanez et al., 2017; O'Gara et al., 2013).

In the context of serial ECG analysis, we earlier proposed subtraction electrocardiography (ter Haar, Man, Maan, Schalij, & Swenne, 2016; Treskes et al., 2015), analysis of the differences between an acute and a previously made nonacute ECG from the same patient. This method uses several ECG features, ECG difference descriptors, e.g., the ST and ventricular-gradient (VG) difference vectors. These variables have shown promising results for ischemia detection (ter Haar et al., 2016; Sbrollini et al., 2019; Treskes et al., 2015). In this study, we hypothesize that subtraction electrocardiography can serve as an alternative for, or can have additional value to conventional analysis of the acute ECG alone. Our present study explores the diagnostic value of subtraction electrocardiography for the detection of myocardial ischemia in a real-world prehospital setting.

2 | METHODS

2.1 | Study design

The here-described research is part of the SUBTRACT study, a multicenter retrospective observational study with the objective of exploring subtraction electrocardiography for the detection of myocardial ischemia in the prehospital phase. This study was conducted in two emergency medical services (EMS) regions in which four hospitals participated. The study protocol has been approved by the medical ethical committees (METCs) of the academic hospitals, the AMC and the LUMC, and by the boards of directors of the other centers.

2.2 | Study population and collected data

The study population consists of patients at least 18 years old, who were urgently attended by one of the participating EMSs, and in whom an ambulance ECG was recorded for ruling-in or ruling-out myocardial ischemia. Further inclusion criteria were as follows: transport to one of the participating hospitals, and availability of an elective previously recorded nonacute ECG in one of the ECG databases of the participating hospitals, to serve as a reference ECG. For each patient, a data set was collected consisting of all ECGs recorded during the ambulance visit/ride, the most recent usable (see

Exclusion criteria) reference ECG, symptoms at EMS presentation and clinical data from the admission (diagnoses, laboratory values, imaging results).

2.3 | Exclusion criteria

Electrocardiograms with poor signal quality, without a regular supraventricular rhythm or with atrial flutter, and also ambulance ECGs that could not be processed (e.g., in case of suspected lead interchange) by the University of Glasgow (Uni-G) ECG Analysis Program (Macfarlane, Devine, & Clark, 2005), were not analyzed. Patients were excluded in case of insufficient information, e.g., due to death before a reliable diagnosis could be established. Patients with a major cardiac event, e.g., open-heart surgery or myocardial infarction, between the time instants at which the reference and ambulance ECGs were recorded, were excluded. Finally, if a patient had multiple ambulance visits by the EMS during the study period, only data regarding the most recent visit were included.

2.4 | Clinical diagnosis

From the medical records (admission and discharge letter), we extracted the clinical diagnosis, which was based on the entire assessment of the patient by the attending physician. We defined the clinical diagnosis as the diagnosis explaining the symptoms at presentation to the EMS. This diagnosis is often the same as the initial diagnosis at admission, but can be altered because of additional diagnostics performed after the initial assessment.

2.5 | Discrimination of myocardial ischemia cases and controls

To retrospectively assess the presence or absence of myocardial ischemia at the time of recording of the ambulance ECG, we defined and applied a myocardial ischemia classification algorithm. The myocardial ischemia classification algorithm aims to retrospectively assess the likelihood of the presence of myocardial ischemia at the time of recording of the ambulance ECG, without using the ambulance ECG itself. The algorithm is based on interpretation of the clinical in-hospital data, with the purpose of retrospectively constructing the prehospital scenario. For instance, when clinically necrosis has convincingly been demonstrated, we estimate a high likelihood of the presence of myocardial ischemia during the immediately preceding prehospital episode. In contrast, if cardiac decompensation is diagnosed accompanied by slightly elevated troponin levels, the presence of myocardial ischemia during the immediately preceding prehospital episode is less likely, although probable. For this purpose, the algorithm uses a 5-point scale, ranging from presumed ischemic, probably ischemic, uncertain, probably nonischemic to presumed nonischemic. The algorithm does not make use of the properties of the ambulance ECG itself, but is based on data from the subsequent hospital admission: on the clinical diagnosis, and additionally, insofar as available and relevant, on troponin samples and on cardiac imaging data. Of note, this ischemia classification algorithm does not distinguish between the supposed mechanism of ischemia (Thygesen et al., 2018). In addition, the algorithm does not estimate the amount of ischemia, only its presence or absence in the ambulance ECG. Because our study is a retrospective observational multicenter study, troponin samples were obtained and interpreted according to the local protocols of the participating hospitals. Since troponin levels are affected by renal function (Gunsolus et al., 2018), we applied a linear correction (Friden et al., 2017). A systematic description of the myocardial ischemia classification algorithm, including examples, is provided below.

