The open artery hypothesis: to open, or not to open, that is the question

In survivors of acute myocardial infarction prognosis is known to depend upon multiple factors which can precede, coincide with or follow the acute event\(^1\). These factors alter prognosis by influencing the single most important determinant of survival, left ventricular function\(^2\). Thus, post-infarction left ventricular function and prognosis will depend upon the interplay of preceding factors such as age, gender, co-morbid conditions and previous myocardial infarction; acute events, such as infarct location, size, transmurality and success/rapidity of reperfusion; and late events that influence the ventricular remodelling process\(^1\)\(^-\)^\(^4\).

The factors that influence post-infarction remodelling are not well understood. However, interventions at this point are attractive since they do not rely on early patient presentation and are therefore likely to be widely applicable. Many years ago it was realized that post-infarction left ventricular aneurysm formation was rare in the presence of a patent infarct-related artery\(^1\). This, and the unexpected benefits of late thrombolysis\(^6\)^\(^-\)^\(^7\), led to the hypothesis that following an acute myocardial infarction an open infarct-related artery is beneficial independent of any limitation of infarct size.

To test the open artery hypothesis the possibility of myocardial salvage must be excluded and therefore reperfusion must occur at a time when no viable myocardium remains in the infarct zone. This hypothesis in its purest form is virtually untestable since the exact time of reperfusion is seldom known and the presence of remaining viable myocardium can hardly ever be excluded. The hypothesis can be tested indirectly by late reperfusion beyond the timepoint traditionally associated with myocardial salvage or by demonstrating that myocardial salvage and subsequent vessel patency have independent effects on prognosis or left ventricular function.

The theoretical benefits of an open artery

An open infarct-related artery allows filling of the epicardial arteries, veins, and the microvasculature within the zone of infarction. This is likely to provide scaffolding-like support to the infarct zone and increase tissue turgor\(^8\)^\(^-\)^\(^9\). In addition, the return of flow may allow adequate perfusion of the border zone.
between infarcted and fully functioning myocardium. Furthermore, the process of reperfusion may induce specific forms of injury within the dead myocytes such as contraction band necrosis that shrink the infarct zone and favourably influence the tensile properties of the scar. Reperfusion also exposed the dead myocytes to blood elements and macrophages crucial for the removal of necrotic debris and the early formation of a healthy scar. In addition, an open infarct-related artery is able to provide collaterals to other vascular territories that may be or may become compromised.

Theoretically, by altering the properties of the scar and diminishing the ischaemic burden in non-infarcted myocardium, a patent infarct-related artery should have a beneficial influence on the remodelling process. These beneficial effects will decrease the likelihood of transition, from a physiological post-infarction remodelling process to the pathological process that leads to progressive left ventricular dilatation. A similar explanation may also account for the long-term electrophysiological stability that accompanies an open infarct-related artery.

Animal studies

In the laboratory it is possible to precisely control the moment of coronary artery occlusion and reperfusion. By ensuring the duration of ischaemia is sufficient to cause transmural infarction with little or no salvage investigators can test the open artery hypothesis in its purest form.

A number of independent studies have compared temporary coronary ligation, of sufficient duration to cause almost complete necrosis of the risk zone, with permanent ligation.

In the rat, a 2 h coronary ligation and a 90 min ligation did not limit infarct size, but at 2 weeks of reperfusion, temporary occlusion was associated with less infarct expansion than permanent occlusion. Similar results have also been seen by other groups in the conscious and unconscious rat where late reperfusion was associated with a more rapid infiltration of neutrophils and resorption of infarcted tissue than no reperfusion (permanent ligation). In dogs, late reperfusion compared to permanent ligation was also associated with a more rapid absorption of necrotic myocytes and a more mature scar 2 weeks post-infarction but by 6 weeks scar appearances were similar. Miura et al. have also observed in the rabbit that late reperfusion accelerates the organization of the infarcted tissue independent of any effect on the size of the necrotic zone. The disadvantages of these studies are that the temporal characteristics of ischaemia and the open pericardium differ from the situation seen in patients where coronary thrombus formation and dissolution is relatively slow and the intact pericardium may alter the ventricular filling pattern.

