Prognostic importance of myocardial infarct characteristics

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Introduction

Left ventricular (LV) systolic function and volumes are independent predictors of long-term survival after myocardial infarction (MI).1,2 The prognostic importance of LV pump function is mainly based on the association between systolic function and future risk of cardiac mortality related to heart failure and its consequences. Furthermore, the evidence-base for post-MI cardioprotective drug therapies, such as beta-blockers3 and angiotensin-converting enzyme inhibitors,4 is at least in part attributable to improvements in LV systolic function and attenuation of remodelling.5,6

This commentary focuses on the additive clinical utility of infarct characteristics, in addition to LV function, for prognostication after MI. Our commentary is stimulated by the publication by Lønborg et al.,7 who studied the prognostic importance of final infarct size 3 months after MI. To appreciate how their paper might be important, one must first understand the strengths and limitations of what is currently known about the clinical significance of infarct characteristics.

Until recently, the assessment of myocardial infarct characteristics, such as infarct scar, microvascular obstruction (MVO), and myocardial haemorrhage, was the exclusive domain of pathologists at post-mortem examination. Since the clinical significance of these problems in vivo was not known no specific treatments exist. Cardiac magnetic resonance imaging (CMR) provides pathological information non-invasively. CMR reveals infarct scar as a bright area of late gadolinium enhancement (~15 min after gadolinium contrast administration).7 MVO is delineated by a central dark area within the hyper-enhanced infarct zone and occurs in about two-fifths of patients after MI.8,9 Focal haemorrhagic transformation within the infarct zone is revealed by a central dark zone on T2- or T2*-weighted CMR10,11 and occurs in about one-third of patients.12–14 Myocardial salvage is the amount of ischaemically injured, but viable tissue that is amenable to recovery within the area at risk,14,15 and salvage is also independently predictive of event-free survival after MI.16

In the past 3 decades, CMR has been used in vivo to determine the prognostic significance of myocardial salvage,17 infarct size,17 MVO,10 and haemorrhage.12 Now that infarct pathologies can be detected, two important questions arise. First, is the prognostic significance of specific infarct pathologies for adverse outcome after MI additive over and above LV ejection fraction (the gold standard for prognostication in clinical practice)? Secondly, since infarct characteristics share a common pathological basis, do these abnormalities simply have interchangeable clinical significance?

To date, several CMR cohort studies of STEMI survivors have reported that infarct characteristics have an independent prognostic value over and above other clinical characteristics. Wu et al.10 imaged 44 STEMI patients on average 10 days after MI and follow-up information was obtained up to 2 years. MVO predicted major adverse cardiovascular events independent of infarct size. Although MVO was associated with larger infarct size and worse function and remodelling, the multivariable analysis did not include LV ejection fraction. In the largest study to date, Eitel et al.12 included a cohort of 342 STEMI survivors with CMR performed a median of 3 days after MI with follow-up for adverse events up to 6 months. They found that compared with either MVO or haemorrhage (as revealed by a hypointense core on T2-weighted CMR) alone, the occurrence of both MVO and haemorrhage was associated with the highest rate of adverse cardiac events. In a multivariable analysis for survival free of adverse cardiac events, the presence of MVO and haemorrhage and LV ejection fraction and age (but neither area at risk nor infarct size) were independent predictors of outcome. Not all studies of myocardial haemorrhage have found that it is an adverse prognostic factor.18 Indeed, since bleeding is a consequence of several evidence-based therapies after MI, myocardial haemorrhage could be a marker of treatment efficacy. Taking all of these studies together, infarct characteristics provide additive prognostic information beyond LV ejection fraction. Since MVO is associated with infarct size, its prognostic value may become more important in the presence of myocardial haemorrhage.14

The story does not end here, however. Infarct size changes dynamically after acute MI. Initially, the infarct tissue is increased in size because of oedema, inflammatory cell infiltrates, and haemorrhage. As healing progresses, these acute pathologies resolve and...
are replaced with collagen scar tissue such that the size of infarction diminishes with time. CMR with late gadolinium enhancement tracks these changes since gadolinium is an extracellular contrast agent. Therefore, the size of infarction as revealed by late gadolinium enhancement within the first week after MI may over-estimate actual infarct size, whereas the extent of infarction imaged 1 week and 6 months after MI are similar. Since the prognostic utility of infarct size has been based on CMR studies typically performed within the first 10 days after MI, the prognostic value may not be the same compared with infarct size measured at a later time-point.

To address this uncertainty, Lønborg et al. enrolled 309 STEMI survivors who had been enrolled in two randomized trials of therapeutic interventions (post-conditioning and exenatide, a GLP-1 analogue) in Denmark. Infarct size was measured at 3 months using late gadolinium enhancement and the median follow-up period was 807 days (inter-quartile range 669–1117). Thirty-five events occurred including 5 non-cardiac deaths, 3 cardiac deaths, and 27 hospitalizations for heart failure. The proportion of patients with an infarct size > median value who experienced at least one adverse cardiac event was higher than in patients with an infarct size < median. In a multivariable analysis with a broad range of clinical characteristics, final infarct size was an independent predictor of all-cause mortality and heart failure hospitalization. Furthermore, the chi-squared statistic increased when infarct size was included in addition to clinical characteristics (including peak troponin as a biochemical measure of acute infarct size), and LV ejection fraction and volumes.

