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EDITORIAL COMMENT

Cardioprotection, Autoretroperfusion, and Therapeutic Hypothermia*

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One of the major challenges in clinical cardiology and primary percutaneous coronary intervention (PPCI), particularly in patients with ST-segment elevation myocardial infarction (STEMI) and an occluded coronary artery, is to limit reperfusion injury. Although description of the complex mechanisms responsible for such injury are beyond the scope of this editorial, reperfusion injury may undo a considerable part of the recovery of the ischemic myocardium achieved by timely reperfusion through PPCI (1). Therefore, the importance of endeavors to limit reperfusion injury remains undisputed.

In this issue of *JACC: Basic to Translational Science*, an interesting study by Choy et al. (2) is presented to assess the protective effects of selective autoretroperfusion (SARP) by a coronary sinus technique and mild hypothermia (MH) for cardioprotection of ischemic myocardium in swine. Choy et al. (2) propose their technique as an approach to be translated to the catheterization laboratory before PPCI of an obstructed coronary artery in STEMI patients or as a way of effective cardioprotection during elective high-risk PCI.

In this experimental study, the left anterior descending artery of 20 swine was occluded for 1 h. In a number of the pigs, SARP was instituted after 30 min, and in another group, this was combined with MH. In the animals with (MH-)SARP, a dramatic decrease of infarct size was found, with concomitant attenuation of multiple biochemical markers in the acute phase and with a better preservation of ejection fraction at 4 weeks.

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Choy et al. (2) should be commended for this meticulously performed study. However, some conceptual and translational limitations should be emphasized.

First, the time of coronary occlusion was limited to 1 h, and in the groups with (MH-)SARP, this protective therapy was already started at 30 min. In other words, the ischemic time in the intervention groups might have been 30 min shorter than in the control group. Therefore, it is well possible that the observed differences are mainly due to a shorter time of ischemia. A duration of ischemia of—factually—30 min might be too short to create a meaningful myocardial infarction, and it is not unlikely that in the (MH-)SARP groups, only stunning was present, rather than myocardial necrosis. In the control group, on the contrary, true necrosis might have occurred. Consequently, what this study shows anyway is that by SARP, at least adequate tissue oxygenation is guaranteed as a way of effective cardioprotection during coronary artery occlusion.

Second, the translation of this technique to the use in humans with STEMI, treated by PPCI in the catheterization laboratory, is not trivial. Choy et al. (2) claim that the SARP catheter can be introduced quickly and hence would not significantly delay the

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door-to-balloon time. However, in clinical practice, anterograde cannulation of the occluded coronary artery during STEMI, and placing a stent will generally take less time than will coronary sinus cannulation.

As such, for translation of this technique to patients with STEMI in the catheterization laboratory, a more suitable comparison between the different groups would have been to maintain the coronary occlusion in all swine for 60 min and to start the retroperfusion with or without hypothermia in the (MH-)SARP groups just shortly before (anterograde) reperfusion.

Importantly, these limitations do not apply in case of elective complex or high-risk coronary interventions, when sufficient time is available for introduction of the SARP catheter and starting (MH-)SARP before the onset of ischemia.

One of the strong features of the (MH-)SARP technique described by Choy et al. (2) is the opportunity to (retro)perfuse and protect the ischemic myocardium even while the coronary artery is still obstructed. This overcomes an important limitation of previous cardioprotective studies in patients with acute myocardial infarction.

So far, all attempts to provide cardioprotection aiming to reduce reperfusion injury in humans with STEMI—irrespective of whether it was by hypothermia or by administration of presumably protective drugs such as cyclosporine—yielded disappointing results. The paramount limitation shared by all those studies is that the protective agent (including hypothermia) came everywhere in the body except at the location where it is needed (i.e., the threatened myocardium distal to the coronary occlusion). Furthermore, reperfusion injury arises mainly in the first few minutes after opening of the occluded coronary artery (i.e., before the protective agent has the chance to be active in the area at risk of infarction).

On the contrary, by SARP, the ischemic myocardium is already reached during persistent anterograde occlusion, and its protective effect might be present and active at the time of restoration of anterograde reperfusion by PPCI.

In this respect, the method of selective anterograde intracoronary hypothermia during STEMI, as recently introduced by Otterspoor et al. (3), also comes into perspective, as discussed subsequently.

Some additional notes should be made about the use of hypothermia in the study by Choy et al. (2). Experimentally, it has been well proven that therapeutic hypothermia (4°C to 5°C decrease in myocardial temperature of the area at risk) is protective and limits infarct size in acute myocardial infarction, when started before reperfusion (4). In humans, on the contrary, such effect has never been demonstrated. By the technique described by Choy et al. (2), hypothermia was induced in the ischemic myocardium retrogradely and rapidly (within 4 min) after installation of the system. However, its magnitude in their study was probably too mild (1°C to 2°C) to be effective. Only a minor and nonsignificant benefit of MH-SARP was found compared with SARP alone.

In this context—and as an area of future development—the seminal work by Otterspoor et al. (3) should be mentioned, showing the safety and feasibility of inducing therapeutic hypothermia of at least 6°C below body temperature in patients with STEMI by selective anterograde infusion of cooled saline distal to the occlusion started 10 min before opening of the obstructed coronary artery, and using standard PCI equipment. By this technique of selective intracoronary hypothermia, local cooling (29°C to 32°C) was obtained within 60 s after starting the infusion, without noticeably affecting the temperature in the adjacent healthy myocardium and without systemic side effects. With that technique, instantaneous monitoring of distal coronary pressure and temperature is provided by a regular sensor-tipped guidewire and used for adjustment of the rate of saline infusion (3). Currently, the clinical benefit of this method is being investigated in a European, multicenter, randomized controlled, proof-of-principle study (EURO-ICE [EUROpean Intracoronary Cooling in ST-Elevation myocardial infarction]; NCT03447834) in patients with anterior wall STEMI (5).

In conclusion, the work by Choy et al. (2) addresses an important clinical problem and, despite some methodological and translational limitations, is a valuable contribution to the development of effective techniques for cardioprotection in high-risk PCI and to limit reperfusion injury in patients with STEMI.

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