ORIGINAL ARTICLE

Ischemic QRS prolongation as a biomarker of myocardial injury in STEMI patients

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Abstract

Background: Patients with acute coronary occlusion (ACO) may not only have ischemia-related ST-segment changes but also changes in the QRS complex. It has recently been shown in dogs that a greater ischemic QRS prolongation (IQP) during ACO is related to lower collateral flow. This suggests that greater IQP could indicate more severe ischemia and thereby more rapid infarct development. Therefore, the purpose was to evaluate the relationship between IQP and measures of myocardial injury in patients presenting with acute ST-elevation myocardial infarction (STEMI).

Methods: Seventy-seven patients with first-time STEMI were retrospectively included from the recently published SOCCER trial. All patients underwent a cardiac magnetic resonance (CMR) examination 2–6 days after the acute event. Infarct size (IS), myocardium at risk (MaR), and myocardial salvage index (MSI) were assessed and related to IQP. IQP measures assessed were; computer-generated QRS duration, QRS duration at maximum ST deviation, absolute IQP and relative IQP, all derived from a pre-PCI, 12-lead ECG.

Results: Median absolute IQP was 10 ms (range 0–115 ms). There were no statistically significant correlations between measures of IQP and any of the CMR measures of myocardial injury (absolute IQP vs IS, $r = 0.03$, $p = 0.80$; MaR, $r = -0.01$, $p = 0.89$; MSI, $r = -0.05$, $p = 0.68$).

Conclusions: Unlike previous experimental studies, the IQP was limited in patients presenting at the emergency room with first-time STEMI and no correlation was found between IQP and CMR variables of myocardial injury in these patients. Therefore, IQP does not seem to be a suitable biomarker for triaging patients in this clinical context.

KEYWORDS

acute coronary occlusion, electrocardiography, ischemia, QRS

1 | INTRODUCTION

Ischemic heart disease is one of the leading causes of death in the western world (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Acute myocardial infarction (AMI) usually results from an acute

coronary occlusion (ACO), requiring immediate revascularization in order to minimize infarct size (Reed, Rossi, & Cannon, 2017). Electrocardiography (ECG) is the most widely used method for triaging patients with suspected AMI in the emergency room as well as in pre-hospital settings. Ischemia-related ST-segment deviation on the

FIGURE 1 Depiction of ischemic QRS prolongation measurement method. During ischemia, when no J-point could be clearly distinguished due to ST-elevation a line was drawn through the peak of the R (or R' if it was present) wave and along 40% of the downslope between the R peak and the nadir of the ST segment. Reprinted from Almer et al. (2016), copyright (2016), with permission from Elsevier

presenting 12-lead ECG accompanied by symptoms and release of biochemical markers of myocardial injury, such as cardiac Troponin T (cTnT), constitute the diagnostic foundation for AMI (Kumar & Cannon, 2009).

Several studies have shown that acute myocardial ischemia is not only manifested as ST-segment deviation on the ECG, but can also affect the QRS complex in situations with severe ischemia, usually seen as terminal QRS distortion (Balci, 2009; Surawicz, Orr, Hermiller, Bell, & Pinto, 1997). Garcia-Rubira et al. have shown a relationship between terminal QRS distortion and poor collateral flow, using the Sclarovsky-Birnbaum ischemia severity grading system where grade 3 of ischemia (G3I) is associated with terminal QRS distortion (Birnbaum, Birnbaum, & Birnbaum, 2014; Garcia-Rubira et al., 2008). Recently, terminal QRS distortion, assessed as ischemic QRS prolongation (IQP) was shown to be related to lower collateral flow in a dog model of acute myocardial ischemia (Almer et al., 2016). This suggests a relationship between ischemia-related IQP and severity of ischemia and, potentially, the speed at which the infarction develops in the ischemic myocardium. To what extent these findings translate to patients in a clinical setting is yet to be determined.

Cardiovascular magnetic resonance imaging (CMR) is currently considered the reference standard for assessment of myocardium at risk (MaR), final infarct size (IS), and myocardial salvage index (MSI) in the setting of ACO. Previous studies in STEMI patients have shown that G3I is associated with larger IS (acute and 4 months post STEMI), larger MaR, lower MSI and more severe microvascular obstruction. (Hassell et al., 2016; Rommel et al., 2016; Valle-Caballero et al., 2016; Weaver et al., 2011) Furthermore, low collateral flow, and thereby more severe ischemia, has been correlated to lower MSI and more rapid infarct development on CMR (Hedström et al.,

2009). Thus, IQP might enable identification of STEMI patients with severe ischemia and at risk of rapid infarct development.

