Angiographic estimates of myocardium at risk during acute myocardial infarction: validation study using cardiac magnetic resonance imaging

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Aims Global angiographic scores have been developed to determine the extent of myocardium jeopardized by significant coronary stenosis. We adapted these scores to quantify the anatomic area at risk during acute myocardial infarction. We used contrast-enhanced magnetic resonance (CMR) infarct imaging to measure the portion of myocardium that developed necrosis within the so defined angiographic area at risk.

Methods and results In 83 subjects presenting for primary percutaneous intervention, the myocardium at risk was estimated angiographically using the Myocardial Jeopardy Index (BARI) and a modified version of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) scores. CMR was performed within a week to measure infarct size, infarct endocardial surface area (infarct-ESA), and infarct transmurality. As infarct transmurality increased, the infarct size closely approximated the myocardium at risk by angiography. In 35 subjects with transmural infarcts, the area at risk by BARI and APPROACH scores matched the infarct size ($r = 0.90$ and $r = 0.92$, $P < 0.001$). Additionally, BARI and APPROACH scores matched the infarct-ESA in all subjects independently of collateral flow and time to reperfusion ($r = 0.90$ and $r = 0.87$, $P < 0.001$). The presence of early reperfusion, collaterals, or both was associated with a progressive decrease in infarct transmurality ($P < 0.001$ for trend) with no difference in the infarct-ESA.

Conclusion The myocardium at risk of infarction can be determined angiographically as validated in subjects with transmural myocardial infarcts. Salvage provided by early reperfusion or collaterals occurs by limiting infarct transmurality, thereby the extent of endocardial infarct involved also allows estimation of the myocardium at risk in patients presenting with STEMI.

Keywords Myocardial infarction; Area at risk; Coronary angiography; Collaterals; Time to reperfusion; Cardiac magnetic resonance

Introduction

In the absence of collateral flow, the myocardium supplied by an acutely occluded coronary artery defines the area at risk of infarction.1–3 If the myocardium at risk could be reliably estimated and the actual infarct size precisely determined, then the myocardium salvage could be assessed, allowing evaluation of the effectiveness of reperfusion therapies. Nuclear perfusion imaging with a technetium tracer injection before reperfusion has been the most widely practiced technique for assessing the area at risk, and has been successfully used to compare the efficacy of various reperfusion strategies.4,5 However, this approach is limited by its low spatial resolution and the need for radioactive tracers injection prior to reperfusion in an emergency department setting, which makes this approach difficult during off hours.

Given that the anatomical distribution of the coronary arteries cannot be altered by reperfusion therapy, it is a constant predictor of potential infarct size and could be retrospectively used as a surrogate of anatomical myocardium at risk. The myocardium at risk for infarction distal to any point in the coronary artery tree can be determined from the sum of the lengths of all distal coronary branches or the cross-sectional area of arterial lumen just proximal to the site of occlusion seen on angiography.6,7 The Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index (BARI-score),8 a score system based upon an individualized assessment of the length and caliber of the coronary arteries, and the Alberta Provincial Project for...
Outcome Assessment in Coronary Heart Disease (APPROACH-score) may be clinically useful to estimate the anatomic territory at risk of infarction. Previous experimental studies showed that as early as 40 min after coronary occlusion, the extent of necrosis is established and encompasses the lateral boundaries of the territory at risk. Subsequent increases in infarct size are dependent on the transmural wave-front progression of necrosis from endocardium to epicardium, modulated by the presence of collateral flow and time-to-reperfusion. However, there is little evidence of this phenomenon in humans. Delayed contrast-enhanced cardiac magnetic resonance (CMR) enables precise characterization of myocardial infarction providing an unique opportunity to clinically quantify the lateral boundaries as well as transmural extent of necrotic myocardium with improved accuracy and reproducibility when compared with other tomographic techniques.

