Proximal embolic protection and biomarkers of reperfusion in ST-segment elevation myocardial infarction
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Quantitative blush evaluation during primary percutaneous coronary intervention predicts functional and contrast-enhanced cardiovascular magnetic resonance outcomes in patients with ST-segment elevation myocardial infarction


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Catheter Cardiovasc Interv.; accepted
Abstract

Objectives
We investigated whether the Quantitative Blush Evaluator (QuBE) value predicts functional and contrast-enhanced cardiovascular magnetic resonance (CMR) outcomes at 4-6 months after primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI).

Background
QuBE is a computer-assisted open source program to quantify myocardial reperfusion. While a higher QuBE value is associated with improved myocardial reperfusion measures and lower 1-year mortality, the association with intermediate functional parameters after STEMI has not yet been investigated.

Methods
QuBE values were quantified retrospectively on angiograms of patients enrolled in the ancillary CMR study of the PROximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation (PREPARE) trial. QuBE en CMR outcomes were independently assessed by reviewers blinded to clinical data.

Results
A higher QuBE value was significantly associated with a smaller left ventricular (LV) end-diastolic and end-systolic volume, a higher LV ejection fraction and systolic wall thickening in the infarct area, and a smaller final infarct size and extent of transmural segments (p≤0.008). In a multivariable model including age, gender, infarct location, time to treatment, history of myocardial infarction, and post-procedural Thrombolysis In Myocardial Infarction flow grade, only the QuBE value and infarct location remained as independent predictors of LV ejection fraction (p=0.018 for QuBE value).

Conclusions
Higher QuBE values are independently associated with improved functional and contrast-enhanced CMR outcomes including LV ejection fraction at 4-6 months after primary PCI and may therefore aid in identifying high-risk patients who benefit most from adjunctive therapies sustaining myocardial function after PCI.
Introduction

Reperfusion of the myocardial microvasculature is an important prognostic factor in the short- and long-term outcome of patients with ST-segment elevation myocardial infarction (STEMI) after successful primary percutaneous coronary intervention (PCI). In patients undergoing primary PCI, suboptimal myocardial reperfusion is associated with a larger enzymatic infarct size, a lower left ventricular (LV) ejection fraction prior to hospital discharge, and increased long-term cardiac mortality.\textsuperscript{1,2} The Quantitative Blush Evaluator (QuBE) is a computer-assisted quantification technique to measure myocardial reperfusion after primary PCI on the coronary angiogram in STEMI patients. We have previously reported that determination of the QuBE value using this freely available program is feasible and reproducible on angiograms from STEMI patients at various primary PCI centers.\textsuperscript{3,4} Furthermore, a higher QuBE value was strongly associated with improved angiographic and electrocardiographic markers of reperfusion, smaller enzymatic infarct size, and lower 1-year mortality. In this study, we investigated whether the QuBE value could predict intermediate functional outcomes as determined with the current golden standard cardiovascular magnetic resonance (CMR) in STEMI patients at 4 to 6 months after primary PCI.

Methods

Patient selection

We studied STEMI patients undergoing primary PCI who were enrolled in the ancillary CMR study of the PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation (PREPARE) trial.\textsuperscript{5,6} This was a two-centre randomized clinical trial, in which patients with STEMI were assigned to primary PCI with combined proximal embolic protection and thrombus aspiration (Proxis, St. Jude Medical, St Paul, MN, USA) or to primary PCI alone. The detailed study design and results have been published previously.\textsuperscript{5,6} In brief, patient inclusion criteria consisted of onset of symptoms less than 6 hours before presentation, electrocardiographic evidence of persistent ST-segment elevation of at least 0.2 mV in two or more contiguous
leads, Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 to 1 on diagnostic angiography, and a coronary anatomy suitable for application of the Proxis system. Patient exclusion criteria included age under 18 years, contraindications to the use of glycoprotein IIb/IIIa receptor antagonists, a co-existent condition associated with a limited life expectancy, prior coronary artery bypass grafting or thrombolytic therapy, previous myocardial infarction in the same myocardial area, and an ECG unsuitable for ST-segment resolution analysis. Angiographic exclusion criteria were left main occlusion or stenosis of more than 30%, severe proximal calcifications, an infarct-related artery <2.5 mm in diameter, and a proximal lesion location resulting in an insufficient landing zone for the Proxis system.

