JULY | 2020

corpuls.science

ESSAYS, RESEARCH AND INFORMATION

22-LEAD ECG

Standard 12-lead ECG plus posterior, right cardiac and orthogonal leads

CARDIAC ELECTRICAL BIOMARKER

Realtime non-invasive indicator for cardiac injury

TELEMEDICINE

Online calculation, sharing and forwarding of ECGmax

CONTENTS

3 EDITORIAL

4 THE ACS ALGORITHM

7 ECG FILTERING

8 HOW FILTERING INFLUENCES THE ECG MORPHOLOGY

9 HOW THE ECG SIGNAL GETS FROM THE PATIENT TO THE MONITOR

10 corpuls.mission

13 22-LEAD ECG

14 DERIVATION OF THE 12-LEAD ELECTROCARDIOGRAM AND 3-LEAD VECTORCARDIOGRAM

19 MATHEMATICAL MODELING AND UTILITY OF THE DERIVED 22-LEAD ELECTROCARDIOGRAM

20 VECTOR LOOPS

21 APPLICABILITY OF THE ELECTRO-VECTORCARDIOGRAM IN CURRENT CLINICAL PRACTICE

27 THE CARDIAC ELECTRICAL BIOMARKER – CEB®

28 DETECTION OF ACUTE MYOCARDIAL ISCHEMIC INJURY BY GENDER USING A NOVEL CARDIAC ELECTRICAL BIOMARKER

32 AUTOMATED ANALYSIS OF THE 12-LEAD ECG IN THE EMERGENCY DEPARTMENT: ASSOCIATION BETWEEN HIGH-SENSITIVITY CARDIAC TROPONIN I AND THE CARDIAC ELECTRICAL BIOMARKER

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DEAR LADIES AND GENTLEMEN

Dr. Christian Klimmer, CEO

Michael Heller, Director

In the second **corpuls.science** we have chosen one of our most core technologies. This issue will focus on electrocardiograms. It has become the standard in Emergency Medicine to just attached a bunch of electrodes to the patient for monitoring reasons. For at least 25 years, whenever a patient presents with symptoms possibly indicating that something is not quite right with the heart, the patient receives a diagnostic ECG. Nowadays the 12-lead ECG is part of every guideline and recommendation to do with Acute Coronary Syndromes and is usually referred to as the "gold-standard". In 1992 **corpuls** pioneered 12-lead ECG in Emergency Medical Services with the **corpuls 08/16**. The 12-lead ECG method has not changed much during the past few decades and it leaves some vectors of the heart in the dark. There have recently been some ideas on how to overcome this, most of which were never popularised, possibly due to complexity or simply just the time which is required to gather this additional information. In EMS the recommendations regarding whether, and especially where, to transport the patient is decided predominately by the patient's symptoms. In the various different hospital environments patients with symptoms receive several troponin tests. Whilst troponin tests have become available for out of hospital use, it never really broke through. Again, most likely due to time and complexity reasons, but also presumably due to the high costs of disposables.

corpuls now has a solution to all of these problems with none of the disadvantages. The **ECGmax** technology which **corpuls** has just released, gives you all the additional ECG-leads and more. You can now get up to 22-leads without the need for any additional electrodes or any change in electrode placement. This includes the posterior leads V7-V9, the right cardiac leads V3r to V6r and the orthogonal leads X, Y and Z with the vector loops. This is all carried out by an evidence based algorithm which runs on the **corpuls.mission** server and can be sent from there to any device on scene, whether this is be a phone, tablet or electronic patient care record device. As this is part of the **corpuls** telemedicine solution, the diagnostic ECG is also available in real time where it can be measured and forwarded to a receiving hospital or a specialist for consultation.

On top of the additional ECG-leads, the **ECGmax** technology includes something which might just be the next big thing when it comes to diagnosing Acute Coronary Syndromes. The Cardiac Electrical Biomarker (CEB®) promises to give medical practitioners a real time value, comparable to troponin, without requiring any additional interventions and it is as easy to interpret as a traffic light. According to studies the CEB® has a similar sensitivity and specificity to troponin tests. Everything you need to know about this, and a lot more, is what this issue of **corpuls.science** is all about.

Thank you very much and enjoy the articles.

Dr. Christian Klimmer
CEO

Michael Heller
Director Medical Research and Application

THE ACS ALGORITHM

The classic 12-lead ECG represents a snapshot of the electrical activity of the heart. With this snapshot it is possible to diagnose various rhythmological and structural diseases of the heart. Due to this fact, the 12-lead ECG is the most important diagnostic tool for myocardial ischemia and infarction and is the basis for further therapeutic and diagnostic measures (Wagner et al. 2009). Myocardial infarction (MI) leads to muscular injury (scarring) and consequently to a change in the conduction properties in the heart. In the ECG, it is often associated with a T-wave change, a so-called ST segment elevation and/or depression, changes in the QRS complex or an inverted T-wave. The ST segment changes result from the voltage differences at the borders between ischemic and non-ischemic tissue. Due to the bioelectrical principles of the ECG, an ST segment elevation in one lead usually leads to a reciprocal ST segment depression in the lead with opposite polarity. Consequently, an ST segment elevation in the posterior leads V8 and V9 can be seen as an ST segment depression in the reciprocal leads V1 and V2 (Wagner et al. 2009).

As the posterior leads are not part of the standard 12-lead ECG, a distinction is normally made between two classes of ACS (acute coronary syndrome), STEMI (ST-elevation myocardial infarction) and NSTEMI (non-ST-elevation myocardial infarction). The STEMI typically has an ST segment elevation at the J point, while the NSTEMI shows an ST segment depression in the corresponding leads. (Wagner et al. 2009)

In a STEMI (patients with acute chest pain and ST segment elevation) there is an acute and total occlusion of a coronary artery. These patients must immediately receive reperfusion therapy or fibrinolytic therapy (Steg et al. 2012). Accordingly, patients presenting with acute chest pain without persistent ST segment elevation have NSTEMI. This is a subacute course and must first be confirmed by laboratory diagnostics to then move on to further therapy.
In order to make a well-founded therapy decision, the ECG is the most important option for a quick and safe diagnosis, as well as adequate risk assessment.

Myocardial ischemia remains the leading cause of death worldwide. Even though this trend has decreased in Europe over the past three decades, heart attacks still caused 1.8 million deaths in 2018. This represents 20% of all deaths (Ibanez et al. 2018). In Germany alone, 60,000 people die of an acute heart attack each year. For this reason, the guidelines recommend an ECG is preformed and interpreted no later than 10 minutes after first medical contact (Kelm et al. 2018; Ibanez et al. 2018).

To be able to offer the patient the fastest and best possible therapy, the **corpuls3** contains a computer-aided ECG analysis. With the **corpuls** ACS algorithm, the ECG can be analysed according to the STEMI or NSTEMI criteria (see Figure 1). **corpuls** has based this on the current European Society of Cardiology guidelines.

Fundamentally, the change in the ST segment is measured from the J point. The following criteria are considered to indicate sustained acute occlusion of a coronary artery (STEMI) (Thygesen et al. 2012).

- Two adjacent leads with ST elevation of 0.25 mV in men < 40 years
- Two adjacent leads with ST elevation of 0.2 mV in men > 40 years
- Or two adjacent leads with ST elevation of 0.15 mV in women in leads V2-V3
- And/ or ST elevation of 0.1 mV in all other leads
- In the absence of LV hypertrophy or LBBB

According to the guidelines, an NSTEMI is characterized by an ST depression of 0.05 mV in two adjacent leads. However, as a depression of 0.05 mV (0.5 mm) is usually difficult to diagnose, a segment depression of more than 0.1 mV in a single lead, or even more relevantly by 0.2 mV, is also a clear characteristic (Thygesen et al. 2012; Achenbach et al. 2012; Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V. 2011, 2012). For the **corpuls** ACS algorithm, a segment depression of 0.15 mV was chosen as the NSTEMI limit value. This value should avoid too many false positives yet still recognize an actual NSTEMI.

Furthermore, the T-wave inversion above 0.1 mV is a clear characteristic for a NSTEMI (Thygesen et al. 2012; Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V. 2012). The **corpuls** ACS algorithm also checks this characteristic, as shown on the flowchart (Figure 1).

Nevertheless, NSTEMI is a disease that is very difficult to detect in a 12-lead ECG. Over half of all NSTEMI display either a normal or a diagnostically unusable ECG (pacemaker, bundle branch block). ST segment depressions only occur in approx. 20% of patients, whereas a T-wave inversion can be found in around 25% of all NSTEMI patients (Arastéh et al. 2012). Accordingly, the guidelines recommend that a measurement of the posterior and the right-precordial leads should also be integrated into everyday clinical practice as routine (Kelm et al. 2018).

FLOWCHART CORPULS ACS ALGORITHM

Version 1.7

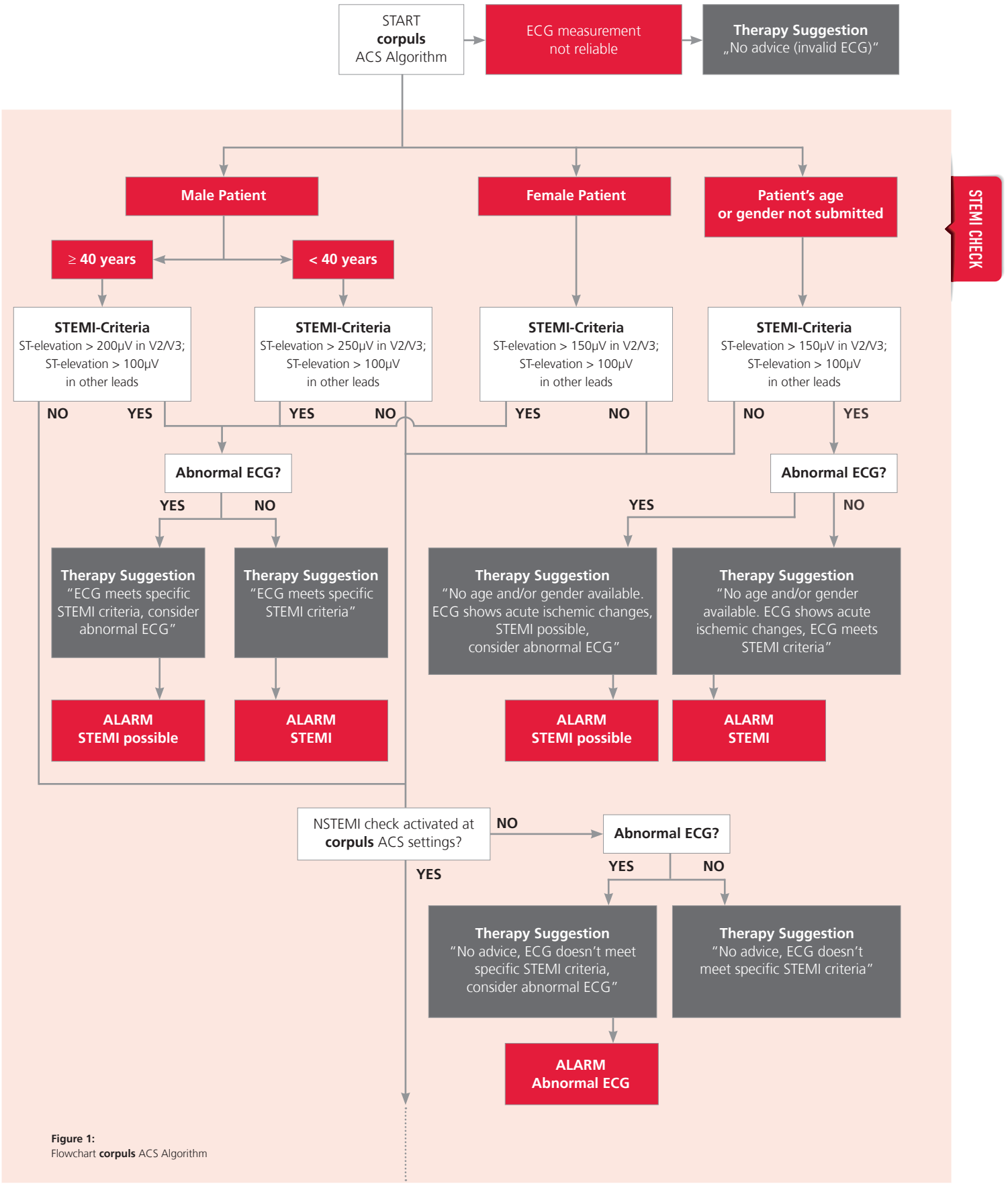
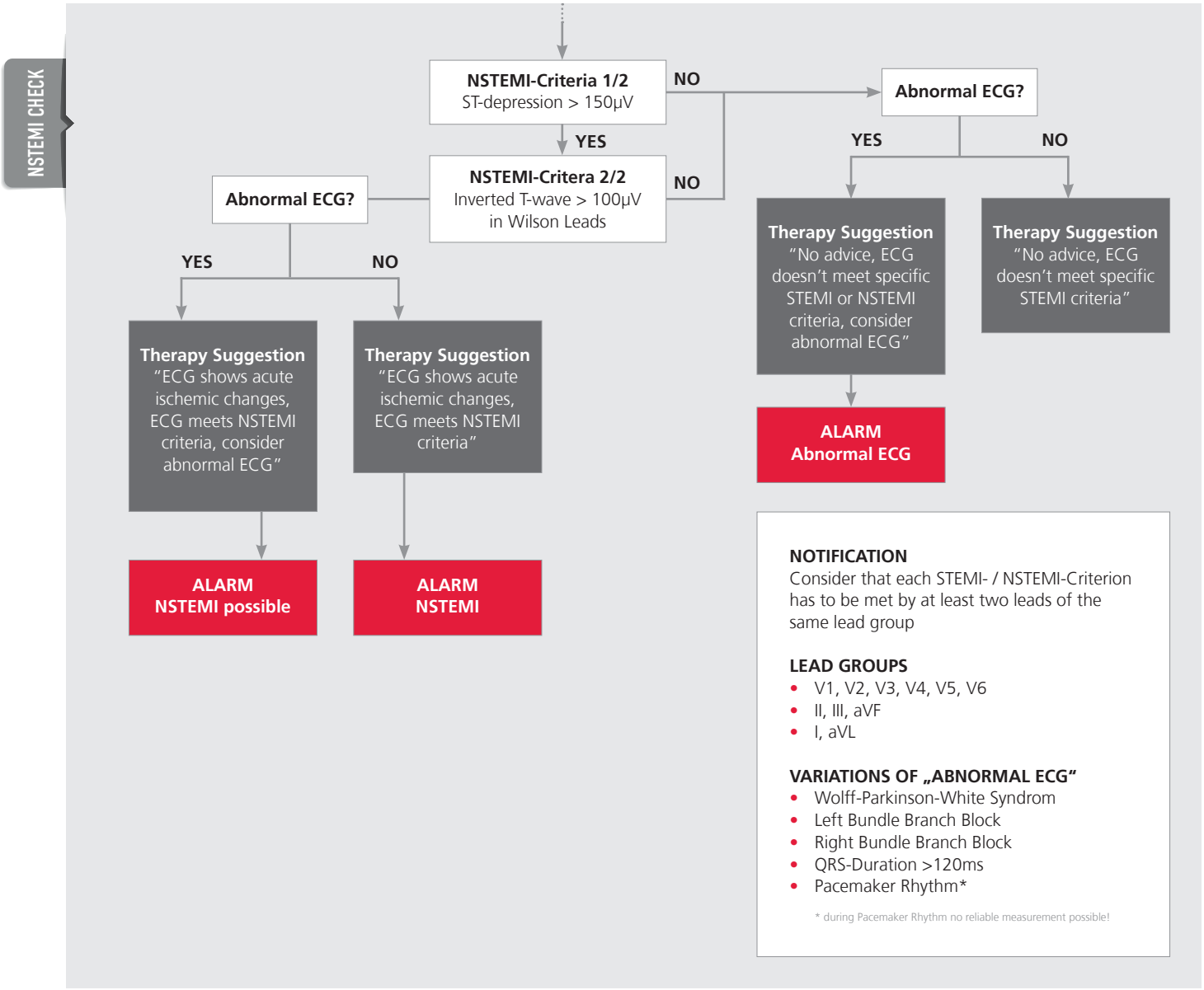


