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EDITORIAL

Searching myocardial rescue through intermittent upper arm occlusion and lizard saliva

Hans Erik Bøtker[1]

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The prognosis following ST-segment myocardial infarction (STEMI) has improved significantly for the vast majority of patients by implementation of rapid reperfusion therapy [24, 33, 35]. Just now, the decline in mortality seems to level out [35]. Cardiac and non-cardiac comorbidities may contribute to this trend, because comorbidity increases short- as well as long-term mortality following myocardial infarction [32]. Nevertheless, the relationship between infarct size and clinical outcome persists in the reperfusion era [34]. Moreover, some patients experience increased mortality or post-infarction heart failure symptoms due to profound ischemic damage caused by extended treatment delay [36] or peri-procedural events that prolong the duration of myocardial ischemia. Consequently, a continued effort to reduce infarct size remains an important task for improvement of clinical outcome in STEMI patients undergoing rapid reperfusion [20].

Substantial experimental evidence indicates that a variety of pharmacological and mechanical conditioning treatments are effective cardioprotective modalities to reduce ischemia reperfusion injury. The concepts mainly address reperfusion injury, which may induce myocardial injury beyond the ischemic injury and account for a significant quantity of the final infarct size [19, 39]. Despite robust infarct size reduction by a variety of cardioprotective interventions in adjunct to primary percutaneous coronary intervention (pPCI) in proof-of-concept clinical studies, translation into a clinical benefit for the patients has failed until now [3, 17]. As a consequence, a multi-target approach has been proposed to intensify the cardioprotective capacity [8]. Indeed, the concept may have been implemented subconsciously in clinical practice already. STEMI patients undergoing mechanical reperfusion are treated with $P2Y_{12}$ inhibitors. Beyond their antithrombotic action, these compounds have revealed inherent cardioprotective effects albeit of varying effectiveness [7, 25, 30, 31, 37, 38].

In this light, the result of a complementary multi-target approach presented by the COMBAT-MI authors in the current issue of Basic Research of Cardiology [9] is timely and appropriate. Given the premises that exenatide activates separate cardioprotective pathways and has additive effects beyond remote ischemic conditioning (RIC) on infarct size reduction in pigs [1], the neutral results of the clinical trial, studying the individual effect of RIC, exenatide, and their combination, are disappointing. As for previous cardioprotection studies that have exposed difficulties in translating promising experimental results into a clinical benefit, we urge for valid explanations.

Transferring results from healthy young experimental animals to an aged patient population with multi-morbidity and co-medication is a trivial challenge, because a variety of concurrent diseases and drugs are well-known confounders of cardioprotective interventions [11, 26]. However, the study cohort in the COMBAT-MI trial did not seem to differ significantly from previous studies demonstrating a cardioprotective effect of RIC [5] and exenatide [27], so other factors may contribute.

The COMBAT-MI trial was a two-by-two factorial, randomized controlled, blinded, multicentre, clinical trial conducted according to current recommendations [4]. Admittedly, no trends in efficacy by any of the individual treatments or their combination are obvious. Even so, the

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✉ Hans Erik Bøtker
heb@dadlnet.dk

[1] Faculty of Health, Aarhus University, Vennelyst Boulevard 4, 8000 Aarhus C, Denmark

power of the study remains a concern because demonstration of a 20% reduction in infarct size from 24% of the left ventricle with an SD of 14% would require at least 274 patients. Only 222 patients were available for analysis mainly because more patients than expected encountered the exclusion criterion of TIMI flow > 1.

The primary outcome was infarct size measured by late gadolinium enhancement in cardiac magnetic resonance (CMR) performed 3–7 days after pPCI. The imaging-based primary outcome variable is superior to measurement of circulating biomarkers of myocardial necrosis due to a higher sensitivity and precision. Although a use of myocardial salvage indexes as end point might reduce patient need to enhance power, because it takes advantage of relating infarct size to individual area at risk and hence eliminates inter-individual variability, infarct size is superior as area at risk quantification by CMR is inaccurate [12, 13, 28]. Infarct sizes in the COMBAT-MI appeared slightly larger, on average 24% of the left ventricle, than in some but not all comparable studies averaging between 11 and 25% of the left ventricle by CMR or SPECT [5, 22, 27]. This is surprising because ischemia duration seemed shorter (137 min) than in previous STEMI studies. The difference may relate to the fact that ischemia duration was defined as time from initial symptoms to arrival to the catheterization lab, whereas other studies have used symptom to balloon time, which is in the order of magnitude of 180 min [5, 22, 27]. A reliable explanation for the larger infarct sizes in the COMBAT-MI study might be the timing of the CMR examination, which was 3–7 days following pPCI, whereas other studies have measured final infarct size after 30 or 90 days [5, 27]. Quantification of infarct size by late gadolinium uptake and CMR has been recommended at 5 ± 2 days after reperfusion [23], because several key variables have stabilized reasonably and because of its prognostic value. As a consequence of shrinkage and myocardial remodelling, the size of necrotic myocardium may still evolve over time and influence quantification of final infarct size and thus explain the discrepancies.

