EDITORIAL

Myocardium at risk: Reasons and methods for measuring the extent

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MYOCARDIUM AT RISK

If a coronary artery is acutely occluded, the downstream myocardium becomes severely under-perfused and at risk of necrosis. The area of myocardium at jeopardy of infarction is usually referred to as area at risk. It is intuitive that the extent of myocardium at risk downstream from an occluded coronary artery does not have the dimension of an area, but rather that of a volume or a mass. Indeed, the extent of myocardium at risk is usually expressed in grams or in percentage of ventricular myocardium. However, because the initial experiments were carried out by injecting dyes or radionuclide-labeled microspheres upstream from the occluded coronary artery, and because the myocardium at risk was defined postmortem as the non-stained or non-labeled area in cross-sectional slices of the heart, the term area at risk has become common and hence entered the medical dictionary.[1,2]

If a flow tracer is injected into a coronary artery proximal to its occlusion, and a second flow tracer is injected after the occlusion upstream the occluded artery, it becomes evident that the extent of myocardium perfused by a given open artery is larger than the myocardium at risk when the same vessel is occluded (Figure 1A, B). This difference is on average 20% in the canine heart, and is due to the collateral circulation.[3] It has been traditionally assumed that coronary arteries are functional end-arteries under physiological conditions. However, even in the absence of coronary stenoses or in entirely normal hearts, brief periods of coronary occlusion produced by balloon inflation are not followed by electrocardiographic signs of myocardial ischemia in 20%-25% of patients. This is attributed to collateral circulation.[4] This phenomenon is more prominent in the case of preexisting collaterals, as observed in patients with chronic coronary artery disease. Thus, the extent of the area at risk after coronary occlusion is influenced both by an anatomical factor (the size and hierarchy of the occluded vessel) and by a series of functional factors (largely related to the collateral circulation). For this reason, an acute coronary occlusion causes a smaller infarction and a less severe hemodynamic impairment in an older patient with extensive coronary atherosclerosis and well-developed collaterals than in a younger patient without preexisting collaterals. Another functional factor is how rapid is the occlusion. If the occlusion is very slow (as it can be obtained in experimental animals and as it occurs in patients with coronary lesions slowly evolving toward total occlusion), collaterals have the time to develop and to minimize the extent of myocardium at risk. This goes in parallel with the common observation of patients with even complete occlusion of a proximal coronary artery and absence of myocardial infarction. Finally, if the perfusion territory is small, as when a secondary branch is occluded, collateral vessels can totally obscure the area of myocardium at risk.

WHY MEASURE THE EXTENT OF MYOCARDIUM AT RISK

There are several reasons for measuring the extent of the area at risk in the clinical setting. First of all it is important to have an idea of how large the infarction can become. It is well known that the size of a myocardial infarction depends upon several factors, including duration of coronary occlusion, presence of a residual stenosis, myocardial preconditioning, and myocardial oxygen consumption during occlusion (as seen with the effects of beta blockers). However, the infarction can never become larger than myocardium at risk. In other words, knowing the area at risk of necrosis during coronary occlusion provides us information on the worst-case scenario, which could be useful in clinical decision-making. If this information was available,

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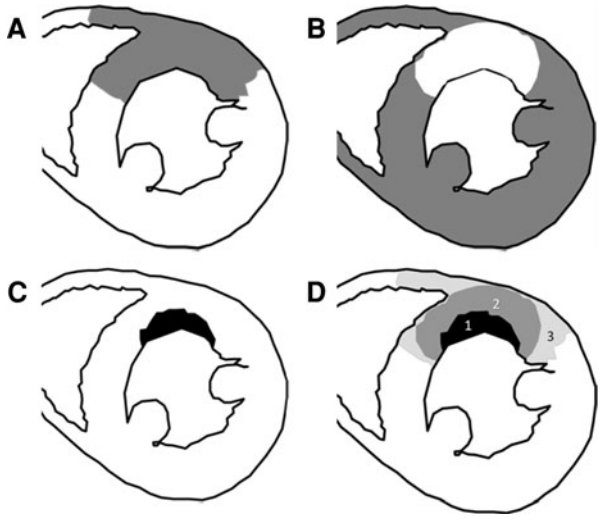

Figure 1. **A** Schematic drawing of the myocardium perfused by left anterior descending coronary artery enhanced by injecting a tracer directly into the open artery. **B** Schematic drawing of the area at risk (not enhanced area) obtained by injecting a tracer into the left atrium after occlusion of the left anterior descending artery. **C** Schematic drawing of the infarction area at tissue staining. **D** Schematic representation of the infarction (1), the area at risk (2), and of the myocardium perfused by the same vessel (3).

prompt revascularization could be indicated in case of a large risk area not accompanied by clear electrocardiographic changes; alternatively, revascularization could be postponed in the case of a very small risk area.

Other information that can be derived from the assessment of the area at risk is the extent of salvaged myocardium, which requires an estimate of myocardial infarct size as compared to the area at risk (Figure 1C, D). This information has been very useful in evaluating the different reperfusion strategies over the past few decades.

Finally, the location of the myocardium at risk (rather than its extent) can be useful in identifying the infarct-related artery. This is mostly true in patients with extensive coronary artery disease in whom information on the culprit vessel to be revascularized is not obvious.