Figure 1:
Flowchart **corpuls** ACS Algorithm



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ECG FILTERING

With the increase in diseases of the cardiovascular system, the electrocardiogram (ECG) is an essential tool for preclinical diagnostics in modern emergency medicine. It is recommended to continuously monitor patients with such diseases so to quickly detect life-threatening arrhythmias. [1] In the preclinical setting, the recorded ECG may show artifacts due to various environmental factors. These can affect the interpretation of the ECG signal. [5] Artifacts can be caused by the patient's muscle activity, transport movements or electrical coupling of the mains frequency, for example. To reduce the quantity of different artifacts in the ECG recording, **corpuls** devices offer the possibility to use different ECG filters.

The human ECG spectrum covers the frequency range 0.05 Hz - 100 Hz, the main part of the QRS complex being in the range 0.5 Hz - 45 Hz. [9] Most of the time the ECG signal is overlaid by the mains frequency of 50 Hz/60 Hz. The mains frequency portion of an ECG can be reduced with a notch filter that can selectively filter individual frequencies. Low-pass filters are used to reduce high-frequency interference such as muscle tremors. These artifacts lie within the range from 5 Hz to 450 Hz. [10] High-pass filters in turn dim low-frequency interference signals that arise, for example, from breathing movements. These are between 0.05 Hz and 1 Hz. [11] This means that high and low frequency interference overlaps the frequency range of the ECG signal. Due to these technical reasons, filtering not only reduces interference, but also changes the ECG morphology. [3] The combination of low- and high-pass filters is known as a bandpass filter.

The principle of ECG filtering is shown in Figure 1. First, the mains frequency in the ECG is reduced with a notch filter. The notch filter must be set to the local mains frequency.

The intended use plays a decisive role in the selection of the bandpass filter. For diagnostic interpretation, the ECG signal must not be affected by the filtering. Therefore, it is recommended for diagnostic purposes to use a high-pass filter with 0.05 Hz and a low-pass filter with 150 Hz. [4] With this bandpass filter setting, the ECG is displayed with the maximum available frequency bandwidth. If the ECG is displayed with a reduced frequency bandwidth, the ECG morphology will be changed. Adjustment to the low-pass filter affects the amplitude of the R wave. Adjusting the high-pass filter can result in shifts in the ST segment. [3] If the bandpass filter impairs the interpretation ability of the ECG signal, it will be shown on the ECG printout.

The aim of ECG monitoring is the detection of life-threatening arrhythmias such as ventricular fibrillation, ventricular tachycardia or asystole. [1] The detection of such rhythms can be impaired by various interferences during patient transport. [7] If rhythm detection is no longer possible, the bandpass filter with the smallest frequency bandwidth should be used. With this filter setting, the maximum possible number of interference frequencies is filtered from the ECG signal. The ECG is shown with less noise but can only be used for rhythm analysis. [8]

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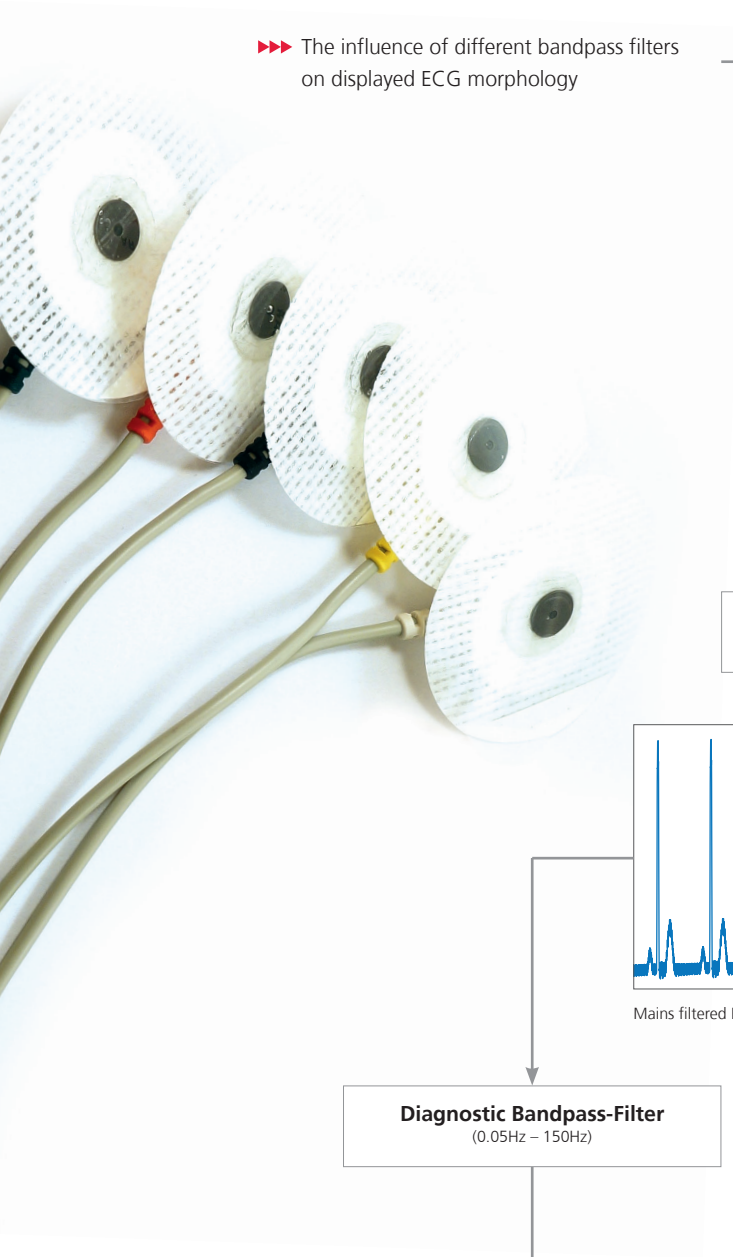
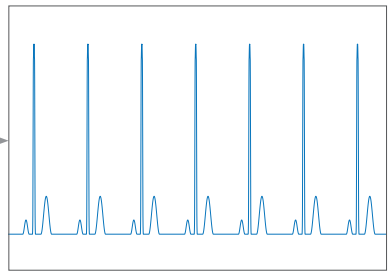
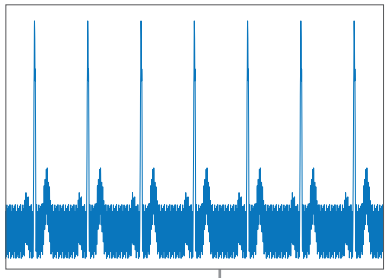
HOW FILTERING INFLUENCES THE ECG MORPHOLOGY



▶▶▶ The influence of different bandpass filters on displayed ECG morphology

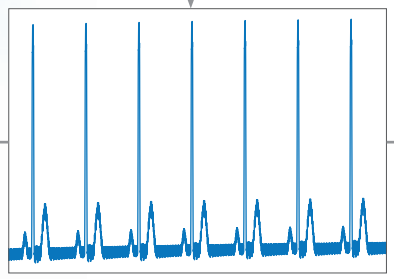


Native ECG without noise



ECG at device input

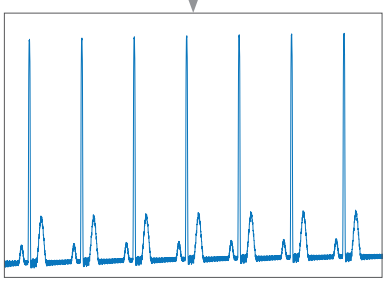
Mains Filter
(50Hz / 60Hz)



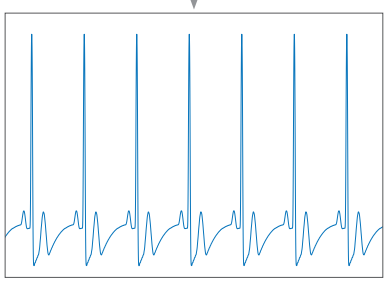
Mains filtered ECG

Diagnostic Bandpass-Filter
(0.05Hz – 150Hz)

Monitoring Bandpass-Filter
(0.67Hz – 20Hz)



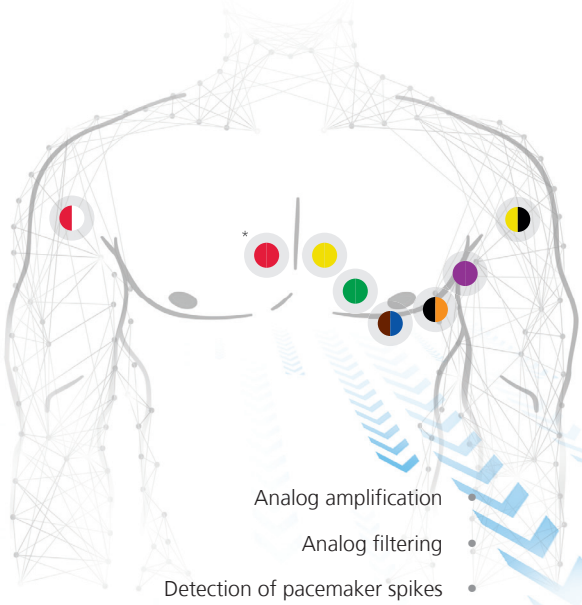
Filtered with diagnostic bandpass filter



Filtered with monitoring bandpass filter

Figure 1 (as referred to in the text ECG FILTERING)

HOW THE ECG SIGNAL GETS FROM THE PATIENT TO THE MONITOR

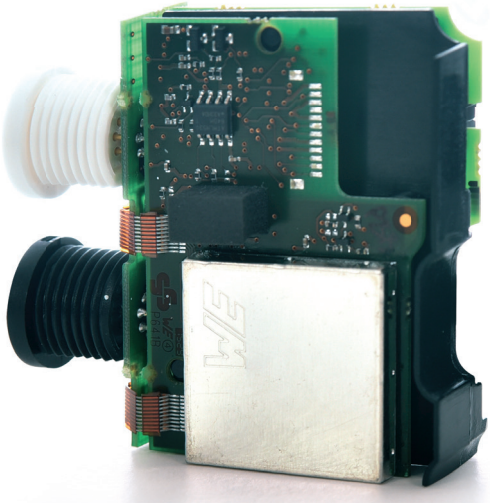


◂◂◂ A change in electrical potential arising from the heart's myocardial tissue can be detected on the skin

◂◂◂ Electrodes link the human body to the **corpuls3 TOUCH** / **corpuls3** CLASSIC

- Analog amplification
- Analog filtering
- Detection of pacemaker spikes
- Analog to digital conversion

- **Calculation of augmented ECG leads**
- **Digital filtering**
  (notch filter, high-pass and low-pass filter)
- **General signal processing**
  (VF Detection, QRS Detection, Heart Rate calculation)



Transmission via infrared or wireless to **corpuls3 TOUCH** / **corpuls3** CLASSIC monitor/printer/cf-card

▸▸▸ Transmission to **corpuls.mission** via WLAN or GSM

* IEC Color coding (left)
AHA Color coding (right)

corpuls.mission

corpuls.mission is a medical communication platform designed with the patient as the main focus. It enables knowledge to be collected where it can be best utilised: during a mission.

Above anything else, adequate patient treatment requires specific knowledge, often stemming from different disciplines and selected experts.

However, this complexity of medicine cannot rest on the shoulders of a single specialist. By combining medical data, chat, video and documentation, all relevant information is found in one place – one software, intuitive and central. Available for web, iOS and Android.

Designed for the unique demands of preclinical missions, **corpuls.mission** stands out from previous classic communication channels. It offers the possibility to view diagnostic ECGs and photos of medication plans or the incident scene in addition to the live curves and vital parameters of the **corpuls3**. All this in the usual **corpuls** quality.

corpuls.mission consists of the three combinable tools.

LIVE, CONFERENCE and **REPORT**

LIVE

LIVE, approved as medical-device software, is responsible for telemedical connection. The live connection provides vital parameters and curves in real time. It also displays trends and events from the connected device. The Live Board feature makes it possible to monitor multiple devices and for the visual display of events. Automated forwarding, flexible interfaces for data export and notification options round out the functions. Naturally, LIVE is also suitable for measuring the resting ECG.

