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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Prediction of troponin elevation by means of intracoronary electrocardiogram during percutaneous coronary intervention of coronary bifurcation lesions (from COronary SIde Branch Residual IschemiA and COllateralization Assessment Study; COSIBRIA & Co Study)

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Abstract

Background: The influence of periprocedural ischaemia on coronary artery bifurcation stenting (percutaneous coronary intervention [PCI]) remains uncertain.

Aim: To determine the differences in rates of end procedural ischaemia after bifurcation lesion PCI detected with intracoronary electrocardiography (icECG).

Methods: Unipolar icECGs were recorded before, during, and after stent placement and at the end of procedure in side branch (SB) and main branch (MB). Coronary wire was placed in all distal vessels with diameter > 1.5 mm to "map" the distal zones of ischaemia. The patient population consisted of patients with stable/unstable angina with troponin I evaluated before and after PCI.

Results: We studied 147 patients (68% males) with mean age of 64 ± 9 years. One hundred and forty-two patients had icECG recordings at the end of PCI from all locations of the treated region; 36% of patients had MB ST segment elevation (STE) and 31% had icECG STE in the SB region ($p = 0.378$). The icECG had sensitivity of 82% and specificity of 81% to detect troponin I elevation, with positive predictive value of 81% and negative predictive value of 83%. The independent predictors of troponin increase (> 5 × N) were: sex (for female gender, OR = 0.130, CI 0.017–0.995, $p = 0.049$), previous myocardial infarction (OR = 33.23, CI 2.802–394.1, $p = 0.005$), and icECG STE in MB or SB or occlusion of secondary SB (OR = 7.877, CI 2.474–25.07, $p < 0.001$) and for any troponin elevation were double product — SBPxHR (OR = 0.999, CI 0.999–1.00, $p = 0.022$) and icECG STE in MB or SB or occlusion of secondary SB (OR = 9.762, CI 3.273–29.12, $p < 0.001$).

Conclusions: Intracoronary electrocardiography is a highly sensitive and specific method for determination of ischaemic regions and prediction of elevated troponin I.

Key words: ischaemia, percutaneous coronary intervention, ST segment elevation, main branch, side branch

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INTRODUCTION

Coronary bifurcation lesions remain a major therapeutic challenge with high early and late complication rates. It has been shown that angiographically high grade ostial side branch (SB) stenosis is not flow limiting and may not cause ischaemia. Our studies with delayed gadolinium enhancement magnetic resonance imaging before and after bifurcation percutaneous coronary intervention (PCI) demonstrated that occurrence of angiographic stenosis of more than 70% in diameter is associated with periprocedural myonecrosis in the region of SB [1]. Moreover, the post-procedural myocardial injury after uncomplicated PCI is not uncommon [2–4] with a frequency of 5% to 30%. Although this is thought to have no clinical significance, clinical trials demonstrated an increased risk of adverse cardiac events in patients with periprocedural myonecrosis [5].

The unipolar intracoronary electrocardiogram (icECG) recording from angioplasty guidewire represents local epicardial ECG and has been shown to be more sensitive and more reliable in detecting regional myocardial ischaemia during balloon inflation than standard ECG [6–10]. The icECG detects earlier ischaemia and the changes are more prominent than surface ECG. The wire tip can be positioned directly in different regions and hence it can "map" regional ischaemia. An icECG can also differentiate residual ischaemic changes in distal main vessel and SB as sources of both prolonged ischaemia and periprocedural myonecrosis [11, 12].

The aim of this study is to evaluate the relation between ischaemia detected by icECG in different areas of myocardium below bifurcation lesion and its relation with postprocedural myonecrosis as assessed by increase of troponin I. The limitations and diagnostic implications of the prospective clinical trial for bifurcation lesions are enumerated.

METHODS

The subjects were included into the study if they were at least 18 years of age, and they all had to provide written informed consent prior to any study related procedure. Patients with stable or unstable angina were included. The selection criterion for inclusion was angiographic bifurcation lesions located in a native coronary artery with diameter ≥ 2.5 mm and ≤ 4.5 mm and SB with diameter ≥ 2.0 mm. We excluded patients with ST-segment elevation (STE) myocardial infarction (MI) and those with non-cardiac co-morbid conditions with life expectancy < 1 year. The following patients were also excluded: 1) left main coronary artery stenosis, 2) total occlusion before occurrence of SB, 3) lesion of interest located at infarct-related artery, 4) subjects with left ventricular ejection fraction < 30%, 5) subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and 6) patients with bundle branch blocks and atrial fibrillation/flutter with no identifiable isoelectric line. The patients were recruited in centres 1, 3 and 5 of the authors' affiliations. The Local Ethics Committee of those sites approved the study protocol.

Definition of endpoints

The postprocedural MI was defined as postprocedural troponin I concentration more than five times the upper normal limits (troponin I reference values are ≤ 0.06 ng/mL at our institution) [13]. Significant troponin rise was defined as postprocedural troponin concentration increase more than 20% of initial concentration.