Primary end point of the PREPARE trial was ST-segment resolution assessed from continuous digital 12-lead ECG/Holter monitoring at an independent core lab. As part of an ancillary study, patients underwent CMR at 4 to 6 months after the index procedure. CMR imaging was performed with a 1.5T clinical scanner (Sonato/Avanto, Siemens, Erlangen, Germany). Functional assessment was studied with a standard cine steady-state free precession sequence and late gadolinium enhancement (LGE) images were acquired after administration of a gadolinium-based contrast agent (0.2 mmol/kg, Magnevist, Schering AG, Berlin, Germany). All functional and LGE images were analyzed as described previously. The CMR data were analyzed by a single experienced physician (JDEH) who was blinded to clinical and angiographic data using the MASS software (version 5.1, MEDIS Medical Imaging Systems, Leiden, The Netherlands). Clinical follow-up was performed at 6 months after the index event. All reported clinical end points have been previously defined. Clinical end points included death, spontaneous or procedural myocardial infarction, stroke, and percutaneous or surgical target vessel revascularization. The current retrospective analysis included all patients who were enrolled in the ancillary CMR study with an angiogram suitable for QuBE.

Angiographic analysis with the QuBE program

The QuBE program (available as open-source software at http://qube.sf.net) has been developed and described previously by Vogelzang et al. In brief, the operator indicates a polygonal shape (the region of interest) that contains the infarct-related
Quantitative blush evaluation predicts cardiac function in STEMI

area on the angiogram acquired immediately after PCI (Figure 1, left panel). Each frame is corrected for panning motions and all pixels in the polygon are divided into blocks of 5 x 5 pixels. The value of each pixel block is proportional to the amount of darkening compared to a wider area around that block. This automatically marks larger structures such as the diaphragm and large vessels as part of the background. The value of a single frame is calculated as the average of the most darkened 50% of pixel blocks. The QuBE value is obtained by summing the maximum increase and decrease of the single frame values during the first 10 seconds (125 frames in our configuration). This representation of the myocardial contrast density in the area of interest shows a typical curve (Figure 1, right panel). Adequate measurement of the QuBE value could be performed if data acquisition begins before the start of contrast injection and continues at least 10 seconds thereafter. A right anterior oblique (RAO -30°) projection was used for assessment of the myocardial blush. For the left anterior descending artery, a left anterior oblique (LAO -60° to 90°) was also suitable for the QuBE measurement. Angiographic projections that deviated from those proposed up to 10° were allowed as well.

Coronary angiograms (Philips Medical Systems, Best, The Netherlands) were acquired at two catheterization laboratories (Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, and Institut de Cardiology de Montréal, Montréal, Canada). The QuBE value was measured by a single experienced physician (YLG) blinded to clinical and CMR data at the core lab (University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands).
Figure 1. Screenshot of the QuBE program. Image showing coronary angiograms of a right coronary artery (upper) and left anterior descending artery (lower). On the left, a specific blush run is loaded into the QuBE program and a polygonal shape is drawn containing the infarct-related area. The myocardial contrast density in the area indicated on this run in each single frame is represented graphically on the curve on the right, which shows a typical curve. The QuBE value is calculated as the sum of the maximum increase and maximal decrease of the single frame values during the first 125 frames. QuBE = Quantitative Blush Evaluator.
Quantitative blush evaluation predicts cardiac function in STEMI

Statistical analysis
Values are expressed as mean (±standard deviation) or median (25th – 75th percentile) for continuous data and as counts (percentage) for categorical variables. For the baseline characteristics, the QuBE values were divided into tertiles and treated as an ordinal variable. Outcomes over ordered categories were compared using the Jonckheere-Terpstra test for continuous data and the Cochran-Armitage test (p for trend) for categorical data. To investigate clinical predictors of the QuBE value, we performed multivariable linear regression analysis with a backward selection procedure including all significant variables as reported previously and baseline variables of the current study if p<0.10. Associations between the QuBE value and CMR outcomes were assessed with univariable linear regression analysis. To identify parameters independently associated with LV ejection fraction, we composed a multivariable linear regression model using a backward selection procedure that included the variables age, gender, infarct location, time to treatment, a history of myocardial infarction, post-procedural TIMI flow as well as the QuBE value. Statistical significance was considered as a two-tailed p value less than 0.05. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.2 was used for all statistical analyses.