Granting that all patients obtained four inflations for the RIC treatment, about half of the patients in the COMBAT-MI trial received only two or fewer cycles before flow restoration. Detailed information about the post hoc sub-analysis of the patients receiving ≥ 3 cycles at the time of reperfusion ($n = 117$), who also gained no infarct size reduction, would be of benefit because the optimum timing of RIC protocol in humans is unknown. The efficacy appears to be superior in terms of infarct size reduction when given earlier than in the catheterization lab, e.g. in the ambulance during transportation to pPCI [5]. Similarly, although exenatide infusion was started before coronary artery opening in all patients, the exact time at which infusion was started is not available. Hence, neither the actually administered dose nor the plasma exendin-4 (the active component of exenatide) concentration at the time of reperfusion is available to document bioavailability of the drug, which has previously documented efficacy in a similar clinical setting [27].

Given recent disappointing results for the clinical efficacy of cardioprotective interventions in relatively low-risk STEMI patients undergoing pPCI, the question arises whether the patient cohort in the COMBAT-MI trial was an ideal target population for adjunctive cardioprotective treatment. The patients were characterized by short admission time, uncomplicated rapid reperfusion and favourable Killip status (86% Killip-I). The clinical event rates, among which cardiac death and admission for heart failure are most relevant, were really low, i.e. 1.4% for all-cause death and 3.2% for heart failure. Acknowledging that the COMBAT-MI trial was not powered for clinical outcome data, the event rates were lower than in observational all-comer studies [35] and in randomized clinical trials [10, 15, 34]. Despite the relatively large average infarct size in the COMBAT-MI trial, the finding suggests that the selection bias inherent to randomized clinical trials is a constraint for the potential of demonstrating a clinical benefit in STEMI patients undergoing pPCI. Mainly uncomplicated stable patients, who are able to give written informed consent, are recruited. Because patients at high risk for a compromised outcome and a benefit by the tested intervention include patients that experience complications, such a cardiogenic shock or cardiac arrest [6], implied or conditioned consent is necessary to ensure recruitment of the appropriate target cohort in future STEMI studies.

A recent meta-analysis revealed a median infarct size of 28.3% [17.9%, 39.5%] of the left ventricle in patients, who experienced death or heart failure vs. 17.6% [8.0%, 29.5%] in patients, who did not [34]. These findings confirm that adjunctive cardioprotective intervention should address a target population with extensive tissue damage [3, 21]. The temporal window of opportunity for modifying infarct size may be limited [14]. However, more recent data indicate that the cardioprotective effect is preserved with extended duration of ischemia beyond 6 h [29]. Thus, future studies should also investigate patients with extensive myocardial ischemia due to long symptom duration.

Nonetheless, the infarct size observed in the COMBAT-MI trial with the average magnitude of 24 ± 12% of the left ventricle should be modifiable by an effective intervention as previous studies in humans have documented a reduction within this range of infarct sizes [5, 22, 27]. The setting should therefore be useful for a proof-of-concept study. Even though the absent expected additive effect is implicit given the puzzling absence of a cardioprotective effect by any of the individual treatments in the COMBAT-MI, recruitment of cardioprotective signaling must address the multifactorial origin of an acute myocardial infarction. Thus, an effective multi-target approach probably needs to involve not only the

cardiomyocyte [18] but also the coronary microcirculation [16] and other cellular compartments of the heart, including platelets, fibroblasts, endothelial and smooth muscle cells, and immune cells [2]; optimally in an additive way.

The annoying results from the COMBAT-MI trial should not discourage future exploration of comprehensive adjunctive multi-target cardioprotective approaches beyond rapid reperfusion. The need for further infarct size reduction is still evident in high-risk patients with extensive myocardial ischemia.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

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