- Classification "Presumed ischemic": Clinical diagnoses where either necrosis is inherent to the diagnosis, e.g., ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI), i.e., any type of myocardial infarction, or if the diagnosis could involve myocardial ischemia, e.g., pulmonary embolism, in combination with supporting evidence for myocardial necrosis (elevated troponin levels and/or positive cardiac imaging) (Douketis, Crowther, Stanton, & Ginsberg, 2002).
- Classification "Probably ischemic": Clinical diagnoses that could involve myocardial ischemia, in combination with troponin levels or imaging results that are slightly, but not clearly, pointing in the direction of myocardial necrosis, e.g., cardiac decompensation with moderately elevated troponin levels (Januzzi, Filippatos, Nieminen, & Gheorghiade, 2012).
- Classification "Uncertain": Assigned in case of insufficient diagnostics, or if the actual occurrence of ischemia during the recording of the ambulance ECG remains unknown due to presumed fluctuations in myocardial perfusion, e.g., with the diagnosis of unstable angina pectoris (Sheridan & Crossman, 2002).
- Classification "Probably nonischemic": Clinical diagnoses that could be associated with myocardial ischemia, but neither troponin levels nor cardiac imaging results were available to definitely exclude myocardial ischemia, e.g., severe pneumothorax (Janssens, Koch, Graf, & Hanrath, 2000), with a single nonrepresentative low troponin level; in this case myocardial ischemia cannot be excluded, and hence the resulting classification is "probably nonischemic."
- Classification "Presumed nonischemic": Clinical diagnoses which are not associated with myocardial ischemia, e.g., hyperventilation syndrome (Wheatley, 1975), or possibly associated with myocardial ischemia but for which there is no support by the troponin levels and/or imaging, e.g., cardiac decompensation with negative representative troponin levels (Januzzi et al., 2012).

In case of multiple diagnoses in one patient, ischemia classification is based on the diagnosis with the highest probability of causing myocardial ischemia.

For the current study, we combined the patients with classifications "Presumed ischemic" or "Probably ischemic" as cases, and the patients with classifications "Presumed nonischemic" or "Probably

nonischemic" as controls. Hence, patients with the classification "Uncertain" were excluded since it was impossible to decide about the presence or absence of myocardial ischemia at the moment of the ambulance ECG recording.

2.6 | ECG processing

Electrocardiograms (10 s, 12 leads) were obtained as raw (unfiltered) data. Ambulance ECGs (recorded with the LIFEPAK 12, Physio-Control, now part of Stryker) were extracted from the EMS databases. Reference ECGs were acquired from the ECG databases of the participating hospitals; they had been recorded by different electrocardiographs (GE, Schiller, Mortara, Siemens/Dräger). Before further processing, ambulance ECGs (recorded with Mason-Likar electrode positions) were converted to standard 12-lead ECGs with the Leiden matrix (Man et al., 2008).

2.7 | ECG analysis

2.7.1 | LEADS program

All ECGs were analyzed by the LEADS program (Draisma et al., 2005). This software synthesizes a vectorcardiogram of the averaged dominant QRST-complex after automated and manually reviewed/edited deselection of noisy or abnormal beats, e.g., extrasystoles. Subsequently, the automatically determined default onset-QRS, J-point and end-T settings were reviewed and manually corrected if necessary. The LEADS program then outputs a wide variety of ECG and VCG variables, of which the user can make a selection, depending on the particular research purpose.

2.7.2 | Computation of ECG difference descriptors

The differences between the ambulance and reference ECGs of each patient were expressed as 28 difference descriptors (see Table 1), each of which was obtained by subtracting LEADS reference ECG output variables from LEADS ambulance ECG output variables (Sbrollini et al., 2019). In patients in whom multiple ambulance ECGs had been recorded, the ambulance ECG with the largest VG difference vector with respect to the reference ECG was selected for further analysis. This choice is motivated by the notion that VG differences reflect changes throughout the QRST-complex.

2.7.3 | State-of-the-art traditional ECG analysis: Uni-G algorithm

The ambulance and reference ECGs were analyzed by the Uni-G ECG Analysis Program (Macfarlane et al., 2005). First, this was performed to obtain a general description of the ECGs in terms of diagnostic categories needed for application of the exclusion criteria. Second, in the reference ECGs, we used the Uni-G program to assess pre-existing ECG pathology. Finally, for the ambulance ECGs, we used the Uni-G algorithm for comparison with our new methods, i.e., this program served as a standardized and objective equivalent of a cardiologists' expert panel for electrocardiographic myocardial ischemia detection based solely on the acute ECG. The Uni-G algorithm gives a wide range of myocardial ischemia diagnostic statements concerning ischemia probability. For the current study, all statements including ischemia were considered a positive score for ischemia.

2.8 | Statistical analysis

2.8.1 | Descriptive statistics, univariate analysis

All statistical computations were performed in Matlab (Matworks, version R2018a). As descriptive statistics, the medians of the difference descriptors were computed for both myocardial ischemia cases and controls, and statistically compared by the Wilcoxon rank-sum text. p-values < .05 were considered statistically significant. We constructed, for each variable, receiver operator characteristics (ROCs) for the univariate discrimination of cases and controls including the computation of corresponding areas-under-the-curve (AUCs) with 95% confidence intervals (95%CIs).

