Intravenous Beta-Blockade for Limiting Myocardial Infarct Size
Rejuvenation of a Concept*

Robert A. Kloner, MD, PhD,a,b Eugene Braunwald, MD,c,d

After coronary thrombosis, the quantity of heart muscle that becomes necrotic (i.e., myocardial infarct size [MIS]) is an important determinant of left ventricular (LV) function and long-term clinical outcome (1). Clearly, early reperfusion of the occluded artery limits MIS and improves LV function and post-infarction survival. Substantial efforts have been directed toward developing adjunctive pharmacological therapies to further limit MIS. Numerous agents showed promise in experimental animal models, but many of these drugs failed to reduce MIS or improve outcomes in clinical trials (2). However, recent work by investigators at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) in Madrid and Mount Sinai Hospital in New York suggest that drugs tested in animal experiments and clinical studies more than 40 years ago now deserve renewed attention (3).

In 1969 and in the early 1970s, studies by Braunwald et al. (4), Maroko et al. (5), Reimer et al. (6), and Rasmussen et al. (7) showed that in open-chest anesthetized dogs, early intravenous (IV) administration of beta-blockers reduced MIS. One mechanism suggested at the time was that beta-blockers reduce the oxygen demand of ischemic, but not yet irreversibly injured, myocytes within the occluded coronary artery bed. Animal models showed that when administered either before or during coronary artery occlusion, beta-blockers reduced epicardial ST-segment elevation and preserved myocardial creatine kinase concentration (5), intramural partial pressure of carbon dioxide (8), structural damage of mitochondria (9), and microvasculature injury (7,10). Propranolol exerted an even more robust reduction of MIS when it was begun early rather than late after coronary occlusion (7). Subsequently, we demonstrated that 2 IV beta-blockers, timolol (11) and the ultra–short-acting esmolol (12), administered after the occlusion but before reperfusion reduced MIS in experimental models. These salutary effects were not observed in the presence of permanent coronary artery occlusion (i.e., in the absence of reperfusion) (13).

Clinical trials before the use of fibrinolytic therapy to induce reperfusion provided mixed results regarding the ability of IV beta-blockers to reduce MIS. Some studies were encouraging (14,15), but others showed no effect (16), which may have been related to late administration of the drug at a time when all myocytes in the occluded artery were already irreversibly damaged. Even if their viability had been temporarily preserved by the beta-blocker, “rescue” by subsequent reperfusion did not occur. Also, in some trials, use of IV beta-blockade was not randomized, making it difficult to interpret the results (17). The situation changed when myocardial reperfusion became possible. In 1991, in the TIMI II (Thrombolysis in Myocardial Infarction II) trial, Roberts et al. (18) compared the effect of immediate IV metoprolol to oral metoprolol started on day 6 in patients with ST-segment elevation myocardial infarction (STEMI) who were receiving fibrinolytic therapy. Patients receiving early IV metoprolol...
exhibited a significantly lower incidence of reinfarction and recurrence of ischemic chest pain. Based on several large randomized trials, clinicians generally agree that oral beta-blockers should be (and are) used routinely for secondary prevention in patients with post-myocardial infarction (19), but opinions remain divided regarding IV beta-blockers in the acute phase (20). Although a large number of patients have been studied in clinical trials of this therapeutic option, overall results have been mixed (21).

A new chapter regarding the role of early IV administration of a beta-blocker for limiting MIS was opened by Ibáñez et al. (22), who carried out a series of rigorous animal and clinical studies. First, using cardiac magnetic resonance imaging (CMR) to measure MIS in a pig model of STEMI, these investigators showed that IV metoprolol administered before reperfusion reduced MIS and improved LV ejection fraction (LVEF) (22). Subsequently, they reported the results of the METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial (3). They studied 270 patients with acute anterior wall STEMI undergoing percutaneous coronary intervention within 6 h of the development of symptoms. Patients were randomized to receive either IV metoprolol or a saline control solution before reperfusion; all patients received oral metoprolol commencing on the first day and continuing thereafter. MIS, assessed by CMR 5 to 7 days after STEMI, showed that infarcts were smaller in the metoprolol-treated patients (25.6 g) compared with the control group (32.0 g; p = 0.012). Additionally, MIS estimated from the area under the creatine kinase release curve was reduced, and at 5 to 7 days, LVEF was higher in the IV metoprolol group. At 6 months, LVEF remained higher in the IV metoprolol group than in the control group (48.7% vs. 45.0%; p = 0.025). The IV metoprolol group also exhibited a significantly lower rate of hospital admission for heart failure (23).

