



Changes in Cardiac Electrical Biomarker in Response to Coronary Arterial Occlusion: An Experimental Observation

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Abstract

Cardiac electrical biomarker (CEB), an indicator of ischaemia-induced change in myocyte polarity, has been proposed for diagnosis of acute coronary syndrome. However, effect of coronary occlusion on CEB has not been demonstrated. CEB was acquired before (CEB0), during maximal adenosine hyperaemia (CEBhyp), balloon inflations (CEBmax) and 1 (CEB1h), 2 (CEB2h) and 3 (CEB3h) h after percutaneous coronary intervention along with pre- and post-procedural troponin-I. CEB of subjects with non-cardiac chest pain without risk factors was used as controls (CEBc). “Late recovery” (LR) of CEB was defined as CEB3h > median-CEB0. CEB was recorded in 75 patients undergoing stenting (group 1) including 8 with FFR < 0.8 (group 1a), 25 with FFR ≥ 0.8 (group 2) and 49 controls. In group 1, CEB0 (median, IQR) was higher than CEBc (48.0; 29.5–88.3 vs 30.0; 17.0–44.0; $p < 0.001$). CEBmax (185; 105.0–331.0) was higher than CEB0 ($p < 0.0001$). CEB1h (78.0; 31.5–143.8; $p < 0.0001$) and CEB2h (63.0; 31.5–114.3; $p = 0.039$) were higher than CEB0 while CEB3h (54.0; 24.3–94.8, $p = 0.152$) was similar. LR occurred in 50.7% patients. CEBmax predicted LR (OR 1.01, 95% CI 1.00–1.01, $p < 0.001$) (AUC 0.759, $p < 0.001$). CEB0 in group 1a and group 2 were similar ($p = 0.524$). CEBhyp was higher than CEB0 in group 1a (126.0, 109.5–266.0 vs 47.5, 20.5–73.5; $p = 0.016$) and group 2 (44.0, 27.8–104.8 vs 39.0, 24.0–90.3; $p = 0.014$). CEBhyp was higher in group 1a than 2 ($p = 0.039$). CEBhyp (AUC 0.75, $p = 0.017$) accurately predicted FFR < 0.8. Coronary arterial occlusion increases CEB that retains a “memory” of the ischaemic event. CEBhyp was higher only when FFR was ischaemic and accurately identified FFR < 0.8.

Keywords Cardiac electrical biomarker · Hyperaemia · Adenosine · Percutaneous coronary intervention · Fractional flow reserve

Background

The diagnosis of myocardial ischaemia at presentation to the emergency department (ED) is often uncertain in the absence of symptoms, its atypical nature, inconclusive

surface electrocardiogram (sECG), immediate non-availability of troponin (Tn), the need to re-measure it, its non-diagnostic levels when available and limitations in its interpretation. In addition, normal Tn does not exclude unstable angina (UA), defined as increased frequency or severity of known stable angina, angina at rest and angina after revascularisation procedure as percutaneous coronary intervention and coronary bypass surgery in the absence of myonecrosis. A diagnostic modality that can be used immediately upon medical contact to rapidly diagnose myocardial ischaemia would be valuable. “Cardiac electrical biomarker” (CEB), a novel ECG index, may have such a potential.

Altered polarisation behaviour of cardiomyocytes during myocardial ischemia results in voltage gradient between ischaemic and non-ischaemic regions changing the normal dipolar cardiac electrical field to multipolar [1, 2]. The Vectraplex ECG System (VectraCor, Inc., Totowa, NJ), derives a 12-lead ECG (dECG) from 3 monitoring leads based on a

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universal patient transformation matrix that is constructed using a non-linear optimisation technique. The eigenvectors of the normalised, calibrated dECG voltage–time data is calculated using abstract factor analysis to construct a unit-less proprietary numerical index, CEB. CEB performed well in detecting acute myocardial injury (AMI) when tested against 12-lead ECG interpretation by blinded physicians as reference [3]. CEB also accurately detected cardiologist adjudicated diagnosis of non-ST elevation myocardial infarction (NSTEMI) [4], improved the diagnostic accuracy when used with sECG [5] and correlated with Tn levels [6]. However, CEB thresholds to “rule-in” and “rule-out” AMI [3] have not been confirmed in subsequent studies [5] with widely varying levels reported [3–5]. The “normal” value of CEB has not been determined, and none of the studies directly demonstrate the effect of myocardial ischaemia on CEB.

To be useful in emergency departments (EDs), CEB should detect ongoing and remote myocardial ischaemia, even without ongoing symptoms, ischaemic sECG and biochemical evidence of myonecrosis. We examine the direct effect of transient coronary occlusion, not severe enough to cause myonecrosis, on CEB and time-course of its recovery.