In the current study, we adapted the BARI-score and a modified version of the APPROACH-score to estimate the anatomic territory at risk for infarction. We hypothesized that the percentage of left ventricular (LV) myocardium at risk determined by coronary angiography would correlate with the percentage of LV endocardial surface area affected by the infarct independently of the infarct transmurality. It was also hypothesized that the angiographic scores would finally predict the infarct size in cases of completed transmural infarcts.

Methods

From December 1999 to May 2006, we prospectively enrolled 119 subjects with their first ST-segment elevation acute myocardial infarction admitted for primary percutaneous coronary intervention (PCI). This is a retrospective analysis from a cohort of subjects prospectively enrolled to look at LV remodelling. We excluded subjects who did not agree to undergo a CMR study within the first week post-infarction. We did not include subjects with haemodynamic instability precluding the CMR study or subjects with either documented clinical history or electrocardiographic evidence of prior myocardial infarction. Criteria for inclusion in the current study were (1) more than 30 min of chest pain and electrocardiographic ST-segment elevation greater than 0.1 mV in at least two adjacent leads or suspicion of true posterior infarction, (2) PCI within 24 h from symptom onset, and (3) presence of a completely occluded artery at the time of PCI [Thrombolysis in Myocardial Infarction (TIMI) grade 0]. We excluded 23 subjects with pre-procedural TIMI flow >0 in the infarct related artery (IRA) and 12 subjects in whom symptoms-to-reperfusion time could not be precisely determined. An additional subject was excluded because of uncertain identification of the IRA. Among the remaining 83 subjects included in the study, the identification of the culprit lesion was easily made based upon the angiographic findings and the clinical information available, including electrocardiograms and response to treatment. The Northwestern University Institutional Review Board approved the study, and all individuals included in the study gave written consent for their participation.

Coronary angiography

All subjects where pre-treated with 324 mg of aspirin and 50 U/kg of unfractionated heparin. The use of glycoprotein IIb–IIIa receptor inhibitors, adenosine, and calcium channel antagonists was left to the angiographer’s judgment. A standard catheterization procedure with multiple selective contrast injections in the right and left coronary artery system was performed before PCI of the culprit lesion.

With the exception of one failed procedure, all subjects received at least one stent. Sixteen subjects underwent an additional PCI for a lesion other than the culprit lesion at a later time, in all cases before the CMR study.

Two angiographers who were blinded to the CMR images reviewed all angiograms. Angiographic collateral flow was assessed before PCI by visual inspection using Rentrop’s classification, a four-grade scale where 0 represents absence of identifiable collateral channels and 3 indicates complete retrograde filling of the epicardial segment of the IRA to the site of occlusion. Antegrade flow in the IRA before and after PCI was characterized using the TIMI system and disagreement in the final TIMI flow between observers was resolved by consensus with a third angiographer. The anatomic myocardial at risk solely dependent upon the infarct culprit lesion was independently evaluated by the two angiographers and the consensus was used for the analysis using the following scores.

Modified APPROACH-score

This system is based on a score developed at the Green Lane Hospital, Auckland, New Zealand. The left ventricle is divided into regions according to pathological studies in humans evaluating the relative proportion of myocardium perfused by each coronary artery. Considering the location (proximal, mid or distal) of the culprit lesion and the assumptions described by Graham et al., we created a template that calculates the jeopardized myocardium for a given site of occlusion (Figure 1). In this modified version of the APPROACH-score, the vessel dominance, site of occlusion and size of the major branches of the IRA were taken into consideration.

BARI-score

In this system, all terminating arteries—the terminal portion of the left anterior descending, left circumflex, and right coronary arteries, as well as the ramus, diagonals, obtuse marginals, posterior descending, and posterolateral branches—are graded based on vessel length and caliber according to specific criteria. A score of 0 indicates an insignificant or inconspicuous artery, and a score of 3 represents a large artery extending more than two-thirds of the distance from base to apex. Septal branches are arbitrarily assigned a maximum total score of 3. Right ventricular marginals and posterior descending artery septal branches are not scored. All scores exclusively affected by the culprit lesion in the IRA are summed and divided by the global score supplying the entire left ventricle to calculate the jeopardized myocardium as a percentage of LV myocardial volume. (Figure 2A).

