Contributions of myocardial ischemia and heart rate to ST segment changes in patients with or without coronary artery disease

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Background: ST changes related to ischemia at different heart rates (HRs) have not been well described. We aimed to analyze ST dynamic changes by vectorcardiography (VCG) during pacing-induced HR changes for subjects with proven coronary artery disease (CAD) and without (non-CAD).
Methods: Symptomatic CAD patients scheduled for elective surgery were enrolled along with a non-CAD group. During anesthesia, both groups were placed at multiple ascending levels. VCG ST data, and in particular in ST change vector magnitude (STC-VM) from baseline, along with arterial and great coronary artery vein (GCV) blood samples were collected to determine regional myocardial lactate production.
Results: A total of 35 CAD and 10 non-CAD patients were studied over six incremental 10 beat/min HR increases. STC-VM mean levels increased in the CAD group from 9 ± 5 to $131 \pm 37\,\mu V$ (standard deviation) compared with non-CAD subjects with 8 ± 3–$76 \pm 34\,\mu V$. Myocardial ischemia (lactate production) was noted at higher HRs and the positive predictive value for STC-VM to detect ischemia was 58% with the negative predictive value being 88%. STC-VM at $54\,\mu V$ showed a sensitivity of 88% and a specificity of 75% for identification of ischemia.
Conclusions: Both HR and ischemia at higher HRs contribute to VCG ST elevation. Established ST ischemia detection concerning HR levels is suboptimal, and further attention to the effects of HR on ST segments is needed to improve electrocardiographic ischemia criteria.

E LECTROCARDIOGRAPHY (ECG) is widely used as a non-invasive method to detect and monitor Myocardial ischemia (1, 2). Continuous vectorcardiography (VCG) is one form of ECG that allows measurement of both ST segment magnitude and vector direction change (3). ECG ST analysis, similar to all diagnostic methods, has limitations concerning sensitivity and specificity for ischemia.

This study concerns the detection of ischemia and the relation of electrocardiographic ST changes to heart rate (HR) both during ischemia and in non-ischemic conditions. ST changes in relation to increased HR have been reported, even in patients who do not have coronary artery disease (CAD) (4),

though the mechanism for this is unclear. Different methods for improvement of the diagnostic accuracy of ST analysis, including adjustments for HR, have been proposed (5–9) generally in the context of exercise testing for ischemia detection, when a reference method for detection of ischemia is not present. ST segment deviation can occur independently, or in the absence of increased HRs, although it is common that when myocardial ischemia occurs, HR increases as well. In the clinical context of ischemia diagnosis, interpretation of ST changes, where ischemia is strongly suspected based on risk factors or other indicators, is made more difficult by the presence of high HRs. The specificity of VCG ST changes for ischemia at different HRs has not been well established, and a ST change in magnitude or threshold for ischemia has not been well validated.

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We hypothesized that changes in VCG ST vector parameters during increased HR can be distinguished from changes due to myocardial ischemia, and that the relative ST change vector magnitude (STC-VM) can detect progress of myocardial ischemia at higher HRs. We aimed to measure and compare ST vector changes during pacing-induced HR changes in subjects with and without myocardial ischemia.

Materials and methods

Inclusion and exclusion criteria

With approval from the Umeå University Research Ethics Committee, 54 pre-operative adult thoracic or vascular surgery patients, who met the inclusion criteria and provided verbal informed consent, were included in the study either in a group for symptomatic CAD scheduled for elective coronary bypass surgery ($n = 44$) or in a group without CAD ($n = 10$). Inclusion criteria for the CAD group included disabling angina pectoris, with a positive exercise ECG and coronary angiogram with 'two or three vessel' disease, including coronary artery stenosis in the left anterior descending (LAD) artery, no pathological Q waves pre-operatively and no left ventricular hypertrophy as defined by ECG or by echocardiography. Subjects from the CAD group were excluded from further study if they had signs of myocardial ischemia before or at the start of the protocol, non-sinus rhythm, left- or right-bundle branch block, or if they did not complete at least three pacing steps. Inclusion criteria for the non-CAD group included scheduled elective cardiac valve replacement or abdominal aortic surgery without signs of CAD (no angina), with normal coronary angiogram and no pathological Q waves pre-operatively (normal rest ECG). Of the 44 CAD subjects included in the study, four subjects were excluded due to pacing non-capture before completing a third pacing step. Another five CAD subjects were excluded because non-ischemia conditions at the baseline pacing measurement could not be confirmed (by both ECG and lactate measurements).