Results
Out of the 284 patients enrolled in the PREPARE trial, CMR imaging was performed in 200 patients (Figure 2). In 35 patients, the angiogram was not assessable with the QuBE program due to excess movement of the diaphragm or panning motions, absence of a specific blush sequence, technical quality problems, or too much overlap of a non-infarct-related artery in the blush area of interest. The remaining 165 patients (83%) were included in the present analysis.
Figure 2 Flow chart of PREPARE patients. Of the total 284 patients included in the PREPARE trial, 200 patients were included in the ancillary CMR study. After exclusion of 35 patients who had a coronary angiogram not assessable with QuBE, the remaining 165 patients entered the current analysis. PREPARE = PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation; CMR: cardiovascular magnetic resonance; QuBE = Quantitative Blush Evaluator.

Baseline characteristics and predictors of the QuBE value
The baseline clinical and angiographic characteristics of these patients are summarized in Table 1 according to tertiles of QuBE values (first tertile 10.5 (range 4.1 – 12.8), second tertile 15.4 (12.9 – 17.6), third tertile 20.1 (17.6 – 32.9)). Patients with a lower QuBE value were more frequently women and had a slightly higher body mass index (BMI), higher heart rate, and a higher rate of infarction in the left coronary system. In a multivariable regression model including age, BMI, heart rate, baseline as well as post-procedural TIMI flow, and infarct location, the independent predictors of the QuBE value were BMI (coefficient = -3.5, SE 0.1, p=0.002) and infarct location (coefficient = -2.2, SE 0.9, p=0.012, r squared 0.12).
**Functional cardiovascular magnetic resonance outcomes by QuBE tertiles**

A higher QuBE value was significantly associated with improved functional CMR outcomes at 4 to 6 months including LV end-diastolic and end-systolic volumes, LV ejection fraction, and systolic wall thickening in the infarct area (p≤0.008, Table 2). As illustrated in Table 3, patients had a lower LV end-diastolic volume with increasing tertiles of QuBE (192±59mL, 190±46mL, and 170±37mL, respectively). Similarly, the LV end-systolic volume was lower for a higher QuBE tertile (102±53mL, 97±35mL, and 81±28mL, respectively). Patients in the first QuBE tertile had an LV ejection fraction of 49±13%, those in the second tertile 50±9%, and those in the third tertile had an LV ejection fraction of 53±9%. Patients in the third tertile had better systolic wall thickening in the infarct area compared with patients in the first and second tertile (1st QuBE tertile 1.8±1.2mm 2nd QuBE tertile 2.1±1.1mm, and 3rd QuBE tertile, 2.6±1.3mm, respectively).
Table 1  Baseline Characteristics of the 165 PREPARE patients with QuBE and CMR data according to tertiles of QuBE