Procedures

Provisional stenting was the default PCI in all patients if significant stenosis before or after SB occurred. Heparin was given in a standard dose (100 U/kg, i.v.) at the beginning of the procedure. The patients with stable coronary artery disease were pretreated with 600 mg of clopidogrel and at least 300 mg aspirin. The patients with acute coronary syndrome without STE were pretreated with 180 mg ticagrelor or 60 mg prasugrel plus aspirin. The application of glycoprotein (GP) IIb/IIIa inhibitor was left to the discretion of the operator. Two guidewires were inserted into both distal branches in most of the cases. Predilatation of main vessel was obligatory. The final kissing balloon inflation (KBI) or sequential balloon inflation were at the discretion of operator. In general, it was recommended that in the case of SB icECG STE (see below), balloon dilatation of SB should be performed. The SB was stented in the case of flow less than Thrombolysis in Myocardial Infarction (TIMI) 3 where high grade ostial stenosis was not eliminated with KBI and the patient was still symptomatic. All lesions were stented with everolimus-, sirolimus-, or zotarolimus-eluting stents. Angiographic success was assessed as the end procedural main vessel diameter stenosis (DS) less than 20% and SB ostial stenosis less than 70% without significant dissection and flow impairment. Procedure success included angiographic success in the absence of in hospital major adverse cardiac events (excluding asymptomatic troponin I increase).

Ischaemia mapping using coronary PCI guide wire

We used workhorse PCI guidewire for recording of intra-coronary electrocardiographic signals (BMW Universal II, Abbott Vascular, USA; Runthrough, Terumo, Japan; Cruiser Hidro, Biotronik, Germany; Prowater and Sion, Asahi, Japan). The proximal end of the wire was connected to unipolar lead, used for recording of V1–V6 on surface ECG. The signal was calibrated at 1 mV = 1 cm. The speed of recording varied between 12.5 mm/s and 100 mm/s, depending on operator intent. At the beginning of the procedure, the wire was placed in every segment of coronary artery. The size of the recording (exploring) electrode is the last 3 cm of every workhorse coronary guidewire. We verified this conclusion by checking the change in signal using a microcatheter; i.e. when the

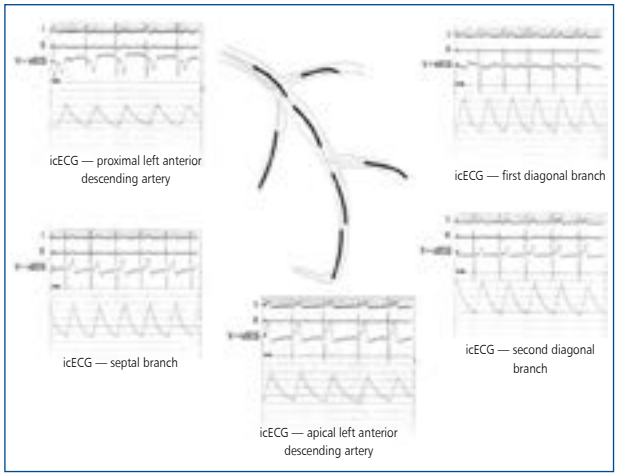

Figure 1. The intracoronary electrocardiography (icECG) signals recorded from patient — mapping of left anterior descending artery before percutaneous coronary intervention. The icECG line is on the third row

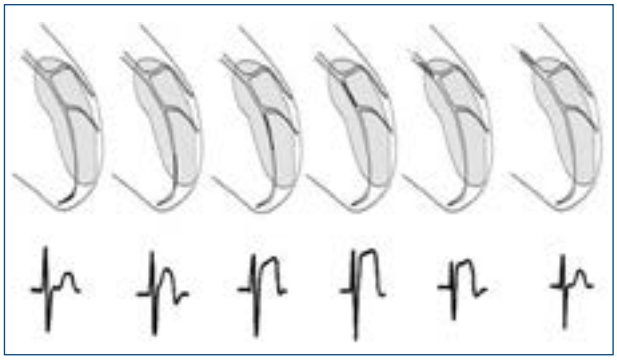

Figure 2. Intracoronary electrocardiography (icECG) mapping — the wire is pulled back, and icECG signals are recorded. The diagonal/septal branches were used as markers for comparison of ECG changes during different time points

catheter tip started to cover the radiopaque distal 3-cm part of the wire and the signal configuration (amplitude, shape) changed. By pulling back the microcatheter, the signal does not change unless the final 3 cm are not covered. Hence, the distal 3-cm part of the wire was placed in every segment of explored coronary artery. Several procedural guidelines were followed:

— the wire tip was required to be largely straight, the tip was not in more than 90° J-configuration;
— the tip of the wire was allowed to move freely. If the tip of the wire was wedged, the lesion current appeared from wire tip, which would erroneously be interpreted as ischaemic changes. Hence, the operator had to turn the wire clockwise-counter-clockwise to be sure that the tip was freely moving. The tip touched the epicardial surface, but had to be unconstrained.

The locations from which records were made were noted by using bifurcation points as the local anatomical markers; i.e. the beginning of the radiopaque distal 3 cm part of the coronary wire was placed exactly against the carina tip of every bifurcation. This gave exact reference points and permitted consecutive changes in icECG. The records in two time points were compared, based on anatomical landmarks. In the case of bifurcation lesion treatment, it was possible to monitor icECG from the distal tips of guidewires placed in main vessel and SB. For this purpose, the outer ends of both wires were connected to two unipolar V-leads. An example of records in different parts of coronary artery tree from left anterior descending artery are presented in Figure 1.

The size of ischaemic area was determined by wire pull-back recordings. The ECG was recorded at a paper speed of 12.5 mm/s or 25 mm/s. The tip of the wire was placed as distal as possible in the vessel of interest. The continuous recording was then turned on and the wire was slowly pulled back. In the case of ischaemia, there was either STE or ST-segment depression (rarely observed).