Method

Patients

VECTRA is a clinical trial programme designed to evaluate the role of CEB in assessment of suspected myocardial ischaemia. VECTRA-PCI arm of this programme evaluates changes in CEB during acute ischaemia induced by balloon occlusion of coronary arteries during percutaneous coronary intervention (PCI).

The study included consecutive adults undergoing elective PCI for chronic stable angina. Patients with allergy to ECG electrode, previous CABG, severe left main stem stenosis, severe LV systolic dysfunction, suspected septicaemia, pulmonary embolism or aortic dissection, recent history of trauma to thorax and eGFR < 30 ml/min, undergoing multi-vessel PCI or revascularisation of chronic total occlusion, were excluded. Other exclusion criteria were ECGs with ventricular or atrial arrhythmias including frequent ectopics, QRS duration > 120 ms, Q waves (except positional Q waves checked by deep inspiration), resting ST-segment deviation or T-wave inversion and artefacts that could not be rectified despite appropriate preparation, e.g. muscle tremor, wandering baseline and respiratory variations. Baseline CEB, of individuals without any modifiable risk factors for coronary artery disease (CAD), past history of ischaemic heart disease (IHD), ECG or haematological or biochemical abnormalities and with normal vital signs

presenting to ED with chest discomfort deemed non-cardiac recruited to the VECTRA-ED arm of the study, were used as controls (CEBc). Ethics approval was obtained from the South East Coast—Surrey Research Ethics Committee (Ref. No. 16/LO/1973) (trial registration number NCT03498105). Informed consent was obtained from all patients.

Age, sex, previous medical history including previous MI, CVA, revascularisation and heart failure, risk factors for CAD, pre-hospital and discharge medications, indication for the PCI, coronary anatomy, baseline heart rate and blood pressure, height, weight, lipid profile, full blood count, electrolytes, urea, creatinine, eGFR and random blood glucose were recorded. Heart rate, rhythm, axis, QRS duration, ST-T changes and QTc were acquired from baseline sECG. This data was obtained from clinical notes, during clinical examination and from the hospital database. Baseline, 1-, 2- and 3-h post-procedural troponin-I were measured as Tn-I was the standard assay used in the hospital.

CEB Acquisition

Coronary angiogram was performed through the radial or femoral artery using a 6F sheath and appropriate coronary catheters after intra-arterial administration of heparin and glyceryl trinitrate. Standard angiographic views were obtained. The radiological equipment used for coronary angiography underwent daily calibration before use. The PCI was performed as standard practice. The ostium of the coronary was engaged using an appropriate guide catheter. Intracoronary glyceryl trinitrate was administered in 200 µg aliquots. The stenosis was crossed using a 0.014-in angioplasty guidewire. Suitably sized pre-dilatation balloon was inflated to pressures high enough to occlude the artery. Stent of required length and diameter were inflated in the stenosis and post-dilated with appropriately sized non-compliant balloons. Occlusive balloon inflation was confirmed by absence of flow distal to the balloon on contrast injection. Balloon inflation was maintained for up to 90 s or till significant ST-T segment deviation or typical chest discomfort appeared whichever was the earliest.

Before fractional flow reserve (FFR) measurements, the pressure transducer was zero-ed to the atmospheric pressure. A 0.014-in pressure–temperature sensor-tipped guide wire (PressureWire X, Abbot Vascular, St. Paul, MN) was equalised in the aorta and advanced beyond the stenosis. Intracoronary nitrate (200 mcg) was administered. The resting mean arterial pressure proximal and distal to the stenosis was recorded via the Coroventis CoroFlow Cardiovascular System (Abbot Vascular, St. Paul, MN), an advanced platform to measure intracoronary physiological indices. Following 2 min of intravenous infusion of adenosine (half-life ~ 8 s), the measurements were repeated. The standard cut-off of FFR < 0.8 was considered flow limiting.

VectraplexECG System underwent daily visual calibration pulse check to ensure the combined sensitivity (1-mV vertical height) and speed (100-ms horizontal width) before use. The device user manual is explicit that user calibration is not necessary. The device was maintained and managed by the electro-biomedical engineering department of the hospital according to set protocol. VectraplexECG System was connected to the patient via 3 electrodes, the pre-procedural positions of which were unchanged during and after the procedure. Resting 12-lead ECG was acquired ensuring stable baseline trace without artefacts and rhythm abnormalities. Pre-procedural CEB (CEB0) was recorded. In the catheterisation laboratory, multiple (10-s datasets) ECGs and associated CEB were captured from good-quality traces at first contrast injection, intra-coronary nitrate administration and maximal hyperaemia (CEBhyp) if FFR was being measured. CEB was recorded during every occlusive coronary balloon inflation during pre-dilatation, stent deployment and post-dilatation and at the end of the procedure. Maximum procedural CEB (CEBmax) during balloon occlusion was used. Recordings were taken 1 (CEB1h), 2 (CEB2h) and 3 h (CEB3h) after the end of the procedure. Troponin-I was measured before and 1, 2 and 3 h after the procedure (Fig. 1). Peri-procedural myocardial infarction was defined as troponin 5 times higher than the upper limit of normal.