In this issue of the Journal, García-Ruiz et al. (24), from the same research group, report on an important post hoc analysis of the METOCARD-CNIC trial, coupling it with a pre-specified experimental validation study. They divided the patients enrolled in METOCARD-CNIC by the time interval between the first metoprolol bolus and reperfusion. Short interval was defined as a metoprolol-to-reperfusion time shorter than the median of 53 minutes; long interval was a metoprolol-to-reperfusion duration longer than the median. MIS, expressed as grams of LV mass determined by CMR 5 to 7 days post-infarction, was 32.4 g in the saline control group, 28.1 g in the short-interval beta-blocker group, and 22.9 g in the long-interval group (p = 0.014, analysis of variance). LVEF was improved in the longer-interval group (48.3%) compared with the saline control group (43.4%) or the short-interval group (43.9%; p = 0.01, analysis of variance). The beneficial effect on LVEF associated with longer-duration metoprolol exposure before reperfusion was maintained at 6 months. Additional analyses showed that for patients randomized to IV metoprolol, “every 10 minutes of onboard metoprolol reduces infarct size by 1.1 g,” according to the investigators (24).

Importantly, the investigators then confirmed these clinical findings in pigs subjected to 45 min of occlusion of the proximal left anterior descending coronary artery, followed by treatment with either vehicle or IV metoprolol, the latter begun either 25 min before reperfusion (long-interval group) or 5 min before reperfusion (short-interval group). At 7 days, MIS, expressed as a percentage of the left ventricle, was 27.3% in the control group and significantly smaller in the long-interval IV metoprolol group (23.3%); the short-interval metoprolol group did not produce reduced MIS. These findings by García-Ruiz et al. (24) suggest that the protection offered by the beta-blocker depended on the time interval between its administration and myocardial reperfusion; this extends to patients and pigs the findings of studies in dogs that were performed in the 1970s showing that MIS reduction is more robust when beta-blocker therapy is present during the entire period of ischemia rather than when it is administered late (7).

Therefore, consideration should be given to starting IV beta-blockade as early as possible in the course of STEMI. This could be in the ambulance, if possible, as was done by Mateos et al. (25) in a subgroup of patients in the METOCARD-CINC trial, or as soon as the patient presents to the emergency department, rather than after coronary anatomy has been defined just before reperfusion.

The finding that the longer that beta-blockade is “onboard” during the period of ischemia, the more myocardium is salvaged parallels animal data demonstrating that hypothermia, another intervention that protects ischemic myocardium by reducing myocardial oxygen needs, must be present during ischemia to reduce MIS (26,27); the longer it is present during ischemia, the smaller the infarct (28). However, the exact timing of early IV beta-blocker use in relation to coronary occlusion and reperfusion remains controversial, because a recent study with the short-acting beta-blocker esmolol found that a 24-h infusion begun immediately after the patient was transferred from the catheterization laboratory.
(thus after reperfusion was induced) significantly reduced release of enzymatic biomarkers of necrosis (29). It is unknown whether starting esmolol even earlier (during ischemia) would have resulted in an even greater reduction of necrosis.

Many adjunctive cardioprotective agents that showed promise in animal models have lacked benefit in clinical trials (2,30). The concept that early IV beta-blockade can reduce MIS was developed more than 4 decades ago and was supported by experiments that were quite primitive by contemporary standards. It is refreshing to learn that as a consequence of the rigorous animal and clinical studies carried out by Garcia-Ruiz et al. (24), this concept has been rejuvenated. Hopefully, a phase III trial looking at late clinical outcomes with the approach that they have used will now be conducted.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Robert A. Kloner, Huntington Medical Research Institutes, 10 Pico Street, Pasadena, California 91105. E-mail: kloner@hmri.org.

REFERENCES


KEY WORDS cardioprotection, metoprolol, myocardial infarct size, myocardial ischemia/reperfusion, ST-segment elevation myocardial infarction