Cardiac magnetic resonance studies

Subjects were imaged in a 1.5 T Sonata or Avanto scanner (Siemens, Erlangen, Germany) at a mean of 2.6 ± 1.5 (range 1–7 days) after admission. All images were gated to the electrocardiogram and acquired during repeated breath holds using a body phased-array receiver coil. Fifteen minutes after intravenous administration of 0.2 mmol/kg gadopentetate dimeglumine (Berlex, Montville, New Jersey), contrast-enhanced images were acquired in contiguous 6 mm short-axis slices every 10 mm throughout the entire left ventricle using a T1-weighted segmented inversion-recovery TurboFLASH gradient-echo sequence. Inversion-time was set to null normal myocardium and the typical voxel size was 1.4 × 1.4 × 6 mm3 with a gap of 4 mm between consecutive slices. Images were cropped, interpolated by a factor of three, de-identified and randomized for further measurements. Using ImageJ software (National Institutes of Health, Bethesda, Maryland) an experienced observer, masked to the catheterization results, manually traced the borders of the epicardium and endocardium on short-axis slices at end-diastole to calculate LV myocardial volume. The areas of hyperenhancement (HE) were manually planimetered on short-axis contrast-enhanced images. Areas of microvascular obstruction, defined as those areas with late hypo-enhancement.\n
within a hyperenhanced region, were included in the infarct area. The infarct areas on sequential short-axis slices were summed and divided by the total LV myocardial volume to calculate the infarct size as a percentage of the LV myocardial volume. Similarly, the LV endocardial border of HE was also traced, and the infarct endocardial surface area (infarct-ESA), expressed as percentage of the left ventricle endocardial surface area, was calculated as follows: 

\[
\text{Infarct-ESA} = \left( \frac{\text{summed endocardial HE infarct length}}{\text{total LV endocardial length}} \right) \times 100. \quad (\text{Figure 2B})
\]

At the time of CMR analysis, an additional area of HE not corresponding to the IRA territory was identified in nine cases. These areas were surrounded by normal myocardium and were clearly isolated from the acutely infarcted area (see Supplementary material online). Five subjects with acute occlusion of the left anterior descending artery and a chronic occlusion of an obtuse marginal or right coronary artery showed HE in the lateral or inferior wall. Two subjects with acute right coronary occlusion also had HE in the anterior wall. The angiogram showed a chronic occlusion in the left anterior descending artery and a diagonal, respectively. An additional subject with acute circumflex occlusion and a severe stenosis in the anterior descending artery had HE in the anterior wall, and only one subject with anterior infarction had HE in other territory without any additional significant coronary lesion. As was with the APPOACH and BARI-scores, these remote areas of HE blindly attributed to a coronary artery other than the IRA were retrospectively excluded from the infarct size at the time of CMR reading.

Using a 17-segment model, the transmural extent of HE was visually assessed by consensus of two experienced observers who were blinded to the subjects’ identity and angiographic data. The transmural extent of HE was categorized as 0 (no infarction), 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100% of LV wall thickness). Only segments graded 4 were considered transmural. The mean infarct transmurality score for each study was calculated as the sum of all segmental scores divided by the number of segments with HE.

<table>
<thead>
<tr>
<th>Culprit lesion location</th>
<th>Infarct related artery side branches</th>
<th>Diagonal for LAD occlusion only or Posterior lateral for all others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Small or absent</td>
</tr>
<tr>
<td>LAD (RD or LD)</td>
<td>Distal</td>
<td>13.75</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>Proximal</td>
<td>41.25</td>
</tr>
<tr>
<td>Proximal LCx (RD)</td>
<td>OM</td>
<td>Small or absent</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>15.25</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>21.25</td>
</tr>
<tr>
<td>Proximal LCx (LD)</td>
<td>PDA</td>
<td>Small or absent</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>35.5</td>
</tr>
<tr>
<td>Mid LCx (LD) or RCA (RD)</td>
<td>PDA</td>
<td>Small or absent</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>15.25</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>21.25</td>
</tr>
<tr>
<td>Mid LCx (RD)</td>
<td></td>
<td>3.25</td>
</tr>
</tbody>
</table>