CONFERENCE

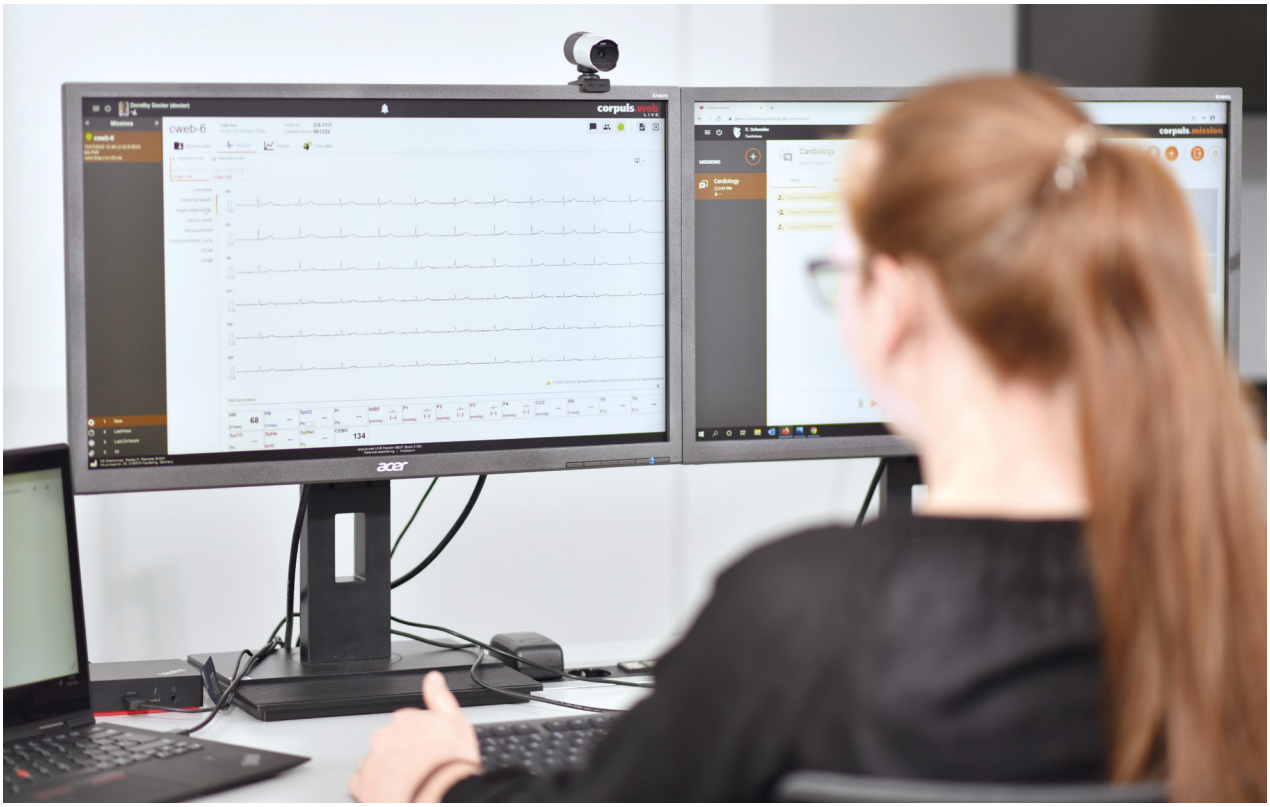
CONFERENCE ensures patient-oriented communication. Here you can get live advice from doctors or specialists via video and audio calls and chat. The ability to send pictures, videos and voice messages completes a modern communication solution. Tactical units such as the dispatch centre, ambulance and duty doctors, rather than individuals allow easy selection of the communication partners that are required.

REPORT

REPORT ensures true and correct mission documentation. So that everything from patient medical history to handover is documented correctly and according to the standards. If requested, the documentation can be collaborative, so that there is only one set of mission documentation for a patient. In this instance, the report naturally indicates who contributed which content. Interfaces to third-party systems round out the possibilities.

Safety is the top priority at **corpuls.mission**. By encrypting all patient data, conformity with the strict data protection requirements is guaranteed. The servers are operated according to relevant standards, such as ISO 27001.

In addition, the development of the entire product is subject to strict observation by an external control authority and is in compliance with the latest standards for IT security.



Posterior part of a 22-lead ECG being assessed by a telemedical doctor via **corpuls.mission LIVE**

Emergency physicians, cardiologists or any other specialist that is required, can precisely access the mission via **LIVE**. With the direct transmission of the cell phone number, team ID, radio ID, as well as the device ID, there is no chance for confusion. For better communication possibilities, **CONFERENCE** offers the option of scanning a QR code on the **corpuls3** using a smartphone. With this QR code, both devices are automatically associated to the same mission, ensuring correct assignment. With the options that **CONFERENCE** offers in addition to **LIVE**, the emergency physician or the future treating physician in the hospital can view all vital parameters, ECG data and trends. In addition, the rescue team can exchange information via chat and video conference, transmit photos of medication plans and wounds or breathing sounds and much more. Even before arriving at the hospital, patient treatment measures can be initiated by the emergency services and specifically prepared.

But **corpuls.mission** can do even more. **LIVE** now also offers the **ECGmax** feature via a telemedical solution. As part of the resting ECG, a holistic picture can be presented by means of an electrocardiological measurement.

In addition to the 12-lead ECG, **ECGmax** offers the option of displaying posterior leads, the precordial leads on the right and the orthogonal X, Y and Z leads. With **ECGmax** you get 22 leads for an all-round view of the entire heart. Vector loops are also displayed. This rarely used yet diagnostically valuable method of vectorcardiogram (VCG) can now be used at the same time and without any additional effort.

With **ECGmax**, the CEB® is also introduced as a new feature. A Cardiac Electrical Biomarker that measures the extent of myocardial ischemia based on the multipolar parts of the actual dipolar electrical field of a heart. The CEB® delivers a single numerical value in almost real time, requiring only 10 seconds of resting ECG measurement. If the CEB® exceeds 95, this strongly indicates myocardial problems. Using a tachometer display directly in the software, the CEB® provides quick and easy indication of the patient's myocardial health.

corpuls.mission supports the user so that they can effectively and professionally help the patient throughout the mission.

22-LEAD ECG

ECG diagnostics must be well trained. But despite good knowledge of the peaks illustrating potential differences of the heart, some diseases are still quite difficult to recognize on a standard 12-lead ECG.

A typical marker for an acute transmural myocardial infarction is the characteristic ST segment elevation. For an isolated posterior myocardial infarction however, this ST segment elevation is not seen on standard 12-lead ECG (Brown et al. 2003), as no specific leads represent this area (Levis 2015). Nevertheless, up to 20% of cases of acute myocardial infarction are acute posterior wall myocardial infarction (Levis 2015). The inevitable result is frequently missing the diagnosis of posterior myocardial infarctions – at least at first. Using additional leads, such as the posterior leads (V7–V9), increases the ability to identify a posterior myocardial infarction significantly (Brown et al. 2003; Levis 2015). Therefore, the ESC Guidelines recommend the routine recording of additional leads such as the posterior and the right precordial leads, despite the additional effort of new electrode positioning. Nevertheless, this is surely not reality in Germany. (Kelm et al. 2018; Ibanez et al. 2018) Equally in Canada, only 11% of cardiologist and just 9% of emergency physicians use the right precordial and posterior leads (Brown et al. 2003). An explanation for this may be the additional effort, time and materials needed for application.

Based on a factor analysis Schreck et al. (1998) showed that three leads are theoretically enough to calculate a 22-lead ECG. All additional leads are more or less redundant and give very little information to the system. Consequently, in 2004, Schreck et al. described a method to derive a 12-, 19- or 22-lead ECG from 3 measured standard leads using a universal patient coefficient matrix. Based on this technique we are able to derive 22-leads out of a standard 12-lead set. Without the necessity of any additional electrodes and without losing the representation of any other area of the heart while observing another. Furthermore, the calculations are based on leads I, II and V2, which are the leads with the least variability in electrode positioning (Schreck and Fishberg 2013). This promises high reliability of the derived leads. However, to keep the routine and compatibility to currently used systems, the **ECGmax** by **corpuls**, which provides 22-lead ECG, will keep the standard 10 electrodes. Consequently, the 12-lead ECG will still be displayed as the measured ECG. The right precordial, the posterior, as well as the X, Y and Z leads, including the vector loops, will be additionally available.

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DERIVATION OF THE 12-LEAD ELECTROCARDIOGRAM AND 3-LEAD VECTORCARDIOGRAM (shortened version)

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ABSTRACT

Objective: The cardiac dipolar field is represented by the measured 12-lead electrocardiogram (ECG) and 3-lead vectorcardiogram (VCG). The objective is to derive the 12-lead ECG and 3-lead VCG from 3 measured leads acquired from only 5 electrodes.

Methods: This is a retrospective blinded study comparing measured and derived ECG and VCG tracings. A nonlinear optimization model was used to synthesize the derived 12-lead ECG and 3-lead derived VCG from leads I, II, and V2. A total of 367 measured 12-lead electrocardiograms and 3-lead vectorcardiograms of varying morphologies were acquired from archived digital ECG databases. All tracings were interpreted by 2 blinded physician reference standards. The derived vs measured tracings were compared quantitatively using Pearson correlation and root mean square error. Qualitative comparisons were determined by physician percent agreement analysis and adjudication.

Results: The correlations between the measured and derived ECGs and VCGs were high (r = 0.867). No clinically significant differences were noted in 98.1% of cases. Electrocardiographic rate, rhythm, segment, axis, and acute myocardial infarction interpretations showed 100% correlation. Root mean square error compared favorably against other synthesis techniques. Overall percent agreements for the various ECG morphologies were noted to be 98.4% to 100%.

Conclusions: The 12-lead ECG and 3-lead VCG can be derived accurately from 3 measured leads with high quantitative and qualitative correlations. These derived tracings can be acquired instantaneously and displayed in real time from a cardiac rhythm monitor. This will allow for immediate, on-demand, convenient, and cost-effective acquisition and analysis of the 12-lead ECG and 3-lead VCG in areas of acute patient care.

1. INTRODUCTION

Cardiac electrical activity is reported to be highly dipolar [1,2] and is clinically represented by both the scalar measured 12-lead electrocardiogram (ECG) (mECG) and 3-lead spatial measured vectorcardiogram (VCG) (mVCG) [3]. In theory, if the cardiac electrical field is dipolar, then only 3 measured leads should be necessary to actually derive this composite 15-lead ECG [4] from just 5 body surface electrodes that are connected to a cardiac rhythm monitoring device. This will allow usual and customary continuous cardiac rhythm monitoring with the added simultaneous advantage of acquiring the derived 12-lead ECG (dECG) and scalar 3-lead derived VCG (dVCG), a composite 15-lead ECG, instantaneously and in real time using 1 cardiac rhythm monitoring device.

It would be highly desirable to record these 15 scalar ECG leads, along with the corresponding cardiac rhythm data, from a reduced lead set, thereby making the acquisition process more timely and efficient.

The objective of this study is to derive with accuracy the standard 12-lead dECG plus 3-lead dVCG, from just 3 measured leads using 5 body surface electrodes that are a subset of the 12-lead mECG, connected to a new continuous cardiac rhythm monitoring device (VectraplexECG System with VectraplexAMI; VectraCor, Inc, Totowa, NJ) using a nonlinear optimization (NLO) constructed universal patient transformation matrix (UPTM).

2. METHODS

This study is a blinded retrospective observational design comparing the quantitative and qualitative correlations between the mECGs and mVCGs with their corresponding dECG and dVCG tracings.

The standard 12-lead ECGs and 3-lead VCGs were acquired using a Marquette MAC-15 machine (GE Healthcare, Waukesha, WI). These ECG records were retrospectively reviewed.

Two independent physician readers, a board-certified emergency physician (EP) and board-certified cardiologist, served as the blinded reference standards. The physicians were blinded to (1) the ECG acquisition and signal processing, (2) the patient's disease state, (3) to each other's interpretation, and (4) to whether the 12-lead ECG and 3-lead VCG were measured or derived.

The basis measured 3-lead set (I, II, V2) is used to derive the remaining leads being studied. Leads I, II, and V2 are measured but are not an orthogonal set of lead vectors. However,

substituting lead aVF for lead II yields an orthogonal set of leads. Lead aVF can be calculated from leads I and II using accepted geometric formulae [7]. The derived ECG results from the multiplication of the NLO [8] constructed UPTM by the basis 3-lead measured voltage-time data matrix. This UPTM was constructed a priori from an independent set of men and women with variable ECG and VCG morphologies.
The quantitative measures of similarity between the original mECG and mVCG and the corresponding dECG and dVCG were determined using Pearson r correlation [4,9] and root mean square error (RMSE – not shown) analysis [10,11] for each derived lead. The Pearson r was considered to show high positive correlation [12] at $r \geq 0.7$. Statistical significance for Pearson r was calculated at $\alpha = .025$ (1-tailed, positive correlation only). The RMSE is a parameter that indicates the average voltage error (microvolts) across the ECG leads studied.
Qualitative measures of similarity and reproducibility between the measured and derived ECG and VCG were determined using percent agreement analysis [13] of the interpretations by the blinded physician reference standards.
The primary outcomes were the quantitative correlations of the measured and derived ECG and VCG tracings based on the Pearson r correlation and RMSE statistics described above and the qualitative methods based on blinded physician percent agreement methodology.