When the wire tip (the very end of the wire) exited the border of ischaemic territory, the ST-segment suddenly normalised. This point was precisely identified on coronary angiogram. Quantitative and qualitative analyses were made of icECG changes taking into account initial record and anatomical landmarks. Thus, the border of ischaemic territory can be identified by simple pull back. However, the severity (transmurality and severity of metabolic changes) of ischaemia could not be deduced from this record (Fig. 2).

icECG analysis

The absolute ST-segment shift in intracoronary ECG lead and surface leads I, II, and aVF was determined immediately before and at the end of any coronary balloon occlusion (for SB, main branch [MB] pre- and/or postdilatation, stent implantation) and at the end of procedure. The recorded intracoronary and surface leads ECG, with simultaneously recorded aortic blood pressure curves, were printed and analysed consecutively. The paper speed was 50 mm/s and ECG amplitude was calibrated as 10 mm/mV. Several points were traced on every ECG: beginning of P wave, beginning of QRS complex, peak Q, peak R, peak S, end of QRS complex, J point (60 ms after end of QRS), end of T-wave, beginning of subsequent P-wave, and beginning of subsequent QRS complex. The points were connected and constituted the isoelectric line. If some hallmark points were not distinct, definition of the isoelectric line was based on two hallmark points. The ST-segment shift was calculated as the distance of the corresponding point from the isoelectric line in a perpendicular direction. The STE at the end of the first balloon inflation (or stent implantation in the case of direct stenting) was considered as the maximum icECG STE in the main and side branches, recorded usually 30–45 s after the beginning

of vessel occlusion. An 0.5-mV STE or ST-segment depression above or below J-point was accepted as the threshold for defining ischaemia occurrence.

Angiographic analysis

Quantitative angiographic analyses were performed using commercially available software (Medis QCA version 5.0, Leiden, the Netherlands; Dicom Works version 3.1.5b, Paris). Catheter calibration was used in all cases. Bifurcation lesions were classified according to the Medina classification using an index of 1 for stenosis greater than 50% and an index of 0 for no stenosis. The lesions with ostial significant stenosis of SB (percentage DS > 50%) were classified as true bifurcation lesions. The changes of SB percentage DS (SB%DS) before procedure, after stenting, and at the end of PCI were assessed. At follow-up, target lesion restenosis was divided as restenosis (more than 50% DS) in proximal main vessel — MB stent region and 5 mm proximal or distal from stent edges or restenosis in SB, involving the ostium and 5 mm distally. As more than 50% residual DS at SB ostium was regarded as an acceptable procedure result, restenosis in SB was defined as more than 20% increase of ostial DS.

Statistical analysis

All data are presented as means ± standard deviation. Differences between groups were examined with paired or unpaired t-tests as appropriate, with normal distributions. If the distribution was not normal, Wilcoxon sign-ranked test and Mann-Whitney U-tests were performed. Analysis of variance (ANOVA) was used for multiple comparisons of data, when parameters were distributed normally. Otherwise, Kruskall-Wallis test was performed. Multiple regression analysis with backward elimination process was used to identify predictors of postprocedural myonecrosis. All univariate predictors with $p < 0.1$ were included in a multivariate model. Chi-square tests were applied for qualitative data. Based on results from fractional flow reserve (FFR) studies and previous studies for icECG changes in the relation with postprocedural myonecrosis [11, 12], we assumed that 30% of our patients would have residual ischaemia in distal MB and the same proportion would have residual ischaemia in the SB region. This gives a sample size of 72 patients for each event to be detected and a total sample size of 144 patients, with significance level of 0.05 and study power of 85%.

RESULTS

From January 2011 to December 2012, 147 patients were selected for inclusion into the study group. The mean age was 64 ± 9 years and 68% were males. More than half of the patients had high degree stable or unstable angina (52%). Almost half of patients had previous PCI (47.6%) and 38.4% had previous MI. The presence of diabetes was 34%, and 47% were smokers. Only three patients had previous coronary artery bypass operation.

Angiographically, 64.4% of the patients had multivessel disease, and the left anterior descending artery was treated in 78% of the population. More than half of the patients had true bifurcation lesions; 54% — Medina type xx1. Overall, KBI was applied in 25.4% of the cases, the SB was balloon dilated only after stenting in 22%, and main vessel stent was postdilated in 44% of the procedures. Tables 1–3 present demographic, procedural, and angiographic characteristics of the study group according to increase of postprocedural troponin > 5 × normal (N). In general, a post PCI troponin I > 5 × N appeared in 28 (19%) patients and the rest had less than this cut-off value of troponin. Female gender was significantly associated with troponin I elevation and patients with previous MI expressed less troponin I after PCI (Table 1). There were no significant differences between groups regarding procedural and angiographic characteristics.

Table 1. Demographic characteristics

Patient characteristics	Troponin > 5 × N [%]	Troponin ≤ 5 × N [%]	P
Age [years]	66 ± 10	64 ± 9	0.182
Sex — males	50%	71%	0.032
Hypertension	93%	98%	0.143
Hyperlipidaemia	82%	94%	0.061
Diabetes	28%	36%	0.313
Renal failure	7.7%	7.5%	0.624
Smoking	47%	52%	0.554
Previous myocardial infarction	14%	45%	0.003
Previous PCI	50%	45%	0.407

Renal failure defined as calculated glomerular filtration rate according to Cockroft-Gault formula < 60 mL/min; N — normal; PCI — percutaneous coronary intervention