| QuBE value (range) | 1st QuBE tertile (n=56) | 2nd QuBE tertile (n=54) | 3rd QuBE tertile (n=55) | p  
|--------------------|--------------------------|--------------------------|--------------------------|----
| Age, yrs           | 56 (49 - 67)             | 56 (46 - 61)             | 58 (49 - 64)             | 0.785  
| Male sex           | 41 (73%)                 | 49 (91%)                 | 49 (89%)                 | 0.022  
| History            |                          |                          |                          |  
| Diabetes mellitus  | 3 (5%)                   | 7 (13%)                  | 0 (0%)                   | 0.244  
| Hypertension       | 12 (21%)                 | 9 (17%)                  | 15 (27%)                 | 0.461  
| Hypercholesterolemia | 4 (7%)                  | 9 (17%)                  | 6 (11%)                  | 0.531  
| Myocardial infarction | 2 (4%)                 | 4 (7%)                   | 0 (0%)                   | 0.321  
| PCI                | 0 (0%)                   | 4 (7%)                   | 2 (4%)                   | 0.303  
| Cerebrovascular disease | 2 (4%)                 | 2 (4%)                   | 1 (2%)                   | 0.592  
| Cardiovascular disease in family | 19 (34%)          | 20 (37%)                  | 27 (49%)                 | 0.105  
| Smoking            | 5 (9%)                   | 11 (20%)                 | 6 (11%)                  | 0.752  
| Current smoking    | 39 (70%)                 | 32 (59%)                 | 36 (66%)                 | 0.641  
| Preinfarction angina | 0 (0%)                  | 5 (9%)                   | 2 (4%)                   | 0.338  
| Body mass index    | 27.2 (25.3 - 29.3)       | 26.3 (24.9 - 29.8)       | 25.6 (24.1 - 27.8)       | 0.010  
| Systolic blood pressure, mm Hg | 136 (120 - 156) | 121 (107 - 155) | 131 (117 - 153) | 0.472  
| Diastolic blood pressure, mm Hg | 80 (68 - 92) | 77 (70 - 89) | 80 (70 - 88) | 0.812  
| Heart rate, bpm    | 75 (65 - 91)             | 70 (58 - 78)             | 66 (56 - 83)             | 0.019  
| No. of diseased vessels | 1         | 39 (70%)                 | 38 (70%)                 | 39 (71%)  
| 2                  | 14 (25%)                 | 14 (26%)                 | 12 (22%)                 |  
| 3                  | 3 (5%)                   | 2 (4%)                   | 4 (7%)                   |  
| Infarct-related vessel | 23 (41%)          | 17 (32%)                  | 16 (29%)                 | 0.011  
| Left anterior descending artery | 7 (13%)         | 2 (4%)                    | 2 (4%)                   |  
| Left circumflex artery | 26 (46%)          | 35 (65%)                  | 37 (67%)                 |  
| Right coronary artery | 0 (0%)          | 1 (2%)                    | 2 (4%)                   | 0.052  
| Baseline TIMI flow | 0                  | 54 (96%)                  | 51 (94%)                 | 48 (87%)  
| 1                  | 2 (4%)                   | 2 (4%)                   | 5 (9%)                   |  
| 2                  | 0 (0%)                   | 1 (2%)                   | 2 (4%)                   |  
| Symptom onset to balloon, min | 163 (138 - 230) | 160 (128 - 227) | 150 (116 - 219) | 0.087  

Data are expressed as mean±SD, median (interquartile range), or number of patients (percent). Data for angiographic signs of distal embolization were available in 227/229 patients. GP = glycoprotein; TIMI = Thrombolysis in Myocardial Infarction.
Table 2 Univariable association of the QuBE value with functional and contrast-enhanced CMR characteristics

<table>
<thead>
<tr>
<th>QuBE Coefficient (SE)</th>
<th>p</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>-1.908 (0.692)</td>
<td>0.006</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>-1.984 (0.573)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>0.490 (0.147)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic wall thickening in infarct</td>
<td>0.064 (0.023)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Late gadolinium enhancement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct size (g)</td>
<td>-0.411 (0.137)</td>
<td>0.003</td>
</tr>
<tr>
<td>Extent of transmural segments (% of segments)</td>
<td>-0.558 (0.156)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. CMR = cardiovascular magnetic resonance; LV = left ventricular.

Table 3 Functional Cardiovascular Magnetic Resonance Outcomes by QuBE tertiles

<table>
<thead>
<tr>
<th>QuBE value</th>
<th>LV end-diastolic volume (mL)</th>
<th>LV end-systolic volume (mL)</th>
<th>LV ejection fraction (%)</th>
<th>Systolic wall thickening in infarct area (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>0.050</td>
<td>p</td>
<td>0.042</td>
</tr>
<tr>
<td>1st tertile</td>
<td>192 ± 59</td>
<td>102 ± 53</td>
<td>49 ± 13</td>
<td>1.8 ± 1.2</td>
</tr>
<tr>
<td>2nd tertile</td>
<td>190 ± 46</td>
<td>97 ± 35</td>
<td>50 ± 9</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>3rd tertile</td>
<td>170 ± 37</td>
<td>81 ± 28</td>
<td>53 ± 9</td>
<td>2.6 ± 1.3</td>
</tr>
</tbody>
</table>

Data are expressed as mean (±SD). LV=left ventricular; QuBE=quantitative blush evaluator.