The CEB measurement was acquired by a fellow (FA) trained in doing so on dedicated laptop connected to the ECG leads and loaded with the VectraplexECG software. The fellow was blinded to the clinical characteristics of the patient. It was not possible for the operator to be blinded to this information to maintain safety of the procedure. Blinding during acquisition was also not possible as the fellow had

to be prompted to acquire the CEB when the balloon was inflated. Multiple 10-s ECGs were obtained during inflations. Care was taken to avoid recording ECGs with movement artefacts, respiratory variations, ventricular ectopic beats, baseline interferences, etc. All acquired ECGs and associated CEB were reviewed by two authors (SC and FA) for quality of the trace in batches. Any ECG with artefacts, ectopics or noise was rejected. The maximum CEB associated with a “clean” ECG trace acquired during each time point was recorded along with the time stamp of the acquisition. As the ECGs and CEB acquisitions were fully anonymised with only the time stamps on it, both authors were blinded to the clinical and the procedural data when reviewing and selecting the best traces.

Follow-up

Patients were followed up at 30 days and 12 months. Death, non-fatal myocardial infarction or hospitalisation for heart failure was registered.

Statistics

Continuous variables are presented as means \pm SD for parametric and medians and inter-quartile range (median; 25th–75th percentile) for non-parametric data. The categorical variables are presented as counts and proportions (%). Categorical data was compared using chi-squared test. Non-parametric paired and independent sample comparisons were made using Wilcoxon rank and Mann–Whitney test. CEBs acquired for each patient at different time-points were compared with Friedman test. The patients who did and did not (as the FFR was normal) undergo stenting were separately analysed. “Late recovery” of CEB was defined as CEB3h higher than median CEB0. Univariate association between late recovery and age, sex, BMI, CAD risk factors, smoking status, diabetes, family history, hypertension, previous IHD (history of previous MI or revascularisation), drug therapies (ACEI/ARB, beta-blocker, Ca channel blocker, diuretics, statin), vital signs (heart rate, systolic and diastolic BP), total cholesterol, LDL and HDL, CEBmax and the difference between CEBmax and CEB0 (δ CEB) were determined. All variables with $p < 0.25$ were included in a multivariate logistic regression model after testing for collinearity (variable inflation factor < 4). Multiple regression was used to determine the adjusted predictors of CEB0, CEBmax, CEB1, CEB2 and CEB3. Receiver operator curve (ROC) was analysed to determine diagnostic accuracy of CEB0, CEBmax and δ CEB in determining late recovery and ischaemic FFR. Optimal cut-off values were selected based on the Youden index. The area under the ROC curves (AUC) was compared. All statistics were computed using the MedCalc Statistical Software (version 17.0.4, Ostend, Belgium). Two-tailed p values < 0.05 were considered significant.

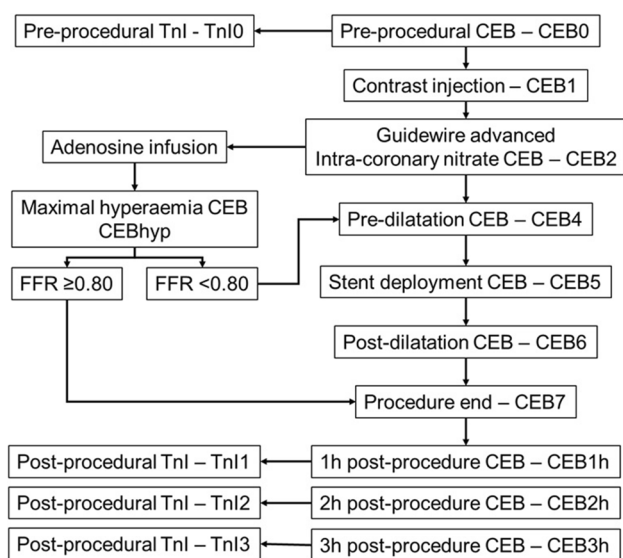


Fig. 1 Flow chart showing the protocol for CEB acquisition

As there was no available data to gauge the difference between the CEB at rest and during acute ischaemia, either in publications or from our own pilot study, we are unable to ascertain the expected changes in CEB with coronary occlusion. Thus, a formal sample size could not be calculated. We decided to recruit 50–100 patients as stated in the protocol (ClinicalTrials.gov ID NCT03498105). The rationale for this wide range is as follows. We were expecting some, though not quite how many, procedural ECGs to be uninterpretable. So, to acquire interpretable data on at least 50 patients, we decided to recruit about 100. Based on expected recruitment rate, catheterisation laboratory availability and resource allocation, we felt it would be difficult to recruit many more than 100. The number of uninterpretable ECGs was low allowing us to use most of the data. There was no interim analysis to prompt us to change our intended recruitment numbers.