Preparation

All subjects received a standard premedication (morphine and scopolomine), and pre-operative β-receptor blocking drugs (10) and nitroglycerin orally were given as ordered by the primary physician the morning before surgery. The anesthesia was standardised (intravenous, opiate and benzodiazepine based) and managed by the responsible anesthesia personnel. Arterial, central venous and pulmonary artery catheters (all three Arrow, Reading, PA) were placed. Intraoperative normoxia and normocapnia were confirmed using intermittent blood gas analysis (ABL 5, Radiometer, Copenhagen, Denmark). Before the start of surgery, a coronary sinus catheter, which had a bipolar pacing electrode 2 cm from the tip (CCS-7U-90A, Webster Labs, Altadena, CA), was placed into the great cardiac vein (GCV) using fluoroscopy and contrast (Omnipaque®, Nycomed, Oslo, Norway).

Measurements

Blood pressures were recorded (Siemens Sirecust 1280, Dräger Medical, Lubeck, Germany). Blood flow in the GCV was measured using the retrograde thermodilution technique (11) (CBA-210 Wheatestone bridge, Webster Lab. Inc.) and a multi-channel amplifier/graphic recorder (Graphtec Linearcorder WR 3310, Graphtec Corp. Yokohama, Japan).

A 12-lead ECG (Mingograph 62, Siemens-Elema AB, Stockholm, Sweden) was recorded for each measurement sequence. The sum of absolute ST deviation values from all 12 leads (ECGST$_{sum}$) was measured as well as the separate sum for leads V5 and II, derived from the same 12-lead ECG recordings (12). Less than 0.5 mm (0.05 mV) ST change in a single lead was measured as zero change. We averaged measures of ST change from three heart cycles.

Eight additional electrodes were placed according to the lead system for VCG described by Frank (13) and signals at 500 Hz were recorded (MIDA 1000, 2.74 software, Ortivus Medical, Täby, Sweden). Heart cycles were averaged for periods of 15 s in three orthogonal planes (X, Y, and Z), and the VCG ST measurement was the combined magnitude (and direction) of these three orthogonal signals (1, 14). Lactate concentration was measured for arterial and coronary sinus whole blood (Yellow Springs Lactate Analyzer 1500, OH) for each pacing step.

Protocol

Pacing (Pacesetter 3077, Osypka, Rheinfeld-Herten, Germany) was started at anHR that was 10–15 beats/min (b.p.m.) higher than the subjects' resting HR. A baseline VCG-averaged complex was established, then a second VCG measurement was acquired at the same HR. After this, 6 min

pacing steps with 10 b.p.m. increments were employed. A set of general circulatory measurements was acquired, including a 12-lead ECG and GCV flow at the end of each HR period. Arterial and GCV blood samples were drawn at 5 min into each HR period. Whole-blood lactate analyses were immediately performed in the operating room, to determine whether net lactate production in the coronary circulation was evident. The protocol was ended if myocardial ischemia was confirmed either by $[lactate_{gcv}] > [lactate_{arterial}]$ or by ST changes (≥ 0.2 mV) in two adjacent leads in the 12-lead ECG (a different ST measurement level was defined for the purposes of analysis of results). If no myocardial ischemia was detected, the pacing level was increased by steps of 10 b.p.m. with measurements until either pacing was characterised by non-capture or lactate production/significant ECG ST changes occurred.

VCG ST measurements

VCG ST magnitudes were calculated using the following formulae (1): $ST\text{-}VM = \sqrt{X^2 + Y^2 + Z^2}$ in microvolts (μV). The ST vector change angle (STC-VA) was calculated as the angle between the reference ST vector and the current ST vector. The relative spatial difference between the reference and the current ST vector was calculated as follows:

$$STC\text{-}VM = \sqrt{(X_i - X_0)^2 + (Y_i - Y_0)^2 + (Z_i - Z_0)^2}$$

in μV with 0 (baseline reference) and i (current) measurements. The median VCG ST point during the last minute of each pacing step was chosen for measurement. All ST measurements were made at J+20 ms. Vector planes and a representative example of orthogonal lead and ST signals are shown in Fig. 1 to illustrate the derivation of the VCG ST measurements.

Analysis and calculations

Left ventricular myocardial oxygen consumption (LV MVO_2) was calculated as GCV flow × myocardial arterio-venous oxygen content difference (ml $O_2 \times min^{-1}$) (15). Myocardial lactate extraction (MLE, %) was calculated as $([lactate]_{arterial} - [lactate]_{GCV})/[lactate]_{arterial} \times 100$ (%). Transcoronary lactate flux was calculated as $([lactate]_{arterial} - [lactate]_{GCV}) \times$ GCV flow (ml × min^{-1}). For *post hoc* analysis of myocardial ischemia by 12-lead ECG, a threshold of ST change ≥ 1 mm

in two adjacent precordial leads was used (16). Rate-pressure product (RPP) was calculated as HR × systolic arterial blood pressure.

Myocardial ischemia by lactate analysis was defined as decreasing MLE, which was also at levels less than 10% (17–19). In subjects where progressive lactate production was documented confirming adequate coronary sinus sampling of ischemic myocardial areas, pacing steps before ischemia (by lactate results) were categorised as non-ischemia.