Contrast-enhanced cardiovascular magnetic resonance outcomes by QuBE tertiles

LGE measurements were available in 161 of the 165 patients. A higher QuBE value was related to a smaller final infarct size and extent of transmural segments (p≤0.003, Table 2). As shown in Table 4, patients in the first QuBE tertile had a mean final infarct size of 13.7±11.6g, whereas those in the third tertile had a final infarct size of 9.7±8.1g. The patients in the second tertile had a mean final infarct size of 11.3±8.6g. Segmental analysis of the contrast-enhanced CMR images showed that patients in the third tertile had less extent of transmural segments compared with patients in the first and second tertile (1st QuBE tertile 10.9±13.4% of segments, 2nd QuBE tertile 7.6±9.2% of segments, 3rd QuBE tertile 5.1±9.1% of segments, respectively).
Table 4 Contrast-enhanced Cardiovascular Magnetic Resonance Outcomes by QuBE tertiles

<table>
<thead>
<tr>
<th>QuBE value</th>
<th>Final infarct size (g)</th>
<th>p</th>
<th>Extent of transmural segments (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st tertile</td>
<td>13.7 ± 11.6</td>
<td>0.095</td>
<td>10.9 ± 13.4</td>
<td>0.027</td>
</tr>
<tr>
<td>2nd tertile</td>
<td>11.3 ± 8.6</td>
<td></td>
<td>7.6 ± 9.2</td>
<td></td>
</tr>
<tr>
<td>3rd tertile</td>
<td>9.7 ± 8.1</td>
<td></td>
<td>5.1 ± 9.1</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean (±SD). QuBE=quantitative blush evaluator.

**Predictors of LV ejection fraction**

In a multivariable model including age, gender, infarct location, time to treatment, history of myocardial infarction, post-procedural TIMI flow grade as well as the QuBE value, the QuBE value remained an independent predictor of LV ejection fraction at 4 to 6 months (coefficient=0.329 for every unit increase in QuBE, SE=0.138, p=0.018, r squared 0.218) next to infarct location. The test for interaction between infarct location and the QuBE value was not significant (p=0.252).

**Clinical follow-up at 6 months by QuBE tertiles**

At 6 months’ follow-up, 4 patients died: 2 in the first tertile, and 1 in each of the higher tertiles (p=0.55). Major Adverse Cardiac en Cerebral Events occurred in 8 (10%) of the patients in the first tertile, in 6 (5%) in the second, and in 5 (7%) in the third tertile (p=0.39).

**Discussion**

The principal finding of this study is that higher QuBE values quantified after primary PCI are associated with improved functional as well as contrast-enhanced CMR outcomes at 4 to 6 months. In the STEMI patients studied, a higher QuBE value was linearly associated with smaller LV end-diastolic and end-systolic volumes, a higher LV ejection fraction and systolic wall thickening in the infarct area, and a smaller final infarct size and extent of transmural segments. After correction for known predictors of LV function and infarct size including age, gender, infarct location, time to treatment, a history of myocardial infarction, and post-procedural TIMI flow grade,
a higher QuBE value remained independently associated with improved LV ejection fraction at 4 to 6 months.

Myocardial reperfusion after primary PCI is an important prognostic factor in STEMI patients and is associated with enzymatic infarct size, LV ejection fraction prior to hospital discharge, and long term survival.\textsuperscript{1,2,9,10} For these reasons, the myocardial blush grade is used as a surrogate or functional end point in randomized clinical trials. However, visual grading is subjective and operator-dependent, and results in a rough classification into four groups. We have previously reported that myocardial blush quantification with the QuBE program is feasible and applicable on angiograms of patients enrolled in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) and achieved excellent intra- and inter-observer agreement rates of 99.7% and 97.7%, respectively.\textsuperscript{3} In these unselected STEMI patients, the QuBE value was associated with conventional measures of myocardial perfusion including visually scored myocardial blush grade, ST-segment resolution, in-hospital enzymatic infarct size, and mortality at one year. Its discriminating power with respect to one-year mortality was also present in the subset of patients with successful and optimal reperfusion therapy (TIMI 3 flow and myocardial blush grade 2 or 3). More recently, we have reported that the QuBE program is also feasible on angiograms from patients included in the PREPARE trial that were acquired at other catheterization laboratories and confirmed the association of the QuBE value with conventional measures of myocardial reperfusion.\textsuperscript{4} The findings of the current study add to this knowledge by reporting the value of QuBE in predicting intermediate functional outcomes.