Observations in the postinfarction period

After thrombolytic therapy a number of trials have shown the importance of an early patent infarct-related artery on survival by univariate analysis. However, in order to exclude a benefit secondary to myocardial salvage it is necessary to take into account left ventricular function in the early post-infarction period because the amount of systolic dysfunction has a marked effect on subsequent ventricular remodelling. When multivariate analysis is used, none of these trials show that patency influences prognosis independent of ventricular function. However, there are a number of drawbacks: in most trials patency is assessed during acute infarction and there is known to be a high early reocclusion rate. In addition, the finding of an occluded vessel often results in aggressive revascularization. Consequently, vessels that were open early post-infarction may be closed later and vessels that were closed early may be open later. To test the open-artery hypothesis, study designs should therefore examine vessel patency days to weeks after acute myocardial infarction and whenever the measured endpoint an effect must be demonstrated that is independent of early left ventricular function. The findings of the recent studies that fulfill these criteria are reviewed below.

In the largest recent study, White et al. examined infarct vessel patency (defined as TIMI 3 flow) and left ventricular function in 312 patients approximately 1 month after first myocardial infarction. On multivariate analysis, ventricular function and patency measured as an occlusion score were independently predictive of survival over the 3 years of follow-up. The beneficial effect of a patent vessel was greatest when the infarct-related artery supplied more than 25% of the myocardium and the ejection fraction was less than 50%. Since serial assessments of left ventricular function were not made, the mechanism for the benefit is unclear.

In a similar study, Leung and Lau assessed infarct vessel patency in 58 patients 7 to 10 days after acute myocardial infarction. In the first week post-infarction, left ventricular function was similar in patients with a patent or an occluded vessel. However, over the subsequent year those with occluded...
vessels developed the most ventricular dilatation and the greatest decrease in ejection fraction, whilst an intermediate effect was seen when the infarct-related artery was patent but possessed a minimal luminal diameter of less than 1.5 mm. These findings not only supported the open-artery hypothesis, but indicated that there was a dose response relationship between the degree of stenosis and the quantity of remodelling, suggesting a role for intervention in stenotic as well as occluded vessels[30].

The importance of the quality of perfusion is further reinforced by a prospective study[31] where infarct vessel patency was defined at 3 to 5 weeks and ventricular function measured over the subsequent 3 years in 70 patients after first myocardial infarction. Progressive dilatation occurred in 20% of patients with a consequent fall in global ejection fraction approximately 1.5 years post-infarction. By multivariate analysis ejection fraction and stroke index at 4 days and ventriculographic infarct size, location and TIMI grade of infarct artery perfusion at 3 to 5 weeks were all significant predictors of progressive ventricular enlargement[31].

The independent effect of a patent infarct-related artery over and above the benefit of thrombolytic reperfusion has also been clearly shown by Popovic et al.[32]. In this study, measurements of left ventricular function in 31 patients were made at four timepoints in the first week as well as at 3 and 6 weeks after infarction, whilst infarct-related artery patency was assessed approximately 1 month after infarction. The findings suggested that thrombolysis resulted in salvage with a benefit in left ventricular function (as measured by left ventricular end diastolic volume index) evident from day 3 onwards whilst the benefit of vessel patency (also by left ventricular end diastolic volume index) was seen from day 21 onwards[32].

The relationship between infarct vessel patency and survival after Q-wave infarction has also been examined[33]. Based upon the predischarge angiograms of 172 patients post-infarction, only left ventricular function and infarct artery patency (defined as TIMI 2 and 3 flow) were independently related to survival. Of the 16 deaths over the 43 month follow-up period, 15 occurred in patients with an occluded artery[33].

The studies above demonstrate that late patency of an infarct-related artery seems to have a positive influence on remodelling and survival and that this effect is independent of any acute reduction in infarct size secondary to reperfusion during acute infarction. The corollary is that a vessel that is patent early and then occludes late after infarction should have a detrimental influence on postinfarction remodelling. A retrospective study of this type was performed by Meijer et al.[34] who compared 95 patients with a patent infarct-related artery both early (within 48 h) and late (at 3 months) after myocardial infarction, to 35 patients who had an asymptomatic reocclusion between these two timepoints. Asymptomatic reocclusion had a detrimental effect on long left ventricular function and this effect was most marked for anterior infarction and for those patients with an early ejection fraction below 50%.

In summary, these studies indicate that if an open infarct related artery carries any advantage it is most likely to be those patients who have had a myocardial infarction involving at least 25% of the left ventricle. This benefit is therefore most likely to be manifest after large anteroseptal infarction.