Statistical analysis

Measured values are presented as the mean ± standard deviation (SD). Repeated measures ANOVA were used to analyse relations between serial measures at different pacing steps. Paired *t*-testing was used to test for differences for paired observations, and between-groups testing was used for grouped measurement with Bonferroni correction for multiple comparisons. For comparison of frequencies, Fisher's exact test or the χ^2 test was used. A *P*-value of < 0.05 was used for statistical significance. ROC analysis was performed to assess the relationship between ischemia (by lactate assessment) and VCG ST levels. Positive predictive value was calculated as the number of true positive (TP) observations divided by the sum of all positive observations, both true and false positives. Negative predictive value was calculated as the number of true negative (TN) observations divided by the sum of all negative observations, both true and false negative.

Results

Thirty-five CAD and 10 non-CAD subjects completed the pacing and measurement protocol for at least three pacing steps, and were included in the analysis. There were no peri-operative myocardial infarctions diagnosed by the clinical teams in any of the subjects as defined by local ECG and enzyme criteria, which were routinely checked in all post-operative patients, and all subjects were alive at 1 year following surgery.

The CAD group was older, had more medical history and medications, and lower functional status than the non-CAD group (Table 1). The non-CAD group included aortic valve replacement ($n = 7$) and abdominal aortic surgery patients ($n = 3$). Five of the 10 subjects in the non-CAD group met criteria for ventricular hypertrophy by
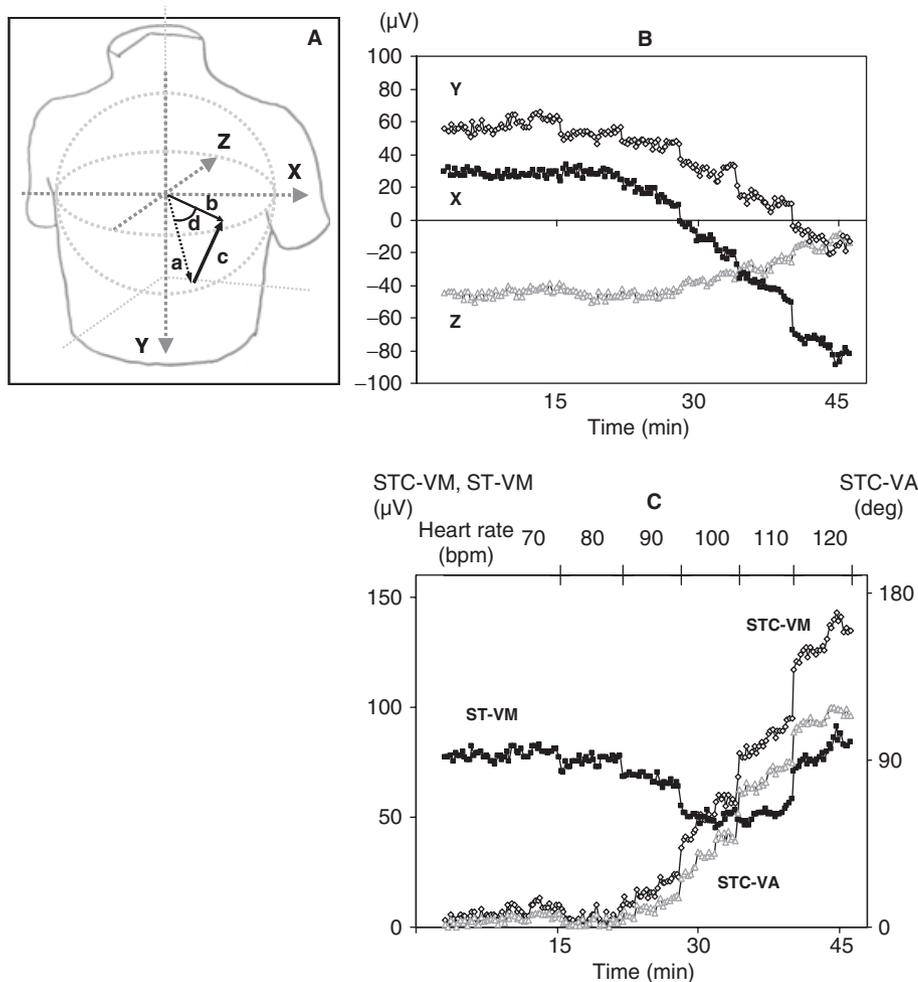
Fig. 1. The ST vector represents the sum of all electrical forces measured 20 ms after the J- point. (A) (a) represents the first recorded ST vector (the reference), (b) represents the current ST vector. ST vector magnitude (ST-VM) is the length of the current ST vector. STC-VM is the spatial distance between the reference ST vector (a), and the current ST vector (b). STC-VA (d) is the spatial angle between the reference ST- vector (a) and the current ST vector (b). (B) orthogonal leads (x, y, and z) are shown for a representative pacing sequence in a coronary artery disease subject. These orthogonal leads are used to calculate vector length and angle, which are presented in (C). Ischemia, in this subject, was noted (by post hoc lactate analysis), first at heart rate 100 b.p.m.

pre-operative echocardiography, though not by ECG. The CAD and non-CAD groups differed for HRs at baseline (Table 2) and responded to pacing with changes in LV MVO$_2$ and GCV flow.