2.8.2 | Building an overall logistic regression model

An initial logistic regression (LR) model was built using all data. This overall model was chosen from 59 LR models that were constructed with the case/control classification based on the ischemia classification algorithm as dependent variable, and the 28 ECG difference descriptors plus age and sex as independent variables (total of 30 independent variables). The first of these 59 LR models was constructed by using solely the independent variable with the largest univariate AUC. The 2nd to 29th LR models were constructed by adding the remaining independent variables one-by-one to the set of variables that had already been entered in the model; each time, the newly added variable was chosen because it yielded the largest AUC together with the variables already entered. The 30th LR model contained all independent variables. The 31st to 59th models were constructed by removing the independent variables from the model one-by-one; each time, the variable that was removed was chosen because the remaining variables yielded the largest AUC. From the 59 thus constructed LR models, the model that had produced the largest AUC was chosen as the final overall model.

2.8.3 | Sensitivity analysis of the overall logistic regression model

The overall LR model, constructed with the complete data set, was subjected to sensitivity analysis. This analysis consisted of the comparison of the AUC of the overall model with the AUCs of the LR models constructed after removal of a specific groups of variables (all QRS-related, J-related, T-wave related, or general variables,

TABLE 1 Subtraction electrocardiography: list of ECG difference descriptors and univariate AUC

Category	#	Symbol	Unit	Description	AUC
QRS	1	ΔQRSdur	ms	QRS-duration difference, signed	0.61*
	2	|ΔQRSdur|	ms	QRS-duration difference, absolute value	0.50
	3	$\left\lvert\Delta\overline{\text{QRSmax}}\right\rvert$	μV	Maximal QRS-vector magnitude difference, signed	0.47*
	4	$\left\lvert\Delta\left\lvert\overline{\text{QRSmax}}\right\rvert\right\rvert$	μV	Maximal QRS-vector magnitude difference, absolute value	0.55*
	5	$\Delta\left\lvert\overline{\text{QRSintegral}}\right\rvert$	mV·ms	QRS-integral vector magnitude difference, signed	0.56*
	6	$\left\lvert\Delta\left\lvert\overline{\text{QRSintegral}}\right\rvert\right\rvert$	mV·ms	QRS-integral vector magnitude difference, absolute value	0.57*
	7	ΔQRScmplx		QRS-complexity difference, signed	0.62*
	8	|ΔQRScmplx|		QRS-complexity difference, absolute value	0.62*
J	9	$\left\lvert\overline{\Delta J}\right\rvert$	μV	J difference-vector magnitude	0.80*
	10	∑|ΔJi|; 8 leads	μV	Summed absolute values of the differences in J-point amplitudes, 8 leads	0.82*
	11	∑|ΔJi|; 12 leads	μV	Summed absolute values of the differences in J-point amplitudes, 12 leads	0.83*
T	12	$\Delta\left\lvert\overline{\text{Tmax}}\right\rvert$	μV	Maximal T-vector magnitude difference, signed	0.59*
	13	$\left\lvert\Delta\left\lvert\overline{\text{Tmax}}\right\rvert\right\rvert$	μV	Maximal T-vector magnitude difference, absolute value	0.62*
	14	$\Delta\left\lvert\overline{\text{Tintegral}}\right\rvert$	mV·ms	T-integral vector magnitude difference, signed	0.58*
	15	$\left\lvert\Delta\left\lvert\overline{\text{Tintegral}}\right\rvert\right\rvert$	mV·ms	T-integral vector magnitude difference, absolute value	0.59*
	16	ΔTcmplx		T-wave complexity difference, signed	0.47*
	17	|ΔTcmplx|		T-wave complexity difference, absolute value	0.55*
	18	ΔTsym		T-wave symmetry difference, signed	0.46*
	19	|ΔTsym|		T-wave symmetry difference, absolute value	0.58*
	20	Δ# leads with positive T waves		Difference in the number of leads with positive T waves	0.43*
	21	# leads with a T-wave polarity change		Number of leads with a T-wave polarity change	0.62*
General	22	ΔQTinterval	ms	QT-duration difference, signed	0.45*
	23	|ΔQTinterval|	ms	QT-duration difference, absolute value	0.57*
	24	$\left\lvert\overline{\Delta VG}\right\rvert$	mV·ms	Ventricular-gradient difference-vector magnitude	0.64*
	25	ΔSA		QRS-T spatial-angle difference, signed	0.53*
	26	|ΔSA|		QRS-T spatial-angle difference, absolute value	0.60*
	27	ΔHR	bpm	Heart-rate difference, signed	0.55*
	28	|ΔHR|	bpm	Heart-rate difference, absolute value	0.56*
Age & Sex	29	Sex	M/F	Sex of the patient, male/female	0.43*
	30	Age	years	Age of the patient	0.58*

Note: Variables used as input for the logistic regression model with corresponding univariate areas-under-the-curve in the overall model.
Abbreviation: AUC, area-under-the-curve.
*Significantly > 0.50.

see Table 1). The drop in AUC upon removal of each of the variable groups characterizes the relative importance of this variable group in the overall LR model.