Table 2
Pearson r correlation for various 12-lead ECG morphologies (I, II, V2 not shown, because they are the measured lead set)

Pearson r	n	III	aVR	aVL	aVF	V_1	V_3	V_4	V_5	V_6	12-lead ECG	95% CI
All cases	366	1.00	1.00	1.00	1.00	0.87	0.90	0.71	0.71	0.75	0.867	0.010
AMI	124	1.00	1.00	1.00	1.00	0.84	0.88	0.62	0.66	0.68	0.855	0.017
Anteroseptal	39	1.00	1.00	1.00	1.00	0.89	0.90	0.68	.068	0.75	0.889	0.018
Inferior	46	1.00	1.00	1.00	1.00	0.78	0.85	0.56	0.68	0.66	0.842	0.033
Lateral	21	1.00	1.00	1.00	1.00	0.84	0.86	0.62	0.53	0.60	0.808	0.045
Posterior	21	1.00	1.00	1.00	1.00	0.78	0.83	0.60	0.58	0.49	0.809	0.056
Non_STEMI/ischemia	63	1.00	1.00	1.00	1.00	0.86	0.88	0.57	0.65	0.67	0.847	0.024
Prior MI (recent or old)	133	1.00	1.00	1.00	1.00	0.87	0.90	0.64	0.63	0.65	0.846	0.016
Control/non-AMI	243	1.00	1.00	1.00	1.00	0.89	0.91	0.75	0.74	0.78	0.873	0.012
LBBB	19	1.00	1.00	1.00	1.00	0.91	0.94	0.53	0.52	0.81	0.881	0.032
RBBB	16	1.00	1.00	1.00	1.00	0.72	0.81	0.59	0.66	0.69	0.852	0.042
LAFB	26	1.00	1.00	1.00	1.00	0.81	0.88	0.64	0.46	0.54	0.850	0.032
IRBBB	21	1.00	1.00	1.00	1.00	0.62	0.89	0.85	0.81	0.76	0.869	0.043
IVCD	41	1.00	1.00	1.00	1.00	0.79	0.88	0.56	0.58	0.74	0.866	0.026
PVC	11	1.00	1.00	1.00	1.00	0.86	0.92	0.74	0.69	0.65	0.845	0.084
Paced rhythm	4	1.00	1.00	1.00	1.00	0.80	0.89	0.74	0.49	0.79	0.913	0.009
NSSTT changes	84	1.00	1.00	1.00	1.00	0.88	0.90	0.70	0.69	0.78	0.857	0.022
LVH	35	1.00	1.00	1.00	1.00	0.96	0.88	0.68	0.80	0.89	0.891	0.021

3. RESULTS

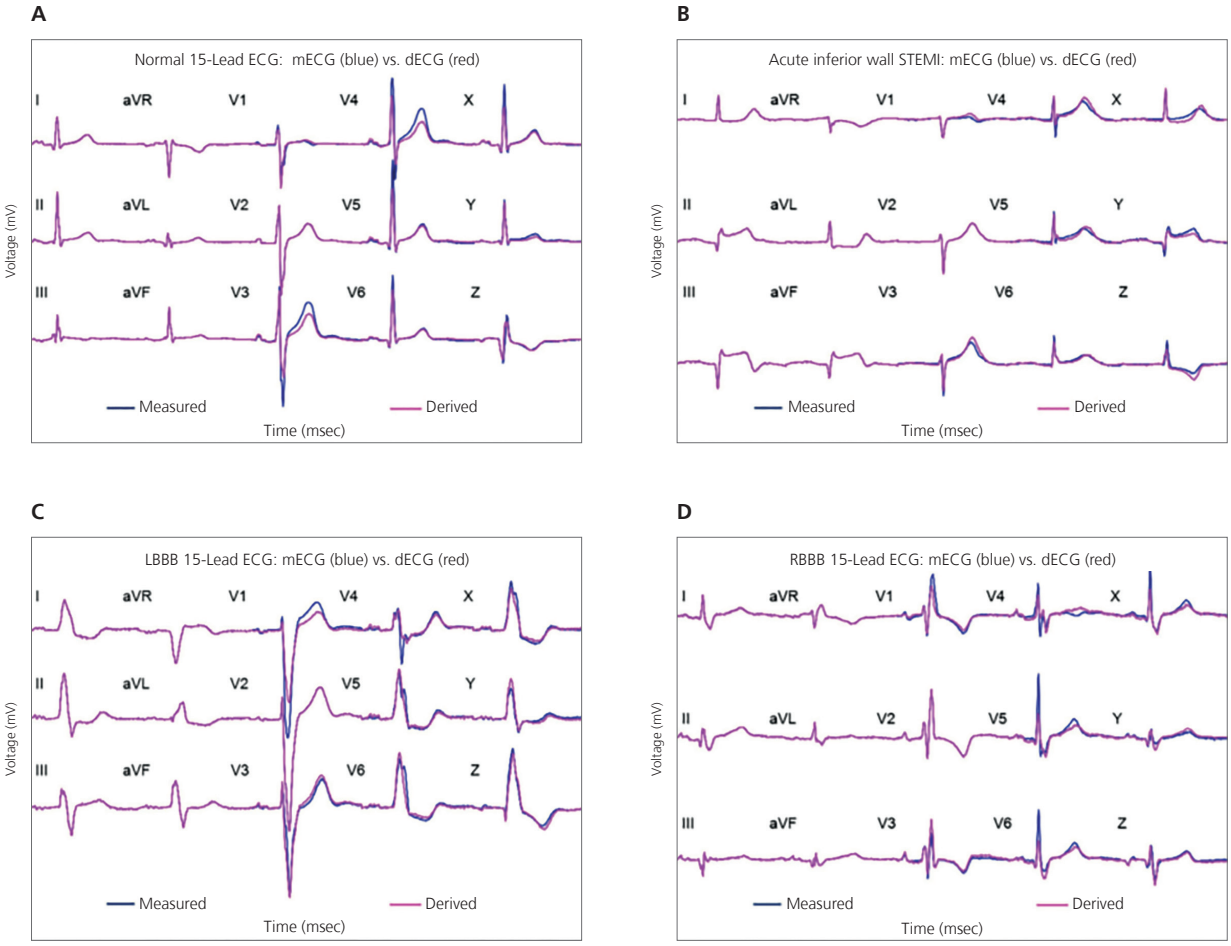
A total of 367 cases were enrolled in this study.
Table 2 describes the Pearson r correlation analysis for a variety of different morphologic ECGs using the NLO method. It should be emphasized that the correlation is only performed on the derived leads. Leads I, II, and V2 are not analyzed because they comprise the measured lead set from which all derivations are constructed and have no error. This is an advantage because these leads are a subset of the 12-lead ECG. As such, additional education on an unfamiliar basis lead set is not required. In addition, the accuracy of the placement of the electrodes for these leads has minimal error. All NLO-synthesized limb leads showed perfect correlations (r = 1.00) suggesting the UPTM should have high accuracy in synthesizing the remaining derived leads. Pearson r for the 12-lead ECG showed high correlations (r = 0.867) for all cases. In addition, all subtype ECG morphologies demonstrated high correlations ranging from 0.823 to 0.913. All derived leads independently show good correlation with the corresponding measured leads across all cases. All correlations were statistically significant at $P < 0.001$.
Table 3 describes the Pearson r correlations for the derived leads at specific points in the ECG and VCG waveforms. All correlations were statistically significant at each portion of the ECG cycle at $P < 0.001$.
For the RMSE analysis for the NLO 12-lead dECG derivation method used by the VectraplexECG System is important to note that there is essentially no error in 7 leads (I, II, III, aVR, aVL, aVF, and V2) using the NLO method. This is due to the NLO method using leads I, II, and V2 as the basis measured lead set from which all other leads are derived.
The consensus interobserver agreement for both blinded physician reference standards reached by adjudication also showed high agreement in diagnostic accuracy between the mECG and dECG. The cardiologist intraobserver agreement between the mECG and dECG for various ECG morpholog-

ic conditions demonstrates high agreement in diagnostic accuracy between the mECG and dECG. The EP intraobserver agreement between the mECG and dECG for various ECG morphologic conditions also demonstrates high agreement in diagnostic accuracy between the mECG and dECG. Figure 4A-4D show comparisons of the scalar mECGs and mVCGs with the corresponding dECGs and dVCGs for several clinical states.

Table 3
Pearson r correlation of measured vs derived leads V1, V3, V4, V5, V6, X, Y and Z at specific waveform peak voltages (P, Q, R, S, J, ST20, ST60, ST80, T+, T-)

	V_1	V_3	V_4	V_5	V_6	X	Y	Z
mP vs dP	0.41	0.73	0.71	0.73	0.75	0.84	0.92	0.57
mQ vs dQ	0.69	0.66	0.76	0.78	0.80	0.81	0.93	0.84
mR vs dR	0.79	0.82	0.63	0.64	0.73	0.68	0.88	0.74
mS vs dS	0.69	0.75	0.62	0.60	0.72	0.80	0.88	0.76
mJ vs dJ	0.86	0.83	0.71	0.71	0.75	0.88	0.92	0.81
mST20 vs dST20	0.89	0.89	0.73	0.71	0.77	0.85	0.92	0.81
mST60 vs dST60	0.90	0.90	0.73	0.74	0.80	0.84	0.88	0.83
mST80 vs dST80	0.89	0.90	0.73	0.75	0.81	0.86	0.92	0.83
mT+ vs dT+	0.81	0.88	0.76	0.78	0.86	0.85	0.91	0.89
mT- vs dT-	0.79	0.89	0.83	0.72	0.73	0.77	0.94	0.83

D.M. Schreck, R.D. Fishberg / American Journal of Emergency Medicine 31 (2013) 1183–1190



ECG	Electrocardiogram	**MI**	Myocardial infarction
mECG	Measured 15-lead ECG (12-lead ECG plus 3-lead Vectrocardiogram)	**STEMI**	ST elevation MI
		LBBB	Left bundle branch block
dECG	Derived 15-lead ECG	**RBBB**	Right bundle branch block

Figure 4.
A, Normal 15-lead ECG: mECG (blue) vs dECG (red). B, Acute inferior wall ST-elevation myocardial infarction: mECG (blue) vs dECG (red). C, Left bundle-branch block 15-lead ECG: mECG (blue) vs dECG (red). D, Right bundle-branch block 15-Lead ECG: mECG (blue) vs dECG (red). MI, myocardial infarction; STEMI, ST-elevation MI; LBBB, left bundle-branch block; RBBB, right bundle-branch block.

4. DISCUSSION

This is the first study describing the process for synthesizing the dECG and dVCG from just 3 measured leads that are a subset of the standard 12-lead ECG, using an NLO technique. The concept of the dECG has been previously reported [15-19]. Schreck et al [20] reported that factor analysis [21] demonstrated that the 12-lead ECG can be derived from just 3 measured lead vectors using a "patient-specific" transformation matrix. However, Schreck et al [22] subsequently demonstrated that a "universal patient" transformation matrix can be computed using an NLO technique that can be used to derive the 12-lead ECG independent of sex, race, age, body habitus, and timing, thus eliminating the need for constructing a patient-specific transformation matrix for each patient. The NLO constructed UPTM allows a "one-size-fits-all" approach to using only 1 UPTM for all patients at any time to derive any patient 12-lead ECG and 3-lead VCG.

The device used in this study uses 3 measured leads, with the least lead placement variability (limb leads and V2), which are a subset of the standard 12-lead ECG and are well known and understood.

The spatial 3-lead VCG was reported by Frank [23] over 50 years ago, and its clinical value has been reported in numerous publications and textbooks [24-28]. In addition, the VCG has been reported to be more sensitive [29-32] in the diagnosis of cardiac pathology, but it is becoming a lost art due to lack of readily available machinery and lack of education of this technology. It would be clinically advantageous in acute care settings to implement the VCG concepts to enhance diagnostic capabilities if the acquisition of the VCG could be accomplished through an accurate derivation process directly from a standard cardiac rhythm monitor.

The clinical application of this research will be advantageous in areas of acute care. The ability to derive a standard 12-lead ECG and spatial 3-lead VCG directly from a standard cardiac rhythm monitor using only 5 electrodes will make the acquisition of these tests much faster, less costly, more easily accessible, and more efficient if clinical accuracy can be demonstrated between the measured and derived ECG and VCG tracings.

The main limitation of this study is its retrospective design. As such, several sources of bias may be present.

Another limitation in this study is that the physician reference standards, although blinded, are an imperfect "truth." In addition, the mECG by itself is also an imperfect truth in that electrode placement variability is very high for the chest leads [33].

One more limitation of this study is that a direct comparison of the NLO method to EASI method of ECG derivation was not performed.

The results of this study demonstrate that the dECG and derived spatial 3-lead VCG using the NLO methodology have high correlation with the corresponding measured scalar leads based on quantitative and qualitative comparisons. This derived composite 15-lead ECG can be constructed from just 3 acquired leads using 5 body surface electrodes connected to a cardiac rhythm monitor. These derived 15 scalar ECG leads are obtained in real-time or on demand directly from the cardiac rhythm monitor. This minimizes the need to obtain frequent serial measured ECGs requiring staff time and numerous electrodes. Application of this device will be advantageous in acute care settings by identifying potential ECG morphology changes in real time in a more convenient and efficient manner.

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MATHEMATICAL MODELING AND UTILITY OF THE DERIVED 22-LEAD ELECTROCARDIOGRAM

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BACKGROUND

The cardiac electrical field is dipolar and is measured by the electrocardiogram (ECG) which may be described by a 3 lead-vector space. There are 22 leads used in clinical practice including the standard 12-lead ECG, right heart leads V3R-V6R, posterior leads V7-V9, and the vectorcardiographic (VCG) leads X, Y, Z. It would be advantageous to derive these 22 ECG leads from just 3 measured leads using a universal patient coefficient matrix (UPCM) that can be computed using simplex optimization (SOP). The objective is to derive the ECG (dECG) from 3 measured leads using a SOP-computed UPCM and calculate the quantitative and qualitative correlations with the measured ECG (mECG).

METHODS

A total of 371 mECGs of varying morphology for both men and women age 18 and older were acquired including 371 standard 12-lead ECGs, 353 VCGs, 75 right heart ECGs, and 34 posterior ECGs. The ECG morphologies included normals, acute MIs, LVH, bundle branch blocks, paced beats, PVCs, and non-specific STT types. Each ECG was interpreted by 2 physicians who were blinded reference standards. The SOP technique was used to derive a UPCM from an additional training set of 20 ECGs. Leads I, aVF, and V2 from the mECGs were chosen as the 3 lead-vector basis orthogonal lead set from which the dECGs were synthesized. The derived vs. measured test case ECGs were compared using Pearson and Kappa statistics.

RESULTS

The dECGs showed high correlation with mECGs overall by Pearson correlations (0.84-0.88). No clinically significant differences were noted in 98.1% of the dECGs. ECG rate, rhythm, segment, and axis interpretations showed 100% correlation. Acute MI differentiation showed 100% correlation. Kappa analysis of the mECG vs. dECG showed high overall correlations (0.73-1.00).

CONCLUSIONS

The 22-lead ECG can be derived from just 3 measured leads using the SOP technique. The comparison of the mECGs and dECGs shows high quantitative and qualitative correlations. Using this technology a 22-lead derived ECG can be displayed instantaneously in real-time to enhance patient observation capabilities and will allow for a convenient and cost effective acquisition and analysis of the ECG in telemetry and critical care areas of health care.

VECTOR LOOPS

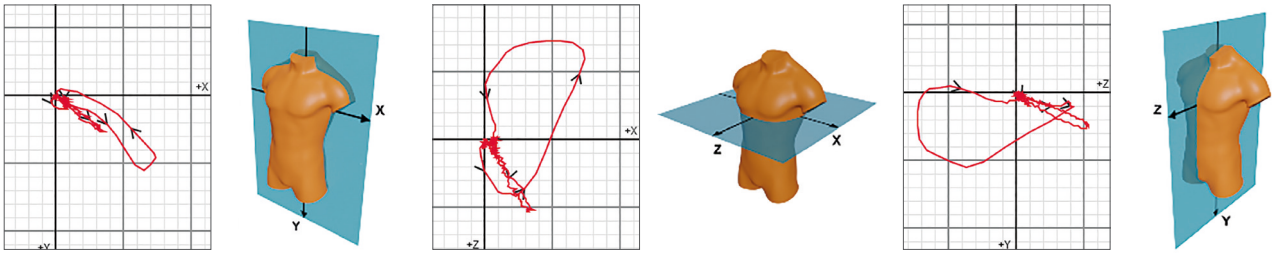
The vectorcardiogram (VCG) is a useful method for cardiac diagnosis. The cardiac cycle is represented in the VCG as three loops. Each loop corresponds to the P, QRS and T wave activities (Bhattacharyya et al. 2020). It contains more information with possible diagnostic significance, it is more sensitive than the conventional ECG and it is useful for the detection and localization of acute myocardial infarction, right ventricular hypertrophy and Tawar arm blockade (Jaros et al. 2019; Bhattacharyya et al. 2020). A healthy myocardium leads to a regular and smooth VCG, but a left ventricular dysfunction might lead to irregular, disorganized or criss-cross propagation. An abnormal ventricular repolarization sequence results in an abnormal morphology of the T wave. (Bhattacharyya et al. 2020)

The diagnostic potential of the VCG is high, but the difficulty and cumbersomeness in constructing a VCG loop prevents its popularity in routine use.