Pacing

In the CAD group, 13 subjects reached a pacing level where they demonstrated incomplete capture. Thirty-four of 35 CAD subjects demonstrated ischemia either by ECG ST deviation or by lactate production. When all 35 CAD subjects and all pacing levels (excluding baseline) were combined, there were 167 measurement points, and of these 80 were positive for ST deviation in the 12-lead ECG, and 55 were positive for ischemia by lactate criteria. Forty-one positive ischemia events were positive both for lactate and the ECG. From all CAD subjects, 28/35 demonstrated positive lactate production during one or more of the pacing steps. For all measurement sequences (167), there were 17 positive ECG events with no positive lactate, and

14 positive lactate events had no 12-lead ECG changes indicative of ischemia.

In the non-CAD group, there were 57 measurements (excluding baseline). Of these, 11/57 measurements (including eight measurements from hypertrophy subjects) and six of 10 subjects at some point in the pacing sequence demonstrated ST change (>1 mm in two adjacent leads) in the 12-lead ECG, while one showed myocardial ischemia by lactate criteria.

At max pacing levels, mean 12-lead ECGST$_{sum}$ (all leads) for the non-CAD group ($n = 10$) was 0.07 mm $\pm$ 0.04 (SD), and for the CAD group, it was 1.07 $\pm$ 0.44 mV. At the same max pacing levels, the sum of ST change in leads II and V5 was 0.01 $\pm$ 0.01 for the non-CAD group, and 0.24 $\pm$ 0.10 mV for the CAD group.

Transcoronary lactate during pacing

For the non-CAD group, there was more transcoronary lactate consumption at higher HRs (Table 2, data shown for baseline and peak pacing levels only),

while in the CAD group lactate extraction decreased and regional myocardial lactate production (grouped) developed at HR baseline +30 and above. Twenty-six subjects in the CAD group exhibited decreasing and low-lactate extraction, progressing toward and reaching (in 22/26) absolute lactate production.

ST-VM, STC-VA, STC-VM and $ECGST_{sum}$

ST-VM (Fig. 2) for the CAD group showed a broad range of initial values, which increased at highest HRs, although individual ST-VM courses were heterogeneous, and this was not well represented by mean ST-VM values. STC-VM demonstrated increases related to HR steps from baseline at the highest three HRs for CAD subjects compared with non-CAD subjects. STC-VA demonstrated a similar pattern with greater increases for pacing step at the highest two HRs for CAD compared with non-CAD groups.

ST-VM, STC-VM and ischemia

The relation of ischemia (presence or absence defined by lactate technique) to ST-VM and STC-VM observations (all patients, all sequences) was analyzed using ROC (Fig. 3). The absolute ST-VM level demonstrated a weak relation to ischemia (area under the ROC curve 0.61, 95% CI of area 0.52–0.70, $P = 0.008$). The STC-VM level, on the other hand, had a stronger relation to ischemia (area under the ROC curve 0.862, 95% CI of area 0.81–0.92, $P < 0.0001$). The STC-VA-level relation to ischemia was also analyzed using ROC (area under curve 0.83, 95% CI of area 0.77–0.88, $P < 0.0001$). The STC-VM relation to ischemia was further analyzed for predictive value for ischemia incorporating baseline levels plus 50 µV as suggested by other investigators (20, 21) as an ischemic limit, as

Table 1

Subject characteristics by group.

	CAD group	Non-CAD group
	($n = 35$)	($n = 10$)
Age (years)	61 ± 8	52 ± 4[a]
Age, range (years)	44–73	45–59
Gender, male (n)	26	9
BMI (kg m^{-2})	26.2 ± 3.2	25.7 ± 2.4
Previous medical history (n)		
Angina Pectoris	35	0[b]
Myocardial Infarction	15	0[b]
Hypertension	16	5
Diabetes	3	0
NYHA function class (n)[c]		
I	0	8
II	2	2
III	33	0
Cardiac medication (n)		
β adrenergic blocking drugs	25	2[b]
Calcium channel blocking drugs	12	1
ACE-inhibitors or All antagonists	13	4
Nitrates	33	0[b]
Diuretics	1	0
Vasodilators	7	0
Digitalis	0	0
Antiarrytmic drugs	0	0

[a]$P < 0.05$ with t-test between groups.
[b]$P < 0.05$ with Fishers' exact test.
[c]$P < 0.05$ with χ^2 test.
BMI, body mass index; NYHA, New York Heart Association; ACE, angiotensin converting enzyme; CAD, coronary artery disease; SD, standard deviation. Data are presented as mean ± SD or number of patients.