2.8.4 | Learning and testing performance evaluation

Using the same procedure that was used to construct the overall model, 100 LR models were built during a learning and testing evaluation procedure. Each of these 100 times, the LR model was built on the basis of a random selection of 70% of the total data and then tested on the remaining 30% of the total data. Finally, ROCs and AUCs of each of the 100 randomly selected test data sets were calculated as well as the mean ROC and AUC of these 100 realizations.

2.8.5 | Comparison of the logistic regression model and the Uni-G algorithm

To statistically compare the diagnostic performance of the Uni-G algorithm and the LR model, we computed, for each of the 100 randomly selected test data sets, confusion matrices of the Uni-G algorithm. The sensitivity-specificity score of the LR model was found

by computing the intersection of the line that connected the Uni-G median performance point and the top-left corner of the ROC plot box and the mean LR model ROC. Finally, we computed the median and the 5th and 95th percentiles of the sensitivity and specificity values of the Uni-G algorithm and of the LR model and compared these using the paired Wilcoxon test.

3 | RESULTS

3.1 | Study group characteristics

A total of 3,261 patients were included in the SUBTRACT study. After application of the exclusion criteria (Figure 1) 1,425 patients remained. The exclusions were mainly due to unusable ambulance ECGs (n = 1,419). The study group's demographic and anthropomorphic data and the medical history are listed in Tables 2 and 3, respectively. There were slightly more men than women in the study group (52% vs. 48%). The median age was 69 years. About

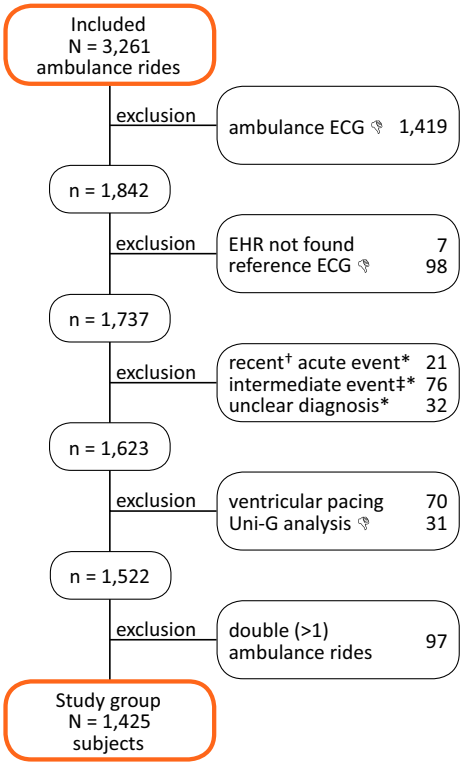

FIGURE 1 Exclusion flowchart. Flowchart illustrating the exclusion steps leading from the patients who satisfied the inclusion criteria (1. urgent transport by the emergency medical services to one of the participating hospitals in the regions Hollands Midden and Amsterdam; 2. and at least one ECG recording was made during the ambulance ride; 3 to include or exclude myocardial ischemia) to the composition of the patient group studied in the here-described research project. = not usable, † = <7 days before acute event, ‡ = major cardiac event between the recording of the reference ECG and the ambulance ECG, * = categories may overlap. EHR, electronic health record

two-third of the study group had a cardiac medical history, while almost 10% had no relevant medical history. In 79% of these EMS presentations, chest pain was one of the symptoms while 21% of the patients had only other symptoms, e.g., acute upper abdominal pain that was also recognized as a symptom suggestive of acute myocardial ischemia. Table 4 lists the clinical diagnoses and the corresponding ischemia classification as assessed by the ischemia classification algorithm. The ischemia status of 196 patients was classified as "Uncertain," leaving 1,229 patients for the current statistical analysis. Table 5 provides clinical characteristics of the study population stratified by myocardial ischemia classification. There was a striking difference between the percentages of the presumed ischemic and the presumed nonischemic patients who were admitted to the hospital: 99% (one patient died preceding intended admission) of presumed ischemic patients was admitted in contrast to 40% of the presumed nonischemic patients. Although 33% of patients with the myocardial ischemia classification "Uncertain" underwent coronary angiography and 16% had positive troponins according to the attending physician, it remained unknown whether myocardial ischemia was indeed present at the very moment of recording of the ambulance ECG due to the dynamic situation, e.g., in unstable angina pectoris or after a resuscitation.