Table 2. Procedural characteristics

Procedure details	Troponin > 5 × N	Troponin ≤ 5 × N	P
LAD/Diagonal	78%	80%	0.601
LCX/Marginal	11%	14%	
RCA — PD/PL	11%	6%	
Multivessel disease	63%	59%	0.886
Stent diameter [mm]	3.31 ± 0.38	3.22 ± 0.37	0.249
Stent length [mm]	27 ± 12	25 ± 8	0.235
Implantation pressure [atm]	13 ± 2	13 ± 2	0.601
Kissing balloon inflation	22%	25%	0.864
Second stent (T — stenting)	10%	9%	0.648

LAD — left anterior descending artery; LCX — left circumflex artery; N — normal; RCA — right coronary artery; PD — posterior descending artery; PL — postero-lateral branch artery

Table 3. Angiographic results

	Troponin > 5 × N	Troponin ≤ 5 × N	P
MV RVD [mm]	3.50 ± 0.33	3.38 ± 0.34	0.106
MV %DS [%]	57% ± 30%	50% ± 33%	0.268
MV %DS final [%]	3% ± 7%	3% ± 6%	0.524
MB RVD, mm]	2.99 ± 0.37	2.95 ± 0.27	0.487
MB %DS [%]	72% ± 29%	72% ± 26%	0.977
MB %DS final [%]	3% ± 7%	3% ± 5%	0.717
SB RVD [mm]	2.25 ± 0.42	2.30 ± 0.37	0.347
SB %DS [%]	45% ± 32%	42% ± 31%	0.650
SB %DS, post stenting [%]	69% ± 27%	71% ± 22%	0.618
SB %DS, final [%]	60% ± 28%	56% ± 26%	0.501

%DS — percentage diameter stenosis; MB — main branch, after side branch; MV — main vessel before side branch; N — normal; RVD — reference vessel diameter; SB — side branch

icECG changes during PCI

One hundred and forty-two patients had icECG recordings at the end of PCI from all locations of treated region. Of these, MB only STE on icECG occurred in 20 (14%) patients and in SB only STE was recorded in 27 (19%) patients ($p = 0.734$ for comparison). In both branches, icECG final STE occurred in 24 (17%) patients. In total, 36% of patients had MB STE and 31% had icECG STE in the SB region ($p = 0.378$). Nine patients had occlusion of secondary SB with reference vessel diameter 1.0–2.0 mm (6.3%). In distal MB, it was possible to record icECG in all patients. In 20 patients, there were artefacts in recordings of the stent region, which made identification of the isoelectric line difficult and reduced the number of used criteria for definition of isoelectric line. These patients were included taking into consideration only records from distal MB and SB. Nine (6%) patients had icECG STE only in the region below the stent, 21 (16%) patients had icECG changes in distal region only, and 20 (14%) patients had icECG ST shift in both the distal region and below the stent regions.

Maximal STE during procedure

In distal MB, the maximum icECG STE was significantly higher than maximal STE in SB region (10 ± 9 mV vs. 8 ± 7 mV, $p = 0.020$). There was a significant correlation between maximal STE in MB and SB ($\rho = 0.231$, $p = 0.047$). The maximal STE in MB during balloon inflation significantly correlated with final absolute STE in distal MB ($\rho = 0.323$, $p = 0.004$) and below the stent region ($\rho = 0.301$, $p = 0.047$), as well as with final absolute SB icECG STE ($\rho = 0.248$, $p = 0.049$). The maximum MB icECG STE correlated significantly with creatine kinase (CK)-MB increase post PCI ($\rho = 0.318$, $p = 0.014$) and with absolute increase in CK-MB after intervention ($\rho = 0.288$, $p = 0.028$), but not with troponin I. The maximal SB icECG STE during balloon inflation did not cor-

relate significantly with final absolute icECG STE in the same region. The SB maximum icECG STE correlated significantly with SB%DS after stent implantation (ρ = 0.300, p = 0.012), diastolic blood pressure before beginning of PCI procedure (ρ = 0.291, p = 0.048), and heart rate during maximum STE in the same region (ρ = 0.273, p = 0.044). For maximum icECG STE (MB and SB) there was a strong trend associated with hypertension (p = 0.056 and p = 0.052, accordingly).

Final STE

The final icECG STE in MB significantly correlated with post PCI troponin I concentration (ρ = 0.471, p < 0.001), as well as with post procedural troponin increase more than five times normal (ρ = 0.357, p < 0.001). It also correlated significantly with final main vessel %DS (ρ = 0.195, p = 0.021), MB final %DS (ρ = 0.230, p = 0.006), and stent implantation pressure (ρ = –0.183, p = 0.032). On multivariate logistic regression analysis, only MB final %DS was independently associated with end procedural MB icECG STE (OR = 1.082, CI 1.013–1.156, p = 0.019). The end procedural SB icECG STE correlated significantly with postprocedural troponin concentration (ρ = 0.437, p < 0.001), postprocedural troponin increased more than five times normal (ρ = 0.256, p = 0.003), SB%DS after stent implantation (ρ = 0.176, p = 0.038), previous PCI (ρ = 0.205, p = 0.025), and low density lipoprotein concentration (ρ = –0.223, p = 0.031), as well as ejection fraction (ρ = –0.185, p = 0.036) and mitral regurgitation degree (ρ = 0.185, p = 0.033) from echocardiography. Independent associates on multivariate analysis were SB%DS after stenting (OR 1.028, CI 1.001–1.056, p = 0.048) and previous PCI (OR 0.210, CI 0.057–0.770, p = 0.019).

Side branch compromise, icECG changes, and postprocedural myonecrosis

There was significant increase in SB diameter stenosis (SB%DS) after stenting (p < 0.001, Table 3), with subsequent decrease at the end of PCI (p < 0.001). As mentioned above, the SB%DS after stent implantation (but not final SB%DS) correlated significantly with maximal icECG STE and final STE in SB region. Neither of the angiographic parameters from the SB region correlated significantly with troponin I. During predilatation of bifurcation lesion or stent implantation (in case of direct stenting), there was always STE > 2 mm in the SB region after 15 or more seconds of vessel occlusion.