In 1956, Ernest Frank introduced the VCG lead-system based on 7 electrodes (A, C, E, I, M, H and F) to derive three equal-length, orthogonal image vectors which are stable for individual anatomical variations, called the VCG. The orthogonal image vectors represent the right-to-left axis, the anteroposterior and the caudal to cranial axis of the human body. The electrodes A, C and I measure the potential difference Vx, which corresponds to the right-to-left axis. The z-axis (anteroposterior lead) is based on the electrodes A, C, E, I, and M. All five are necessary for the reliability of the lead and for stability against dipole-location changes. The last axis from cranial to caudal, the y-axis, is derived from electrodes H, M and F. For measurement of the VCG in addition to the ECG, you needed to attach these 7 electrodes together with the standard 12-lead ECG, which means 17 electrodes for each patient (Schreck and Fishberg 2013). Consequently, the VCG is not commonly used in clinical practice due the effort required in its application and the complex, specific interpretation (Jaros et al. 2019).

Nowadays these vectors can be derived from a reduced set of the standard 12-lead ECG electrode set (Schreck and Fishberg 2013). There is no need for any additional electrodes or to change current routines, yet all benefits of this method can be reaped. It can easily be compared to the ECG at the same time, resulting from the same electrode set. This is the chance to implement the VCG into clinical routine and to learn more about the loops, their meaning and their potential.

The literature cited and the following review article by Carlos Alberto Pastore and colleagues offers a good overview of the VCG and its diagnostic potential.



Visualization of the electrical activity of the three ortogonal leads (X,Y,Z) in the shape of vector loops

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APPLICABILITY OF THE ELECTRO-VECTORCARDIOGRAM IN CURRENT CLINICAL PRACTICE

(Review article - shortened version)

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ABSTRACT

The electrocardiogram (ECG) has been reinvigorated by the identification of electrical alterations that were not definitely clarified before. In this context, and mainly regarding the definition of arrhythmogenic substrates, the association of the ECG with the vectorcardiogram (VCG) has gathered much more information about the cardiac electrical phenomena, thus allowing us to differentiate potentially fatal cases from benign ones. Obtaining a VCG concomitantly with the performance of an ECG has led to a significant gain in the definition of extremely sophisticated pathologies, which function suffer some type of structural or dynamic alterations, involving either the reduction or enhancement of ionic channels and currents.

The classic aspects of the ECG/VCG association in the differential diagnosis of myocardial infarctions, conduction disorders, atrial and ventricular hypertrophies, and the correlations between these electrical disorders are still valid and assertive. The association of these pathologies is further clarified when they are seen through the ECG/VCG dyad.

The three-dimensional spatial orientation of both the atrial and the ventricular activity provides a far more complete observation tool than the ECG linear form. The modern analysis of the ECG and its respective VCG, simultaneously obtained by the recent technique called electro-vectorcardiogram (ECG/VCG), brought a significant gain for the differential diagnosis of some pathologies. Therefore, we illustrate how this type of analysis can elucidate some of the most important diagnoses found in our daily clinical practice as cardiologists.

INTRODUCTION

The study of vectorcardiography began during the 1940's and publications reached a peak between the 1960's and 1970's, correlating this method with the heart diseases best known at that time. The great difficulty then was linked to the fact that the VCG device could not be easily moved around. The images were thus not immediately obtained, and so the vectorcardiogram was a tool to be used a posteriori to resolve doubts about specific electrocardiograms in some special situations. A temporal gap, associated to a diminished interest in electrovectorcardiography, resulted in a significant decrease in the number of cardiology centers capable of performing and interpreting a vectorcardiogram.

However, with the development of invasive electrophysiology (electroanatomic mapping), genetics and molecular biology, many electrical conditions have been unveiled, resulting in the identification of their clinical/electrocardiographic patterns, since such conditions can lead to sudden death.[1-7]

The technological developments seen during the 1990s also affected electrovectorcardiography. The sophistication brought by the use of computers, algorithmic systems and Fourier transforms allowed us to obtain vectorcardiographic information in a much simpler and quicker form, in color, and as three-dimensional images.

The electrocardiogram (ECG) was therefore reinvigorated by the identification of electrical alterations. Mainly regarding the definition of arrhythmogenic substrates, it was observed that the association of the ECG and the vectorcardiogram (VCG) methods could provide much more information about the cardiac electrical phenomena, thus increasing its employment and allowing us to differentiate potentially fatal cases from benign ones.[8-10]

Our team is involved with the teaching of electro-cardiography to undergraduate and postgraduate students in the medical area. Therefore, we feel there is an urgent need to teach vectorcardiography, considering that its spatial visualization of the cardiac electrical activation makes it a lot easier to understand and memorize the basic and more complex electrocardiographic notions.[11]

Obtaining a VCG concomitantly with the performance of an ECG has led to a significant gain in the definition of extremely sophisticated pathologies, of which genetic mutations cause their function to suffer some type of structural or dynamic alterations, involving either the reduction or enhancement of ionic channels and currents.

The classic aspects of the ECG/VCG association in the differential diagnosis of myocardial infarctions, conduction disorders, atrial and ventricular hypertrophies, and the correlations between these electrical disorders are still valid and assertive.[12,13] The association of these pathologies is further clarified when they are seen through the ECG/VCG dyad. (Figure 1)

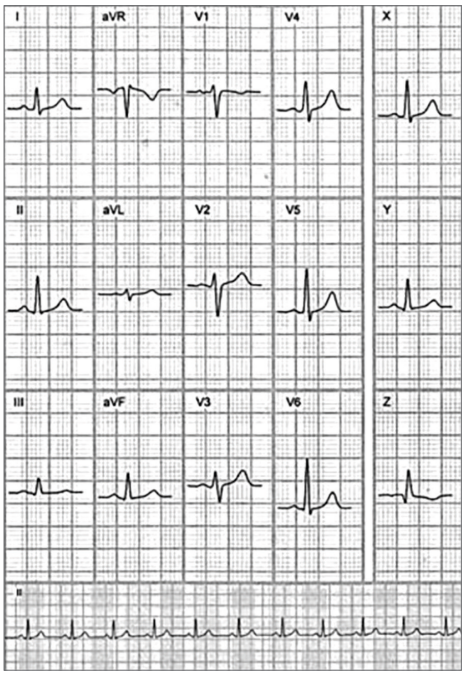
Based on the abovementioned facts, during the last decade we were able to develop the performance of the binomial electrovectorcardiogram in the context of the most varied

pathologies. This binomial can add sophistication to the already known clinical entities, in addition to a greater accuracy of the recent electrocardiographic definitions (such as Brugada, early repolarization, etc.)

Our experience, both academic and scientific, led us to join these new ECG/VCG acquisitions, and to open a window into the observation of the electrical phenomena of the heart. The literature has shown that the more sophisticated vectorcardiogram makes it easier for us to observe punctual phenomena that are not defined by the ECG.

Figure 1: Normal Electrocardiogram and Vectorcardiogram

Electrocardiology Electrocardiogram



Vectorcardiogram

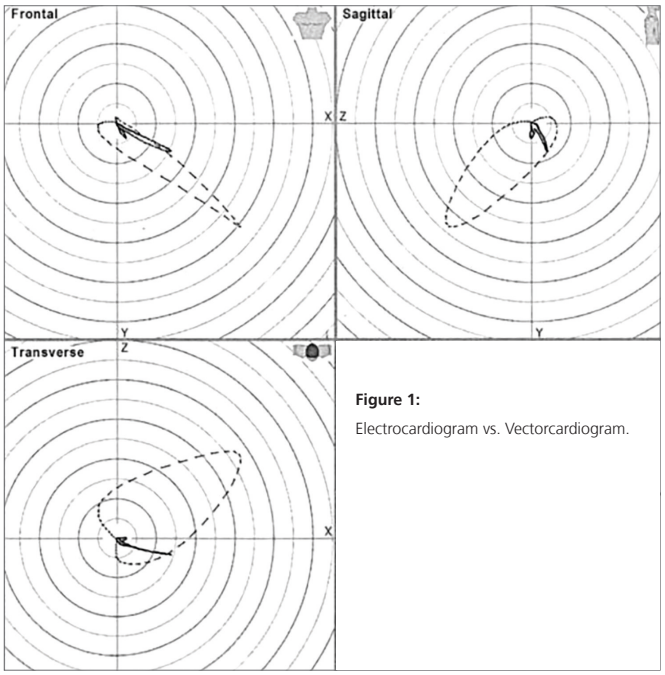


Figure 1:
Electrocardiogram vs. Vectorcardiogram.

The electrovectorcardiography binomial

The experience with the VCG during these last decades shows the greater specificity and sensitivity of this method to detect the subtleties of these diagnoses. In comparison with the ECG, the VCG shows some advantages; however, when in association, they can help us differentiate between some very ordinary situations in clinical practice.

The three-dimensional spatial orientation of both the atrial and the ventricular activity provides a far more complete observation tool than the linear form of the ECG. The modern analysis of the ECG and its respective VCG, simultaneously obtained by the recent technique called electro-vectorcardiogram (ECG/VCG), brought a significant gain for the differential diagnosis of some pathologies.[1,3,4,8,14,15] (Figure 2)

The electro-vectorcardiographic analysis is very rich and consistent for the diagnosis of myocardial infarctions (MI), since the difficulties in defining pathological Q waves or the loss of R waves in the ECG can be very clearly visualized in the ECG/VCG. This association helps us to define the real changes in the direction and orientation of the vectorcardiographic loops created by the areas of myocardial infarction, in both the transverse and the frontal planes.[16-18] (Figure 3)

Another important differential aspect obtained by the elec-

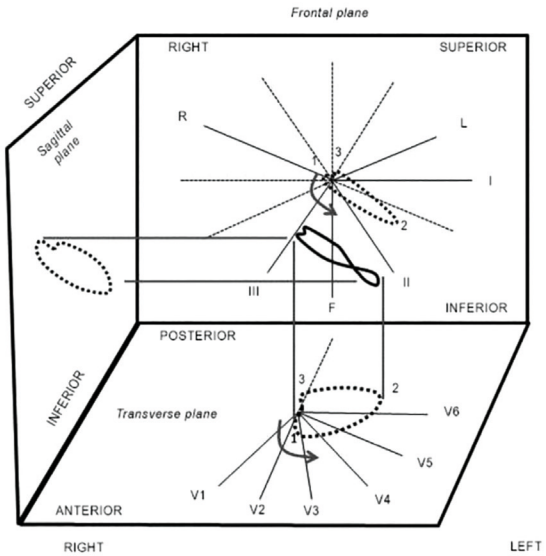
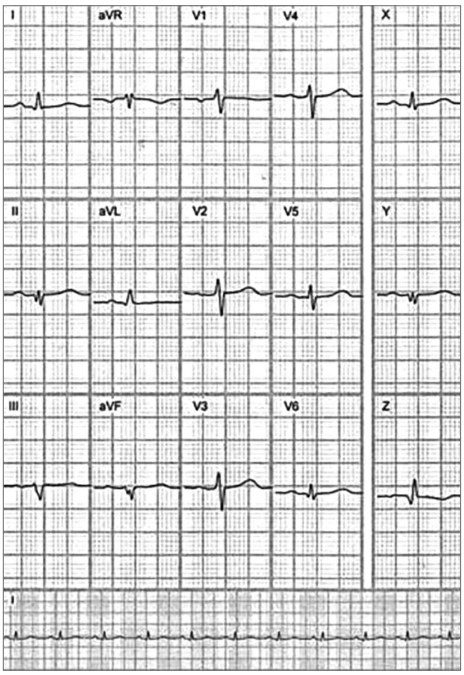


Figure 2: Orthogonal planes

trovectorcardiogram is the investigation of the presence of a myocardial infarction area in the inferior wall, of a left superior fascicular block, or the association of both pathologies. The association of MIs with the presence of fascicular or troncular blocks can be fully characterized by the ECG/VCG association. The inferior MIs with a left anterosuperior fascicular block (LASFB), and the anterior MIs with a right bundle-branch block (RBBB) are typical examples of the importance of the ECG/VCG association for a differential diagnosis.[19,20] (Figure 3A and 4A)

Figure 3A: Old inferior myocardial infraction (MI)

Electrocardiology Electrocardiogram



Vectorcardiogram

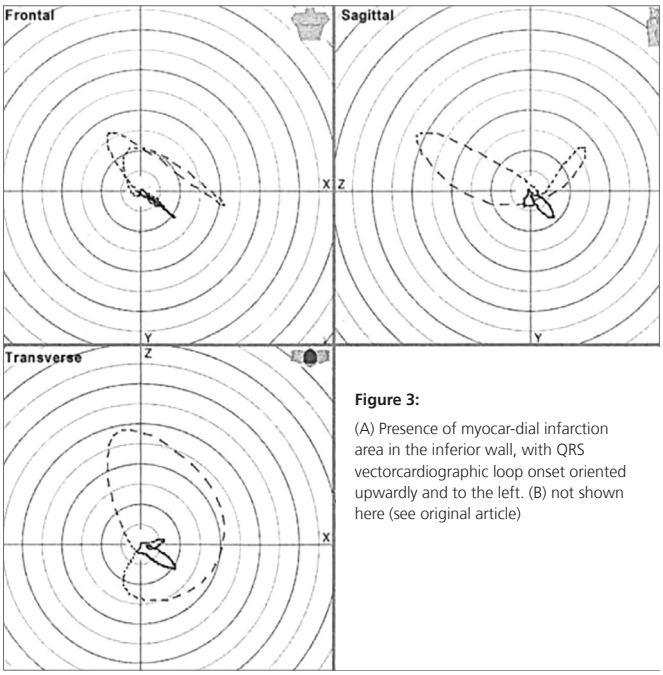


Figure 3:
(A) Presence of myocar-dial infarction area in the inferior wall, with QRS vectorcardiographic loop onset oriented upwardly and to the left. (B) not shown here (see original article)

The spatial orientation of the fascicular blocks can be better understood through the electro-vectorcardiogram. The septal vector orientation and the direction of the vectorcardiographic loop activation neatly characterize the fascicular blocks and their associations through the ECG/VCG, since they define the electrical path of this phenomenon, thus characterizing exactly the position of the blocks.[21-24] (Figure 4A and 5(A and B not shown)

The VCG complements the ECG in the analysis of acute myocardial infarctions and makes the differential diagnosis of the associations with blocks and chamber hypertrophies. Furthermore, the ECG/VCG is capable of characterizing the presence of: [22-27] (Figure 5B, 6[A, B, C (not shown) and D])

a) Left anteromedial fascicular block (LMFB)
b) Right ventricular hypertrophy (RVH)
c) Lateral infarction
d) Ventricular pre-excitation syndrome (WPW)
e) Brugada syndrome

The ECG/VCG is the gold standard to identify com-plete and fascicular blocks, because it can differen-tiate them either in isolation or in association with other blocks. The electrical path marked by the ventricular activation loops can identify the blocks, as well as other associations.[21,23,28] (Figure 7)

The end-conduction delays, previously denominated incomplete right bundle-branch blocks, are neatly defined by the ECG/VCG. These findings can be mistaken for the left phenomena and also can mimic a myocardial infarction area. Thus, the association of ECG/VCG solves the doubts that arise from the presence of these delays, which can be either the variants from the normal, or even suggest a conduction disorder in specific areas of the right ventricle.

