Risk area, infarct size, and the exposure of the wavefront phenomenon of myocardial necrosis in humans

Bernhard L. Gerber

Division of Cardiology, Department of Cardiovascular Diseases, Cliniques Universitaires St Luc, Université Catholique de Louvain, Avenue Hippocrate 10/2806, B-1200 Woluwe St Lambert, Brussels, Belgium

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This editorial refers to ‘Angiographic estimates of myocardium at risk during acute myocardial infarction: validation study using cardiac magnetic resonance imaging’ by J.T. Ortiz-Pérez et al., on page 1750

In the 1970s, Reimer and Jennings1 performed a multitude of studies in dogs after acute coronary occlusion in which they examined the relation between duration of ischaemia, area at risk, collateral blood flow, and final infarct size. The results of their experiments were summarized by the concept of ‘wavefront phenomenon of myocardial death’. In summary, this concept states that infarct size increases in a transmural wavefront extending from the endocardium to the epicardium with increasing duration of coronary occlusions and with increasing severity of ischaemia. Coronary occlusions lasting <6 h result in subendocardial infarcts, in which infarct size is smaller than the ischaemic area at risk, because some epicardial rim of viable tissue is spared. When coronary occlusion exceeds 6 h, infarcts become transmural with an infarct size encompassing the entire area at risk.

The concept of Reimer and Jennings is fundamental to current revascularization therapy of acute ST-elevation myocardial infarcts (STEMI). Indeed, modern treatment strategies of STEMI aim at opening the infarct-related artery as quickly as possible, in order to reduce the duration of ischaemia and to save viable myocardium in the risk area.

The importance of saving such viable myocardium was underscored by the recent OAT trial,2 which demonstrated the benefit of opening the infarct-related artery by PTCA in patients having suffered an STEMI more than 3 days ago, likely because in such subacute STEMI the window of action for saving residual viable myocardium had expired.

Experimental studies indicate that additional myocardial injury may occur at the time of reperfusion or shortly thereafter.3 This suggests that the relation between risk area and final infarct size for a given duration of occlusion could be still modified at the time of reperfusion by administration of ‘cardioprotective’ drugs. Such ‘cardioprotective’ effects have indeed been suggested in experimental studies for a variety of drugs, for instance K-ATP channel blockers,4,5 or fibrin targeting peptides.6 It remains, however, unknown whether any of these drugs might have beneficial effect in humans with acute STEMI. Therefore, it would be of great interest to be able to evaluate such drugs by studying their effect on the relation between area at risk and final infarct size in patients with acute STEMI.

For the measurement of infarct size in humans, cardiac MR (cMR) after injection of Gd-based extravascular contrast agents is currently considered the reference standard. Indeed, the technique offers high spatial resolution and excellent correspondence with histological necrosis.7 However, the measurement of risk area in humans remains difficult. Although several methods have been proposed for this purpose, all of these methods have limitations. The most developed method for assessment of risk area in humans is nuclear imaging after injection of 99mTc-sestamibi. Indeed, 99mTc-sestamibi is a radiopharmaceutical which is rapidly taken up by normal myocardium in direct proportion to regional myocardial perfusion. Unlike 201Tl, the agent remains trapped in the myocardium and does not washout and redistribute. The area at risk of acute STEMI can thus be measured if 99mTc-sestamibi is injected before revascularization therapy. SPECT imaging can be performed up to 8 h after revascularization, once the patient has been stabilized, and the size of the perfusion defect obtained at that time will still reflect the initial distribution of the tracer, thus risk area, irrespective of the therapeutic interventions performed between the injection of the tracer and image acquisition. Using SPECT for assessment of risk area has however several limitations. Indeed, the technique requires the injection of the tracer at the time of the presentation of the patient and SPECT imaging within few hours after revascularization. Since STEMI frequently occurs ‘off-hours’, availability of nuclear facilities is often problematic. In addition, SPECT suffers from poor spatial resolution, resulting in...
partial volume effects. These effects are exacerbated by abnormal segmental contraction in the infarcted region, if ECG gating is not used. Another technique which has been proposed for measuring area at risk is contrast echocardiography with intravenous or intracoronary injection of microbubbles before revascularization of the infarct-related artery. The advantage of this technique over SPECT imaging is its clearly higher spatial resolution, and the ability to quantify perfusion in the risk area in absolute terms. Also the assessment of risk area can be performed immediately before revascularization in the cathlab or coronary care unit. However, the technique is currently limited to two-dimensional echo imaging. Three-dimensional echo would allow certainly more precise estimation of risk area than two-dimensional imaging alone, however, perfusion imaging modes have not yet been successfully transposed to three-dimensional echo.