Figure 1. Data represents percentage of left ventricular myocardium volume. In this system, the culprit lesion location, dominance, and major side-branches size of the infarct related artery were taken into consideration. For example, a subject with a left-dominant system and a proximal left circumflex lesion who has a medium-sized posterior descending artery and small posterolateral branches has a area at risk of 29.5% of the left ventricular myocardium. LAD, left anterior descending artery; LCx, left circumflex artery; LD, left dominance; OM, obtuse marginal; PDA, posterior descending artery; RCA, right coronary artery; RD, right dominance.

Statistical analysis

The agreement between angiographic estimates of anatomical area at risk and infarct-ESA as well as infarct size was examined using Pearson’s correlation, standard error of the estimate, and Bland-Altman analysis. Comparisons of quantitative variables between groups of subjects were done with unpaired Student’s t-test or ANOVA with Bonferroni correction for multiple comparisons. The interobserver agreement for angiographic area at risk by BARI and APPOACH scores was assessed using Lin’s concordance correlation coefficient. The transmurality ratio score and the number of segments with transmural infarct were not normally distributed. In this case, U of Mann-Whitney or Kruskal-Wallis tests were used for comparison between groups when appropriate. SPSS 11.0 software package (Chicago, IL) was used for the analysis. A two-tailed P-value, 0.05 was considered statistically significant.

Results

Table 1 shows the clinical and angiographic characteristics of the population. An occlusion in the left anterior descending artery was found in 42 subjects. Forty-one of these subjects had HE in the anterior or septal wall. With the exception of one subject who had HE in the infero-apical region and occlusion in the mid-LAD, all subjects with HE limited to the inferior or inferoseptal wall had a culprit lesion in the RCA. All subjects with a left circumflex artery infarction had HE in the anterolateral or inferolateral regions. The mean anatomic area at risk as a percentage of the LV myocardial volume by BARI-score, APPOACH-score, and infarct-ESA according to the site of occlusion are shown in Table 2.
A total of 82 out of 83 subjects included in the study had symptoms-to-reperfusion time \( \leq 1 \) h. Among them, the infarct-ESA highly correlated with the anatomical area at risk by both BARI (Pearson \( r = 0.90, P \leq 0.001 \)) and APPROACH scores (\( r = 0.87, P \leq 0.001 \)) (Figure 3A and B). Bland–Altman analysis showed a bias of 2.16\% of the left ventricle (95\% confidence interval: 2.61–0.70) and 2.81\% of the left ventricle (95\% confidence interval: 3.88–1.75) between infarct-ESA and anatomical area at risk by BARI and APPROACH scores, respectively (Figure 3C and D).

Among 35 subjects with transmural infarcts, defined as a mean transmurality score \( \geq 3 \), the anatomic area at risk closely matched the final infarct size by CMR (\( r = 0.90, P < 0.001 \) for BARI-score; \( r = 0.90, P < 0.001 \) for APPROACH-score). (Figure 4A and B; filled circles). In this subgroup of patients, Bland–Altman analysis showed a bias of 2.42\% L V myocardial volume (95\% confidence interval: 3.98–0.85) for BARI and 1.14\% L V myocardial volume (95\% confidence interval: 2.67–0.38) for APPROACH when compared with infarct size (Figure 4C and D).