Results

We recruited 104 patients (1 withdrew consent, procedure was abandoned in 3). Seventy-five underwent coronary stenting, and 25 had normal FFR not requiring stents.

Baseline characteristics of the patients are shown in Table 1. We identified 49 controls (age 48 ± 13.1 years, 55% male, CEBc (30.0; 17.0–45.0)) from 413 individuals in the VECTRA-ED arm of the study.

CEB in Obstructed Coronary Arteries

All CEB0s were obtained. CEB was not measured during intra-coronary contrast injection in 10 (10%) and nitrate injection in 8 (8%) patients due to ECG artefacts, pre-dilatation in 5 (6.7%) patients undergoing direct stenting and post-dilatation in 5 (6.7%) patients not needing post-dilatation. CEBs were measurable in 60 patients at all time-points. FFR was measured in 33 patients; 8 were ischaemic needing stents.

The CEB0 (median; IQR) in patients with obstructive CAD (angiographic and $FFR < 0.8$) was higher than the control (Table 1). Contrast-CEB (76.0; 32.3–141.0, $p < 0.0001$) and nitrate-CEB (76.5; 47.0–184.0, $p < 0.0001$) were higher than CEB0. CEB at pre-dilatation, stenting and post-dilatation was higher than CEB0 (overall $p < 0.0001$) (Fig. 2A). The CEBmax was recorded in 29 (42.6%) patients during pre-dilatation compared to 22 (30.1%) during stenting and 12 (17.9%) at post-dilatation ($p = 0.086$). The duration of

Table 1 Baseline characteristics

	Coronary artery stent <i>n</i> = 75	FFR without stent <i>n</i> = 25	<i>p</i>	Total study cohort <i>n</i> = 100	Controls <i>n</i> = 49	<i>p</i> *
Male, <i>n</i> (%)	61 (81.3)	15 (60.0)	0.031	76 (76.0)	27 (55.1)	0.009
Age (years)	66.0 (56.3–72.0)	69.0 (57.0–71.5)	0.664	66.0 (63.2–69.0)	48.0 (41.3–57.0)	<0.001
BMI (kg/m ²)	28.6 (25.9–31.1)	30.4 (24.7–33.3)	0.481	28.8 (27.9–30.3)	27.0 (24.0–31.2)	0.180
Smoker	16 (21.3)	3 (12.0)	0.303	19 (19.0)	-	
Diabetes	16 (21.3)	4 (16.0)	0.564	20 (20.0)	-	
Family history	40 (53.3)	12 (48.0)	0.644	52 (52.0)	-	
Hypertension	44 (58.7)	12 (48.0)	0.352	56 (56.0)	-	
Previous IHD	49 (65.3)	13 (53.0)	0.234	62 (62.0)	-	
ACEI/ARB	26 (34.7)	9 (36.0)	0.904	35 (35.0)	-	
Beta-blocker	43 (57.3)	17 (68.0)	0.346	60 (60.0)	-	
Ca channel blocker	14 (18.7)	5 (20.0)	0.883	19 (19.0)	-	
Diuretics	4 (5.3)	3 (12.0)	0.258	7 (7.0)	-	
Statin	63 (84.0)	20 (80.0)	0.645	83 (83.0)	-	
Heart rate	69 (60.0–76.0)	69 (64.7–76.5)	0.602	69.0 (66.7–73.0)	68 (56.8–80.5)	0.931
Systolic BP	137.0 (124.0–154.7)	141.0 (125.0–153.3)	0.656	139.0 (133.7–143.0)	130.0 (120.5–143.3)	0.016
Diastolic BP	81.0 (73.0–89.0)	79.0 (69.0–90.0)	0.387	80.0 (77.0–85.0)	82.0 (75.0–86.0)	0.918
Total Cholesterol	4.1 (3.3–4.7)	4.0 (3.2–5.0)	0.854	4.1 (3.6–4.3)	5.1 (4.3–5.4)	0.023
LDL-cholesterol	1.8 (1.2–2.5)	1.7 (1.1–2.5)	0.873	1.8 (1.6–2.0)	3.0 (2.6–3.6)	0.002
HDL-cholesterol	1.2 (0.9–1.4)	1.4 (1.1–1.6)	0.047	1.2 (1.2–1.3)	1.3 (1.1–1.6)	0.442
Triglyceride	1.8 (1.3–2.5)	1.1 (0.95–2.4)	0.070	1.7 (1.5–1.9)	1.1 (0.8–1.7)	0.038
Baseline CEB	48.0 (29.5–88.3)	39.0(24.0–90.3)	0.524	47.5(40.7–64.3)	30.0 (17.0–44.3)	<0.001

IHD ischaemic heart disease, *BP* blood pressure, *ACEI/ARB* angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *BMI* Body mass index.