Studies involving Intervention to restore vessel patency late after acute myocardial infarction

The studies cited above suggest a clear advantage, in terms of survival and left ventricular function, associated with long-term patency of an infarct-related artery that opened spontaneously or as a result of thrombolytic therapy. This need not necessarily mean that opening an occluded infarct-related artery late after infarction confers benefit. Firstly, a vessel may occlude or have poor TIMI flow because of no-reflow[35] within the zone of infarction. Thus, revascularization will be of no value in the absence of a discrete arterial lesion. Secondly, opening blocked arteries is often technically difficult[32] and not without complications[36] that may influence the risk benefit ratio. There is evidence that interventions to achieve reperfusion between 6 h and 1 week (mean of 5 days) post-infarction are associated with a reduction in abnormal wall motion and left ventricular size at 3 months[37]. However, the interpretation of this study is clouded by the fact that some patients were revascularized because of continuing pain making it difficult to conclude that there was an advantage independent of myocardial salvage. In addition, other similar studies where the incidence of late intervention was high have failed to show any advantage in favour of intervention[38,39], perhaps because of follow-up periods that were too short.

The trials of thrombolysis given beyond 6 h after the onset of chest pain are also difficult to interpret. These trials suggest that thrombolysis 13 to 24 h following the onset of pain may still have a small benefit[40] but the number of patients treated was relatively small[40] and the likelihood of achieving long-term vessel patency seems inversely related to the duration of chest pain prior to treatment[22].
Restoring vessel patency and ventricular arrhythmias

The considerations so far have concentrated on the beneficial effects that restoring vessel patency has on left ventricular contractile performance. More difficult to predict are the consequences that late reperfusion may have on susceptibility to arrhythmia.

Brugada et al. have described ventricular tachycardia in patients with either collateral or antegrade flow to infarcted myocardium. In addition on the basis of superselective infusions of cold saline it seemed likely that these tachycardias involved viable tissue within the infarct zone. Following coronary artery occlusion the presence of collateral myocardial blood flow is able to preserve myocardial tissue. In this circumstance necrotic, abnormal but viable, and normal and viable, tissue may coexist within the infarct zone. This may provide a substrate for infarct expansion and infarct remodeling. Reperfusion of such tissue may therefore predispose to re-entrant arrhythmias that would adversely influence the risk/benefit ratio of restoring vessel patency.

Unfortunately, there is no information available that has directly addressed whether late reperfusion increases arrhythmia. However, late potentials post-infarction are less common with a patent rather than an occluded infarct-related artery. In addition, other therapies that favourably influence the post-infarction remodelling process such as angiotensin converting enzyme inhibitors seem to decrease the likelihood of arrhythmia. Therefore, at present there is no direct or indirect evidence to support the contention that late reperfusion increases the tendency to arrhythmia.

Conclusions

In patients with coronary disease small changes in left ventricular function can have a profound effect on survival, for example death rates increase six-fold with a change in end-diastolic volume index from ≥ 90 to ≤ 111 ml.m⁻². Although differences of this magnitude exist between groups according to whether they possess or lack a patent infarct-related artery, the question remains whether opening an occluded vessel late post-infarction confers any long-term advantage? A benefit is suggested by the indirect descriptive studies reviewed above which suggest that interventions, even as late as 1 month post-infarction, will improve the remodelling process and that the greatest benefit is likely to be seen in those patients with anterior infarction and poor left ventricular function. Unfortunately, it may be many months or even years before this advantage is manifest and it is unclear if it will be additive to that of ACE inhibition which is already of proven benefit in this group of patients.

Currently late revascularization of occluded infarct-related arteries is not recommended in the absence of ischaemia. Nonetheless, the weight of experimental and clinical evidence indicates the urgent need for a prospective randomized trial of the open artery hypothesis.

M. S. MARBER*, D. L. BROWN† R. A. KLONER†

*The Rayne Institute, St Thomas' Hospital, London SE1 7EH, U.K.
†UCSD Medical Center, San Diego, U.S.A.
‡Hospital of the Good Samaritan, Los Angeles, U.S.A.

References

[12] Boyle MP, Weisman HF. Limitation of infarct expansion and ventricular remodeling by late reperfusion. Study of time


Clinical Perspectives

Eur Heart J, Vol. 17, April 1996