### Anatomic area at risk vs. infarct-endocardial surface area

A total of 82 out of 83 subjects included in the study had symptoms-to-reperfusion time \( \leq 1 \) h. Among them, the infarct-ESA highly correlated with the anatomical area at risk by both BARI (Pearson \( r = 0.90, P < 0.001 \)) and APPROACH scores (\( r = 0.87, P < 0.001 \)) (Figure 3A and B). Bland–Altman analysis showed a bias of 1.66\% of the left ventricle (95\% confidence interval: −2.61–0.70) and −2.81\% of the left ventricle (95\% confidence interval: −3.88–1.75) between infarct-ESA and anatomical area at risk by BARI and APPROACH scores, respectively (Figure 3C and D).

### Anatomical area at risk vs. infarct size

Among 35 subjects with transmural infarcts, defined as a mean transmurality score \( \geq 3 \), the anatomic area at risk closely matched the final infarct size by CMR (\( r = 0.90, P < 0.001 \) for BARI-score; \( r = 0.90, P < 0.001 \) for APPROACH-score). (Figure 4A and B; filled circles). In this subgroup of patients, Bland–Altman analysis showed a bias of 2.42\% L V myocardial volume (95\% confidence interval: 3.98–0.85) for BARI and 1.14\% L V myocardial volume (95\% confidence interval: 2.67–0.38) for APPROACH when compared with infarct size (Figure 4C and D).
For the remaining 48 subjects, who had non-transmural infarcts (mean transmurality score, 3), the infarct size by CMR was significantly smaller than the anatomic area at risk by BARI (17.3 ± 8 vs. 30.5 ± 10% LV myocardial volume) and APPROACH scores (17.3 ± 8 vs. 29.6 ± 10% LV myocardial volume), respectively (Figure 4A and B; open circles). As depicted in Figure 5, the infarct size by CMR progressively approximated the angiographic area at risk.

**Table 2** Angiographic anatomical area at risk and infarct-ESA in subjects with symptoms-to-reperfusion ≥1 h according to culprit lesion location

<table>
<thead>
<tr>
<th>Culprit lesion</th>
<th>BARI-score</th>
<th>APPROACH-score</th>
<th>Infarct-ESA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD (n = 41)</td>
<td>38.19 (20.83–60.00)</td>
<td>37.00 (22.40–47.75)</td>
<td>41.14 (21.03–63.89)</td>
</tr>
<tr>
<td>Proximal LAD (n = 22)</td>
<td>43.71 (21.05–60.00)</td>
<td>42.52 (22.40–47.75)</td>
<td>46.06 (28.12–63.89)</td>
</tr>
<tr>
<td>Mid-LAD (n = 19)</td>
<td>31.80 (20.83–42.80)</td>
<td>30.60 (27.50–41.25)</td>
<td>35.7 (21.03–47.13)</td>
</tr>
<tr>
<td>LCx (n = 9)</td>
<td>22.75 (13.04–31.82)</td>
<td>19.53 (12.00–26.66)</td>
<td>25.92 (11.65–32.73)</td>
</tr>
<tr>
<td>Proximal LCx (n = 1)</td>
<td>31.82</td>
<td>21.25</td>
<td>31.12</td>
</tr>
<tr>
<td>Mid-LCx (n = 3)</td>
<td>27.05 (24.00–29.20)</td>
<td>25.47 (23.25–26.66)</td>
<td>30.04 (28.64–32.73)</td>
</tr>
<tr>
<td>Distal LCx (n = 1)</td>
<td>23.07</td>
<td>19.66</td>
<td>28.80</td>
</tr>
<tr>
<td>Obtuse marginal (n = 4)</td>
<td>17.17 (13.04–20.80)</td>
<td>14.61 (12.00–19.44)</td>
<td>20.80 (11.65–31.09)</td>
</tr>
<tr>
<td>RCA (n = 32)</td>
<td>23.71 (9.09–32.00)</td>
<td>23.34 (12.00–27.75)</td>
<td>23.36 (10.13–35.07)</td>
</tr>
<tr>
<td>Proximal RCA (n = 13)</td>
<td>23.74 (9.09–32.00)</td>
<td>23.10 (12.00–27.75)</td>
<td>23.40 (10.13–32.75)</td>
</tr>
<tr>
<td>Mid-RCA (n = 10)</td>
<td>24.82 (18.18–32.00)</td>
<td>23.77 (18.50–27.75)</td>
<td>23.33 (16.73–33.20)</td>
</tr>
<tr>
<td>Distal RCA or PDA (n = 9)</td>
<td>22.42 (13.04–30.77)</td>
<td>23.17 (18.00–27.75)</td>
<td>22.95 (14.43–35.07)</td>
</tr>
</tbody>
</table>

