Free wall rupture in the elderly: deleterious effect of fibrinolytic therapy on the ageing heart

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This editorial refers to 'Effect of thrombolytic therapy on the risk of cardiac rupture and mortality in older patients with first acute myocardial infarction'† by H. Bueno et al., on page 1705

Free wall rupture (FWR) is a catastrophic mechanical complication of ST segment elevation myocardial infarction (STEMI), which occurs in up to 8% of patients and is responsible for nearly 20% of all infarction-related deaths. In fact, next to cardiogenic shock due to pump failure, FWR is the most common mechanical cause of death in STEMI patients, occurring eight to 10 times more frequently than rupture of a papillary muscle or rupture of the interventricular septum. Although the vast majority of FWRs occur within the first week following symptom onset, up to half occur within the first 24 h. FWR primarily affects the left ventricle and complicates anterior and inferior infarctions similarly. When FWR occurs, the clinical presentation is dramatic, with the rapid development of hypotension, cardiac tamponade, pulseless electromechanical activity, and death. Unfortunately, the mortality rate is >90%, and few patients can be salvaged by anything other than heroic measures, including emergent pericardiocentesis and surgical repair.

Both the choice and the timing of reperfusion therapy for STEMI have been implicated in the development of FWR. Early studies of STEMI patients randomized to fibrinolytic therapy (FT) or placebo showed a paradoxical increase in early mortality in those treated with FT, which could not be explained by an increase in stroke or major bleeding; this early mortality was attributed to the development of FWR.

More recently, data from studies comparing primary percutaneous coronary angioplasty (PCI) with FT showed a significantly lower risk of FWR in patients treated with primary PCI.1 Several possible mechanisms have been proposed to explain the increased risk for the development of FWR with FT. First, animal studies have shown that reperfusion with FT results in interstitial and myocyte oedema, contraction band necrosis, and intramyocardial haemorrhage consistent with reperfusion injury, findings not seen to the same extent with mechanical reperfusion. Secondly, autopsy studies in humans have shown an association between the systemic lytic state induced by FT and the occurrence of haemorrhagic infarction, a phenomenon associated with severe microvascular injury and extravasation of erythrocytes into reperfused myocardium.2 Interestingly, the intramyocardial haemorrhage seen with the administration of FT is not seen when coronary artery occlusion occurs without reperfusion or when reperfusion is achieved mechanically by primary PCI.

Finally, although the efficacy of FT to achieve thrombolysis in myocardial infarction (TIMI) grade 3 flow decreases with increasing time to treatment, primary PCI achieves TIMI grade 3 flow in >90% of STEMI patients regardless of the length of time from symptom onset to balloon inflation. The increased patency rate seen with primary PCI results in greater myocardial salvage and smaller infarct size which may protect against FWR. Although data from 23 randomized controlled trials show that primary PCI is superior to FT by significantly decreasing short-term death, non-fatal re-infarction, stroke, and the combined endpoint of death, non-fatal re-infarction, and stroke,3 the majority of STEMI patients still receive FT because of the limited availability of primary PCI. Therefore, it is crucial to know which STEMI patients are at high risk for developing the lethal complication of FWR, so that transfer for primary PCI can be considered.

Bueno et al.4 provide convincing evidence that FT markedly increases the risk of FWR in the elderly. In their analysis of 706 consecutive STEMI patients ≥75 years presenting with a first STEMI, the incidence of FWR was 17.1% in patients treated with FT when compared with 7.9% in patients who did not receive any form of reperfusion therapy and 4.9% in patients treated with primary PCI, (P < 0.0001). In multivariate analysis, elderly patients treated with FT had more than a three-fold increase in the risk of FWR when compared with those not treated with reperfusion therapy (OR = 3.62, CI 1.79–7.33), whereas primary PCI was not found to increase the risk of FWR (OR = 0.90, CI 0.34–2.34). The other predictors of FWR, female gender (OR = 1.79, CI 1.01–3.17), anterior location (OR = 2.08, CI 1.20–3.62), and longer time from symptom onset to presentation (OR = 1.92, CI 1.01–3.62), have also been shown by others to be associated with FWR in patients treated with FT.1 No
significant interaction was observed based on the type of FT agent used.