*Control group vs total study cohort

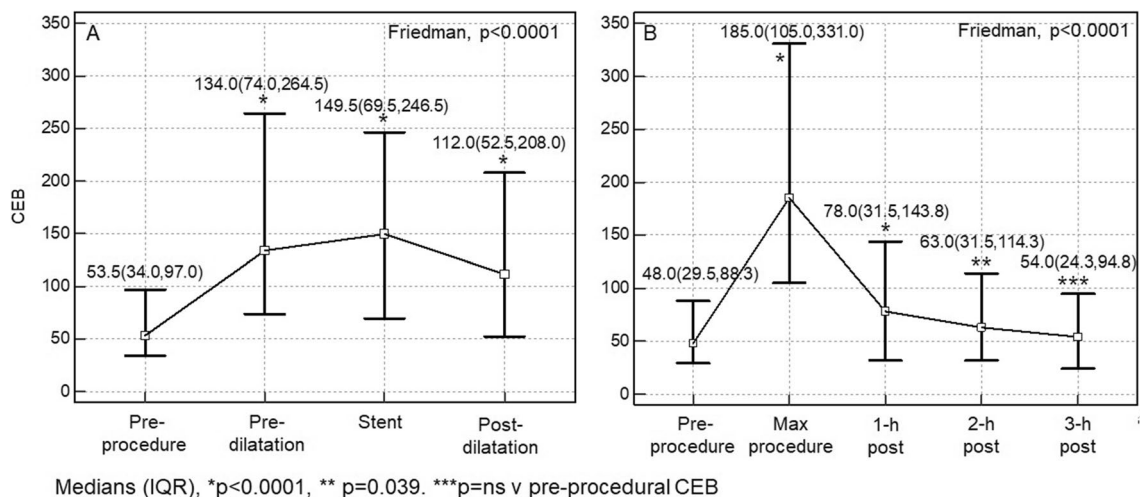


Fig. 2 Median (95% CI) CEB before and (A) during balloon occlusion at pre-dilatation, stent deployment and post-dilatation and (B) 1, 2 and 3 h after the end of the procedure

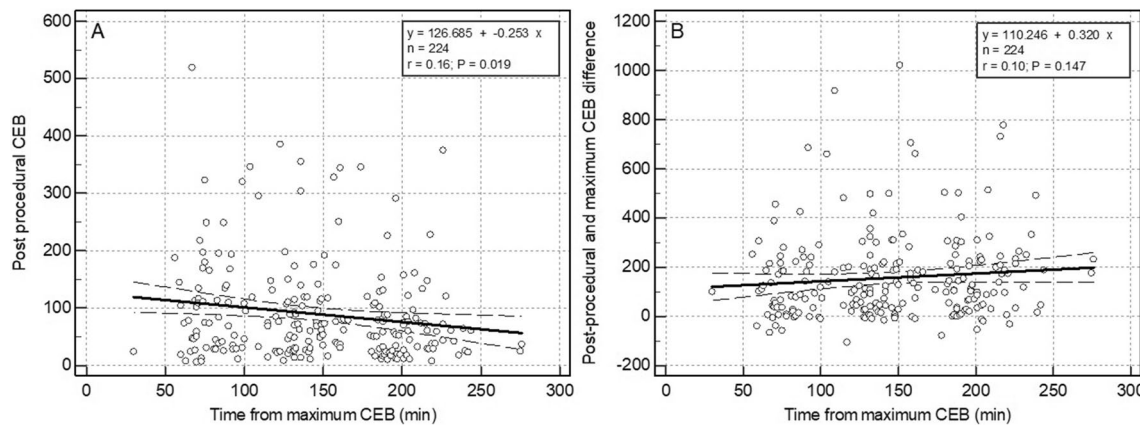


Fig. 3 Relation of the duration after the maximum CEB when post-procedural CEB was recorded to post-procedural CEB level (A) and the difference between the post-procedural and maximum CEB level (B)

balloon inflation yielding CEBmax was similar during pre-dilatation, stenting and post-dilatation ($p = 0.779$). The CEBmax was higher than CEB0 ($p < 0.0001$) (Fig. 2B). CEBmax reached in any of the three procedural stages was similar ($p = 0.439$) (Fig. 2A).

The CEB1h, CEB2h and CEB3h were recorded 63.1 ± 16.0 , 122.1 ± 12.1 and 182.1 ± 12.4 min after the end of the procedure and 86.7 ± 22.3 , 145.7 ± 19.9 and 205.7 ± 20.4 min after CEBmax was recorded. The CEB peaked during balloon occlusion ($p < 0.0001$) and decreased progressively over time ($p = 0.003$). The CEB1h and CEB2h were higher than CEB0 and returned to pre-procedural level at 3 h (Fig. 2B). There was a weak but significant inverse relation between post-procedural CEB and time when it was recorded (Fig. 3A), although the rate

of reduction did not change (Fig. 3B). CEB3h was higher than CEB0 in 38 (50.7%) patients. Late recovery was seen in 41 (54.6%) patients. The CEB0 (83.0; 54.0–150.3) and CEBmax (265; 155.3–444.3) in these patients were higher than those without ($p = 0.0001$).