HOW TO MEASURE THE EXTENT OF MYOCARDIUM AT RISK

Although a variety of methods is currently available to measure the risk area, each of them shows several limitations in the clinical setting. An elevation of the ST segment in the electrocardiographic leads reflecting the area of myocardium at risk is the typical sign of acute injury, while a fall in ST segment elevation can indicate successful myocardial reperfusion.[5] Although one can reasonably assume that the more precordial leads show ST segment elevation, the larger is the area at risk, ST segment analysis still does not provide reliable measurements of the risk area.[6] The inaccuracy of the electrocardiogram is even higher in the case of myocardial infarctions involving the inferior or the lateral wall of the left ventricle.[7]

Detecting ventricular wall motion abnormalities by echocardiography is becoming a routine method to assess the area at risk in patients with an acute coronary syndrome. However, regional wall motion abnormalities can be present even in normally perfused segments (outside of the area at risk) due to tethering phenomena.[8] In addition, perfusion deficits generate wall motion abnormalities only if their transmural extent overcomes a given threshold.[9] In some cases, sharp borders, separating a normally contracting wall from a hypokinetic ventricular one, can hardly be identified. Moreover, ventricular wall motion during acute ischemia is also influenced by loading conditions of the heart.[10] Thus, although diagnostic ultrasound is wide available, highly feasible, has a low cost, and uses clean energy, echocardiography provides only gross semi-quantitative information on the extent of the risk area. It should be noted that clear images of the risk area were obtained by myocardial contrast echocardiography in experimental animals and in subsets of patients.[3,10,11] However, the variety of artifacts, the low signal-to-noise ratio, and the complexity of the approach have limited the use of this method in the clinical setting.

Detecting hypoperfused myocardium by single-photon emission computed tomography (SPECT) after intravenous injection of a radioactive tracer during coronary occlusion is the most commonly accepted method to measure the extent of myocardium at risk. The injection of the same tracer after reperfusion provides us with an estimate of myocardial infarct size, and hence of salvaged myocardium. In contrast to the earlier studies involving thallium-201,[12] technetium-99m-based perfusion tracers undergo minimal redistribution, allowing image acquisition several hours after injection.[13-15] Another advantage of Tc-99m over Tl-201 is the higher peak energy window, which allows a more accurate identification of the boundaries of a perfusion defect and increases accuracy of gated images. However, the limited availability of tracers in the emergency room and intensive care units, the need of injecting isotope in the acute setting and of scanning patients with a gamma camera, let alone radiation exposure for the patient and the operator, limits the actual utilization of SPECT for measuring the area at risk and salvaged myocardium. Last but not least, all information provided by SPECT is available only when reperfusion strategies have already been planned, so that medical decision-making cannot be altered.

Myocardial ischemia leads to an accumulation of fluid in the ischemic myocardium.[16] Using T2-weighted cardiac magnetic resonance (CMR), it is possible to visualize edema in the myocardium retrospectively, even several days after coronary occlusion.[17,18] Experimental studies have demonstrated that the extent of edema is comparable to histopathological and fluorescein measurements of the area at risk.[19] Furthermore, the quantification of irreversible myocardial injury using delayed contrast-enhanced CMR has been extensively validated in acute and chronic settings.[20,21] Thus, CMR is now considered the gold standard for measuring the area at risk, myocardial infarct location, size, and transmural infarct extent, as well as extent of salvaged myocardium. However, moving a patient with an acute coronary syndrome to a CMR laboratory can sometimes be problematic. Moreover, CMR can be performed only when diagnostic questions have already been addressed and therapeutic decisions made. Therefore, although ideal under several points of view, in real world clinical situations, CMR is rarely utilized to assess the area at risk and salvaged myocardium.

The angiographic approach to measure the area at risk is based on the extent and the distribution of the coronary arteries and their major branches. Using the Bypass Angioplasty Revascularization Investigation (BARI) score, each vessel is graded depending on its length from base to apex and on its caliber according to specific criteria.[22] The scores of the vessels downstream from the culprit lesion in the infarct-related artery are summed and divided by the global score of all the arteries supplying the entire left ventricle. The area at risk is expressed as a percentage of left ventricular myocardial volume. Applying a modified version of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) score, vessel dominance, occlusion site, and size of the major branches of the infarct-related artery are also taken into consideration.[23]

In the present issue of the *Journal*, Rodríguez-Palomares et al[24] have compared the area at risk for necrosis measured by coronary angiographic scores with that obtained by SPECT. They found that the area of risk determined by SPECT correlated well with the area at risk as measured by the coronary angiographic score. On the one hand, angiographic scores are a valid method for estimating the area at risk: their main advantage is to provide a timely answer which can orient medical decision-making. On the other hand, although many of these patients independently undergo an invasive diagnostic and therapeutic strategy, this approach remains invasive.

A few considerations should be taken into account regarding the angiographic approach. First of all, the distribution and caliber of an occluded or stenotic coronary artery (in addition to anatomical factors) depend on functional factors (e.g., perfusion pressure). Second, even if patients with angiographic evidence of collateral circulation were excluded from this study, collateral vessels can exist even without being angiographically apparent. Third, the accuracy of the angiographic score is higher in the left anterior descending artery perfusion territory. This suggests that despite correction of coronary prevalence the different anatomical distributions of the right and circumflex coronary artery in the different subjects do play a role.

CONCLUSION

While several methods are available to measure the extent of myocardium at risk during coronary occlusion, none of them is entirely satisfactory in the clinical setting. Despite the fact that ST segment analysis lacks accuracy, and echocardiography only provides semi-quantitative information, these two methods should be extensively utilized in such setting.

SPECT is theoretically perfect, but has a limited feasibility in the acute setting and provides cardiologists with correct but belated information. CMR is also very accurate, but documents what has already happened to the patient and is not widely available. Angiographic scores to measure the area at risk are strictly invasive, but ready for clinical use. In the present issue, Rodríguez-Palomares et al have demonstrated that measurement of the risk area obtained by coronary angiography is closely related with that obtained by SPECT. In the future, angiographic methods could be implemented with the evaluation of myocardial tissue perfusion and the direct assessment of the risk area, as nuclear medicine does at present.

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