Table 2

Circulatory and cardiac parameters for baseline and highest pacing level.

	CAD patients ($n = 35$)		Non-CAD patients ($n = 10$)	
	Baseline	Maximum pace	Baseline	Maximum pace
HR (b.p.m.)	68 ± 6	115 ± 14*	77 ± 7[#]	133 ± 11*
MAP (mmHg)	81 ± 9	87 ± 11*	81 ± 10	89 ± 10*
CVP (mmHg)	7 ± 3	7 ± 3	6 ± 2	8 ± 3
PAP (mmHg)	14 ± 4	19 ± 5*	17 ± 3[#]	24 ± 7*
PAOP (mmHg)	8 ± 3	13 ± 6*	11 ± 2[#]	19 ± 8*
GCVF (ml/min)	75 ± 44	118 ± 80*	128 ± 50	264 ± 128*
Lactate flux (nmol/min)	− 13.3 ± 13.0	− 4.0 ± 22.0*	− 21.3 ± 18.7	− 40.7 ± 31.1*
Lactate extr. (%)	17.9 ± 11.9	2.9 ± 15.9*	25.9 ± 20.6	25.3 ± 18.1
RPP (mmHg*b.p.m.)	7297 ± 1056	12672 ± 2475*	8965 ± 1451[#]	15830 ± 2243*
LVMVO$_2$ (O$_2$ ml/min)	7.5 ± 4.3	14.0 ± 13.3*	15.7 ± 6.1[#]	27.9 ± 12.0*

*Denotes significant difference $P < 0.05$ between paired measurements baseline and maximum pace.
[#]Denotes comparison between groups at baseline.
HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PAP, mean pulmonary artery pressure; PAOP, mean pulmonary artery occlusion pressure; GCVF, great coronary venous flow; extr., extraction; RPP, rate-pressure product; LVMVO$_2$, left ventricular myocardial oxygen consumption; CAD, coronary artery disease; SD standard deviation. Data are presented as mean ± SD.
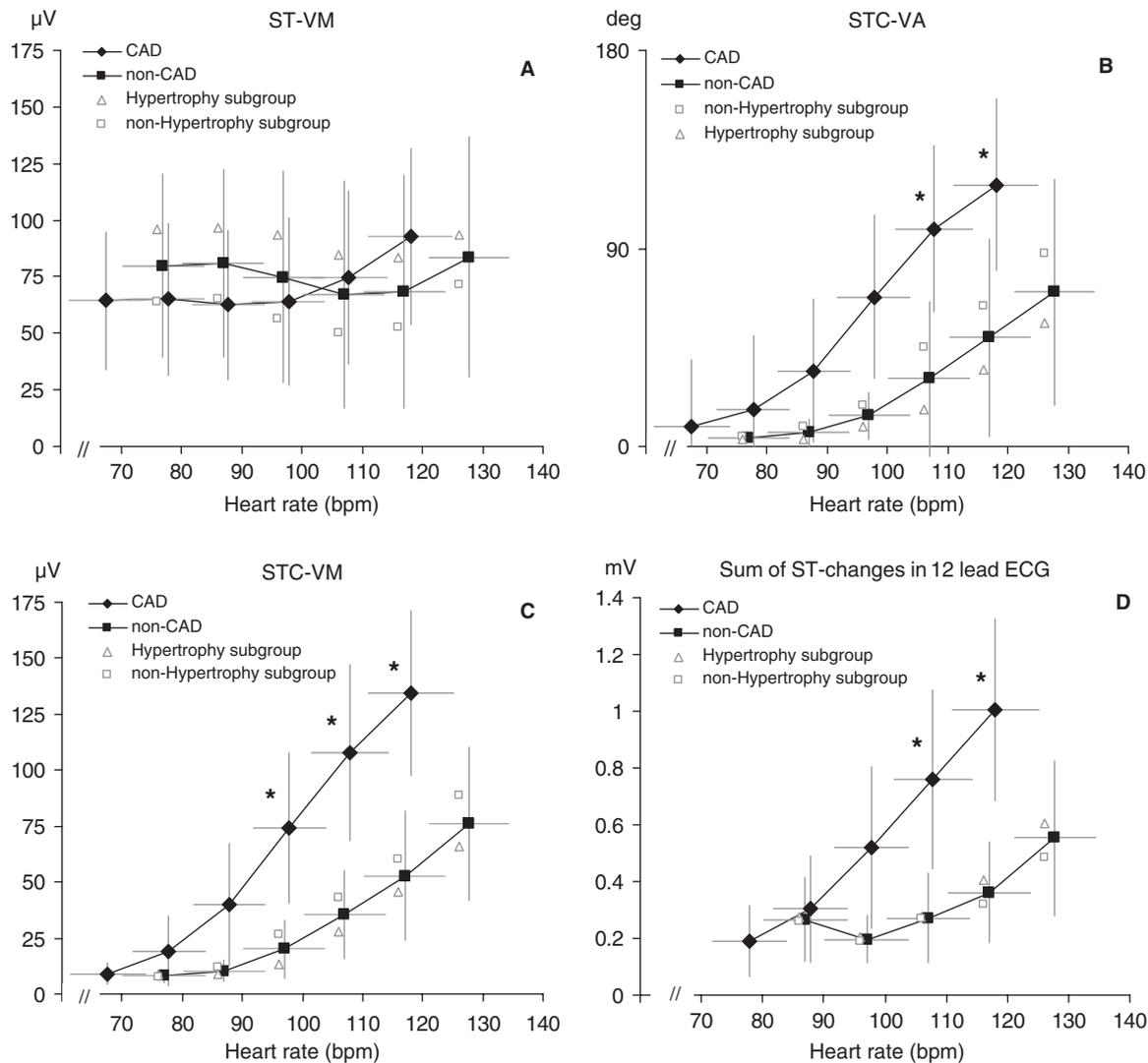
Fig. 2. These panels demonstrate mean vectorcardiography- and electrocardiography-based ST sum values, grouped for heart rates (HR), in the coronary artery disease (CAD) (solid diamonds, n = 35) and non-CAD patients (solid squares, n = 10, open diamonds and open squares, n = 5). STC-VA (B), ST change vector magnitude (STC-VM) (C) and 12-lead ECG ST sum (D) levels all increased in relation to HR during the pacing sequence, and findings for the CAD group were higher at higher HR compared with non-CAD subjects. ST-VM (A) demonstrated no systematic change related to HR for either group, though there was a significant increase in ST-VM for the CAD group at the highest HR. Data are presented as mean ± standard deviation. *P < 0.05 using t-test between groups at each pacing step, with Bonferroni's correction for multiple comparisons.