The rate of FWR was higher in this study than in some previous reports, which may reflect the authors' longstanding interest in this area and heightened attention to this diagnosis in their practice. However, given the careful diagnostic criteria used in the present study, when combined with probable underdiagnosis in previous reports, these remarkably high rates of FWR in the elderly are likely to reflect contemporary practice and are in accord with those reported by the GISSI investigators.5

These findings with respect to FWR add to the growing list of concerns with regard to FT in the elderly. In the Bueno et al.4 study, 30 day mortality rates ranged from 25 to 32%. In multivariate analyses, primary PCI was associated with lower 6–12-month mortality than no reperfusion therapy, but FT was not associated with a significant reduction in mortality. These findings support those of Thiemann et al.4 who observed an increase in adjusted mortality risk for elderly patients receiving FT vs. no reperfusion therapy. Rates of intracranial haemorrhage are also significantly increased in elderly patients who receive FT, particularly when more aggressive adjunctive antiplatelet and anticoagulant therapy is used with tPA-based FT regimens. Interestingly, older age, female gender, and absence of early beta-blocker therapy, several of the same variables that predict FWR, have been shown to predict intracranial haemorrhage.7

It is disconcerting that because of actual or perceived contraindications, most patients who present with STEMI do not actually receive any type of reperfusion therapy. These ‘ineligible’ patients are disproportionately elderly, and as expected, have significantly higher in-hospital mortality rates. Moreover, despite the fact that the elderly population is increasing in size, they have been excluded from most randomized trials for STEMI. Management decisions regarding these patients, therefore, are derived either from data obtained from observational studies or extrapolated from randomized trials enrolling healthier and younger patients. The lack of data pertaining to the growing elderly population often results in this high-risk subgroup not receiving any of the treatments considered to be standard of care. For example, in an analysis of 80 456 Medicare patients >65 years with <12 h of symptoms who were eligible for reperfusion therapy, 59 673 (74.2%) did not receive reperfusion therapy within the first 6 h and 54 989 (68.4%) did not receive reperfusion therapy at any time.8 It is not surprising, therefore, that only 46% of elderly patients with STEMI in the study by Bueno et al.4 actually received reperfusion therapy.

Clearly, this problem should be addressed by performing randomized trials evaluating the timing and type of reperfusion therapy in the elderly population. Two small trials randomized elderly patients to primary PCI or FT. In one study, primary PCI with adjunctive stenting was associated with a significant reduction in the combined endpoint of death, re-infarction and revascularization for recurrent ischaemia and a reduction in major bleeding complications (0 vs. 17%, P = 0.03) in patients >70 years,9 and in the other study, patients >75 years randomized to primary PCI had a significant reduction in the combined endpoint of death, re-infarction, or stroke compared with those treated with FT (9 vs. 29%, P = 0.01).10 A large, multicentre trial, the Senior PAMI trial, is presently randomizing STEMI patients ≥70 years with <12 h of chest pain to FT or primary PCI.

In the absence of available data from adequately powered randomized trials, what should clinicians do when presented with an elderly patient with an evolving STEMI? Clearly, the risk–benefit ratio favours primary PCI over FT and thus we recommend that patients >75 years should be transferred for primary PCI whenever a patient can be transferred in ≤2 h to a ready and waiting cardiac catheterization laboratory at a PCI centre. When this is not possible, we recommend that FT be administered if it can be done within 6 h of symptom onset, but that platelet glycoprotein IIb/IIIa inhibitors be avoided and that only unfractionated heparin (60 U/kg bolus, 12 U/kg/h infusion) be used with t-PA-based FT regimens. Results from ongoing randomized trials such as Senior PAMI will be essential in guiding future therapies for the growing elderly population, who are at remarkably high risk for death and other important complications after STEMI.

References