

# QRS broadening due to terminal distortion is associated with the size of myocardial injury in experimental myocardial infarction

Marina M. Demidova, MD, PhD,<sup>a, b, \*</sup> Alba Martín-Yebra, MSc,<sup>c, d</sup>  
Sasha Koul, MD, PhD,<sup>a</sup> Henrik Engblom, MD, PhD,<sup>a</sup> Juan Pablo Martínez, PhD,<sup>c, e</sup>  
David Erlinge, MD, PhD, FESC,<sup>a</sup> Pyotr G. Platonov, MD, PhD, FESC<sup>a</sup>

<sup>a</sup> Department of Cardiology, Lund University, Lund, Sweden

<sup>b</sup> Federal Research Center, St. Petersburg, Russia

<sup>c</sup> Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Aragón, Spain

<sup>d</sup> Electronics, Information and Bioengineering Department, Politecnico di Milano, Milan, Italy

<sup>e</sup> CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Zaragoza, Spain

## Abstract

**Introduction:** Not only repolarization, but also depolarization ECG indexes reflect the progression of ischemic injury. The aim was to assess the QRS duration and morphology dynamics during the prolonged coronary occlusion and their association with the myocardial area at risk (MaR) and final infarct size (IS).

**Methods:** In pigs, myocardial infarction was induced by inflation of an angioplasty balloon in the left descending artery (LAD), and ECG was continuously recorded. QRS duration was calculated on a beat-to-beat basis during the occlusion period. Single photon emission computed tomography (SPECT) was performed for the assessment of MaR, and IS was assessed by magnetic resonance imaging (MRI).

**Results:** All animals developed an anteroseptal infarction with MaR  $40 \pm 9\%$  and IS  $23 \pm 7\%$ . Two peaks of QRS widening were found in all animals: the early peak immediately after LAD occlusion and the late one  $17.7 \pm 4.1$  min later. No association was found between MaR and IS and either QRS width or the degree of QRS widening at the early peak. QRS duration on the late peak correlated with both MaR ( $r = 0.61$ ;  $p = 0.007$ ) and IS ( $r = 0.55$ ;  $p = 0.018$ ).

**Conclusion:** The QRS widening at the late peak, but not at the early peak, is associated with the size of myocardial injury, suggesting different underlying mechanisms.

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## Keywords:

Myocardial infarction; Ischemia; QRS broadening; QRS distortion; Myocardial injury

## Introduction

ST-segment deviation is well known to reflect ischemia. However, during the progression of ischemic injury, not only ventricular repolarization ECG indices, but also depolarization ones are involved, and changes in QRS complex are believed to be associated with severe ischemia [1].

Sclarowsky-Birnbaum classification has been suggested for grading the severity of acute ischemia, even though its use in clinical practice remains limited. The most severe, grade 3 ischemia is characterized not only by T-wave and ST-segment abnormalities, but also by the presence of terminal distortion of

the QRS complex [2]. It is hypothesized that the presence of terminal distortion is associated with either longer ischemia time or faster ischemia progression [3] due to poor collateral flow or absence of preconditioning [4].

Patients with terminal QRS distortion before reperfusion were shown to have larger infarct size [5,6], more prominent wall motion abnormalities and lower ejection fraction after reperfusion [7], as well as lower myocardial salvage [8,9]. The myocardial segments corresponded to ECG leads showing the QRS distortion had the maximum late gadolinium enhancement score, suggesting that QRS distortion shows severe and prolonged transmural infarction in the area corresponding to these ECG leads [6].

However, the data on the association between the terminal distortion and myocardial area at risk (MaR) before reperfusion are controversial. In some studies MaR was higher in patients with terminal distortion [4,10,11], while in

\* Corresponding author at: Department of Cardiology, Lund University, 22185, Lund, Sweden.

E-mail address: [marina.demidova@med.lu.se](mailto:marina.demidova@med.lu.se)

several other pretreatment MaR in patients with Grade 3 and Grade 2 was comparable [12–14].

In an experimental model of myocardial infarction we previously demonstrated the dynamic nature of changes in QRS duration and morphology and their association with ventricular fibrillation during coronary artery occlusion [15]. The aim of the present work was to assess the association between the degree of dynamic QRS widening during the prolonged coronary occlusion and the size of myocardial injury in porcine model.