Therefore, the purpose of the current study was to evaluate how IQP and Sclarovsky Birnbaum ischemia grade is related to measures of myocardial injury, such as IS, MaR, MSI and left ventricular function as assessed by CMR in patients presenting with first-time acute STEMI.

2 | METHODS

2.1 | Study population

Patients included in this retrospective study were originally a part of the randomized controlled SOCCER (The Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion) trial. This trial was conducted at Skåne University Hospital, Sweden and was approved by the regional ethics committee. Oral informed consent was initially obtained from each patient in the ambulance and later completed in writing after PCI (Khoshnood et al., 2018).

The SOCCER population consisted of 160 normoxic (O_2 -saturation $\geq 94\%$) STEMI patients who underwent primary PCI and randomized to either standard oxygen therapy or no supplemental oxygen in the ambulance. A total of 95 patients underwent CMR 2–6 days after the PCI. Patients with a previous AMI or inability to make the decision to participate were excluded (Khoshnood et al., 2018).

Inclusion criteria in the current study were diagnostic CMR images and STEMI or STEMI equivalent criteria met (Martin et al., 2007; Wagner et al., 2009).

2.2 | ECG acquisition

Details regarding the ECG recordings have previously been described (Khoshnood et al., 2018). Briefly, while resting in a supine position, a 10 s, 12-lead ECG was acquired for each patient in the ambulance, at admission to the hospital prior to PCI and at discharge. For the dataset in the present study, digital ECGs were collected for all patients from the computerized patient records of Region Skåne (Meliör; Siemens, Germany) and from the SWEDEHEART quality registries RIKS-HIA or SCAAR. If no ECG from the ambulance was available, the first ECG (prior to PCI) recorded at arrival to hospital was used for analysis. The signals were digitized at a sampling rate of 1 kHz, with an amplitude resolution of 0.6 μV .

2.3 | ECG analysis

The acute ECG in the ambulance or first ECG after hospital admission before PCI was analyzed for IQP. The computer-generated QRS duration was noted for each ECG. All IQP measurements were made according to a single 12 lead ECG method (Elmberg et al., 2016).

In short, manual measurements were made from print outs of median beats of the ECG at a paper speed of 50 mm/s and gain of 10 mm/mV. The lead with the maximum ST-deviation as well as the

lead with the least ST deviation was determined. The latter was used as the reference lead. QRS duration (QRSd) was calculated for both leads. The difference between the QRSd measurements was calculated with a resulting QRS prolongation, referred to as aIQP (absolute IQP, in ms) and rIQP (relative IQP), normalized to QRSd at the reference lead. In addition, the QRSd in the reference lead was also measured on the discharge ECG and compared with the acute ECG.

If no distinct J point was present due to terminal distortion of the QRS complex, the QRS duration was estimated by superimposing a line descending from the peak of the R wave and following 40% of its amplitude (Almer et al., 2016). The estimated J point was defined as the intersection point of the superimposed line and the isoelectric line (Figure 1). If the final QRS waveform was an S wave, the same method was used but the line was superimposed from the peak of the S wave.

Measurements were made by two observers (JA, VE) blinded to the CMR data. In case of disagreement in the analysis, the differences were adjudicated in consensus together with a third observer (HE).

The Sclarovsky-Birnbaum Ischemia Grade was also determined from the acute ECG using the algorithm of the refined grading system described by Billgren et al. (Billgren et al., 2004). In short, each ECG was analyzed and assigned an ischemia grade from 1–3 where grade 3 of ischemia (G3I) is associated with terminal QRS distortion. The algorithm has previously been described in detail (Billgren et al., 2004).

For estimation of the acuteness of the ischemic ECG changes, the ECGs were also analyzed using the Anderson-Wilkins (AW) acuteness score, which has previously been described in detail (Heden et al., 2003). In short, each standard lead (except -aVR) with ≥ 0.1 mV ST elevation in the precordial leads, ≥ 0.05 mV in the limb leads, or abnormally tall T waves, were considered. An acuteness score (1–4) was assigned to each lead based on the presence or absence of a tall T wave or an abnormal Q wave, where 1 is least acute and 4 most acute. The final AW acuteness score was then calculated as the average score of the included leads.