Table 2 Determinants of late recovery of CEB

Age	1.0023	0.9425 to 1.0659	0.941
Female sex	0.6776	0.1057 to 4.3443	0.681
HDL-cholesterol	1.6403	0.4297 to 6.2610	0.469
Diabetes	5.5636	1.1017 to 28.0974	0.038
Hypertension	0.4039	0.1187 to 1.3741	0.147
CEBmax	1.0094	1.0038 to 1.0150	<0.001
Time from CEBmax to CEB3h	0.9667	0.9346 to 0.9999	0.049

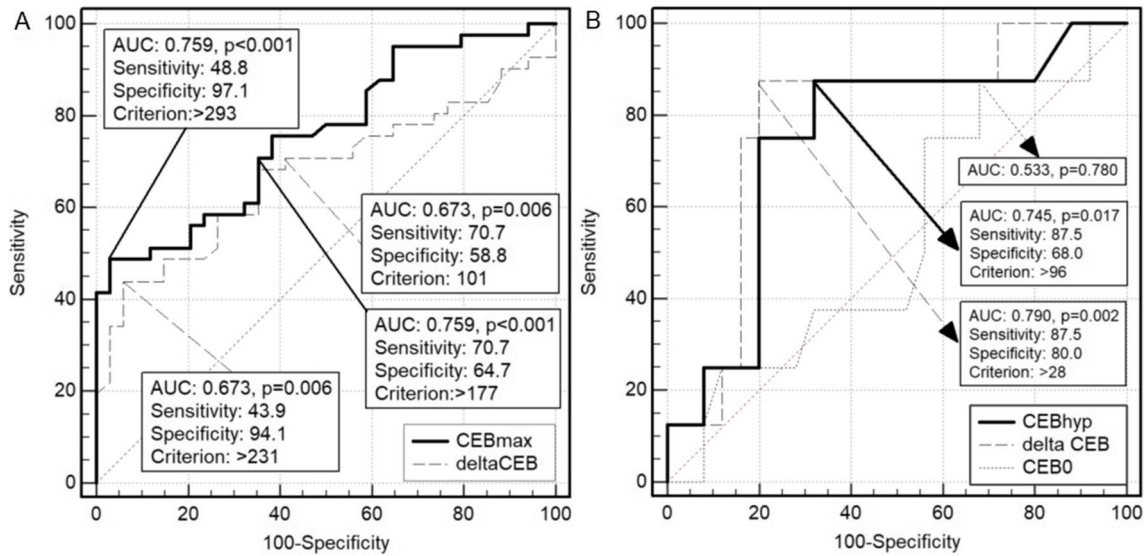


Fig. 4 A ROC curves to determine the diagnostic accuracy of CEBmax and δ CEB in predicting "late recovery" and B the diagnostic accuracy of CEB0, CEBhyp and δ CEB in predicting ischaemic FFR (<0.8)

Determinants of Later Recovery

The strongest predictor of late recovery was CEBmax (Table 2). The area under the ROC curve (AUC) (Fig. 4A)

Table 3 Determinants of pre-procedural, maximum procedural and post-procedural CEB

	<i>r</i>	<i>p</i>
Pre-procedural CEB		
Age	0.2359	0.0445
Cholesterol	-0.1913	0.105
HTN	0.2784	0.0171
Maximum procedural CEB		
HDL	0.153	0.1994
DBP	0.2373	0.0448
Pre-procedural CEB	0.6273	<0.0001
Inflation time for maximum procedural CEB	-0.1817	0.1266
1-h post-procedural CEB		
LDL	-0.1781	0.1317
Pre-procedural CEB	0.5207	<0.0001
Maximum procedural CEB	0.3985	0.0005
2-h post-procedural CEB		
DBP	-0.1709	0.1573
Smoking	-0.156	0.1971
HTN	0.2104	0.0805
Pre-procedural CEB	0.5482	<0.0001
Maximum procedural CEB	0.3342	0.0047
Inflation time for maximum procedural CEB	-0.1597	0.1867
3-h post-procedural CEB		
Pre-procedural CEB	0.6879	<0.0001
Maximum procedural CEB	0.2483	0.0329

was higher for CEBmax compared to δ CEB ($p=0.001$). CEBmax > 177 predicts late recovery with 71% sensitivity and 65% specificity. The CEB0 and CEBmax were the only determinant of the post-procedural CEB (Table 3).