## Methods

### Experimental protocol

The study was performed on a close-chest porcine model of myocardial infarction. The experimental preparation, study protocol and imaging technique were previously described in detail [16]. In brief, ischemia was induced in pigs by inflation of the angioplasty balloon in the left anterior descending coronary artery (LAD), immediately distal to the first diagonal branch. Occlusion was verified by repeated coronary angiography, and the duration of occlusion was 40 min.  $^{99m}\text{Tc}$ -tetrofosmin was administered intravenously at the 20th minute of occlusion for subsequent single photon emission computed tomography (SPECT). After 40 min of occlusion the balloon was deflated. TIMI-3 flow upon balloon deflation was achieved in all animals. The experiment was terminated after 4 h of reperfusion. Gadolinium-based contrast agent was administered intravenously 30 min prior to removal of the heart for subsequent magnetic resonance imaging (MRI). After 4 h of reperfusion the hearts were explanted and *ex-vivo* SPECT for assessment of area at risk (MaR) and MRI for assessment of infarct size (IS) were performed.

The study conforms to the Guide for the Care and Use of Laboratory Animals, US National Institute of Health (NIH Publication No. 85–23, revised 1996) and was approved by the local animal research ethics committee.

### ECG analysis

Continuous 12-lead ECG monitoring (“Kardiotechnica-04-8”, INCART, St. Petersburg, Russia) with a sampling rate of 1024 Hz and an amplitude resolution of 1.4  $\mu\text{V}$  was initiated before the occlusion and lasted throughout all the period of occlusion.

QRS complexes were automatically detected [17] and then visually and manually checked. After applying an automatic wavelet-based ECG delineator [17] to each of the precordial leads, beat-to-beat multilead QRS boundaries were computed. The delineator was set to automatically include the final slurring or notching of QRS, if present in any lead, as a part of the QRS complex.

The multilead boundaries of the QRS complex were then defined as the earliest QRS onset and latest QRS end in the 6 precordial leads. To minimize the effect of noise or delineation errors, a rule-based approach was used, setting the multilead QRS onset annotations at the earliest single-lead annotation in the 6 precordial leads, whose 3

nearest neighbors were within a 50 ms interval. Similarly, the QRS end was set at the latest single-lead annotation with the 3 nearest marks in a 60 ms interval.

This multilead approach, based on the post-processing of single-lead annotations, allows to obtain a robust measurement of the global QRS duration, considering the electrical activity projected in different leads. A more detailed description of the algorithm can be found elsewhere [18].

For each pig, QRS duration was computed on a beat-to-beat basis as the difference between the QRS onset and QRS end multilead marks along the 40-min occlusion period for each experimental animal. These series were then resampled by averaging QRS duration every 10 s. We assessed both the absolute value of QRS duration during the coronary occlusion and the difference between baseline QRS duration and QRS duration at the different time points during occlusion.

### Imaging

Ex vivo imaging of the heart was undertaken according to a previously described protocol [19]. Cardiac MRI and SPECT images were analyzed using freely available software (Segment v1.700, Medviso, Lund, Sweden, <http://segment.heiberg.se>) [20].

SPECT was used to assess the MaR as percent of left ventricular myocardium. 1000 MBq of  $^{99m}\text{Tc}$ -tetrofosmin was administered intravenously at the 20th minute of occlusion. Ex vivo imaging was performed with a dual head camera (Skylight, Philips, Best, the Netherlands) at 32 projections (40 s per projection) with a 64 X 64 matrix yielding a digital resolution of 5 X 5 X 5 mm. Iterative reconstruction using maximum likelihood-expectation maximization (MLEM) was performed with a low-resolution Butterworth filter with a cut-off frequency set to 0.6 of Nyquist and order 5.0. No attenuation or scatter correction was applied. Finally short and long-axis images were reconstructed. The endocardial and epicardial borders of the left ventricle that were manually delineated in the MR images were copied to the co-registered SPECT images (Fig. 1). A SPECT defect was defined as a region within the MRI-determined myocardium with counts lower than 55% of the maximum counts in the myocardium and expressed as a percentage of left ventricle as previously described [21].