The patients were divided into six groups depending on SB ostial stenosis after stent placement, SB balloon dilatation afterwards, and final icECG STE. Group 1 (n = 12, 8%) included patients with SB%DS > 50% after stenting, with icECG STE in SB region, but without further intervention in SB. Group 2 (n = 36, 25%) consisted of patients with SB%DS > 50% after stenting, but without icECG STE; those patients did not receive any additional treatment of SB. Group 3 (n = 39, 27%) included patients with SB%DS > 50% after stenting and icECG STE in the SB region, which received balloon dilatation of SB ostium, and icECG STE was eliminated afterwards. Group 4 was formed from 23 (16%) patients, who were identical to group 3 (SB%DS > 50% after stenting, icECG STE in SB region with consequent ballooning of SB ostium) but in whom there was sustained icECG STE on final record from SB. Group 5 (n = 10, 7%) constituted patients who had icECG STE in the SB region after stenting, but ostial stenosis < 50% and no treatment was performed. Finally, group 6 included 23 (16%) patients with < 50% SB ostial stenosis after stenting and no icECG STE.

The groups 1, 3, and 4 (52% of entire cohort) were patients with significant (> 50% DS) SB stenosis and sustained icECG STE in the SB region after stenting main vessel. Thus, in 63% (39/62) of cases, where SB ostial balloon inflation was performed, it was possible to eliminate ischaemia in the branch region (i.e. the SB ostial stenosis was the sole reason for ischaemia). For the entire patient population, there was no statistically significant difference between the six groups regarding frequency of troponin elevation more than five times normal, but there was a significant difference between groups regarding any significant troponin increase after PCI (p < 0.001). It must be noted that in groups 1 and 4, 91% and 95% of patients had postprocedural troponin elevation. In contrast, only 50% of patients in group 5 developed postprocedural troponin elevation. From the remaining 76 patients, all three (100%) patients in group 1 and all nine (100%) in group 4 had postprocedural myonecrosis. None of the patients in group 3 had postprocedural myonecrosis (0/19, 0%), meaning that SB balloon dilatation eliminates 68% (19/28) of the reasons for ischaemia causing myonecrosis in the branch region. In group 5, 60% (n = 3/5) had postprocedural myonecrosis.

Troponin increase after intervention and icECG ST-segment changes

One hundred and thirty-five patients had complete sets of data with troponin analysis before and 24 h after PCI and icECG recording. Thirteen (9.6%) patients had increased troponin at baseline. Myocardial infarction defined as post-PCI troponin I > 5 × N was observed in 28 (21%) patients, and significant troponin rise after the procedure was demonstrated in 76 (56%) patients. There was no patient with CK-MB increase more than three times the upper normal limit, and 11 (8.1%) patients demonstrated a rise of more than 20% of initial value of enzyme as compared with the value before the procedure. The dynamics of troponin before and after PCI in groups with icECG STE, and in groups with SB icECG STE, MB icECG STE, and in the group with icECG STE in both branches is presented in Figure 3. There is a significant difference between groups, and there is a linear increase of postprocedural troponin concentration with icECG STE (troponin I concentrations: SB vs. MB vs. SB + MB STE –0.61 ± 1.76 ng/mL vs. 1.73 ± 6.16 ng/mL vs. 2.99 ± 7.88 ng/mL, overall

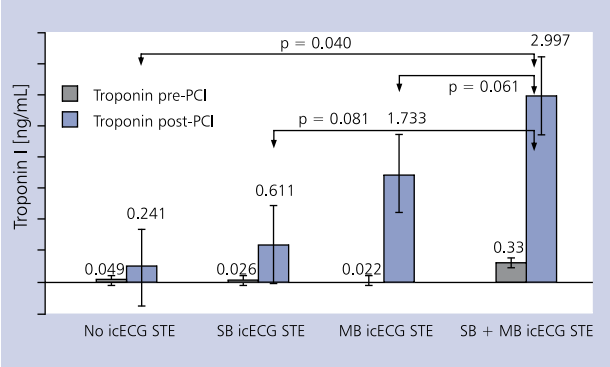

Figure 3. The means plots of the dynamics of troponin concentration in groups with intracoronary electrocardiography (icECG) ST-segment elevation (STE) after percutaneous coronary intervention (PCI), group with icECG STE in side branch (SB), in main branch (MB), and both

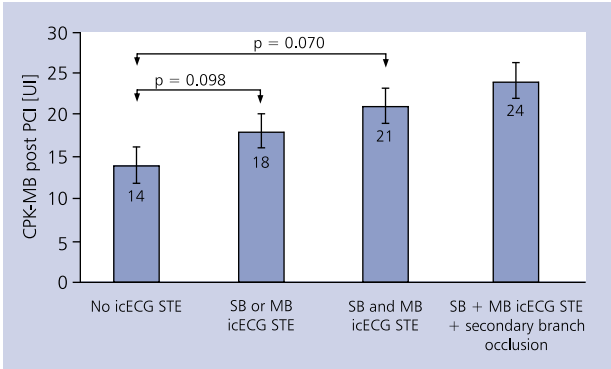

Figure 4. The means plots of the troponin, creatine phosphokinase (CPK)-MB, and total CPK post-percutaneous coronary intervention (PCI) concentration in groups with one intracoronary electrocardiography (icECG) ST-segment elevation (STE) after PCI (side branch [SB] or main branch [MB] STE) or occlusion of secondary side branch