2.4 | CMR image acquisition

The magnetic resonance image acquisition has been described earlier in detail (Khoshnood et al., 2018). In short, acquisition of imaging data was done with a Philips 1.5T Achieva or a Siemens 1.5T Avanto scanner.

First, scout images were acquired to locate the heart. For visualization of MaR, multi-slice and multi-phase contrast-enhanced (CE)-SSFP images were acquired covering the entire left ventricle. The CE-SSFP images were acquired approximately 5 min after intravenous administration of 0.2 mmol/kg of a gadolinium-based extracellular contrast agent (Dotarem, Gothia Medical, Billdal, Sweden). The slice thickness was 8 mm with no slice gap. In-plane resolution was typically 1.5×1.5 mm and the temporal resolution for the CE-SSFP images was 20–30 frames per cardiac cycle. For infarct visualization, late gadolinium enhancement (LGE) images corresponding to the CE-SSFP images were acquired approximately 15 min after injection of gadolinium. The LGE-images were acquired using an inversion-recovery gradient-recalled echo sequence with a slice thickness of 8 mm with no slice gap. In-plane resolution was typically 1.5×1.5 mm. Inversion time was manually adjusted to null the signal from viable myocardium.

2.5 | CMR image analysis

All quantitative CMR analysis was performed on short-axis images using the software Segment v.1.9 (<http://segment.heiberg.se>). MaR was calculated using contrast-enhanced (CE)-SSFP short-axis images for both scanners. This technique has previously been validated both experimentally and in the clinical settings (Nordlund et al., 2017; Sörensson et al., 2010). Endo- and epicardial borders were manually delineated in end-diastole (ED) and end-systole (ES) in all the CE-SSFP short-axis images. Areas with increased signal intensity were manually delineated as previously described (Sörensson et al., 2010). Infarct size was quantified from the LGE images using an automated computer algorithm taking partial volume effects into consideration (Heiberg et al., 2008). MaR and IS were expressed as a percentage of

FIGURE 2 Co-localized mid-ventricular left ventricular slices showing myocardium at risk, infarction and myocardial salvage in a patient after myocardial injury caused by occlusion-reperfusion of the right coronary artery. Green lines delineate epicardium, red lines endocardium, white line myocardium at risk, and orange line infarction. In the image to the right, the infarct delineation has been superimposed upon the myocardium at risk delineation where salvaged myocardium is indicated in white

the left ventricular myocardium and the MSI was quantified as $(1 - \text{IS}/\text{MaR}) \times 100\%$. Figure 2 shows an example of MaR, IS and MSI in a patient with an infarction in the right coronary artery (RCA) vessel territory.

For assessment of left ventricle ejection fraction (LVEF), endo- and epicardial borders were manually delineated in ED and ES in all the CE-SSFP short-axis images. LVEF (%) was calculated as $(100 \times [\text{ED volume} - \text{ES volume}]/\text{ED volume})$.

2.6 | Statistical analysis

Visual evaluation of distribution as well as comparisons of mean to median was used to evaluate if data were normally distributed. For parameters not normally distributed, non-parametric tests were applied. Continuous data are expressed as median (range) and categorical variables as proportions. For correlations of IQP to data from CMR, Spearman's rank correlation coefficient was calculated. When adjusting for timing variables and AW-score, multivariate analysis was used. When comparing groups, the Mann-Whitney *U* test was used. All statistical tests were 2-tailed and a *p*-value of <0.05 was considered to indicate statistical significance. SPSS version 23.0 for Macintosh was used for the statistical analyses.

3 | RESULTS

Ninety-five patients from the SOCCER study population, with CMR examinations of diagnostic quality were subject for inclusion and out of those, 77 patients met STEMI criteria and were ultimately included in the study. Patient characteristics are described in Table 1.