The method used to assess IS by MRI has previously been described in detail [19,22,23]. In brief, a gadolinium-based contrast agent (Dotarem, *gadoteric acid*, Gothia Medical AB, Billdal, Sweden) was administered intravenously (0.4 mmol/kg) 30 min prior to removal of the heart. After removal, the heart was immediately rinsed in cold saline and the ventricles were filled with balloons containing deuterated water. MRI was performed using a 1.5 T MR scanner (Intera, Philips, Best, the Netherlands). T1-weighted images (repetition time = 20 ms, echo time = 3.2 ms, flip angle = 70° and 2 averages) with an isotropic resolution of 0.5 mm covering the entire heart were then acquired using a quadrature head coil.

The endocardial and epicardial borders of the left ventricular myocardium were manually delineated in short-axis *ex vivo* images. This defined the left ventricular myocardium. The infarcted myocardium was defined as the myocardium with a

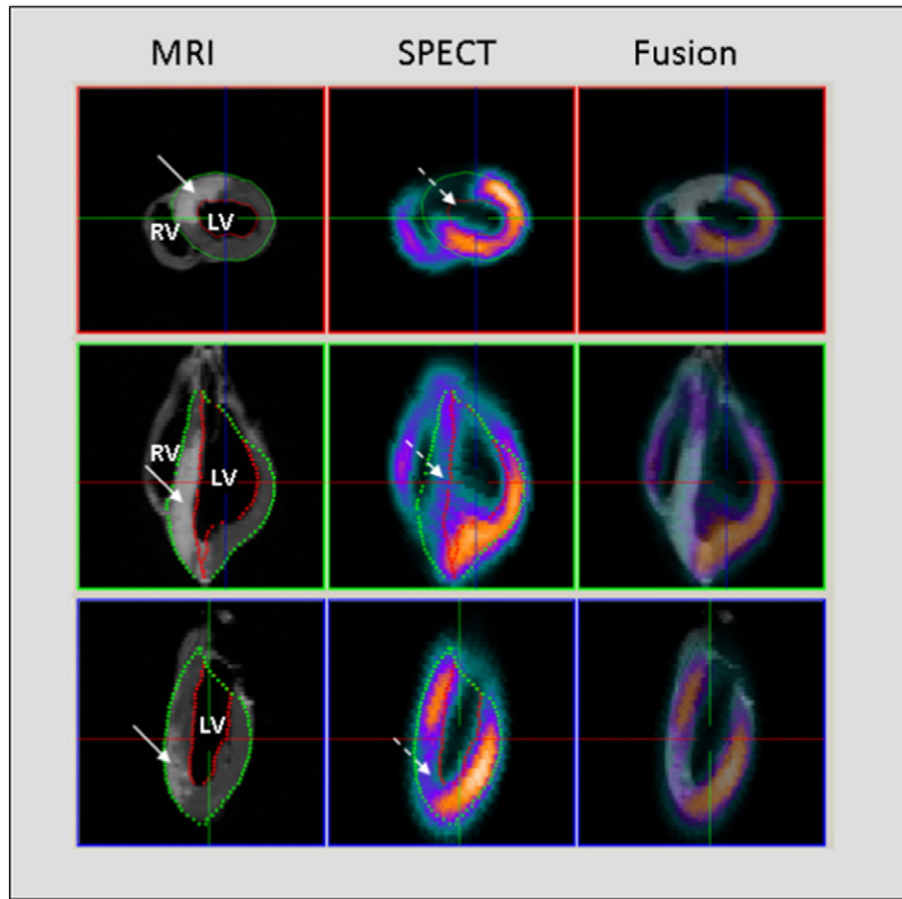


Fig. 1. Imaging of myocardium at risk and final infarct size after experimentally induced ischemia by occluding the left anterior descending coronary artery. **Left column:** Magnetic resonance imaging (MRI) performed for visualization of the anteroseptal infarction (solid arrows). Dark gray myocardium indicates viable myocardium and white indicates infarction. **Middle column:** Single photon emission computed tomography (SPECT) used to assess the myocardium at risk by visualization of the anteroseptal perfusion defect (dashed arrows). Warm colors indicate adequate perfusion and cold/absent colors indicate decreased/lack of perfusion. **Right column:** Fusion of MRI and SPECT images. The upper panel shows a mid-ventricular short-axis slice and the lower two panels show two long-axis slices. Endocardial and epicardial borders of the left ventricle were manually delineated in the MR images and fused with the co-registered SPECT images. LV = left ventricle, RV = right ventricle (from Demidova et al. *J Electrocardiol* 2011; 44 (1):74–81).

signal intensity  $>8SD$  above the average intensity of the non-affected remote myocardium [23]. The infarcted myocardium was then quantified as the product of the slice thickness and the area of hyperenhanced myocardium. The IS was expressed as percent of left ventricular myocardium.