well as previously reported suggestions for an HR adjustment for the ST level (4) above which STC-VM levels should indicate ischemia (see Fig. 4). With these ischemia thresholds, the positive predictive value of STC-VM for ischemia was 0.58 and the negative predictive value was 0.88.

Discussion

In this study, we were able to test the relationship of both HR and ischemia to VCG ST results in subjects with established CAD diagnoses, with controlled HR changes and graded 'demand' myocardial ischemia. There appears to be a relatively large component of the total grouped STC-VM values occuring in the CAD group, with a smaller component contributed by HR, as shown in the non-CAD group in Fig. 2C. Although there may be an interaction between HR and ischemia concerning effects on ST levels, there was no way to separate these components in ischemic subjects with this study design, other than to compare them with non-ischemic subjects at the same HR. These results also confirmed previous work concerning ST behavior during HR increases in
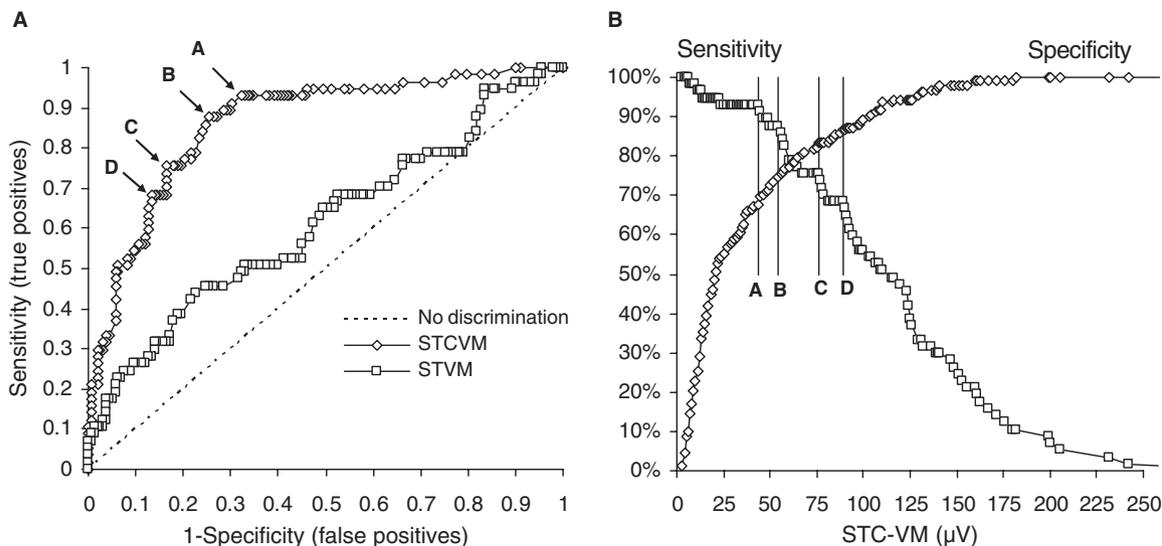
Fig. 3. ROC curves are shown for ST vector magnitude (ST-VM) and STC-VM levels in relation to positive ischemia by lactate analysis (A). ST-VM is little better than chance in this setting for identifying ischemia. In B, sensitivity and specificity for the STC-VM level and positive ischemia are shown, with the same four STC-VM levels identified. It is notable that in the region of these four