3.2 | Reference ECG characteristics

The elective previously recorded reference ECGs had a median "age" (time difference between the recording of the ambulance ECG and of the reference ECG) of 12 months (minimum: 0, Q1: 4, Q3: 34, maximum 332 months). According to the Uni-G algorithm, 32% of the reference ECGs were normal, 33% borderline abnormal and 35% abnormal.

3.3 | Statistical analysis of the complete dataset—overall model

3.3.1 | Descriptive statistics, univariate classification performance

Medians of the cases differed significantly from medians of the controls in all variables except for the absolute value of the QRS-duration difference, signed maximal QRS-vector magnitude difference, signed T-wave complexity, signed T-wave symmetry difference, and the signed QRS-T spatial-angle difference. Univariate ROC analyses of the 28 ECG difference descriptors, as well as the variables age and sex for the discrimination of cases from controls all yielded AUCs that were significantly larger than 0.5 except for the absolute value of the QRS-duration difference (Table 1). The largest AUC was the sum of the absolute values of the differences in J-point amplitudes in all 12 leads: 0.83 (95%CI: 0.82–0.84).

TABLE 2 Demographic and anthropomorphic characteristics of the study group

				Study group *N* = 1,425		
Sex (*n*)	Male/female	(%/%)		736/689	51.6/48.4	
Age (years)	Median	(min–max)	[Q1–Q3]	69	(18–97)	[58–79]
Height (cm)	Median	(min–max)	[Q1–Q3]	171	(141–198)	[164–178]
Weight (kg)	Median	(min–max)	[Q1–Q3]	79	(42–170)	[69–90]
BMI (kg/m^2)	Median	(min–max)	[Q1–Q3]	26.9	(16.6–49.1)	[24.3–30.4]

Note: Demographic and anthropomorphic characteristics of the study group.
Abbreviations: *N*/*n* = number of patients, BMI = body mass index, Q1, first interquartile, Q3, third interquartile.

3.3.2 | Diagnostic performance of the overall model and Uni-G algorithm

After addition and removal of variables to establish the overall LR model with the largest AUC, the best AUC was 0.86 (95%CI: 0.85–0.87), consisting of 21 variables. Removal of groups of difference descriptors (QRS, J, T, General) led only to a statistically significant drop in AUC in case of removal of all J-point related variables: AUC 0.74 (95%CI: 0.72–0.75). The Uni-G algorithm yielded a sensitivity of 67% and a specificity of 81% for detecting myocardial ischemia.

3.3.3 | Misclassifications of the logistic regression overall model

We investigated the clinical characteristics and the ECG characteristics of the most serious misclassifications of the logistic regression overall model (cases for which the model generated a low probability score and controls for which the model generated a high probability score for ischemia). Of the 2.5% lowest probability scores within the cases, 80% of patients had NSTEMI diagnoses due to coronary artery spasm or a transient thrombus. This is presumably due to fluctuations in the degree of coronary artery occlusion and with that its electrocardiographical reflection. The 2.5% highest probability scores within the controls had diverse diagnoses. The most frequent diagnoses in this group were pneumonia (23%) and pericarditis (8%); no other diagnosis occurred frequently. While further attempting to explain these high probability scores within the controls, we noticed prevalent tachycardia-induced ST-deviations and possible deviating electrode placement in combination with pre-existing ST-deviations, causing spurious differences.

3.4 | Learning and testing

3.4.1 | Logistic regression

The 100 learning sets had a mean AUC of 0.88 (95%CI: 0.85–0.88), and the 100 test sets had a mean AUC of 0.80 (95%CI: 0.77–0.82), see Figure 2.

3.4.2 | Uni-G ECG algorithm

Figure 2 also presents the diagnostic performance of the Uni-G algorithm in the 100 learning and test sets. Because the learning sets were randomly drawn from the data, this effectively resulted in a random composition of the test sets as well. Hence, as expected, the performance of the Uni-G algorithm appeared to be similar in the learning and test sets. Mean Uni-G sensitivity and specificity were 67% and 81%, respectively.

3.4.3 | Comparison of the logistic regression model and the Uni-G algorithm

A meaningful comparison of the diagnostic performance of the LR model and the Uni-G algorithm can be made by comparing

TABLE 3 Medical history of the study group

N (%)		
Cardiac disease*	961	(67.4)
Myocardial infarction	420	(43.7)
CAD without myocardial infarction	278	(28.9)
Other cardiac disease	263	(27.4)
TIA/iCVA*	179	(12.6)
Noncoronary or cerebrovascular arterial disease*	158	(11.1)
DVT/Pulmonary embolism*	75	(5.3)
Hypertension*	850	(59.7)
Pulmonary disease*	282	(19.8)
Diabetes mellitus type 2*	354	(24.8)
Chronic kidney disease*	140	(9.8)
Significant disease, any of above	1,291	(90.6)
No significant disease	134	(9.4)

Note: Medical history of the study group. The medical history comprises the patients' health issues and events which are relevant to this study prior to the time of inclusion in the SUBTRACT study (i.e., visit by the EMS).
Abbreviations: CAD, coronary artery disease; CVA, cerebrovascular accident; DVT, deep venous thrombosis; *N*, number of patients; TIA, transient ischemic attack.
*Categories may overlap.