#### Statistical methods

Data are presented as mean values  $\pm$  standard deviations if normally distributed or as median with interquartile range otherwise. Pearson's correlation was used for assessment of relationships between indices of QRS duration and MaR as well as IS. Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, Illinois, USA).

#### Results

Twenty-three experimental animals comprised the study group, 19 of them completed the study protocol. One pig was lost due to unsuccessful resuscitation for ventricular fibrillation during the occlusion period, three more from resistant VF or electromechanical dissociation during the reperfusion period. QRS data was available only for 18 out

of 19 pigs, because of the poor-quality signal. QRS dynamics during coronary occlusion was characterized by two peaks of QRS widening: immediately after LAD occlusion:  $4.4 \pm 1.8$  min and  $17 \pm 4.1$  min after occlusion start (Fig. 2). The QRS duration at baseline was  $76 \pm 11$  ms, at the early peak of QRS widening  $155 \pm 31$  ms, and at the late peak  $123 \pm 16$  ms ( $P < 0.001$ ). Significant interindividual differences were observed with regard to the magnitude of changes in QRS duration. The median difference between maximal QRS duration and QRS duration at baseline was 27 ms (interquartile range 16 ms).

In all experimental animals an anteroseptal infarction was developed as a result of LAD occlusion. The MaR was  $40 \pm 9\%$  (range 28–57%), and the IS was  $23 \pm 7\%$  (range 10–40%) of the left ventricle.

No association was found between the indexes of myocardial injury and either QRS duration or the degree of QRS broadening at the early peak (Table 1). The absolute value of QRS duration on the late peak correlated with both MaR ( $r = 0.61$ ;  $R^2 = 0.37$ ;  $p = 0.007$ ) and IS ( $r = 0.55$ ;  $R^2 = 0.30$ ;  $p = 0.018$ ). The degree of QRS broadening at the late peak was associated with MaR ( $r = 0.55$ ;  $R^2 = 0.31$ ;  $p = 0.017$ ) (Table 1, Fig. 3). We found no correlation

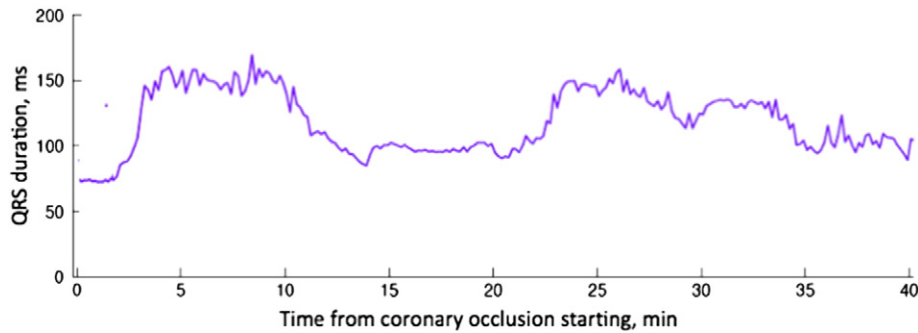


Fig. 2. Example of QRS duration dynamics during 40-min coronary occlusion.

between QRS duration and myocardial salvage index (IS/MaR).

**Discussion**

The main findings of this study are that QRS duration dynamically changed during progression of myocardial ischemia and necrosis with two peaks of QRS-broadening, and that the degree of QRS broadening at the late peak was associated with the size of myocardial injury.

In available literature we could not find any reports on the consecutive QRS duration dynamics during the course of STEMI. In clinical settings, the early QRS-widening might occur before the first contact with health-care professionals. However, the transient QRS broadening associated with alterations in QRS complex was described during short-time coronary occlusions during percutaneous transluminal coronary angioplasty (PTCA) [24–27].

