EDITORIAL COMMENT

Cold Cardioplegia for Acute Infarction

A Viable Adjunct to Reperfusion Therapy?*

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Since antiquity, the myth of being able to freeze the course of
time and perpetuate life has haunted human minds. The
idea does make sense because life is biochemistry, and
biochemical reactions are exquisitely sensitive to tempera-
ture: slowing down when temperature declines and the
opposite when temperature increases. Nature itself has
successfully taken advantage of the conservative capabilities
of cooling, the most advanced and sophisticated protective
mechanisms being found in hibernating animals. In contrast
with non-hibernating animals, where hypothermia is asso-
ciated with severe arrhythmias and contractile arrest, hiber-
nating animals exhibit remarkable tolerance and resistance
to these environmental stresses. Hibernation induces adap-
tive changes in Ca^{2+} handling of myocytes whereby the
contractile force remains preserved (1). In the late 1970s,
Rahimtoola (2) used the metaphor of hibernation to explain
the adaptive contractile mechanisms operating during chronic
myocardial ischemia. Whether or not these chronic
changes, including structural abnormalities, which at best
are only partially reversible upon revascularization (3), truly
represent some form of hibernation remains elusive. How-
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Is There An Unmet Need?

Yes, there is. Although reperfusion therapy has considerably
improved patient outcome after STEMI, the optimal mo-
dalities of reperfusion remain under investigation. Even
though there is evidence that mechanical reperfusion by
direct percutaneous intervention is superior to pharmaco-
logically induced fibrinolysis, treatment delays or unavail-
ability with either therapy continues to prevent significant
myocardial salvage (“infarct size reduction”) to occur, and
reperfusion in itself causes additional damage, largely
through oxidative stress. In the future, depending on avail-
able resources, the most promising scenario may involve
pre-hospital care of STEMI, perhaps using a combined
pharmacomechanical approach. Thus, there remains a need
for adjunctive therapy both prior to reperfusion in order to
increase the tolerance to ischemia and during reperfusion in
order to limit reperfusion damage. However, any adjunctive
therapy of value will have to be compatible with each of these
possible reperfusion scenarios.

Catheter-Based Transcoronary Hypothermia

In the first part of this pre-clinical study, which was
performed in open-chested pigs, Otake et al. (4) have
studied the effect of reducing the local intramyocardial
temperature by some 3°C while coronary artery occlusion
was maintained. As compared with a control group
receiving the same volume (2.5 ml/min) of normothermic
saline, infarct sizes were significantly reduced by an
impressive 75%, as clearly shown by the Reimer (5) plot
of necrotic versus risk area (Fig. 7 of their study). Other
indexes were significantly improved, including reduced
rate of arrhythmias, increased left ventricular dP/dt max,
maintained coronary flow velocity reserve, and reduced
biomarker release.

In the second part of the study, hypothermic saline
(8 ml/min) was delivered at the time of reperfusion. As
compared with a control group receiving no intracoronary
infusion, no significant changes were observed in the in-
dexes related to infarct size. The flow velocity reserve was
improved at 60 min (but no longer at 180 min), and the
release of isoprostans was decreased, as a marker of reduced
oxidative stress.

A detailed analysis of Figure 1 in the study by Otake et al.
(4) reveals that the time required to reach the desired
myocardial hypothermia varies from 20 to 40 min after
starting the infusion, presumably depending on the inter-
play between flow rates of the infusion and the coronary
flow. Most interestingly, when reperfusion was restored in
Study 1, the myocardial temperature returned to baseline
values despite continued infusion of hypothermic saline at
the rate of 2.5 ml/min. This finding has prompted the use
of higher flow rates in Study 2, allowing for a faster
achievement and maintenance of the desired temperature
decrease, despite ongoing reperfusion.

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Because intracoronary flow rates had to be increased up to at least twice the normal baseline coronary flow, as can be estimated from the size of the risk area of the left ventricle, the authors have verified that no excessive edema resulted. Although this represents a worthwhile finding, the authors have introduced a flaw in the design of Study 2. Indeed, the control group of animals did not receive any coronary infusion. Strictly speaking, one cannot exclude that the intracoronary infusion of normothermic saline could have similar beneficial effects on indexes of microcirculatory function than those observed with hypothermia. Indeed, in the presence of angiographic no-reflow, increasing coronary flow by infusion of adenosine or other vasoactive agents was shown beneficial (6).

**Potential Clinical Relevance**

Prior clinical studies on the effect of cooling during reperfusion treatment of STEMI have failed to show significant benefit (7). Limitations of the therapy were related to shivering and systemic effects of reducing total body temperature. Targeted approaches to the myocardium have only been tested in animal models and require access to the pericardium (8). Although feasible, this approach entails an additional invasive procedure that exposes the already acutely ill patient to incremental treatment-related risks. Therefore, the use of a catheter-based transcoronary approach would seem extremely appealing, in particular in patients already submitted to mechanical reperfusion in whom invasive procedures are performed on a routine basis. Also, the current approach was demonstrated not to cause any changes in core body temperature. Thus, from an instrumental viewpoint, catheter-based transcoronary hypothermia as proposed by Otake et al. (4) seems like a potentially useful adjunct to reperfusion therapy for STEMI.

However, the key question remains whether the current pre-clinical data are robust enough to support early translation in the clinic. The most impressive results were obtained in Study protocol 1, which provides strong proof of concept but unfortunately is not relevant to clinical practice. Catheter-based transcoronary hypothermia obviously requires invasive access to the coronaries, under which circumstances coronary occlusion will not be maintained for 60 min (Fig. 1 in Otake et al. [4]). Study protocol 2 is more relevant to the practice of direct percutaneous coronary intervention, but paradoxically, the observed results of hypothermic coronary perfusion are modest, limited to minor microcirculatory changes, and perhaps obtainable with infusion of normothermic saline (not tested). As to the large number of patients treated either with systemic fibrinolysis or in the future during the pre-hospital phase of STEMI, catheter access will not be available, and other approaches than the currently proposed transcatheter delivery of cold saline will be required.

**Summary and Future Investigations**

The current study by Otake et al. (4) adds further evidence to the available data that support the strong cardioprotective effect of myocardial cooling, when applied during coronary occlusion and evolving myocardial infarction. The issue remains whether cardioprotection will be maintained with reperfusion and, if so, by which means selective myocardial cooling will be achievable in the various possible reperfusion scenarios. Of paramount importance and not addressed in the study by Otake et al. (4) is the understanding of the underlying mechanisms. As indirectly demonstrated, one of the protective actions of cooling is probably mediated by a reduction in the oxidative stress. To what extent hypothermia also suppresses the inflammatory response during reperfusion, as was shown in models of ischemia-reperfusion in other organs (9), remains to be investigated.

The current approach could easily be combined with direct percutaneous coronary intervention. However, further positive pre-clinical studies will be required before the potential role of the proposed catheter-based transcoronary hypothermia can be formally tested as an adjunctive therapy to reperfusion in patients with STEMI. It is highly desirable that these future studies are designed as to mimic as closely as possible the clinical scene.

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