TABLE 4 Clinical diagnoses and ischemia classes

n(%) patients with one or more diagnoses in group	totals	presumed ischemic	probably ischemic	uncertain	probably nonischemic	presumed nonischemic
Cardiac	465(32.6)	152(91.6)	24(85.7)	127(64.8)	16(76.2)	146(14.4)
Primary myocardial ischemia	273(19.2)	134(80.7)	9(32.1)	90(45.9)	2(9.5)	38(3.7)
STEMI	68(4.8)	67(40.4)	1(3.6)	0(0.0)	0(0.0)	0(0.0)
NSTEMI	76(5.3)	67(40.4)	8(28.6)	1(0.5)	0(0.0)	0(0.0)
UAP	87(6.1)	0(0.0)	0(0.0)	87(44.4)	0(0.0)	0(0.0)
Stable angina	42(2.9)	0(0.0)	0(0.0)	2(1)	2(9.5)	38(3.7)
Arrhythmia/conduction disturbances	111(7.8)	10(6)	3(10.7)	15(7.7)	1(4.8)	82(8.1)
Cardiac decompensation	74(5.2)	16(9.6)	12(42.9)	25(12.8)	15(71.4)	6(0.6)
Valvular disease	22(1.5)	3(1.8)	2(7.1)	11(5.6)	0(0.0)	6(0.6)
Inflammatory	17(1.2)	0(0.0)	0(0.0)	1(0.5)	0(0.0)	16(1.6)
Resuscitation	12(0.8)	9(5.4)	0(0.0)	3(1.5)	0(0.0)	0(0.0)
Hypotension/hypertension	117(8.2)	4(2.4)	5(17.9)	41(20.9)	1(4.8)	66(6.5)
Noncoronary vessel disease	36(2.5)	6(3.6)	1(3.6)	8(4.1)	0(0.0)	21(2.1)
Pulmonary (excl. PE)	108(7.6)	6(3.6)	3(10.7)	13(6.6)	1(4.8)	85(8.4)
Gastrointestinal	161(11.3)	0(0.0)	2(7.1)	3(1.5)	4(19)	152(15)
Neurology (excl. CVA)	11(0.8)	0(0.0)	0(0.0)	0(0.0)	1(4.8)	10(1)
General infectious disease	32(2.2)	3(1.8)	3(10.7)	13(6.6)	0(0.0)	13(1.3)
ENT/endocrine/urogenital/gynecology	22(1.5)	0(0.0)	2(7.1)	2(1)	1(4.8)	17(1.7)
Dermal/costo/tendo/myogenic	139(9.8)	0(0.0)	0(0.0)	4(2)	0(0.0)	135(13.3)
Psychiatry	61(4.3)	0(0.0)	0(0.0)	3(1.5)	0(0.0)	58(5.7)
No acute pathology nos*	368(25.8)	0(0.0)	0(0.0)	5(2.6)	1(4.8)	362(35.7)
Lab abnormalities other than troponin	23(1.6)	3(1.8)	1(3.6)	11(5.6)	1(4.8)	7(0.7)
Other	22(1.5)	0(0.0)	0(0.0)	4(2)	0(0.0)	18(1.8)
Total *N* patients	1,425(100)	166(100)	28(100)	196(100)	21(100)	1,014(100)

Note: For the total study group and stratified by ischemia class, numbers of patients with one (or more) clinical diagnosis in a group with corresponding percentages. The percentages between parentheses relate to the total number of patients in the study group or ischemia class. Of the presumed ischemic patients, 81%/19% had a diagnosis involving primary/secondary myocardial ischemia, as opposed to 32%/68% of the probably ischemic patients. Hence, secondary ischemia was more often causing a probable ischemic classification rather than a presumed ischemic classification.
Abbreviations: CVA, cerebral vascular accident; excl., exclusive of lab abnormalities, laboratory abnormalities; nos, not otherwise specified; NSTEMI, non-ST-elevation myocardial infarction; PE, pulmonary embolism; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.
*No acute pathology, this refers to diagnoses in which no explicit diagnosis is stated, but in which all relevant acute diagnoses have been excluded by the physician.

the test results of the LR models with the Uni-G results on the same test data. The Uni-G algorithm had a sensitivity of 67% (5th–95th percentiles: 59%–74%) and a specificity of 81% (5th–95th percentiles: 78%–84%). The LR model had a sensitivity of 66% (5th–95th percentiles: 60%–74%) and a specificity of 80% (5th–95th percentiles: 76%–85%). There was no statistically significant difference (*p*-values > .10) between the diagnostic performances as expressed in sensitivity and specificity of the two algorithms. Panel B of Figure 2 shows that the mean performance of the Uni-G algorithm is almost exactly on the mean of the ROC curves.