Since the progression of MI in pigs is approximately 7 times faster than that in humans [28], 20 min of coronary artery occlusion in the porcine model corresponds to approximately 2–2.5 h evolving MI in clinical settings, and the analysis of QRS morphology and duration in this time period could correspond to prereperfusional ECG assessment in clinical settings. The presence of QRS prolongation on ECG before reperfusion was shown to be associated with increased mortality in the clinical settings [29,30]. The terminal distortion on ECG before reperfusion, which is usually classified as Sclarowsky-Birnbaum Grade 3 ischemia, was also shown to be associated with worse prognosis [5,31].

Whether QRS broadening recorded in our study reflects the same processes, as those described by Grade 3 ischemia, is discussible. Some representative examples of QRS

complexes at the different time points of coronary occlusion are shown in Fig. 4. The terminal part of QRS mostly contributed to QRS broadening, and in most cases QRS broadening was accompanied by the appearance of the slurring or notches at the terminal portion of QRS. The recently published consensus paper noticed that the measurement of the QRS duration from the 12-lead ECG should ideally be done from the leads without slurring and notching [32], however it was impossible in our study because of the automated measurement of QRS duration, which was based on multilead approach. It has to be taken into account that significant ST-elevation during acute myocardial ischemia makes delineation of QRS end a challenging task, since it appears as a gradual transition between QRS and ST, which leads to development of alternative methods of QRS measurements [33]. Because of that, the wavelet-based delineator had to be adapted to this model of acute ischemia and automatic delineation was set to include final slurring or notching, if present, into the QRS complex. However, from our study based on the closed-chest porcine model of myocardial infarction, the contribution of repolarization and depolarization abnormalities into QRS broadening could not be elucidated.

The mechanisms of the terminal QRS distortion is believed to be explained by a prolongation of the electrical conduction in Purkinje fibers in the ischemic region [34]. Purkinje fibers are less sensitive to ischemia than the contracting myocytes [35]. The terminal QRS distortion is thought to reflect the conduction delay caused by severe regional ischemia.

Our model of myocardial infarction did not presume preconditioning, and the localization of coronary occlusion and the time since occlusion start was similar in all experimental animals. It is known that QRS prolongation is more typical for left circumflex artery (LCx) occlusions. LCx perfuses the posteriolateral area of the left ventricle, which is one of the last areas to be activated [36]. LAD perfuses ventricular septum, which was shown to be the first area to be depolarized, and thus conduction delay due to LAD occlusion may not be recognizable on the surface ECG if ischemia extent is limited [36–38]. A plausible explanation of marked QRS prolongation in our study is that the great extent of ischemia due to proximal LAD occlusion and, possible, due to differences between species as heart geometry and its position in the chest differs between humans and pigs.

Table 1  
The correlation between indexes of QRS duration during coronary occlusion and indexes of myocardial injury.

	MaR		IS	
	r	p	r	p
Max QRS duration early peak	0.48	0.058	0.38	0.147
Difference QRS duration baseline -early peak	0.50	0.051	0.34	0.197
Max QRS duration late peak	<b>0.61</b>	<b>0.007</b>	<b>0.55</b>	<b>0.018</b>
Difference QRS duration baseline- late peak	<b>0.55</b>	<b>0.017</b>	0.41	0.088

Abbreviations: MaR – myocardial area at risk; IS – infarct size.