identified STC-VM levels, sensitivity for identification of ischemia is rapidly declining while specificity rises. This illustrates why a single specific absolute STC-VM threshold has limitations, and that additional factors (such as heart rate) must be included in interpretation of STC-VM levels and likelihood of ischemia.
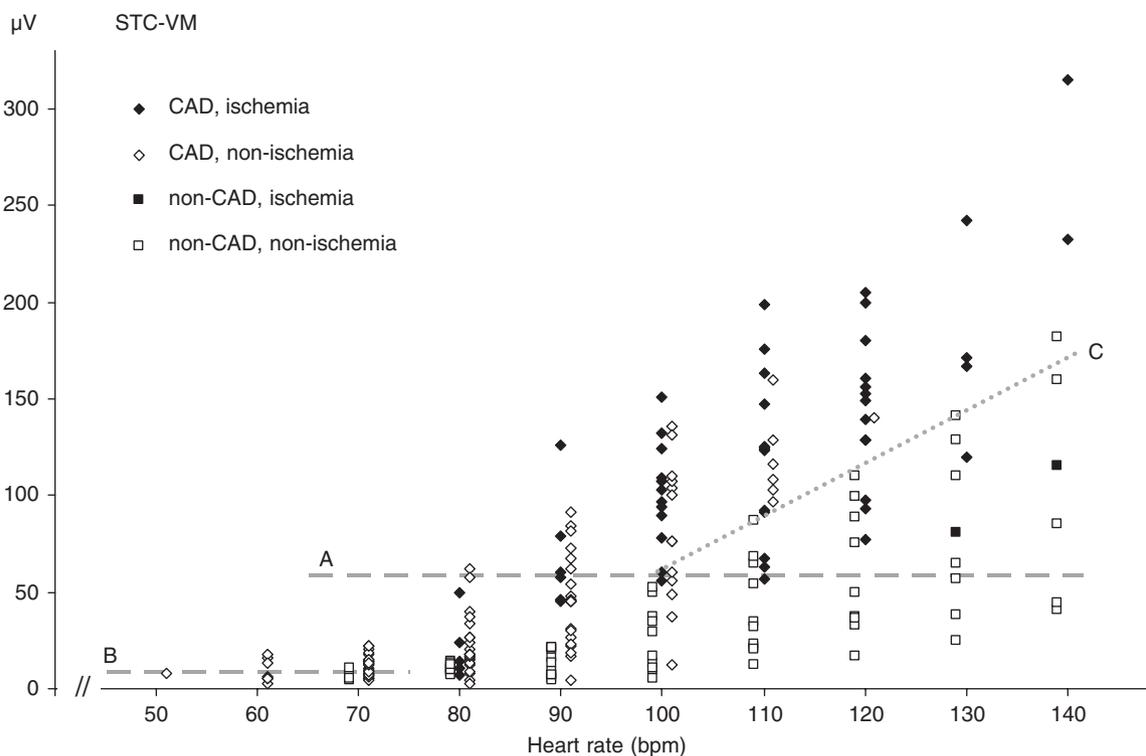

Fig. 4. This figure shows individual measurements, with ischemia and non-ischemia results with ST change vector magnitude (STC-VM) levels marked for both coronary artery disease (CAD) and non-CAD patients. The hatched line labeled 'A' marks a $\Delta 50\,\mu V$ threshold (20, 21), which is placed over the mean 'Baseline' STC-VM value, which is denoted by the hatched line labeled 'B'. The dotted line (C) represents a 2.8 μV change per beat (2.0+0.8 standard deviation) for heart rates (HR)s over 100 b.p.m. (4), as a second HR-related STC-VM threshold for ischemia. These thresholds were used to calculate positive and negative predictive values for ischemia based on the STC-VM level.

non-ischemic conditions (4, 22). While the VCG methodology was chosen because of its strengths as a scientific measurement and analysis instrument, these results examine the same ST phenomena reflected by 12-lead ECG in the multiple single-lead planar format, although we have not attempted a comparison of VCG and 12-lead ECG ST analysis. All the 12-lead ECG ST results suggest changes compatible with the VCG findings.