4 | DISCUSSION

4.1 | Subtraction electrocardiography for detecting myocardial ischemia

In this first exploratory study of subtraction electrocardiography, we found this technique—here, using logistic regression—to be equivalent to an existing automated and validated ECG analysis algorithm addressing the acute ECG alone. Prehospital myocardial ischemia detection, in which the ECG is a key diagnostic, can be challenging. Subtraction electrocardiography has considerable, and when further

TABLE 5 Clinical characteristics in the five ischemia classes

	Presumed ischemic	Probably ischemic	Uncertain	Probably not ischemic	Presumed nonischemic
Male/female (%/%)	108/58 (65/35)	13/15 (46/54)	112/84 (57/43)	11/10 (52/48)	492/522 (49/51)
Median age (years) (min–max) [Q1–Q3]	70 (34–93) [63–79]	78 (42–97) [62–89]	72 (30–95) [63–81]	75 (48–95) [73–80]	67 (18–97) [57–78]
Chest pain at ambulance visit (%)	142 (86)	17 (61)	159 (81)	13 (62)	801 (79)
History of coronary artery disease (%)	88 (53)	17 (61)	127 (65)	14 (67)	452 (45)
Admitted to hospital* (%)	165 (99)	26 (93)	150 (77)	16 (76)	409 (40)
Died during or before hospital admission (%)	11 (7)	3 (11)	10 (5)	0 (0)	3 (0)
Coronary catheterization (%)	128 (77)	9 (32)	65 (33)	1 (5)	44 (4)
Coronary intervention (%)	116 (70)	1 (4)	40 (20)	1 (5)	4 (0)
Elevated troponin levels according physician positive†/negative/missing‡ (%)	132/0/34 (80/0/20)	15/0/13 (54/0/46)	32/98/66 (16/50/34)	1/9/11 (5/43/52)	32/647/335 (3/64/33)
Numbers of patients in each ischemia class	166	28	196	21	1,014

Note: Demographic data and clinical characteristics of the total study population stratified by ischemia class.
Symbols: * = admission of at least 24 hours or in case or for additional tests, e.g., coronary catheterization, were performed. Patients discharged from the emergency room were not classified as admitted. † = elevated, but in some cases the attending physician attributed the elevation to another factor, e.g., renal failure; ‡ = missing either due to the absence of measurements or no mention of the troponin values in the medical letter.

developed possibly even increased diagnostic value, by taking pre-existing ECG abnormalities into account. In parallel to single-ECG analysis, in which J-point amplitudes contain the most important diagnostic information, we found that amplitude differences at the J-point were the most informative. However, removal of all J-point related variables yielded an AUC of 0.74 that was significantly larger than 0.50, and, hence, still valuable for ischemia detection. Hence, broadening of the diagnostic scope beyond the J-point appears useful.

4.2 | Challenges in subtraction electrocardiography

One of the expected pitfalls of subtraction electrocardiography was the difference in electrode placement between the ambulance and reference ECG. In multiple cases, clear differences in precordial P-wave and QRS-complex orientation could be observed between the ambulance and reference ECG, suggesting that also J-point and T-wave differences may be electrode-position related. Moreover, we presume that differences in heart rate and post-tachycardia T-wave changes influence J-point amplitude, hence, negatively affecting our results. This could possibly be addressed by a deep-learning approach (Sbrollini et al., 2019).

It is conceivable that lapsed time between the ambulance and reference ECG influences diagnostic accuracy.(de Jongh et al., 2015) However, the "age" of the reference ECG in our study was, with the exception of a few extremes, rather low (median 12 months). Possibly, day-to-day variation and irreproducible electrode positions have more influence. An approach to at least deal with ECG changes caused by the progression of disease could be to use only recent (e.g., <5 years old) reference ECGs.

4.3 | Further development of electrocardiographic myocardial ischemia detection

While subtraction ECG analysis/electrocardiography is solely based on differences, its performance in our study appeared to equal conventional single-ECG analysis. This demonstrates that intra-individual ECG differences contain valuable information. This information is, however, in daily practice not yet intensively used.

Our current method, LR, assumes a linear interaction of variables, and cannot, for instance, eliminate the use of a variable when another exceeds a certain threshold. The latter, nonlinear interaction would be, for instance, helpful when in case of severe tachycardia global ST-depressions (resulting in a high sum of J-point deviations, but a small ST-vector magnitude due to cancelation) would be eliminated from the analysis. Presumably, an alternative method, e.g., neural networks (Sbrollini et al., 2019), could further improve subtraction electrocardiography's performance.