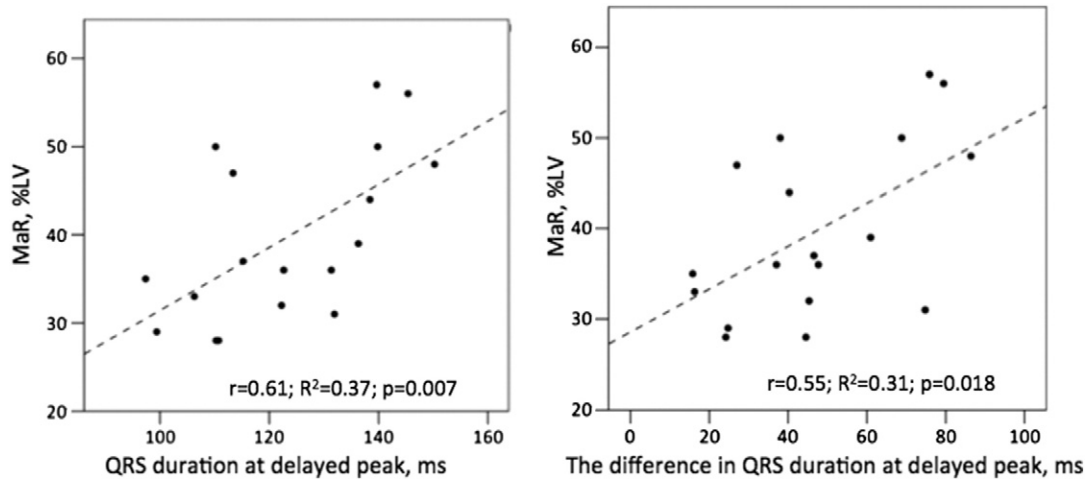


Fig. 3. Association between myocardial area at risk and the degree of QRS-widening at the late peak. Abbreviations: MaR – myocardial area at risk.

The dynamic nature of changes in QRS duration in our study and the absence of association between the indexes of myocardial injury and QRS-broadening in the very early minutes after coronary occlusion allows us to suppose plausible different underlying mechanisms responsible for the early and late peaks of QRS broadening.

The anaerobic glycolytic process would have produced sufficient ATP for survival of the “stunned” myocardial cells during a 15 to 20 min period of coronary occlusion [39]. Therefore, QRS-broadening in the very early minutes after coronary occlusion occurred in the presence of acute ischemia but not due to development of necrotic substrate. It could have been caused by slow “intra-ischemic” conduction in the sub-endocardial layer during the time of maximally severe ischemia. The transience of the first episode of early QRS widening could have been caused by the emergence of collateral blood flow.

The collateral flow has been previously reported to play a crucial role in preventing terminal QRS distortion [40,41]. Unfortunately, the collateral flow, which could influence the ischemia progression, was not assessed during coronary angiography, and therefore has to be considered as study

limitation. On the other hand, collateral flow in pigs comparing to that in dogs is known to be limited [42].

The mechanisms underlying the appearance of the late period of QRS widening are also obscure. It occurred when the onset of myocardial necrosis would be expected. We can speculate that QRS widening at this stage may be directly related to slow peri-infarction conduction, when this layer becomes the very first to infarct. The transience of the 2nd episode could have been caused by spread of the infarction into the deeper myocardial layers.

## Conclusion

In the porcine model of myocardial infarction, QRS duration undergoes dynamic changes during the progression of acute myocardial ischemia and necrosis with two distinct peaks of QRS broadening occurring immediately after coronary artery occlusion and around 20th minute of occlusion. The late QRS broadening, but not the early one, is associated with the size of myocardial injury and myocardium at risk, supposing plausible different mecha-

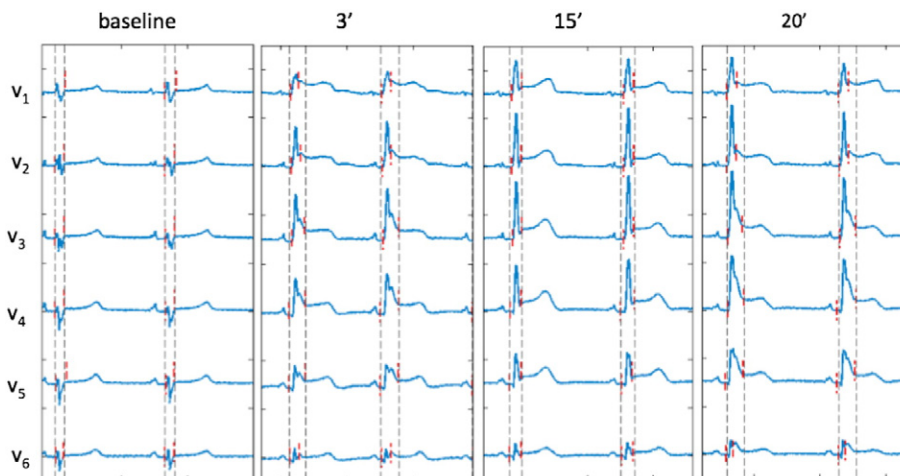


Fig. 4. Some representative examples of QRS complexes at the different time-points of coronary occlusion.

nisms underlying QRS widening at different stages of ischemic injury progression.

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