Data is expressed as mean (range). LAD, left anterior descending artery; LCx, left circumflex; PDA, posterior descending artery; RCA, right coronary artery.

Figure 3 The scatterplots between infarct-ESA and the anatomical area at risk by BARI and APPROACH are shown in (A) and (B). The trend line and r coefficient for 82 subjects with more than 1 h of symptoms-to-reperfusion time is depicted. A single subject reperfused within the first hour of symptoms (asterisk) was excluded from the analysis. The dotted line represents the equality between the two measurements. (C and D) Bland–Altman analysis comparing BARI and APPROACH scores with infarct-ESA among subjects with >1 h of symptom-to-balloon time. The central line represents the bias and the dotted lines the bias ± 2 standard deviations limits between the two measurements.

For the remaining 48 subjects, who had non-transmural infarcts (mean transmurality score <3), the infarct size by CMR was significantly smaller than the anatomic area at risk by BARI (17.3 ± 8 vs. 30.5 ± 10% LV myocardial volume) and APPROACH scores (17.3 ± 8 vs. 29.6 ± 10% LV myocardial volume), respectively (Figure 4A and B; open circles). As depicted in Figure 5, the infarct size by CMR progressively approximated the angiographic area at risk.
risk as the infarct transmurality increased ($P < 0.001$ for the trends).

**Interobserver agreement**

The concordance correlation coefficient for the angiographic assessment of the area at risk by BARI and APPROACH scores was 0.97 (95% confidence interval: 0.95–0.98) and 0.95 (95% confidence interval: 0.93–0.97), respectively.

**Effect of collateral flow and early reperfusion on infarct transmurality**

Those subjects with good collateral flow (grade ≥2, $n = 36$) tended to have smaller infarct sizes ($19.88 \pm 9.14$ vs. $24.22 \pm 12.82\%$ LV myocardial volume, $P = 0.09$), had smaller infarct transmurality score ($2.33 \pm 0.76$ vs. $2.70 \pm 0.70$, $P = 0.03$) and fewer segments with transmural infarct ($1.53 \pm 1.42$ vs. $3.17 \pm 2.47$, $P < 0.001$) in comparison with the group with poor collateral flow (grade ≤1, $n = 47$).

When separating the subjects into two subgroups based upon the median symptoms-to-reperfusion time, the group with early reperfusion ($<3\, \text{h}, \, n = 37$) trended towards smaller infarct sizes ($20.05 \pm 12.79$ vs. $24.17 \pm 10.14\%$ LV myocardial volume, $P = 0.05$), smaller infarct transmurality score ($2.25 \pm 0.83$ vs. $2.77 \pm 0.58$, $P = 0.002$), and fewer segments with transmural infarct ($2.0 \pm 2.47$ vs. $2.83 \pm 1.96$, $P = 0.01$) than the group with late reperfusion ($≥3\, \text{h}, \, n = 46$). There was no significant difference in the anatomical area at risk or the infarct-ESA between groups with or without collaterals and early or late reperfusion.

As seen in Figure 6, increasing infarct transmural extent was associated with a progressive decrease in the difference between myocardium at risk and infarct size (myocardial salvage) ($P < 0.001$ for both BARI and APPROACH-scores). The impact of time from symptoms-to-reperfusion on the infarct size as a percentage of the angiographic area at risk was maximal in the first 4 h of symptoms (Figure 7).