Adding alternative variables, e.g., the direction of the ST-vector instead of merely including the magnitude could further improve the algorithm especially in case ECG changes in the QRS-complex and T

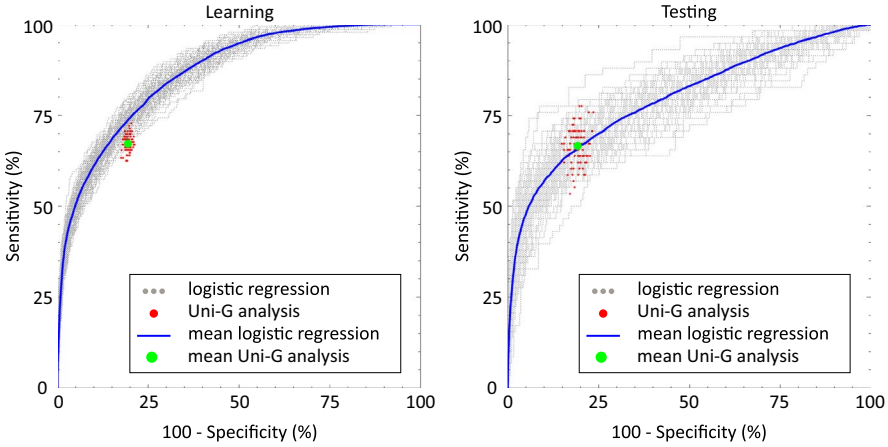

FIGURE 2 Receiver-operating-characteristics of learning and testing. ROCs of the 100 learning and testing realizations. From the plot can be appreciated that the differences with the Uni-G algorithm in the test sets were statistically not significant

wave also manifest in this specific spatial direction. Additionally, the interpretational logic of the Uni-G algorithm could possibly also be improved using the data collected in the current study.

Moreover, integration of the further refined subtraction electrocardiography and the Uni-G algorithm might possibly further enhance the diagnostic performance of current electrocardiographic acute myocardial ischemia detection. Since the information obtained with subtraction electrocardiography and with single-ECG analysis is only partly redundant, and the separate diagnostic performance of both approaches is roughly the same, it is very likely that combining both sources of information can yield a better result than that obtained with either the single or the serial ECG approach. It is also striking that we could reach, by using subtraction electrocardiography, in our initial attempt, a result i.e., comparable with the performance of an algorithm which has been in development already since the early nineties (Macfarlane et al., 1990). Obviously, to be of clinical interest, our method should be further improved, otherwise we should use conventional single-ECG interpretation because it is easier to apply in clinical practice (no earlier-made ECG required).

4.4 | Clinical implications and applications

Guidelines (Ibanez et al., 2017; O'Gara et al., 2013) recommend a comparison of the acute ECG which is under suspicion of myocardial ischemia to an older nonischemic ECG. Our study is consistent with this approach. In the future, after construction of a secure ECG cloud containing reference ECGs, prehospital subtraction electrocardiography could be automatically performed in the prehospital ECG electrocardiograph (Macfarlane & Pahlm, 1988). The paramedic can use the results of subtraction electrocardiography, in addition to, or instead of, visual ECG interpretation, in conjunction with the medical history and physical examinations. Moreover, in case of equivocal probability scores, an attending cardiologist can be consulted.

4.5 | Study's strengths and limitations

This study is, to our knowledge, the first to systematically explore the concept of prehospital serial ECG analysis by subtracting an elective previously recorded ECG of the same patient from the ambulance ECG, while using detailed clinical information of each patient.

Despite our extensive efforts to discriminate myocardial ischemia cases from controls by the ischemia classification algorithm, the (retrospective) objective assessment of myocardial ischemia remains a challenge. Additionally, we have not discriminated between the various underlying pathophysiological mechanisms of acute myocardial ischemia because our study data contain insufficient information to do so and, in our opinion, the first prehospital priority is to detect myocardial ischemia in general.

For this analysis, we only included patients with an available reference ECG, rendering this study nonrepresentative for the total EMS population since not all EMS patients have an earlier ECG available. However, a reference ECG could be found in about half of the patients with an ambulance ECG, rendering subtraction electrocardiography a feasible method.

By only including patients who were transported by ambulance, and not those who were, after initial assessment, left home, we introduced inclusion bias. We assume this bias to be small, since most myocardial ischemia cases initially left at home are eventually, when symptoms increase, brought to a hospital by the EMS, and would then as yet have been included in our study.

Lastly, due to the absence of precise information concerning the presence of complaints and concerning the administration of nitroglycerin during/preceding the recording of the ambulance ECG, as well as concerning the position in which the patient was transported (e.g., torso upright in decompensated patients), we could not correct for the dynamics that these factors may have caused in the ECG.

5 | CONCLUSIONS

Subtraction electrocardiography, which exclusively uses intra-individual ECG differences, is a promising additional method to detect myocardial ischemia. Diagnostic performance of the here-described crude first exploration of subtraction electrocardiography proved equal to current sophisticated single-ECG analysis. Possibly, refinement of both the subtraction electrocardiography algorithm as well

as the Uni-G algorithm, or even integration of the two, could surpass current electrocardiographic acute myocardial ischemia detection.

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CONFLICT OF INTEREST

None of the authors of this manuscript reported any disclosures.

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