The presence of the end-conduction delay (ECD) is clarified in the ECG/VCG by the S_1 S_2 S_3 pattern, with the S wave in D2 greater than the one in D3, qR in aVR and presence of S wave from V1 to V6. The ECG/VCG confirms the ECD position backwardly and to the right in the transverse plane, and up-wardly and to the right in the frontal plane.[25] (Figure 8 not shown)

One of the most recent diagnostic achievements of the ECG/VCG refers to the criteria to establish Brugada syndrome patterns, as well as the early repolarization (ER) phenomenon. It is important to emphasize that, in typical cases, there are no difficulties to make the electro-vectorcardiographic identification of both conditions. Due to the severity of the

first, to the variability of the second between normal cases and other pathologies, and also to the possibility of having an early repolarization pattern located in a more anterior area, it became essential to make an adequate distinction between them. Specific ECG/VCG patterns of the J-wave abnormalities, namely the Brugada syndrome (BrS), and the early repolarization pattern (RP) were studied by our research team. An important qualitative and quantitative analysis of the ECG/VCG was carried out in all the study population, specifically regarding aspects of the area comprising the terminal portion of the QRS loop, the J point and the ST segment. This analysis showed a neat end-conduction delay (ECD) in all the individuals (BrS and RP). This ECD is characterized by a conduction delay greater than 10 ms at the final portion of the QRS in all the planes, either to the right or to the left.

In the transverse plane, the QRS loops showed a counterclockwise rotation, with the ECD beginning posteriorly and ending anteriorly, with the main difference between the groups being the ECD position.

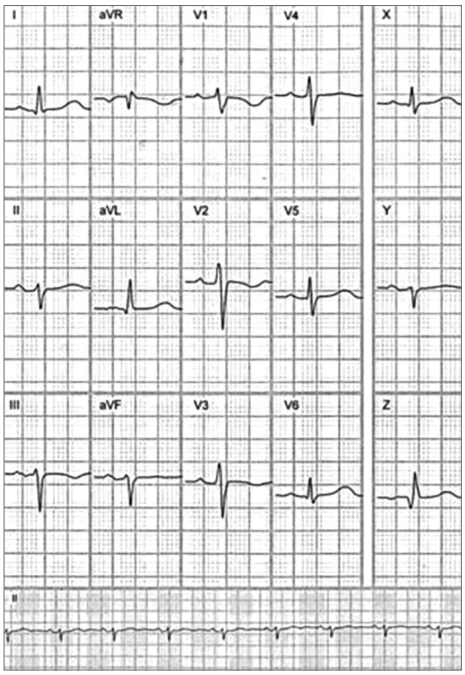
In the ER pattern [9,25] (Figure 10 not shown) we see a clockwise rotation (terminal portion of the QRS) of the same segments, resembling a "fishhook". In all the ER cases the ECD position was in the left quadrant, with a shorter duration. In 100% of the ER patients, the final portion of the QRS loop showed a fishhook pattern.

A very important arrhythmogenic pathology, the arrhythmogenic right ventricle cardiomyopathy (ARVC), has an almost definitive assessment tool in the electrovectorcardiographic diagnosis. The end-conduction delay with low voltage and long duration to the right (forward or slightly backwards) characterizes the phenomenon with great accuracy, with the differential diagnosis being very important, since this pathology may lead to severe arrhythmias. (Figure 11 not shown)

ARVC sometimes presents with an aspect similar to the RBBB, although with a very low voltage that is different from that block. It can also show an ECD aspect on the right and be slightly backwards. The presence of a negative T wave in V_1, V_2, V_3 and left posteriorly located in the transverse plane of the ECG/VCG is crucial for an accurate diagnosis. The Brugada syndrome has shown to be very dynamic regarding its arrhythmogenic substrate, and the ECG/VCG follow-up can be very useful to define this process.[29,30] (Figure 12 not shown).

Figure 4A: LASFB

Electrocardiology Electrocardiogram



Vectorcardiogram

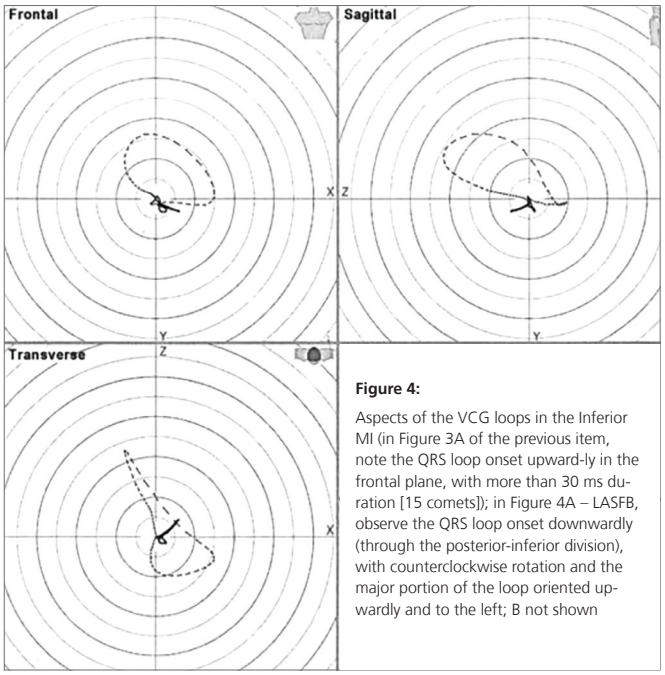
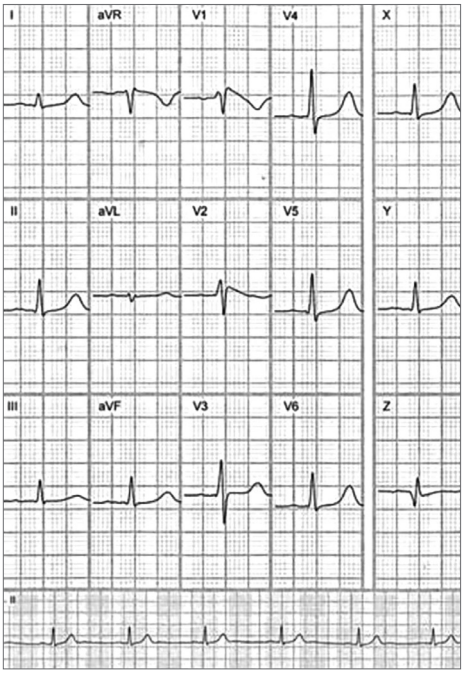


Figure 4:

Aspects of the VCG loops in the Inferior MI (in Figure 3A of the previous item, note the QRS loop onset upward-ly in the frontal plane, with more than 30 ms duration [15 comets]); in Figure 4A – LASFB, observe the QRS loop onset downwardly (through the posterior-inferior division), with counterclockwise rotation and the major portion of the loop oriented upwardly and to the left; B not shown

Figure 6: Burgada Syndrome

Electrocardiology Electrocardiogram



Vectorcardiogram

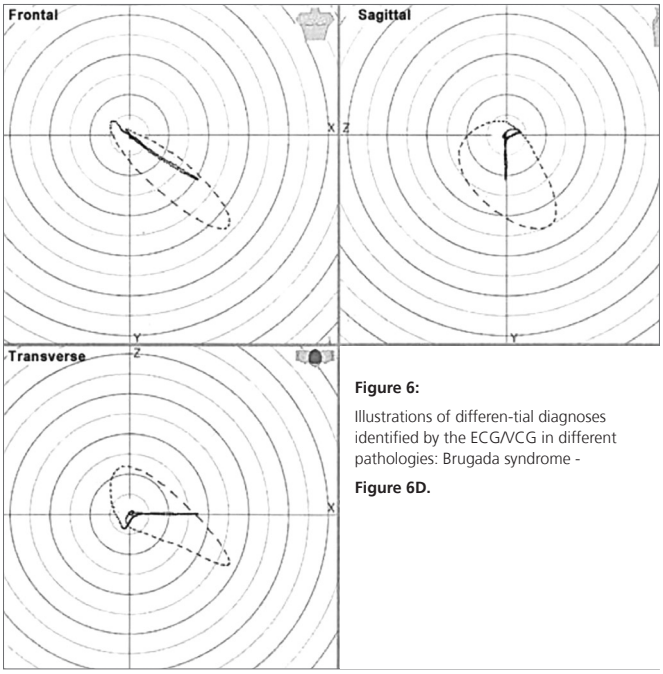


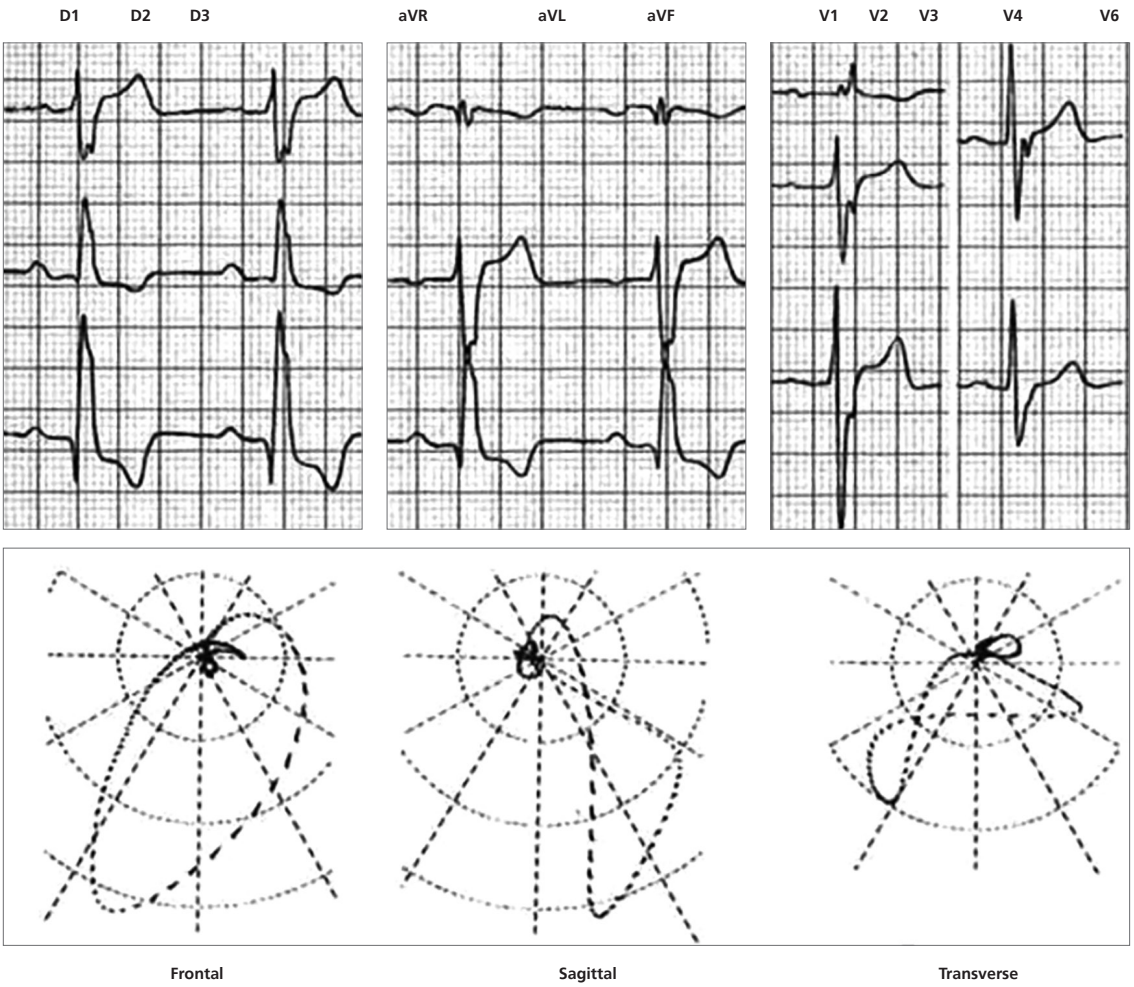
Figure 6:

Illustrations of differen-tial diagnoses identified by the ECG/VCG in different pathologies: Brugada syndrome -

Figure 6D.

Figure 7: LPIFIB + RBBB

Vectorcardiographic aspects of the associ-ation of LPIFB and RBBB: axis to the right in the frontal plane (LPIFB), with most of the QRS loop in the frontal plane, oriented downwardly and to the left, and the QRS loop in the transverse plane, slowly ending forwardly and to the right (RBBB).