More recently, T2-weighted cardiac magnetic resonance imaging (cMRI) has been suggested as another method to non-invasively assess area at risk. Indeed, T2-weighted cMR can highlight the increased water content in oedematous myocardial regions. Such oedema occurs rapidly, and persists for several hours after acute ischaemia, due to the reduced function of Na/K/ATPase pumps in acute ischaemia, resulting in intracellular sodium accumulation. In animals, good correlation between the bright area on T2-weighted cMR measured 2 days after infarction and risk area was shown. Potential advantages of T2-weighted cMR are the high resolution and three-dimensional capabilities of cMR and the possibility to combine assessment of risk area and infarct size in a single examination, which can be performed a posteriori, i.e. after revascularization, when the imaging facilities are more available and when the patient has stabilized. The limitation of the technique is that image quality of T2-weighted images in humans is often less good than in animals, good correlation between the bright area on T2-weighted cMR measured 2 days after infarction and risk area was shown. Potential advantages of T2-weighted cMR are the high resolution and three-dimensional capabilities of cMR and the possibility to combine assessment of risk area and infarct size in a single examination, which can be performed a posteriori, i.e. after revascularization, when the imaging facilities are more available and when the patient has stabilized. The limitation of the technique is that image quality of T2-weighted images in humans is often less good than in animals, making clear-cut definition of risk area more difficult.

Also, it remains unknown how the accuracy of the measurements of risk area is influenced by the delay between reperfusion and MRI. In this context, the study of Ortiz-Pérez et al., which appears in the current edition of the ‘European Heart Journal’ is very appealing. Indeed, Ortiz-Pérez et al. proposed two angiographic score to compute area at risk in patients with STEMI, the BARI score, and a modified APPROACH score and compared such risk area to infarct size measured by cMR. The authors observed that when the time from symptom onset to needle was long in patients with STEMI, infarcts were transmural, and the infarct size measured by cMR corresponded precisely to the risk area estimated by the two angiographic scores. This validated the measurement of the risk area by angiographic score vs. cMR in such patients with transmural infarcts, which do not have any salvageable myocardium. By opposition, when patients were revascularized early, they presented sub-endocardial infarcts and infarct size was significantly smaller than risk area, indicating salvageable myocardium. There are several interesting points to be highlighted in this paper: First of all, the authors demonstrate by this present study the accuracy of assessing risk area in humans using either the BARI or the modified APPROACH angiographic scores. These two angiographic scores were developed based on autopsy studies to estimate the volume of myocardium subtended by a stenosis, thus the amount of myocardium at risk, based on the location and severity of a coronary artery lesion in the angiographic tree. The BARI score was used to correct for area at risk in a study comparing bypass surgery with angiographic revascularization. The advantage of using such angiographic scores is that estimation of risk area can be performed a posteriori, thus even in patients which present with a STEMI in the middle of the night. Further the authors demonstrate that the combination of cMR and the angiographical risk score, allows the estimation of the amount of salvageable myocardium in individual patients. Thus the combination of the angiographic risk score with cMR assessment of infarct size could be used to study the effect of ‘cardioprotective’ medications in patients with acute STEMI. Finally, the study nicely illustrates the wavefront of myocardial necrosis in humans. In this context, the authors make the interesting observation that the endocardial length of myocardial necrosis by itself imaged by cMR could measure risk area. This is because, similar to the observations made by Reimer and Jennings in dogs, in humans extension of infarct size with duration of ischaemia progresses transmurally from the endocardium to the epicardium, with very little extension of infarct size in lateral directions.