CEB, Troponin and ECG Correlates

Post-procedural dynamic increase in TnI occurred in 20 (26.7%) patients; 3 (4%) had peri-procedural infarctions due to side-branch occlusion. The CEBmax in patients with raised TnI was similar to those without (190.5; 123.5–327.0 vs 185.0; 84.7–331.0, $p=0.602$). Compared to pre-procedural values, the post-procedural TnI was higher ($p<0.0001$) with a graded hourly increase irrespective of whether the patient had raised TnI or not. No relation was seen between the CEBmax and post-procedural troponin.

Ischaemic ECG changes during CEBmax were seen in (66%) patients, in 71.4% patients when CEBmax was achieved during pre-dilatation, 60% during stenting and 70% during post-dilatation ($p=0.750$). The maximum CEB in patients with ECG changes (259.0; 155.3–370.8) was higher than those without (90.0; 49.8–213.3) ($p=0.008$).

CEB in Patients with Non-ischaemic Versus Ischaemic FFR

CEB0 in patients with non-ischaemic FFR (39.0; 24.0–90.3) was numerically higher than controls 30.0 (17.0–44.3) ($p=0.051$) though not statistically significant. CEBhyp in patients with non-ischaemic FFR (44.0; 27.8–104.8; $p=0.014$) and contrast CEB (62.0; 40.3–105.8; $p<0.001$)

was higher than CEB0. The CEB1h (38.0, 25.5–123.5, $p=0.536$), CEB2h (45.0, 26.8–121.8, $p=0.339$) and CEB3h (44.0, 20.8–121.8, $p=0.253$) were similar to CEB0.

FFR was ischaemic in 8 patients indicating flow limiting stenoses. CEB0 in these patients (47.5; 20.5–73.5) was similar to controls ($p=0.241$). CEBhyp was higher than CEB0 (126.0; 109.5–266.0), ($p=0.016$). Although CEB0 in these patients was similar compared to those with non-ischaemic FFR (47.5; 20.5–73.5 vs 39.0; 24.0–90.3, $p=0.785$), CEBhyp was higher (126.0; 109.5–216.0 vs 44.0; 27.8–104.8, $p=0.039$). Compared to CEBhyp, CEB2 (57.0; 13.1–94.7, $p=0.039$) and CEB3 (31.5; 21.4–72.3, $p=0.023$) but not CEB1 (91.5; 7.8–150.6, $p=0.195$) were lower. However, CEB1 was similar to the CEB0 ($p=0.161$).

CEBhyp accurately predicted ischaemic FFR (Fig. 4B) with CEB > 96 predicted FFR < 0.8 with 87.5% sensitivity and specificity of 68% (> 107 would give 75% sensitivity and 80% specificity). The change in CEB from baseline to hyperaemia was similarly accurate in predicting FFR < 0.8 ($p=0.570$) with an increase in > 28 units predicting FFR < 0.8 with a sensitivity of 87.5% and specificity of 80.0%.

Discussion

This study establishes the experimental evidence that reduction in coronary blood flow, without resultant myonecrosis induced either by transient arterial occlusion or adenosine stress, increases CEB. The CEB retains “memory” of the ischaemic episode and remains elevated for about 3.5 h. Baseline CEB in patients with asymptomatic obstructed CAD is higher than controls, but not in patients with non-obstructive CAD. The maximum procedural CEB best predicts the late recovery of CEB after the ischaemic event. The hyperaemic CEB predicts ischaemic FFR.

In a retrospective study, the accuracy of CEB in identifying AMI was tested against 12-lead ECG changes as interpreted by two blinded physicians. Based on a training set of only 33 AMI patients diagnosed according to the Universal Definition, CEB thresholds of ≤ 65 and ≥ 95 were identified as thresholds to rule-out and rule-in AMI. These levels performed well in a test set [3]. This study did not determine the accuracy of CEB in diagnosing AMI as Tn was not available for diagnosis, NSTEMI without ECG changes were classed as no-AMI and 68–79% of the patients had STEMI. In a STEMI population, median CEB was considerably higher [4]. In NSTEMI patients, CEB performed well against adjudicated diagnosis of AMI based on clinical history, ECG changes and the Tn levels [5]. The median CEB was 44 for NSTEMI and 40 for UA patients. CEB < 32 “ruled-out” NSTEMI [5]. CEB improved the sensitivity of sECG for diagnosis of NSTEMI. However, NSTEMI was diagnosed

in only 20% of patients in the highest CEB tertile and also in 10% of patients in the lowest CEB tertile. This may relate to the diagnostic uncertainty regarding the ischaemic aetiology of the myonecrosis in some patients with NSTEMI.

As we measured CEBmax at the time of coronary occlusion, the values are higher than reported in other studies [3, 5, 6] where CEB was measured at presentation, a variable and often indeterminable duration after the ischaemic event. Our recordings were tightly timed in a set protocol under controlled experimental conditions and differ from clinical setting under which other recordings were made. Unsurprisingly, CEBmax were nearest to the CEB recorded in patients presenting for primary PCI for STEMI. Even then, a third of the patients in that study had \geq TIMI 2 flow in all arteries and 13% had collateralisation to the infarcted territory. In contrast, all of our patients had TIMI 0 flow during balloon inflation when CEB was recorded.