The authors concluded that final infarct size has more prognostic value than early infarct size; however, the results do not support this assertion. First, early infarct size was not measured with CMR and peak troponin is only moderately correlated with the area under the curve from serial troponin measurements, let alone actual infarct size early after MI. Therefore, the clinical significance of the main result for CMR at 3 months over acute infarct size as measured by peak troponin must be qualified. Secondly, the patients in this analysis were derived from two randomized trial study populations which selected patients based on the inclusion and exclusion criteria of these trials. Therefore, the results of the current analysis may not be entirely applicable to unselected patients in ordinary clinical practice. Finally, 39% of the patients at baseline were lost-to-follow-up implying potential bias with the follow-up results.

So where does this place the clinical relevance of infarct characteristics after MI? Early infarct characteristics have the greatest potential clinical utility since the likelihood of an adverse event is greatest within the first month of the event. Therefore, while the assessment of final infarct size at 3 months or later is relevant to long-term prognosis, it is not relevant to early risk stratification. Considering previous CMR studies with imaging performed within the first few days after MI, infarct size, LV ejection fraction, and MVO associated with haemorrhage are prognostically important. Even though ejection fraction has been established as an evidence-based marker of outcome and guide for therapy, these infarct characteristics increase the power of prognostication and, possibly, the clinical and economic utility of CMR for risk stratification.

Myocardial salvage selectively revealed by subtraction of infarct size (late gadolinium enhancement) from area at risk revealed by T2-weighted CMR provides an objective initial estimate of the potential for LV recovery. However, since salvage is derived from other infarct characteristics, salvage may not have an independent incremental value for event-free survival. Although salvage gives an early indication of the potential for improved systolic function, other factors such as collateral and microvascular function, will influence myocardial recovery vs. infarct expansion.

Overall, there remains a substantial need for treatment advances in secondary prevention since heart failure after MI is a major public health problem ever increasingly associated with an ageing population. Since infarct size and MVO/haemorrhage add incremental prognostic information, future randomized controlled studies are needed to determine whether risk stratification based on selective identification of these abnormalities early after MI (i.e. large infarct size, MVO with haemorrhage) could lead to improved clinical outcomes. Another opportunity to improve long-term clinical outcomes after MI will be selected therapeutic interventions targeted to patients with large MI and/or MVO with haemorrhage. While currently there are no evidence-based therapies for MVO or myocardial haemorrhage, new treatments are being tested that target the pathological basis for these problems, including ischaemia-reperfusion injury (NIAM: NCT 01388504) and matrix remodelling (SOLSTICE: 00910962).

In conclusion, several cohort studies with CMR in post-MI patients have described the prognostic value of infarct burden, salvage, MVO, and haemorrhage. As was the case for LV function some 40 years ago, the key question now is whether new therapeutic interventions (pharmacological or non-pharmacological) might be associated with prognostic benefits and cost-effectiveness when tested in randomized controlled trials which include post-MI patients based on infarct characteristics as revealed by CMR.

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**References**


A large blood cyst of the mitral valve: late presentation in an 80-year-old female

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The ‘blood cyst’ or the ‘blood-filled cyst’ was first reported by Elsa¨sser in 1844. It is relatively common in newborns under 6 months of age, but disappears spontaneously in most cases during infancy, a rare finding in young adults. We present a case of a blood cyst found in an 80-year-old woman with concomitant coronary artery disease.

The patient was admitted with the diagnosis of a solid tumour (20 × 25 mm) of the left ventricle, identified by magnetic resonance (Panels A and B), where homogenous contrast opacification of the tumour was noted. The diagnosis of fibroelastoma or myxoma was proposed.

The transoesophageal examination (mid-oesophageal four-chamber view) revealed a mobile, hyperechogenic lesion (arrow) on the anterior leaflet of the mitral valve (Panels C and D; see Supplementary data online, Movie 1). It originated from antero-lateral papillary muscle and extended in the direction of the mitral annulus (Panels E and F; see Supplementary data online, Movie 2 and 3). The structure was moving together with anterior leaflet causing non-significant outflow tract obstruction (Panel G; see Supplementary data online, Movie 4).

At surgery, a membrane extending from the primary chordae of the antero-lateral papillary muscle along the anterior leaflet was found (Panel H, arrows). The membrane formed a kind of pocket, which, in vivo, was filled with the blood. Histological examination revealed a typical valve tissue with fibrotic areas and pocket-like space covered with endothelium. No sign of inflammation or neoplastic disease was found.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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