Table 4. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of intracoronary electrocardiography to detect troponin > 5 × normal

	Sensitivity	Specificity	PPV	NPV	Accuracy
MB STE, final	70%	72%	40%	90%	72%
SB STE, final	56%	74%	36%	87%	70%
MB or SB STE, final	85%	59%	35%	94%	65%
MB or SB STE or occlusion of secondary SB	89%	59%	36%	95%	65%

MB — main branch; SB — side branch, STE — ST-segment elevation

Table 5. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of intracoronary electrocardiography to detect any troponin increase after percutaneous coronary intervention

	Sensitivity	Specificity	PPV	NPV	Accuracy
MB STE, final	58%	91%	90%	63%	73%
SB STE, final	48%	88%	83%	57%	66%
MB or SB STE, final	78%	86%	88%	75%	82%
MB or SB STE or occlusion of secondary SB	78%	84%	86%	75%	82%

MB — main branch; SB — side branch, STE — ST-segment elevation

$p < 0.001$) in SB, through MB and both branches. In post-hoc analysis, there was a significant difference in post-PCI troponin I concentration between groups without icECG STE and group with icECG STE in both branches ($p = 0.010$) and a strong trend for a significant difference between groups with SB icECG STE and icECG STE in both branches ($p = 0.082$). In this way, we demonstrated that increasing the region of ischaemia is directly related with absolute concentration rise in troponin I postprocedural.

When occlusion of secondary SB was added to the analysis of the relation between icECG changes and postprocedural enzyme rise, the differences between groups became even clearer. By adding occlusion of small secondary SB, there was also a significant difference between groups in postprocedural concentration of creatine phosphokinase (CPK) ($p = 0.001$) and MB-fraction of CPK ($p = 0.023$). Thus, the increase in ischaemic territory detected by icECG changes in ST-segment were directly related to the increase in concentration of enzymes for myocardial necrosis (Fig. 4).

Tables 4 and 5 demonstrate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of changes on icECG in main and SB, as well as occlusion of small size SB to predict troponin-defined MI and significant troponin increase after PCI. If the icECG changes only in MB regions are taken into consideration, the sensitivity and specificity to detect troponin-defined MI was

much better in distal MB (sensitivity/specificity: 58%/76% vs. 40%/72%, respectively). The same was true also for any significant troponin increase (50%/91% vs. 32%/93%). Interestingly, if only the group with undetectable baseline troponin I is considered (< 0.01 ng/mL), the sensitivity of icECG changes for postprocedural troponin rise > 5 × N was 100%, with a specificity of 61%, PPV of 37%, and NPV of 100%. For any troponin rise, the respective values were — sensitivity 82%, specificity 81%, PPV 81%, NPV 83%, and overall accuracy 81%.

Predictors of postprocedural myonecrosis

Univariate associates of increase in troponin > 5 × N were: clopidogrel pretreatment, statin pretreatment, sex (female), previous MI, and systolic blood pressure at the beginning of PCI, as well as double product before PCI (DP = systolic blood pressure × heart rate) and icECG STE in MB and SB or occlusion of secondary side branches. On binary logistic regression analysis independent predictors of troponin increase > 5 × N were: sex (for female gender, OR = 0.130, CI 0.017–0.995, p = 0.049), previous MI (OR = 33.23, CI 2.802–394.09, p = 0.005) and icECG STE in MB or SB or occlusion of secondary SB (OR = 7.877, CI 2.474–25.07, p < 0.001).

Several variables were associated with postprocedural significant troponin increase such as previous MI, serum creatinine concentration and renal failure, main branch %DS before PCI, icECG STE in MB and SB, and occlusion of secondary side branches. On binary logistic regression analysis independent predictors of significant troponin rise after PCI were double product (OR = 0.999, CI 0.999–1.000, p = 0.022) and icECG STE in MB or SB or occlusion of secondary SB (OR = 9.762, CI 3.273–29.12, p < 0.001).

DISCUSSION

There were several major findings in this study. First, a modified method for icECG recording of epicardial electric potentials was introduced for ischaemic zone detection at conclusion of PCI for coronary bifurcation lesions. This method provides a unique opportunity for determining areas of residual ischaemia, which may be possible sources of postprocedural increase in troponin I concentration. Second, this is the first study demonstrating that about one third of patients have ischaemia in at least one distal location (MB, SB, or both) after stenting of coronary bifurcation lesions as detected by means of icECG. We showed that this residual ischaemia is a sensitive and specific marker for postprocedural increase of troponin and for prediction of troponin-defined postprocedural MI according to the third definition of MI [13]. It was also found that the increase in ischaemic territory in bifurcation region (SB region–MB region–both distal regions) is linearly related with postprocedural troponin I concentration. The icECG recording provides a possible mechanism for postprocedural enzyme rise in patients with icECG STE in distal MB only may be distal embolisation from plaque components, while spasm or local thrombosis of microcirculation appeared to be a possible reason for those with icECG changes in both zones (below the stent and distal MB). This is in agreement with magnetic resonance studies that demonstrated late gadolinium enhancement zones in adjacent areas around the stent [2–4].