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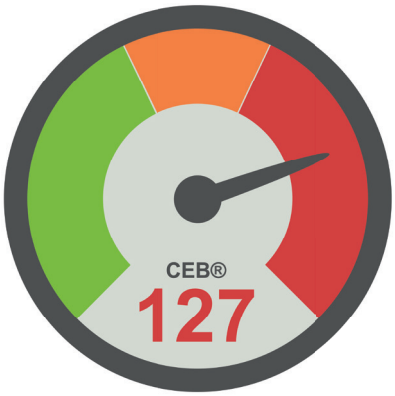
THE CARDIAC ELECTRICAL BIOMARKER – CEB®

A heart beat results in a dipolar electrical field (Strebel et al. 2018; Abaecherli et al. 2017; Chattopadhyay et al.) which is measurable as a vector between electrodes on the body surface. If acute myocardial ischemia occurs, this dipolar field is disturbed by multipolar parts (Strebel et al. 2018). VectraCor developed a method to use these multipolar vectors as a marker for myocardial injury. This cardiac electrical biomarker CEB® is constructed from three ECG leads of the standard ECG electrode set. In addition to the ECG, the CEB® is a tool for detection of acute myocardial ischemic injury with high diagnostic accuracy by analyzing ECG changes (Schreck and Fishberg 2013). The current gold standard for a specific diagnosis of myocardial injury is the highly sensitive cardiac troponin I (Hs-cTnI). Hs-cTnI is a marker for myocardial necrosis. It should be measured at clinical presentation and 3h after admission for a 100% sensitivity and negative predictive value (Thygesen et al. 2012). Therefore, Tereshchenko et al. (2014) analyzed the correlation of troponin and CEB® in 3h-steps. They showed a significant correlation between troponin and CEB® for the second and third 3h-period after presentation of the patient. Strebel et al. (2018) stated a weak but significant correlation between troponin and CEB® also at the time of presentation. Consequently, the CEB® is a marker which correlaes with Hs-cTnI with one major benefit. The CEB® is instantly available the moment an ECG is measured (Schreck and Fishberg 2013; Tereshchenko et al. 2014). Rather than 3h, only 10 seconds is required until an interpretable numerical index is available. The higher the number, the higher the multipolar activity and consequently the probability of acute myocardial ischemic injury (Strebel et al. 2018). A receiver-operating-characteristic analysis showed that a value of 65 and smaller indicates a normal dipolar electrical heart, while a value of 95 and higher is a clear indication to suggest acute myocardial injury. The zone between 66 and 94 is indeterminate, but these cases occurred in only 10% of the patients (Schreck and Fishberg 2013). Even though there were a number of indeterminate CEB®s included as false positive or false negative results, analyzing the correlation of a diagnosis with the CEB® and the diagnosis of different physicians still shows a noninferiority of the CEB®. (Schreck and Fishberg 2013)



CEB indicator showing acute myocardial problems

In summary, the CEB® is simultaneously available with the ECG, it shows high diagnostic accuracy, troponin I correlation and correlation to physicians' diagnostic ECG interpretation. This technology allows immediate identification of patients with AMII on scene (Schreck and Fishberg 2015).

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DETECTION OF ACUTE MYOCARDIAL ISCHEMIC INJURY BY GENDER USING A NOVEL CARDIAC ELECTRICAL BIOMARKER (shortened version)

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ABSTRACT

Objective:

The objective of this study us to stratify by gender a new cardiac electrical biomarker (CEB) diagnostic accuracy for detection of acute myocardial ischemic injury (AMII).

Methods:

This is a noninferiority retrospective, case-control, blinded study of 310 archived measured electrocardiograms (ECGs) acquired from 218 men and 92 women. The CEB is constructed from the derived ECG (dECG) synthesized from 3 leads. Electrocardiograms were included if acquired less than or equal to 1 day from patient presentation. Electrocardiograms were interpreted by 2 blinded physicians and adjudicated by consensus. Standard ST analyses and computerized ECG interpretations were active controls. Electrocardiograms were excluded for noise and baseline wander, age younger than 18 years, and ectopic beats in the 10-second ECG acquisition. Diagnostic accuracy measures of sensitivity, specificity, positive and negative predictive values, and likelihood ratios were stratified by gender. Measured vs derived ECG correlations were quantitatively compared using Pearson correlation and qualitatively by percent agreement methodology.

Results:

The CEB sensitivities for AMII detection in men and women were 93.9% and 90.5%, respectively, and CEB specificities were 90.7% and 95.2%, respectively, and were superior to active controls. Derived and measured ECGs showed high correlation for both men and women with r =0.857 and r = 0.893, respectively. Reference standard intra-agreement analysis for measured ECGs and dECGs with AMII was 99.4%.

Conclusions:

The CEB demonstrates high diagnostic accuracy for detection of AMII in men and women. The ECG can be derived with accuracy from 3 leads. This technology is an efficient real-time method of identifying patients with AMII who are being monitored in acute care settings.

1. INTRODUCTION

The concepts of a new and novel cardiac electrical biomarker (CEB) and the derived 15-lead electrocardiogram (ECG) have been recently reported by Schreck and Fishberg [1,2]. Briefly, cardiac electrical activity is reported to be highly dipolar [3,4], and as such, only 3 measured orthogonal leads should be needed to actually derive this composite 15-lead ECG. This will allow continuous cardiac rhythm monitoring with the added simultaneous advantage of acquiring the derived 12-lead ECG (dECG) and scalar 3-lead derived vectorcardiogram, a composite 15-lead ECG, instantaneously and in real-time using 1 cardiac rhythm monitoring device. The objective of this study is to identify the CEB diagnostic accuracy, stratified by gender, compared to active controls (ACs).

2. MATERIALS AND METHODS

This is a noninferiority, retrospective, blinded, case-control, paired comparator [5] study. These 310 measured ECGs (mECGs) of various morphologies were obtained from 2 databases including an archived National Institutes of Health–funded Physiobank PTBDB database [6] and a database from Muhlenberg Regional Medical Center (Plainfield, NJ). The study ECGs represent a gender stratification subanalysis of a recent prior study by Schreck and Fishberg [1]. Electrocardiograms were included if acquired less than or equal to 1 day from patient presentation.

The dECGs were constructed from 3 measured leads I, II, and V2, which were converted to a 3-lead orthogonal basis set of {I, aVF, V2} [7] using Einthoven triangular geometric relationships. The 15-lead dECGs were synthesized from this orthogonal lead set. The CEB is constructed from the median beat from each dECG using the VectraplexECG System (VectraCor, Inc, Totowa, NJ) and is a measure of the dipolar energy in the cardiac electrical field.

The CEB was compared to each AC that included the 12-lead ECG computer interpretation and the ST analysis voltage parameters ST0 (J point) and ST area under curve (STSUM). The STSUM points included the lead voltages at the J point and at 20, 60, and 80 milliseconds after the J point

(ST0, ST20, ST60, and ST80, respectively).

There were 2 reference standards including 1 board-certified emergency physician (EP) and 1 board-certified cardiologist who independently interpreted the ECGs and were blinded to each other's interpretations. The 2 reference standards also adjudicated the results at study completion. The criteria reported by Thygesen et al [8] were used by the reference standards to interpret ECGs for the presence of ST changes consistent with ST segment elevation myocardial infarction (STEMI) and non-STEMI.

Measured vs derived ECGs correlations were quantitatively compared using Pearson correlation coefficient (r) and qualitatively by reference standard percent agreement methodology [9].

The CEB diagnostic accuracy parameters including sensitivity, specificity, negative and positive predictive values (NPV and PPV), likelihood ratios (LR+ and LR–), and odd ratios (ORs) were identified and compared to the ACs in a noninferiority design [5] and stratified by gender using a 1-sided ($\alpha < .025$, $1 - \beta = 0.90$) interval with 95% confidence statistical analysis.

3. RESULTS

Table 2 shows the CEB sensitivities, specificities, NPV, PPV, LR+, LR–, and OR for acute myocardial ischemic injury (AMII) detection in men and women, also stratified by reference standard and adjudication. The detailed CEB sensitivity analyses, also known as the true-positive rate (TPR), and the 1 – specificity analyses, also known at the false-positive rate, are shown in Figures. 3 to 8.These figures show the analyses of the CEB/AC ratios stratified by gender, AC, and reference standard interpretation with adjudication. The CEB is considered a positive test for AMII if greater than 94 and negative for AMII if less than 66. The CEB is considered indeterminate from 66 to 94. As such, the sensitivity is also stratified by "actual" and "worst" case scenarios. The worst-case scenario is such that any CEB in the indeterminate region is considered a false-positive or false-negative result.

Figure 3 shows the sensitivity (TPR) analyses stratified by gender and AC for the EP reference standard. The CEB was noted to be noninferior by hypothesis testing, but superiority was statistically demonstrated using the actual data compared to the ACs. Figure 4 (not shown) shows the false-positive rate (FPR), also known as 1 – specificity. The CEB was noted to be noninferior by hypothesis testing, but superiority was statistically demonstrated using the actual and worst case data compared to the ACs.

The CEB is shown to be noninferior by hypothesis testing for the TPR analyses. The CEB is shown to superior to ACs in the FPR analyses. Figures 7 to 8 (not shown) show the same TPR and FPR analyses as adjudicated by the reference standards to mimic the real-world situation where the EP and cardiologist both collaborate on the ECG interpretation. The CEB is again shown to be noninferior by hypothesis testing in both the TPR and FPR analyses, but superiority was demonstrated in the actual data TPR analysis. Superiority was also demonstrated for both actual and worst case data FPR analysis.

All CEB diagnostic accuracy measures were significant (P<.025). Derived vs measured 12-lead ECGs showed high correlation for both men and women with r=0.857 and r=0.893, respectively. Because the CEB is constructed from the dECG, it is important to demonstrate the correlation between the mECG and dECG to support the diagnostic accuracy of the dECG for AMII cases. Table 3 (not shown) shows the quantitative Pearson r correlations of the mECGs vs the corresponding dECGs by each derived lead.

Table 4 (not shown) shows reference standard percent inter-agreement and intra-agreement analysis for mECGs and dECGs with AMII.

Table 2
Cardiac electrical biomarker diagnostic accuracy parameters

			AMII	CEB	CEB	CEB	CEB	CEB	CEB	CEB	CEB
		n	Prevalence	Sensitivity	Specificity	NPV	PPV	LR(+)	LR(-)	OR	Utility
EP	Men	222	18.5%	92.7%	91.1%	98.1%	71.7%	10.38	0.08	129.2	92.2%
	Women	92	36.6%	95.5%	91.9%	98.3%	80.8%	11.84	0.05	239.4	91.3%
	Total	314	20.1%	93.7%	91.3%	98.1%	74.7%	10.77	0.07	154.9	93.3%
Cardiology	Men	228	15.4%	82.9%	82.8%	96.1%	48.3%	4.83	0.21	23.2	94.3%
	Women	98	32.1%	94.4%	80.0%	98.2%	54.8%	4.72	0.07	68.0	89.8%
	Total	326	16.3%	86.8%	82.0%	96.7%	50.5%	4.82	0.16	29.9	92.9%
Consensus	Men	218	20.9%	93.9%	90.7%	97.5%	79.6%	10.09	0.07	149.2	94.5%
	Women	92	25.0%	90.5%	95.2%	98.3%	76.9%	19.00	0.10	190.0	91.3%
	Total	**310**	**20.6%**	**92.2%**	**92.9%**	**97.7%**	**78.7%**	**13.02**	**0.08**	**154.9**	**93.5%**

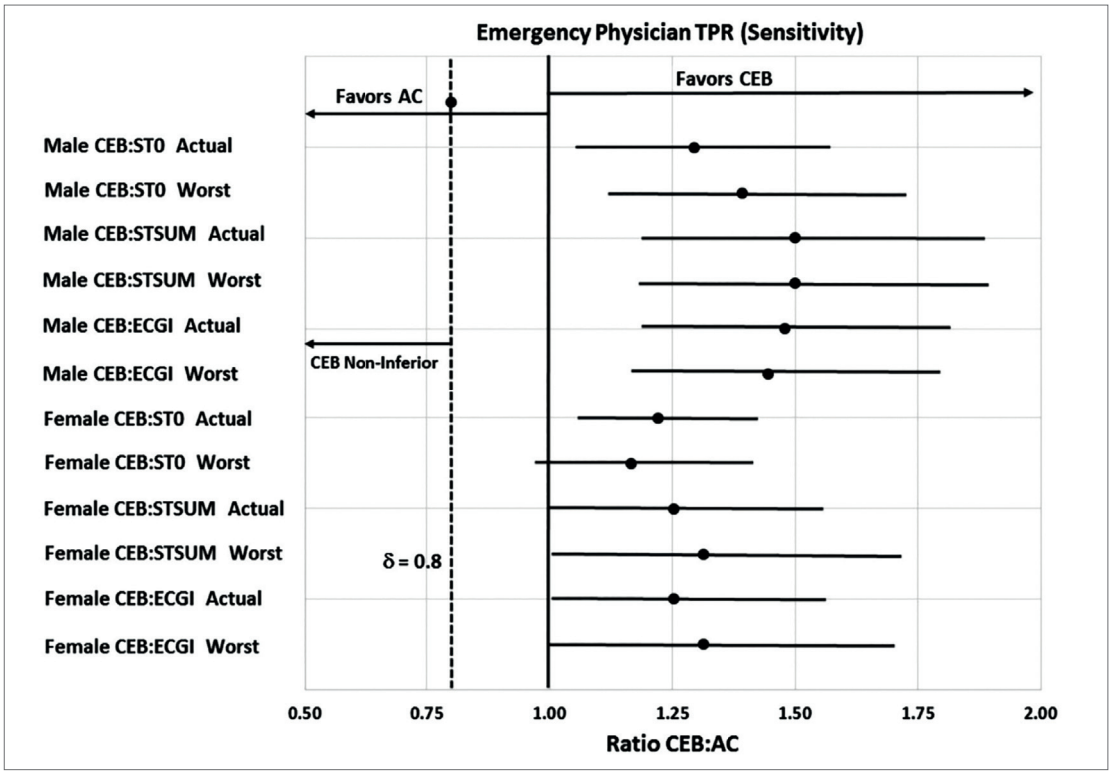

Figure 3: Emergency physician ECG interpretation: CEB:AC actual and worst case sensitivities for men and women. Abbreviations: TPR, true-positive rate (sensitivity); δ,effect margin; ST0,J-point ST voltage; STSUM, area under curve of ST segment voltages at J-point and 20, 60, and 80 milliseconds after J point.

4. DISCUSSION

The concept of the derived ECG is not new and has been reported by several investigators [11-17]. Now that recent guidelines for STEMI [18] and non-STEMI [19] care have called for frequent serial ECGs to be acquired, the utilization of the derived ECG technology may now become more advantageous and clinically useful.

It was very important to note that this study demonstrated high correlations between them ECG and dECG. The high interagreement and intraagreement analysis also lends support for the use of the dECG in the clinical setting.

The concept of the CEB allows a more efficient method for observing patients being evaluated for chest pain equivalents in any acute care setting, particularly the ED. The CEB is obtained continuously and displayed on the cardiac monitor in real time allowing immediate identification of a potential AMII in the proper clinical setting.

It was interesting to note that the CEB diagnostic accuracy parameters were very favorable in both men and women.