**Discussion**

Defining the initial area at risk for infarction has become clinically important since it permits an accurate assessment of myocardial salvage provided by reperfusion therapies. Furthermore, knowing the area at risk of infarction would permit prediction of the potential infarct size, and could be helpful in determining the need for a revascularization procedure when the maximal infarct size is suspected to have occurred. In this study, both the BARI-score and

![Figure 4](image_url)
APPROACH-score accurately estimated the anatomical area at risk for infarction, with sufficiently small variability to be clinically useful in subjects presenting with acute ST-segment elevation myocardial infarction. Single photon emission computed tomography imaging with a technetium perfusion tracer injection prior to acute reperfusion is currently considered the gold standard for the clinical assessment of myocardium at risk and salvage. This approach provides physiological information on those zones of reduced perfusion regardless of anatomy, and accounts for the presence of collateral flow that may limit the hypoperfused ischaemic area. However, perfusion defects attributed to the IRA may be falsely increased due to coexisting perfusion defects from other non-IRA coronary arterial lesions, or underestimated in cases of severe three-vessel disease. In addition, tracer injection must be performed prior to acute revascularization, and imaging must

![Figure 5](image1)

**Figure 5** Infarct size as a percentage of LV myocardial volume in proportion to the initial area at risk by BARI-score (A) and APPROACH-score (B). Infarct size progressively approximates the initial anatomic area at risk as infarct transmurality increases.

![Figure 6](image2)

**Figure 6** Box-plot showing the relationship between myocardial salvage (difference between infarct size and initial area at risk by BARI-score; white bars) and infarct transmurality (grey bars). The presence of collateral flow, early reperfusion or both was associated with an increase in myocardial salvage that reflected the decrease in infarct transmurality ($P < 0.001$ for both trends).

![Figure 7](image3)

**Figure 7** Scatter-plot showing the effect of time from symptoms onset-to-reperfusion to the final infarct size as a percentage of the initial area at risk by BARI (A) or APPROACH score (B). A logarithmic relationship is shown with a major impact in infarct size when the time-to-reperfusion is within the first 4 h of symptoms. Beyond 4 h, the effect of time-to-reperfusion to the infarct size plateaus.
be completed within 6 h. Finally, the requirement for two separate perfusion studies (to measure area at risk and infarct size) is an important consideration in subjects additionally exposed to radiation during primary angioplasty. Other approaches using fatty acid tracers or $^{19}$F-fluorodeoxyglucose with positron emission tomography rely on metabolic disturbances to retrospectively estimate the ischaemic area at risk. However, these alternative techniques are still limited by low spatial resolution.

CMR imaging using T2-weighted scan to determine myocardial oedema constitutes an emerging new surrogate of estimating the area at risk. An increase in T2-weighted signal intensity reflects the increase in water content that occurs in the acute ischaemic area. Several studies have shown that CMR T2-weighted oedema imaging 2 days after acute myocardial infarction and coronary reperfusion can retrospectively delineate the area at risk in an animal model. Along with the standard contrast-enhanced CMR imaging, myocardial salvage can also be calculated in a single study. Initial reports in humans have also shown that the HE region is a subset of the hyperintense area delineated by T2-weighted imaging, the later most likely representing the initial area at risk. Although initial studies are very promising, technical improvements in signal to noise ratio and artifact suppression need to be implemented in order to make this approach robust enough for clinical use.

**Angiographic assessment of anatomical area at risk**

The angiographic scores presented in this study illustrate an alternative for measuring the anatomic myocardium at risk. The anatomic area at risk has been determined using techniques such as autoradiography and post-mortem arteriography. The studies by Seiler et al. established the basis for angiographically measuring the anatomic area at risk. The anatomic approach assumes a certain proportion of LV myocardium supplied by each coronary artery that is dependent upon the length and size of its branches. This relationship between the size of coronary arteries and the supplied myocardium reflects the physical principles of minimal energy loss and limited adaptive shear stress that underlie the branching structure of the coronary tree. This method has the advantage of allowing a retrospective analysis of area at risk attributable to the IRA based on clinical angiography without the need of additional imaging. This estimation is independent of the presence of other perfusion defects related to other coronary lesions different than the IRA. However, the inability to account for the presence of residual flow or contribution of the metabolic factors that modulate the hypoperfused area at risk is the main limitation of the angiographic measure of the area at risk.