The CEBs in controls and patients with non-ischaemic FFR are similar to the group without NSTEMI reported by Strebel et al. [5], most of whom (93%) had unobstructed coronary arteries. Our 3-h CEB was nearer to the CEB of the NSTEMI patients [5]. The temporal relation of the CEB acquisition to the acute ischaemic event is unknown in these patients and may be longer than 3.5 h, the time of our final CEB acquisition.

Temporal Changes in CEB

Temporal recovery of electrical jeopardy with relief of ischaemia is relevant to the interpretation of the CEB. We demonstrate that the recovery of CEB is time dependent and not instantaneous, suggesting that CEB retains an “ischaemic memory” and may be useful in identifying remote ischaemia. Few findings need highlighting. The CEB remained elevated above the median of CEB0 in 55% patients 3.5 h after mild ischaemic insult of short duration not enough to cause myonecrosis. The pattern of recovery of CEB was similar in patients with and without Tn rise. The CEBmax seems to predict late recovery. Thus, it can be inferred that the time interval after an ischaemic insult within which CEB could identify remote ischaemia would depend on the patient’s baseline CEB that is likely to be higher in patients with established CAD and how prolonged and severe the disruption to flow.

Hyperaemic CEB

CEB increased with hyperaemia in patients with and without ischaemic FFR. Despite similar CEB0, CEBhyp was higher in ischaemic compared to non-ischaemic FFR group. In non-ischaemic FFR group, the CEB0, CEBhyp, CEB1, CEB2 and CEB3 were all similar. In ischaemic FFR group, CEBhyp decreased to CEBpre levels within 1 h suggesting

a rapid recovery to baseline after adenosine stress. Both CEBhyp and the change from baseline to hyperaemic CEB diagnosed ischaemic FFR accurately.

Ischaemic Pre-conditioning

Balloon inflation at pre-dilatation, when the lumen is most stenosed, was expected to be most occlusive resulting in higher CEB than later inflations. A degree of ischaemic pre-conditioning was also anticipated to lower the CEB during stenting and post-dilatation. However, CEB at pre-dilatation, stenting and post-dilatation were similar. This may have resulted from a pre-existing degree of ischaemic pre-conditioning at pre-dilatation, from recurrent angina and minimal pre-conditioning from single, 60–90-s inflations rather than multiple 90–120-s occlusions [7] at > 2-min intervals [8] needed to induce pre-conditioning.

Clinical Implication

CEB has a potential to rule-in or rule-out myocardial ischaemic events. To be able to do so, post-ischaemic CEB values may need careful interpretation considering the interval between the event and the recording, baseline CEB, the severity of ischaemia and presence of pre-existing CAD. This needs further validation in a bigger cohort of patients with coronary artery disease. Decay in ischaemic CEB is delayed in patients with pre-existing CAD both due to higher baseline CEB and slower recovery. The ability of hyperaemic CEB to accurately predict ischaemic FFR raises the prospect of using CEB as a non-invasive alternative to ischaemia detection.

Limitation

This is a small study with inherent limitations. The optimal CEB cut-off value for detecting stenoses with ischaemic FFR is derived from a very small number of patients and should be considered hypothesis generating. Vectraplex ECG recording is highly sensitive to minor movement artefacts, breathing, perspiration, inadequate skin preparation, suboptimal contact and ECG changes, e.g. baseline waver and ectopic beats, yielding widely varying and unstable CEB values that are difficult to interpret. This seems to be an inherent limitation of the modality. Thus, further large-scale studies especially including repeat CEB measurements in a short interval are needed to assess the stability of the measurements. To mitigate the risk of deriving CEBs from artefactual ECGs, we repeated the measurements during balloon inflations, albeit within the limitation of inducing prolonged ischaemia, and before and after the procedure. The best tracings were taken. Although we

rejected some ECGs due to artefacts, this should not affect the generalisability of this data, derived from the selected ECGs, to real-world population as the VECTRA-COR user manual clearly advises against using CEBs derived from ECGs with artefacts. As patients with QRSd > 120 ms were excluded, CEB changes that may have been affected by this cannot be commented on. The *p* values are not from pre-specified hypothesis tests and were not adjusted for multiple comparisons or within-subject correlation and should be considered exploratory.

Conclusion

Coronary arterial occlusion, not severe enough to cause myonecrosis, increases CEB. CEB improves over time and seems to retain a memory of the ischaemic event. Temporal resolution of CEB appears to be related to the pre-ischaemic CEB value and severity of the ischaemic jeopardy. CEB values may need to be interpreted in relation to the time interval between the symptom and the recording.

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Declarations

Conflict of Interest The authors declare no competing interests.

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