5. CONCLUSIONS

The CEB demonstrates high diagnostic accuracy for detection of AMII for men and women when compared to standard ST segment analysis and ECG computer interpretation ACs. The 12-lead ECG can be derived with accuracy from just 3 leads directly from the cardiac monitor. The measured and derived 12-lead ECGs show high qualitative and quantitative correlation. This technology will allow an immediate, cost effective, and efficient means of identifying patients with AMII who are being monitored in acute care settings.

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AUTOMATED ANALYSIS OF THE 12-LEAD ECG IN THE EMERGENCY DEPARTMENT: ASSOCIATION BETWEEN HIGH-SENSITIVITY CARDIAC TROPONIN I AND THE CARDIAC ELECTRICAL BIOMARKER (shortened version)

Larisa G. Tereshchenko, MD, PhD, David Gatz, BS, Albert Feeny and Frederick K. Korley, MD

ABSTRACT

Timely detection of myocardial injury is essential for appropriate management of patients in emergency department (ED) evaluated for acute myocardial infarction. A novel electrocardiogram (ECG) metric, the Cardiac Electrical Biomarker (CEB), uses eigenvalue modeling of the 12-lead ECG and quantifies dipolar vs. multipolar forces. The goal of this project was to study association between the CEB and high-sensitivity troponin I (HsTnI). We conducted a retrospective study of patients, evaluated in the ED for acute myocardial infarction [n = 411; 57.6 ± 13.2 years; 186 (45%) men; 266 (64%) African-Americans]. Resting 12-lead ECG and HsTnI were measured at presentation and at 3, 6, and 9 hours after the initial measurement. The CEB was measured by the VectraplexECG System (VectraCor, Totowa, NJ). Patient-specific longitudinal analysis was performed to study association between the CEB with HsTnI changes over time. The CEB indicated myocardial injury in 116 (28.2%) study participants. HsTnI was significantly elevated during ED observation period in patients with myocardial injury, diagnosed by the CEB [median (interquartile range), 10.3 (5.2–31.4) vs. 6.3 (3.5–16.5) ng/L; P = 0.002]. In a mixed-effects linear regression adjusted for age, race, and sex, increasing HsTnI was associated with the CEB elevation [β-coefficient, 0.071 (95% confidence interval, 0.008–0.134); P = 0.027]. In conclusion, in patients in ED evaluated for acute myocardial injury, increasing values of HsTnI were associated with increasing values of the CEB, suggesting that myocardial injury is the mechanism that underlines acute changes in the CEB.

Key Words: electrocardiogram, emergency medicine, acute coronary syndrome, cardiac electrical biomarker (Crit Pathways in Cardiol 2014;13: 25–28)

Each year, a large number of patients are evaluated in emergency departments (EDs) for acute myocardial infarction (AMI). AMI is diagnosed based on the history of present illness, 12-lead electrocardiogram (ECG), and cardiac biomarkers. Failure to identify patients in the early stages of AMI can result in failure to provide beneficial therapies. The third universal definition of AMI1 requires a rise and/or a fall in cardiac troponin, with at least 1 troponin value above the 99th percentile. It is recommended that blood samples for troponin measurement are drawn at presentation and repeated 3–6 hours later to optimize clinical sensitivity for ruling in AMI. Traditional 12-lead ECG is less informative very early in the course of ST-elevation myocardial infarction (STEMI) and especially in non-STEMI. Recently, new ECG technology was proposed to detect myocardial injury. Development of the novel Vectraplex-ECG System with Cardiac Electrical Biomarker (CEB) or VectraplexAMI was based on factor analysis[2] with simplex optimization. Acute myocardial injury may result in heterogeneous electrical field.[3,4] VectraplexAMI index was developed by Schreck,[5] who postulated that CEB measures the degree of the multipolarity of the cardiac electrical field.

We conducted a retrospective study of adult patients in ED with available serial digital 12-lead ECGs and high-sensitivity troponin I (HsTnI) results, with the goal of determining whether myocardial injury is the mechanism that underlines acute changes in CEB. We hypothesized that the CEB correlates with HsTnI in patients admitted to ED with suspected AMI.

METHODS

Study Population

We retrospectively analyzed data from an ongoing prospective observational cohort study of patients in ED evaluated for AMI. Serial ECG and troponin measurements were performed at presentation and at 3, 6, and 9 hours after presentation at the discretion of treating clinicians. The exclusion of patients with STEMI also allows us to evaluate the CEB in patients in whom standard ECG is nondiagnostic.

ECG Analysis

Each 12-lead ECG was reviewed and clinically evaluated by 2 investigators (D.G. and L.G.T.), blinded to all other clinical data. For each ECG, investigators evaluated cardiac rhythm and determined the presence or absence of left bundle branch block, right bundle branch block, pathological Q wave, ST segment elevation or depression, and nonspecific ST-T changes. The first ECG, recorded at the JHH ED, was com-pared with the previously recorded ECG (if available), and observed ECG abnormalities were categorized as "new," or "old." Each ECG was adjudicated and included into 1 of 5 categories: new STEMI, new non-STEMI, new non-specific ST-T changes, unchanged abnormal ECG, and normal ECG. Interreader agreement was evaluated, and in case of disagreement, the final ECG diagnosis was based on the third ECG reader (JHH attending cardiologist) assessment. The CEB for each ECG was calculated automatically by VectraplexECG System, as previously described[5] and provided by Vectracor,

inc. (Totowa, NJ). A predefined threshold was used. We considered that values of the CEB greater than 94 units indicated myocardial injury, as recommended by the manufacturer.

Outcomes

All clinical, laboratory, and ECG data were reviewed by an independent endpoints adjudication committee, blinded to the results of the VectraplexECG analysis. AMI was defined according to the guidelines,[1] clinical setting consistent with myocardial ischemia.

Statistical Analysis

All statistics were computed using Stata 13 (StataCorp LP, College Station, TX). Results are presented as mean ± SD for normally distributed variables and as median and interquartile range for skewed continuous variables. Normally distributed continuous variables were compared using the Student t test. The Wilcoxon rank-sum test was applied to skewed continuous variables—HsTnI and the CEB. Dichotomized variables were compared by Pearson χ^2 test. Spearman rank correlation coefficient r_s was calculated to quantify relations between HsTnI and the CEB. Then HsTnI and the CEB variables were log-10-transformed to normalize distribution, for subsequent regression analysis. To determine whether the patient-specific changes in the CEB are associated with the HsTnI changes during observation in the ED, we ran the generalized least squares random-effects linear regression analysis. We accounted for correlation of the repeated troponin and ECG observations by including a random intercept for each patient and control for the patient's CEB (centered). Adequate fitting of the model was checked to ensure that the specified quadrature has adequately approximated the likelihood. The model was adjusted by age, sex, and race.

RESULTS

Study Population

The study population consisted of middle-aged adults (57.6 ± 13.2 years), 65% were African-Americans (n = 266), and 55% were women (n = 225). Among the African-Americans, there were more women than men [159 (60%) vs. 107 (40%); P = 0.006], whereas an opposite sex composition was observed in non-African-Americans [66 (45.5%) women vs. 79 (54.5%) men; P = 0.006]. Risk factors of coronary heart disease were frequently observed: 263 patients (64%) had hypertension, 131 patients (32%) had diabetes mellitus, and 263 patients (64%) were current or former smokers. Approximately a quarter of study participants (n = 106; 25.8%) were current or former cocaine users.

ECG Analysis: The VectraplexAMI Index

The CEB indicated myocardial injury in 116 (28.2%) study participants. Clinical characteristics of patients with and without myocardial injury are shown in Table 1. Patients with myo-cardial injury as detected by the CEB were older, more likely to have hypertension, hypercho-lesterolemia, and heart failure. HsTnI was significantly elevated during ED observation period in patients with myocardial injury, diagnosed by the CEB (Table 1).

Table 1
Clinical and ECG Characteristics of Patients with and Without Myocardial Injury as Determined by VectraplexAMI Index

	VectraplexAMI ≤94 (N=295)	VectraplexAMI >94 (N=116)	P
Age (SD), yr	**56.7 (12.5)**	**59.9 (14.7)**	**0.039**
Men, n (%)	136 (46.1)	50 (43.1)	0.583
African-Americans, n (%)	186 (63.1)	80 (69.0)	0.259
Hypertension, n (%)	**180 (61.0)**	**83 (71.6)**	**0.045**
Diabetes Hx, n (%)	95 (32.2)	36 (31.0)	0.819
Heart failure, n (%)	**66 (22.4)**	**38 (33.8)**	**0.029**
Current or former smokers, n (%)	186 (63.1)	77 (66.4)	0.527
Current or former cocaine users, n (%)	72 (24.4)	34 (29.3)	0.306
Hypercholesterolemia, n (%)	**126 (42.7)**	**64 (55.2)**	**0.023**
Family Hx CHD, n (%)	105 (35.6)	44 (37.9)	0.657
HsTnI #1, median (IQR)	**6.3 (3.5–16.5)**	**10.3 (5.2–31.4)**	**0.002**
HsTnI #2, median (IQR)	**6.2 (3.2–14.8)**	**9.2 (4.6–28.6)**	**0.021**
HsTnI #3, median (IQR)	**6.55 (3.5–16.0)**	**12 (4.8–30.4)**	**0.018**
HsTnI #4, median (IQR)	6.55 (3.55–13.9)	12.45 (4.7–32.7)	0.076
Pathological Q wave on ECG, n (%)	**38 (12.9)**	**40 (34.5)**	**<0.0001**
Normal ECG, n (%)	**122 (41.4)**	**15 (12.9)**	**<0.0001**
Right bundle brunch block, n (%)	**5 (1.7)**	**15 (12.9)**	**<0.0001**
Left Bundle branch block, n (%)	6 (2.0)	3 (2.6)	0.731

CHD, coronary heart disease; Hx, history; IQR, interquartile range.
Bold indicates statistical findings.

There were no patients with typical STEMI ECG presentation among study participants. Pathological Q wave and right bundle branch block were more frequently observed, whereas a normal 12-lead ECG was less frequent in the myocardial injury group (Table 1).

Association Between High-sensitivity Cardiac troponin I and the Cardiac Electrical Biomarker

During the first 3 hours of observation at the ED, HsTnI and the CEB did not correlate. However, statistically significant correlation was found and strengthened during the next 6 hours of observation ($r = 0.163$; $P = 0.036$ and $r_s = 0.179$; $P = 0.018$), and further at the fourth 3-hour period ($r = 0.227$; $P = 0.026$ and $r_s = 0.217$; $P = 0.034$). Figure 1 illustrates correlation between HsTnI and the CEB.

In the univariate generalized least squares random-effects linear regression model, changes in HsTnI were associated with the changes in the CEB: β-coefficient, 0.083 (95% confidence interval, 0.022–0.144); $P = 0.008$. Thus, increasing HsTnI by an order of magnitude (10-fold in-crease) was associated with 8.3% increase of the CEB value. After adjustment for age, race, and sex, association between HsTnI and the CEB remained significant: β-coefficient, 0.071 (95% confidence interval, 0.008–0.134); $P = 0.027$.

DISCUSSION

This study showed that in patients evaluated for AMI in the ED, increasing by an order of magnitude HsTnI is associated with simultaneously increasing value of the CEB. Therefore, an underlying myocardial injury is an important mechanism of acute changes in the CEB in this study population.

Multipolar vs. Dipolar Forces in the Cardiac Electrical Field

The cardiac electrical field of a healthy subject is primarily dipolar.[7] The vector of myocardial injury current differs from the heart vector. Thus, occurrence of myocardial injury leads to the appearance of multipolar cardiac electrical field.[9] The CEB quantifies the quality of the cadiac electrical field, and in particular, whether the cardiac field is predominantly dipolar, or whether multipolar forces in the cardiac electrical field are present, and how much. VectraplexAMI is provided for the end-user as a single number. In this study, we used the CEB threshold of 94 units, as recommended by the VectraCor, Inc., for detection of myocardial injury.[5] Additional studies are needed to define optimal threshold for discriminating between no AMI and AMI cases.

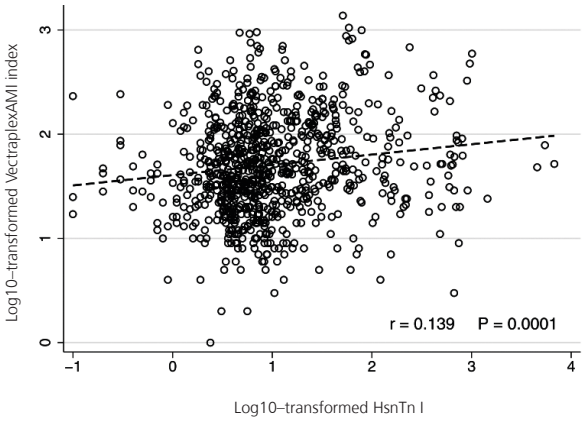

Figure 1
Correlation between high-sensitivity cardiac troponin I and CEB in patients in emergency department.

Simplex optimization (nonlinear optimization technique) was applied to the ECG signal to obtain and reconstruct the ECG signal,[2,10–13] and to calculate a proprietary CEB. This is the first study to examine whether myocardial injury (as determined by changes in HsTnI) is associated with acute changes in the CEB. Our findings suggest that in patients with high pretest probability of AMI, an underlying myocardial injury, as detected by an increasing HsTnI, is associated with elevation of the CEB.

Clinical Implications of Association Between HsTnI and the CEB

Surface ECG is traditionally used for the diagnosis of an acute myocardial injury.[1,14] However, with the advent of cardiac troponins, it has been demonstrated that the sensitivity and specificity of the acute changes in the ST segments on an ECG are modest, with sensitivity ranging from 50% to 100%, and specificity ranging from 71% to 91%,[15,16] and inconsistent among individual readers. Traditional ECG in-terpretation not only suggests the presence or absence of myocardial injury but at the same time determines localization and extent of the myocardial injury, predicting the possible culprit vessel and complications. This was especially important in the era of conservative AMI management. However, it does not make any difference for current therapeutic strategies.[17] In addition, it is worth noting that while cardiac troponin quantifies myocardial injury by a single number, ECG AMI diagnosis is dichotomized (yes or no), and requires complex knowledge of pattern recognition. In the current realm of clinical practice, the CEB offers a simple 1-number quantification of the myocardial injury on the surface ECG. Ease of use, low cost, wide availability, and a possibility of the continuous monitoring of the surface ECG in the ED make the CEB promising for future use.[23]

CONCLUSIONS

In conclusion, in patients in ED evaluated for acute myocardial injury, increasing values of HsTnI were associated with increasing values of the CEB, suggesting that myocardial injury is associated with acute changes in the CEB in the population of patients with high pretest probability of acute myocardial injury.

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