One third of patients had ischaemia in the SB region at the end of coronary bifurcation interventional procedure, not related to the extent of SB final stenosis. The SB ostial stenosis, after stenting, correlated significantly with maximum icECG STE in SB region immediately after stenting, but not with final icECG STE in SB region. Although this parameter, as well as final SB ostial stenosis, did not correlate with either final icECG STE or with postprocedural troponin elevation, almost 60% of patients had icECG STE after stenting in the SB region (nearly half of this ischaemia could be eliminated by balloon inflation at SB ostium). When attempted, balloon inflation at SB ostium was successful in eliminating ischaemia and in preventing further myonecrosis in almost 70% of cases. In cases where SB ostium ballooning is ineffective to alleviate SB ischaemia (even after larger balloon dilatation), application of GP IIb/IIIa inhibitors and vasodilators may be effective, but the hypothesis remains to be validated. In cases where there was no icECG STE after stenting in the SB region, no further treatment of SB was needed regardless of the angiographic appearance of the lesion.

Based on the above findings, we can propose a simple practical method for icECG recording to guide bifurcation PCI, termed the "313" method for ischaemic mapping. At the beginning of PCI, the main vessel wire records icECG from the region below the distal lesion end and thereafter — from the distal end of the main vessel. Then, the SB wire is inserted and the icECG is recorded from the area more than 10 mm away from the ostium (three places for recoding icECG — MB proximal, MB distal, SB; the first "3"). After stenting, one more measurement of icECG is made from the SB region for ongoing ischaemia (the "1" in our "313" method). If there is persistent (> 90–120 s after occlusion) STE, a balloon opening (with or without KBI) of SB should be made. At the conclusion, the icECG is recorded from distal MB, from below the stent region and SB region (the second "3" in our "313" method) (Fig. 5).

It should be noted that icECG and pressure wire-recorded FFR values are different entities — the icECG detects actual, during PCI, ischaemia, while FFR detects the potential for ischaemia appearance. Those two features could coincide during the interventional procedure, but they may not. Our ongoing study will evaluate the relation between icECG changes and fractional flow reserve changes in SB after stenting coronary bifurcation lesions (FFR vs. icECG in Coronary Bifurcations [FIESTA] ClinicalTrials.gov Identifier: NCT01724957).

By using the icECG mapping technique, we were able to predict almost 80% of cases with any troponin I rise after intervention for coronary bifurcation stenosis and 90% of troponin I rise more than five times the upper normal limit,

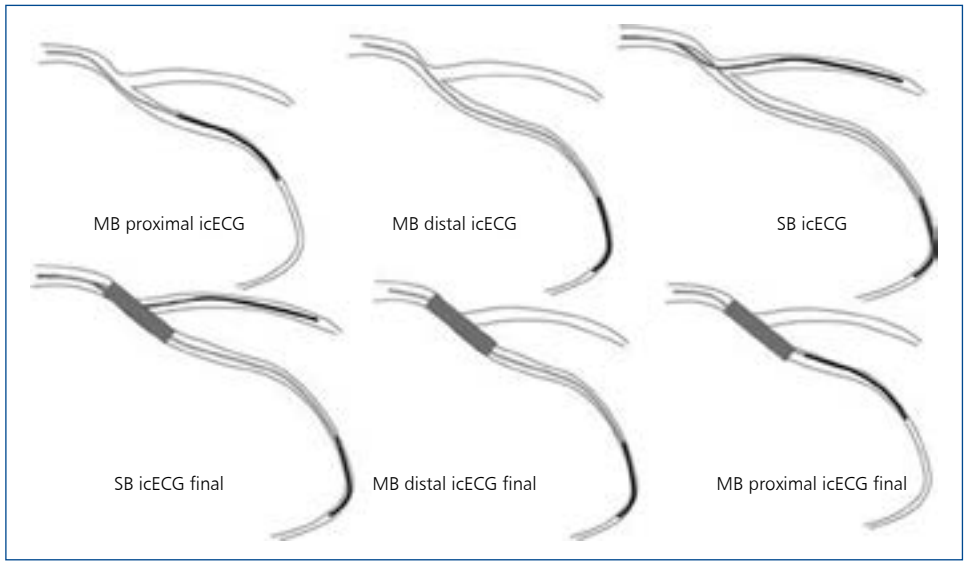

Figure 5. The "3 + 1-point ischaemic mapping" method. At the beginning of percutaneous coronary intervention (PCI), intracoronary electrocardiography (icECG) is recorded from main branch (MB) at the level of distal lesion end and distal end of main vessel. From side branch (SB), icECG is recorded from at least 10 mm below the ostium of the vessel. These are the three main points of record while an additional record is made after stenting across the SB for check of ischaemia. If no ischaemia, the SB should not be further intervened. At the end of PCI, two records are performed in MB — at the distal part of the main vessel and from the region below the stent distal end and one more from SB

with 95% NPV (i.e. if icECG STE is lacking there is 95% probability that troponin I after intervention will be negative). Our results are comparable with the results of previous studies performed in non-bifurcation coronary interventions. Balian et al. [8], in group of 108 stable, low-risk, non-bifurcation coronary patient population, found 74% sensitivity, 95% specificity, and 93% and 81% PPV and NPV, respectively, for any troponin increase. Despite the lower risk patient cohort, the frequency of postprocedural enzyme increase was almost identical to our patient population, although no data were provided about sensitivity and specificity of method regarding $> 5 \times N$ troponin I increase. In 339 patients with non-bifurcation PCI of non-complex lesions probed with icECG, Uetani et al. [10] demonstrated sensitivity of 55%, specificity of 92%, PPV of 69% and NVP of 87% (the absolute number of patients with increase in troponin and relative icECG changes was not provided). Neither of those studies used a reference point, nor was the wire positioning before and after intervention described. The present findings are similar in sensitivity to the two above studies if we consider only data for MB. The present method is more comprehensive, however, as it provides a base for demonstrating the exact zone location source of possible troponin rise after intervention. In the subgroup of our patients with undetectable baseline troponin values, as in the cited studies, we demonstrated higher sensitivity and better negative predictive value (100%) in comparison with previous studies, with a slightly lower specificity (91% in our study vs. 95% in the Balian et al. [8] study and 92% in the study by Uetani et al. [10]). Since a different distribution of icECG shifts exists in the MB, this may explain the different sensitivity and specificity detected in previous studies. In our experience, the site of placing the guidewire tip is mandatory to detect possible ischaemic changes.