Despite all its appeal, the present study has limitations. Indeed, risk area by angiographic scores was not compared with another reference method, such as for instance 99mTc-sestamibi SPECT, contrast-echo, or T2-weighted cMR. Also, the study only included patients with STEMI, with symptoms lasting at least 30 min. The non-invasive assessment of area at risk might be even more important in patients with unstable angina (UA) or in those with NSTEMI, since in such patients the magnitude of salvageable myocardium in the area at risk might be more important than in patients with STEMI. In particular, it is very uncertain if the proposed method of endocardial length of subendocardial necrosis assessed by cMR would allow to accurately estimate risk area in such patients with UA/NSTEMI, at a time when subendocardial necrosis has not yet occurred. Also the angiographically determined methods for assessment of risk area can only be used in such patients at the time of cardiac catheterization. Thus, in such patients with UA/NSTEMI, nuclear cardiology or contrast echocardiography at rest and during stress, are likely better methods to assess salvageable myocardium in risk areas.

In conclusion, the present study by Ortiz-Pérez et al. is very important by demonstrating a simple method to assess risk area and infarct size in humans by combining an angiographically determined risk score with contrast-enhanced cMR. This study allows us to follow the wavefront phenomenon of myocardial necrosis in humans. By offering a simple approach for estimating salvageable myocardium in humans, it offers new opportunities to study ‘cardioprotective’ medications which might favourably influence the relation of risk area to infarct size in humans.

**Conflict of interest:** none declared.

**References**

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Clinical vignette

Bland–White–Garland syndrome: extensive collaterals prevent ischaemia

Ercuement Ercin, Oliver Gammaerti, Philipp Kaufmann, and Franz R. Eberli*

Cardiovascular Center and Nuclear Medicine, University Hospital Zurich, C HOF 109, Raemistrasse 100, CH-8091 Zurich, Switzerland

*Corresponding author. Tel: +41 44 255 2216; fax: +41 44 255 44 01. E-mail address: franz.eberli@usz.ch

A 56-year-old female patient was referred for coronary angiography because of occasional chest heaviness and a positive stress test. Coronary angiography revealed an anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) also referred to as Bland–White–Garland syndrome. The right coronary artery (RCA) supplied the left coronary system through an abundance of predominant septal collaterals. The left main artery (LMA) drained into the pulmonary artery (PA) (Panel A).

On 64-slice CT angiography (Panel B), the left anterior descending artery (LAD) appeared wrinkled and thin walled, due to the low pressure and retrograde flow into the pulmonary artery. The extensive collaterals resulted in a preserved perfusion at rest and almost normal coronary flow reserve of the anterior wall, as documented by $[^{11}N]$NH$_3$ positron emission tomography (PET). Nevertheless, fused PET–CT imaging showed a relative hypoperfusion of the anterior wall (purple colour, Panel C) compared with the preserved perfusion of the inferior wall (orange colour, Panel D).

The Bland–White–Garland syndrome is a rare congenital condition. Eighty percent of affected infants die within 4 months. Survival is critically dependent on the development of collateral circulation. In adulthood, this syndrome is seen with angiina, congestive heart failure, mitral regurgitation, and sudden death.

Panel A. Coronary angiography showing blood flow from RCA to LMA and drainage into the PA.
Panel B. CT angiography.
Panel C. Fused PET–CT imaging showing a relative hypoperfusion of the anterior wall (purple colour).
Panel D. Fused PET–CT imaging showing a privileged perfusion of the inferior wall (orange colour).