Vector angle change was the main component of STC-VM increase during ischemia as well as HR increases without ischemia. STC-VA during demand ischemia at graded HR levels has not been previously reported. At the same time, ST-VM did not demonstrate a strong relation to ischemia, although changes in ST-VM may have come late in the protocol, at higher degrees of ischemia, and were difficult to characterise systematically. STC-VM changes occurred in the same pattern and magnitude as STC-VA, as can be seen in Fig. 2. STC-VA increased at highest HRs while ST-VM means did not increase significantly, even at highest HRs. Vector angle change has been suggested as an early indicator of ischemia and infarction (23), and can be an additional tool for discrimination between ischemic and postural ECG changes (24, 25). In clinical practice, vector angle change is generally not monitored independently.

These results show that the widely employed and empirically established ischemia thresholds for ST-VM and STC-VM do not accurately identify ischemia at HRs 100 and above. More dynamic criteria for VCG ST levels are needed, and particularly with regard to higher HR levels. One may implement an ST-HR index or slope factor similar to those proposed for exercise ECG (9, 26–28). An STC-VM threshold for ischemia will have to be a compromise in test performance for sensitivity and specificity, as our findings demonstrate. Specificity of STC-VM for identifying ischemia in this study was unexpectedly low, although this may have been due to limitations in sensitivity of the lactate method as used here to identify the start of ischemia.

To date, no clearly demonstrated VCG ST threshold for myocardial ischemia has been published. Although without reference to HR, $50\,\mu V$ (change) has been suggested for ST-VM (20) and STC-VM (29–31). For observations from the angioplasty laboratory, with subjects resting steadily in the supine position, an even lower limit for STC-VM ($25\,\mu V$) has been proposed (20, 29). Our material demonstrates a relative contribution of HR to ST magnitude in subjects before and during myocar-

dial ischemia, which reflects many clinical settings. While the model that was employed here probably best fits the clinical setting of exercise testing, this is a unique material in that subjects were anesthetised during the ischemic provocation.

The negative predictive value for the ischemic thresholds as tested (STC-VM $50\,\mu V$ increase along with $2.8\,\mu V$ per beat for HR increase above $100\,b.p.m.$) was high (88%) while the positive predictive value was lower (58%). It is likely that the regional lactate production reference method here was not sensitive enough to identify myocardial ischemia rapidly at its onset (where the ECG ST signal might be quicker), and hence there were measurements where ischemia was present and ST elevations occurred, but no lactate production was noted. Similarly, increasingly higher absolute ST levels show rapid declining sensitivity when identifying ischemia. In the ranges of interest in this study, the rate of change in both sensitivity and specificity was rapid for increasing STC-VM levels (Fig. 3B)

Non-CAD subjects increased their myocardial work, as indicated by RPP and metabolism (by LV MVO_2 and lactate consumption), in response to pacing HR steps. The CAD group did not respond the same way. They demonstrated increased LV MVO_2 at maximum pacing, though at the same time lactate production. Results for transcoronary lactate flux also corroborate findings of increased myocardial work during pacing, with a simultaneous limited myocardial supply of substrates in the CAD subjects. From this we can summarise that the pacing method produced myocardial demand-related ischemia in the CAD group, but not in the non-CAD group. Therefore, pacing was an acceptable method for inducing controlled ischemic steps in the CAD subject group.

Some limitations in the study material include the following. The non-CAD group was heterogeneous for both operation-type and myocardial conditions, where half of the subjects had some degree of LV hypertrophy. Also, there were few women in either group. The non-CAD group did not provide enough material from which to generalise about VCG ST behavior during increased HR. There are published reference levels for VCG ST in this setting in awake subjects (4). The numbers in this group were small due to limited access to elective heart operation subjects with minimal ventricular hypertrophy who did not have CAD. The non-CAD group was younger and had a lower incidence of medication (β-blocker). Left ventricular mass was presumably greater in some of the non-CAD

subjects who had valvular heart disease. Left ventricular mass was not measured in all subjects.

Lactate sensitivity and specificity for ischemia is excellent in the laboratory setting, where location and timing of ischemia is known, and lactate sampling is optimal (32). Clinical experience with coronary sinus lactate measurement for detection of ischemia has been described (17–19), and limitations in sensitivity are most likely related to suboptimal sampling of the ischemic myocardial region (33). Lactate measurement as a clinical screening method for myocardial ischemia is inadequate. Still, the specificity of progressive lactate production for myocardial ischemia is very high, which supports our study design of selecting subjects with demonstrated lactate production in order to further analyse the relation of ST-VM and STC-VM to confirmed myocardial ischemia, independent of HR.

In summary, we present a unique clinical material with metabolic measurement for identification of myocardial ischemia during controlled HR increases where the relation of ST changes is tested for both HR and ischemia. We conclude that during assessment of patients for the presence or absence of myocardial ischemia, HR must be taken into account when interpreting VCG ST findings. The diagnostic implication is that in non-hypertrophic patients, an HR adjustment for the ST level may be motivated at higher HRs in order to increase the diagnostic specificity of ST levels for detection of myocardial ischemia. Further prospective validation is needed to establish HR-related VCG ST thresholds for myocardial ischemia.

Acknowledgements

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