Figure 3 shows example ECGs of patient without (a) and with (b) significant IQP. Median aIQP was 10 (0–115) ms (Table 2). No significant correlations were found between any CMR variable of myocardial injury and computer-generated QRSd, QRSd at max STD or aIQP (Table 3). QRS duration in the reference lead was similar on the acute ECG as on the discharge ECG recorded at 3.3 (1.6–15.2) days from PCI (80 ms [60–120 ms] vs 80 ms [50–100 ms], $p = 0.526$). Anderson-Wilkins score did not correlate to any IQP measure or CMR variable of myocardial injury. Adjusting for the acuteness of the ischemia according to the AW score did not change the results. Adjusting for time from pain onset to ECG or time from ECG to PCI did not affect the results either.

Sixty-seven patients (87%) had a Sclarovsky-Birnbaum ischemia grade of 2 (G2I) and nine patients (12%) had G3I. One patient had only ST-depressions could therefore not be assigned any ischemia grade (Billgren et al., 2004). There was no significant difference between the G2I and G3I groups regarding any measure of IQP or any of the CMR variables for myocardial injury (Table 4).

The J point was distinct in 48 patients and QRSd at max ST-deviation did not differ when using the J point as offset compared to the Almer method offset in these patients (94 [75–190 ms] vs 95 [77–200 ms]; $p = 0.305$).

TABLE 1 Baseline characteristics

	<i>n</i>	Median (Range) or <i>n</i> (%)
Age (years)	77	66 (33–86)
Gender (female)	77	27 (35)
Smoking	77	
Smoker		28 (37)
Ex-smoker		27 (36)
Never smoked		21 (28)
Co-morbidities	77	
Heart failure		0 (0)
Hypertension		29 (38)
Diabetes		10 (13)
CVI		3 (4)
Ischemic heart disease		1 (1)
Atrial fibrillation		1 (1)
CABG		0 (0)
Culprit artery (angiography)	75	
LAD		38 (51)
LCX		5 (7)
RCA		32 (43)
Time from pain onset to ECG (min)	68	70 (6–305)
Time from ECG to PCI (min)	77	94 (63–205)

Note. CABG: coronary artery bypass grafting; CVI: cerebrovascular injury; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery.

4 | DISCUSSION

No correlations were found between IQP and CMR variables of myocardial injury in patients experiencing first-time STEMI. Furthermore, patients with G3I did not differ from G2I with regard to CMR markers of myocardial injury or IQP.

Several measures of the severity of ischemia in ACO have previously been suggested, such as the Sclarovsky-Birnbaum Ischemia Severity Grading System, (Birnbaum et al., 2014) and the morphology criteria of “tombstoning”, presented by Guo et al. (Guo, Yap, Chen, Huang, & Camm, 2000). QRS “tombstoning” morphology has been reported to correlate to mortality, in-hospital cardiogenic shock, ventricular tachycardia and ventricular fibrillation, in patients with anterior AMI (Balci, 2009). Furthermore, Sclarovsky-Birnbaum G3I has been correlated to IS (acute and at 4 months post STEMI), impaired myocardial salvage, and reperfusion injury (Birnbaum et al., 2014; Hassell et al., 2016; Rommel et al., 2016). Thus, although markers of terminal QRS distortion have been shown to be related to myocardial injury, IQP or G3I show no such correlation in the current study. Almer et al. (Almer et al., 2016) have previously shown a mean aIQP of 49 ± 57 ms (mean $\pm$ SD), in patients with a controlled experimental total coronary occlusion, compared to the median of 10 ms within the current study. This could potentially be explained

FIGURE 3 Electrocardiography examples from a patient with a LAD occlusion (a) and a patient with an RCA occlusion (b). (a) Twelve-lead ECG with maximum ST-deviation in lead V2 (1) of 0.525 mV. Since there is a distinguished J-point, it is used as offset, resulting in a QRS duration at maximum ST deviation of 90 ms. Lead V6 (2) was used as a reference, showing a QRS duration of 85 ms, resulting in an absolute ischemic QRS prolongation of 5 ms. (b) Twelve-lead ECG with maximum ST-deviation in lead III (3) of 0.425 mV. Since no clear j point can be determined, the intersect method for QRS duration was applied, resulting in a QRS duration at maximum ST deviation of 150 ms. Lead I (4) was used as a reference, showing a QRS duration of 82 ms, resulting in an absolute ischemic QRS prolongation of 65 ms