Lee et al. reported an excellent correlation between postmortem angiographic vascular bed at risk and histological infarct size. Similarly, we observed that in cases with complete transmural infarct following reperfusion, the anatomical myocardium at risk by angiography closely matched the infarct size. Additionally, the infarct-ESA also matched the anatomical myocardium at risk by angiography independently of the transmural extent of infarction. There are several important clinical implications of these findings. First, combining measurements of anatomical area at risk by angiography and infarct size by CMR may quantify myocardial salvage provided by reperfusion and medical therapies. Secondly, the risk region can potentially be determined by solely measuring the percent of LV endocardial surface area affected by the infarct on CMR images. The lateral boundaries of the infarct are established after the first hour of symptoms independently of the presence of collateral flow. Lastly, the benefit provided by collaterals, time-to-reperfusion, and reperfusion therapies manifests as a reduction in the infarct transmurality rather than a decrease in the lateral boundaries of infarction. Our observations in humans support this wavefront progression of myocardial infarction described by Reimer and Jennings in an animal model.

Both the BARI and APPROACH-scores were developed to describe the extent of significant coronary artery disease and provide prognostic information. There were some differences in the overall performance of the two scores. The BARI-score was more precise throughout the entire range of areas at risk, whereas the modified version of the APPROACH-score underestimated those cases with greater areas at risk. However, the APPROACH-score allows a rapid and simplified semi-automatic quantification of area at risk. The BARI-score requires a more detailed and individualized assessment of the vascular anatomy. For these reasons, the modified version of the APPROACH-score may be a simple and practical way of measuring the myocardium at risk that can have widespread applicability for broad populations in retrospective studies.

**The effect of collateral flow and time-to-reperfusion**

It is well accepted that time-to-reperfusion and the presence of collateral flow are major determinants of infarct size. However, little is known in humans whether salvage provided by these factors occurs in the lateral boundaries of the area at risk in addition to the limitation of transmural extent. Our study suggests that the benefit provided by angiographically well-developed collaterals and symptoms-to-reperfusion time occurs by means of a reduction in infarct transmurality rather than reduction in the lateral boundaries of the infarct. In this cohort, only one subject presented within the first hour of symptoms, and the infarct-ESA was clearly smaller than the anatomical area at risk, denoting extended salvage in the lateral boundaries. This raises the question to whether the infarct-ESA will not be an appropriate measure of area at risk in cases with <1 h of reperfusion.

**Study limitations**

This is an observational retrospective clinical study, and specific medical treatments to reduce the areas at risk or myocardial salvage were not evaluated. Similarly, a more precise method to evaluate total collateral flow like pressure derived collateral flow or contrast echocardiography might have improved our results, especially in cases with undetected angiographic collaterals. The proposed method may not be applicable in non-ST-segment elevation myocardial infarction, where the identification of the culprit lesion may be challenging. Additionally, the presence of previous undiagnosed myocardial infarction in adjacent myocardial areas to the acute infarction may preclude...
appropriate registration between angiography and contrast-enhanced CMR images.

Conclusion
This investigation shows that both the BARI-score and a modified version of the APPROACH-score can be clinically used to determine the anatomical myocardium at risk in patients with acute ST-segment elevation myocardial infarction. In accordance with the wavefront hypothesis, the lateral boundaries of the infarct are established after the first hour of occlusion and further myocardial necrosis results in progressive increase in infarct transmurality depending on the time-to-reperfusion and collateral flow. In patients presenting with STEMI and more than 1 h of symptoms, the infarct endocardial surface area can also be a surrogate measure of the area at risk.

Supplementary material
Supplementary material is available at European Heart Journal online.

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