Limitations of the study

The major limitation in our study, as well as in previous studies, is that there is no stated definition of ST-segment changes on icECG that may be connected to ischaemia. Hence, setting a different threshold for ST segment shift can subsequently improve the sensitivity of the method. Our definition was based on previous studies with icECG recordings and our own patient studies for examination of predictors of periprocedural necrosis [6–12]. Moreover, some of our patients may not have had a sufficiently long bout of ischaemia to cause myonecrosis. We did not wait more than 5 min after completion of the procedure for final registration of icECG, and it is possible that the specificity of this method can be improved with longer waiting time. We did not analyse changes in flow and ostial diameter of small SB (1–2 mm diameter), taking into account only complete occlusion of those branches. It is possible that more detailed analysis of changes in small branches may further improve sensitivity and overall accuracy of our method to detect any troponin increase after the procedure. Finally, we were unable to place PCI wire in all SBs, which can explain some of the missing ischaemic zones. The postprocedural myocardial necrosis enzymes was small, however, which probably has little prognostic implication [5].

CONCLUSIONS

We found a linear relation between the size of residual ischaemic zone (number of places with end-PCI icECG STE) and final absolute troponin concentration. There was no relation between maximal amplitude of STE on icECG inside the ischaemic zone and final enzyme concentration of troponin I. Although the lateral extent of the ischaemic/necrotic zone may be more important for final myocardial necrotic enzyme concentration than eventual transmural extent, icECG may be a useful tool for identifying post-procedural myocardial injury after uncomplicated PCI and may prompt a group of high-risk patients that may require additional therapeutic interventions and longer in-hospital stay.

ClinicalTrials.gov Identifier: *NCT01268228*

Conflict of interest: *none declared*

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Prognozowanie wzrostu stężenia troponiny na podstawie elektrokardiogramu wewnątrzwieńcowego wykonanego w trakcie przezskórnej interwencji wieńcowej w obrębie rozwidlenia tętnic wieńcowych (dane z badania COronary SIde Branch Residual IschemiA and COllateralization Assessment Study; COSIBRIA & Co)

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Streszczenie

Wstęp: Nie określono dotychczas wpływu niedokrwienia okołozabiegowego na wynik wszczepienia stentu w obrębie rozwidlenia tętnic wieńcowych (przezskórna interwencja wieńcowa [PCI]).

Cel: Badanie przeprowadzono w celu ustalenia różnic w częstości występowania niedokrwienia wykrytego za pomocą elektrokardiografii wewnątrzwieńcowej (icECG) po zakończeniu PCI w obrębie rozwidlenia tętnic wieńcowych.

Metody: U chorych wykonano jednobiegunowy zapis icECG przed, w trakcie i po zabiegu wszczepienia stentu, a także po zakończeniu procedury w gałęzi bocznej (SB) i głównej (MB). Cewnik wieńcowy umieszczono we wszystkich dystalnych naczyniach o średnicy > 1,5 mm w celu mapowania dystalnych obszarów niedokrwienia. Badana populacja obejmowała chorych ze stabilną/niestabilną dławicą piersiową, u których stężenie troponiny I było podwyższone przed i po PCI.

Wyniki: Do badania włączono 147 chorych (68% mężczyzn, średnia wieku 64 ± 9 lat). U 142 pacjentów po zakończeniu PCI wykonano icECG z wszystkich leczonych okolic; u 36% chorych stwierdzono uniesienie odcinka ST (STE) w zapisie z MB, a u 31% stwierdzono STE w zapisie icECG z okolicy SB (p = 0,378). Badanie icECG cechowało się 82-procentową czułością i 81-procentową swoistością w wykrywaniu zwiększonego stężenia troponiny, a wartość predykcyjna dodatnia i ujemna wynosiły odpowiednio 81% i 83%. Niezależnymi czynnikami predykcyjnymi wzrostu stężenia troponiny wynoszącego > 5 × N (norma) były: płeć (w przypadku kobiet OR = 0,130; CI 0,017–0,995; p = 0,049), przebyty wcześniej zawał serca (OR = 33,23; CI 2,802–394,1; p = 0,005) oraz STE w zapisie icECG w MB lub SB, lub okluzja drugorzędowej SB (OR = 7,877; CI 2,474–25,07; p < 0,001), a niezależnymi czynnikami jakiegokolwiek wzrostu stężenia troponiny były: produkt podwójny SBPxHR (OR = 0,999; CI 0,999–1,00; p = 0,022) oraz STE w zapisie icECG w MB lub SB, lub okluzja drugorzędowej SB (OR = 9,762; CI 3,273–29,12; p < 0,001).

Wnioski: Badanie icECG jest wysoce czułą i swoistą metodą określania obszarów niedokrwienia i prognozowania zwiększonego stężenia troponiny I.

Słowa kluczowe: niedokrwienie, przezskórna interwencja wieńcowa, uniesienie odcinka ST, gałąź główna, gałąź boczna

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