TABLE 2 Main variables

	n	Median (range)
MaR/LV mass (%)	77	31 (8–57)
IS (%)	77	15 (0–43)
MSI (%)	77	47 (3–100)
LVEF (%)	76	48 (29–73)
Computer-generated QRS duration (ms)	74	95 (76–152)
Reference QRS duration (ms)	77	80 (60–120)
QRS duration at max ST-deviation (ms)	77	95 (75–200)
Absolute IQP (ms)	77	10 (0–115)
Anderson-Wilkins acuteness score (1–4)	77	3.0 (1.0–4.0)

Note. IQP: ischemic QRS prolongation; IS: infarct size; LV: left ventricular; LVEF: left ventricular ejection fraction; MaR: myocardium at risk; MSI: myocardial salvage index.

TABLE 3 Spearman correlations for aIQP

	Correlation coefficient	p-value
MaR/LV mass (%)	−0.02	0.89
IS (%)	0.03	0.80
MSI (%)	−0.05	0.68
LVEF (%)	−0.16	0.34

Note. aIQP: absolute ischemic QRS prolongation; IS: infarct size; LV: left ventricular; LVEF: left ventricular ejection fraction; MaR: myocardium at risk; MSI: myocardial salvage index.

TABLE 4 Mann-Whitney test for Sclarovsky-Birnbaum ischemia grade 2 vs 3

	p-value
Computer-generated QRS duration	0.32
QRS duration at max ST-deviation	0.17
Absolute IQP	0.14
MaR	0.79
IS	0.46
MSI	0.24
LVEF	0.42

Note. IQP: ischemic QRS prolongation; MaR: myocardium at risk; IS: infarct size; MSI: myocardial salvage index; LVEF: left ventricular ejection fraction.

by less severe ischemia in the current study population. In comparison, a 2016 study by Rommel et al. (Rommel et al., 2016) found that G3I was correlated to IS, impaired MSI, and reperfusion injury in a STEMI population. The Rommel cohort consisted of 572 patients of which 186 (32%) had G3I, compared to 9 patients (12%) in the current study. Thus, the study population in the present study seems to differ with regards to the frequency of ischemia-related terminal QRS changes.

The findings in present study suggest that IQP is of limited use in the clinical context of ACO. It would, however, be of clinical importance to investigate if IQP could be used as an indicator of severe ischemia in the pre-hospital setting, when the patient is earlier in the ischemic injury process, which more resembles the experimental situation where IQP has been shown to be useful (Almer et al., 2016).

4.1 | Limitations

The results must be viewed in the light of several limitations. First, the small sample size could mean that the study was too underpowered to detect any correlation between IQP and CMR markers. Second, the ECG waveforms change as the infarct evolve which complicates the interpretation of the analysis. There are several factors that can have an effect on the infarct evolution; opening and closing of the culprit artery because of vasospasm, (Lanza, Careri, & Crea, 2011) lysing of the thrombus at the obstruction point, downstream embolic obstruction and hypotension impacting flow in the culprit artery but also in other diseased but non-obstructed arteries which may be suppliers of collaterals. Thus, an ECG obtained at a certain time point pre-PCI in this dynamic pathophysiological evolutionary process might not reflect the overall disease state and lead to misinterpretation of the severity of ischemia. Third, although there was a maximum time of 6 hr between pain onset and the analyzed ECG, this period varied among the patients. Thus, if the ECG was recorded late in the infarct evolution process, it is possible that severe ischemia, initially causing significant IQP, has resulted in infarction and less IQP at the time of the recording. In order to try to compensate for this, the AW acuteness score was assessed but did not change the results. Fourth, time from ECG to PCI varied. Adjusting the correlation between IQP and MSI with this time did, however, not change the results. Fifth, two methods were used for estimating the QRS complex offset, either with a distinct J point or using the "Almer method". As shown in simulation studies, the end of depolarization can be shifted to the ST segment even when the J point is distinct (Bacharova, Szathmary, & Mateasik, 2013). However, QRS duration at max ST-deviation did not differ between the two methods in the present study.

5 | CONCLUSION

Unlike previous experimental studies, there was only a small IQP in patients presenting at the emergency room with first-time STEMI and no correlation was found between IQP and CMR variables of myocardial injury in these patients. Therefore, IQP does not seem to be a suitable biomarker for triaging patients in this clinical context.

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