CMR imaging is considered the golden standard in the assessment of the combination of LV ejection fraction and final infarct size,\textsuperscript{11-13} both of which are related to long-term mortality. However, this comprehensive technique is technically demanding, time-consuming, and expensive. In contrast, QuBE is a readily available simple computer program that can be used in the catheterization laboratory by anyone with knowledge of the coronary anatomy and usually requires no longer than a minute to assess. In the current study, the QuBE program was applicable in 83%, a rate almost similar to that reported in the TAPAS trial,\textsuperscript{3} while these angiograms were acquired at 2 different PCI sites and were also not specifically recorded for quantitative analysis. To further
improve its clinical applicability, several issues should be taken into account. First, diaphragm or panning movement, accounting for more than half of the excluded angiograms, can be put to a minimum by instructing the patient to hold his breath and by keeping the table still. Second, dedicated blush sequences should be recorded in all patients. Finally, overlap of a non-infarct-related artery into the area of interest can usually be minimized by choosing a different projection. Therefore it is expected that, with these efforts, a QuBE value can be obtained from almost all patients.

The relationships between QuBE and functional and contrast-enhanced CMR parameters observed in this study could have been weakened as a result of the PREPARE inclusion criteria, requiring a landing zone for the Proxis system. Patients with a myocardial infarction related to an ostial coronary artery occlusion were therefore not included. This resulted in more myocardial infarctions related to a right coronary artery (RCA) (60%) compared with a general STEMI population and led to exclusion of very proximal infarct-related left anterior descending artery (LAD) and left circumflex artery (LCx) lesions. The RCA typically perfuses a much smaller amount of LV myocardium and as such is associated with much smaller final infarct size. Also, patients with a non-proximal LAD- or LCx-related lesion have a much smaller LV myocardium at risk. Nevertheless, the QuBE value was highly associated with several functional CMR outcomes in this cohort with a relatively small expected variability in functional outcomes.

Considering the deleterious effect of impaired myocardial perfusion on infarct size, LV function and long-term clinical outcome, its clinical course may be improved by identifying high-risk patients as early as possible and developing and intensifying specific treatment regimens in this subgroup. The QuBE program can be adopted easily in the catheterization laboratory and enables quantitative risk assessment in clinical practice. Next to being readily available once implemented, the QuBE value provides a risk indicator (long) before other indicators including enzymatic infarct size during hospital stay and functional recovery at follow-up can be determined. QuBE may not replace more technically sophisticated techniques, but may serve as a practical marker for myocardial perfusion and as a surrogate end point in clinical trials, where a functional or surrogate end point is necessary that is able to detect a difference between treatment groups, especially with small numbers of patients.
Further investigations should be directed at the reproducibility of these findings in other centres, validation of the prognostic utility in larger-scaled studies, and cut-off values that assist in interpretation in clinical practice.

**Study limitations**

First, as quantitative analysis with the QuBE program was not available when this clinical trial was designed, this analysis was not pre-specified. Nevertheless, QuBE was still applicable in the majority of these angiograms that were not specifically made for quantitative analysis. Second, any quantification tool suffers from some level of subjectivity. QuBE is dependent on some actions of the operator, such as the choice of angiographic view and determined region of interest of the infarct-related artery. However, excellent intra- and inter-observer agreement has been reported with the QuBE program. Furthermore, several operator- and site-specific parameters are not standardized that may influence the QuBE value including type and volume of the contrast agent, speed of injection and specific settings on the acquisition machines. Third, with the low number of clinical events at follow-up, there was inadequate power to compare the clinical outcome of patients between the QuBE tertiles. Finally, the QuBE tertiles generated in this population are not representative to a general STEMI population. This study included patients presenting with TIMI flow grade 0/1 and excluded patients with an ostial lesion.

**Conclusions**

Higher QuBE values are independently associated with improved functional and contrast-enhanced CMR outcomes including LV ejection fraction at 4 to 6 months after primary PCI in STEMI patients. Early identification of high-risk patients may select those who can benefit from adjunctive therapies targeted at sustaining myocardial function after PCI.
Reference list


