

Authors: E. AGABITI-ROSEI - G. AMBROSIO - L. BADIMON - J.P. BASSAND - A. BAYÉS DE LUNA - M.E. BERTRAND - E. CHAZOV - S. CHIERCHIA - J. CLELAND - D. CLEMENT - D. COKKINOS - N. DANCHIN - R. DIETZ - P. DOMINIAC - I. EDES - E. ERDMANN - R. FERREIRA - H.R.FIGULLA - W. FLAMENG - I. GRAHAM - G. JACKSON - W. JANUSZEWICZ - J.C. KASKI - P. KEARNEY - W. KLEIN - F. KOLBEL - M. KOMAJDA - W. KÜBLER - J.L.LOPEZ-SENDON HENTSCHEL - G. MANCIA - W.J. MCKENNA - T. MEINERTZ - J.MLCZUCH - D. MULCAHY - E. O'BRIEN - A. OTO - J. PAPP - W.J. PAULUS - J. POLONIA - I. PRÉDA - L.A. PROVIDENCIA - J. REID - W.J. REMME - W. RUZYLO - Z. SADOWSKI - P. SERRUYS - P. SLEIGHT - J. SOLER-SOLER - J. SOMERVILLE - P.G. STEG - H.A.J. STRUIJKER BOUDIER - B. SWYNGHEDAUW - L. TAVAZZI - M. TENDERA - P. TOUTOUZAS - A. VAHANIAN - J.L. VANOVERSCHELDE - J. WIDIMSKY - M. YACOB

New therapies to protect the heart from reperfusion injury in acute myocardial infarction

Effective treatment of ST-elevation myocardial infarction involves reperfusion with primary percutaneous coronary intervention (PCI) or thrombolysis, which limits the necrotic area, thus preserving left ventricular function.¹ Myocardial reperfusion, however, can have detrimental consequences, as it can per se cause myocardial injury ("myocardial reperfusion injury").² Protecting the heart against this additional form of injury would be desirable, as it can account for up to 50% of the infarct area. Interestingly, although the molecular basis of ischemia-reperfusion injury is relatively well understood, attempts to antagonize the deleterious effects of molecules that appear to mediate myocardial damage during reperfusion have not been extremely successful.²

New approaches have been suggested to tackle this important problem. One of these is "ischemic postconditioning," which has been shown to reduce the size of the myocardial infarction (MI), and consists on delivering several low-pressure inflations of the angioplasty balloon during primary PCI to temporarily reocclude the coronary artery. Of interest, the beneficial effects of ischemic postconditioning can be achieved by pharmacological interventions, ie, adenosine and atrial natriuretic peptide, that activate "endogenous prosurvival protein kinases of the reperfusion-injury salvage kinase pathway."^{2,3}

Recently it has been suggested that the protective actions of ischemic postconditioning and some pharmacological interventions are mediated by their effects on the mitochondrial permeability-transition pore.⁴ As reported by Hausenloy and Yellon,⁴ under certain pathologic conditions, the inner mitochondrial membrane can undergo changes in permeability⁵ that make it permeable to protons and solutes that alter the mitochondrial membrane potential, affect oxidative phosphorylation, and lead to cell death.⁴ The immunosuppressant cyclosporine is an inhibitor of the opening of the mitochondrial permeability-transition pore⁶ and first implicated the mitochondrial permeability-transition pore as a major factor in ischemia-reperfusion injury.

Of interest, Piot et al⁷ showed, in a small randomized pilot study involving 58 AMI patients, that the administration of cyclosporine (intravenous bolus of 2.5 mg/kg of body weight before undergoing PCI can limit infarct size, as assessed by the release of creatine kinase and troponin I and magnetic resonance imaging [MRI] on day 5 after infarction).

The cyclosporine and control patients did not differ regarding ischemic time, the area at risk, and ejection fraction before PCI. The release of creatine kinase was significantly reduced in the cyclosporine group compared with control patients, but troponin I was not significantly reduced. On day 5 of the AMI, the absolute mass of the infarcted tissue on MRI was significantly reduced in the cyclosporine group compared with the control group. Of interest, cyclosporine was not associated with serious side effects.

These findings suggest that the administration of cyclosporine at the time of reperfusion may have important clinical implications, as the use of this agent was associated with a smaller infarct by some measures than that seen with placebo. Piot et al's findings⁷ are also consistent with those of other clinical studies that showed that the cardioprotective benefits of these types of interventions are almost restricted to patients with large anterior AMIs, as pointed out by Hausenloy and Yellon³ in a recent editorial article.

Thus in patients undergoing primary PCI, acting on the mitochondrial permeability-transition pore can have a protective effect against reperfusion injury and result in reduced AMI size. The Piot study⁷ is likely to stimulate large, multicenter studies to establish whether this new form of treatment that targets the opening of the mitochondrial permeability-transition pore will truly benefit patients with ST-elevation AMI. Undoubtedly, if these findings are confirmed in future studies, patient outcome may improve significantly with the use of this new therapeutic strategy.

J.C. KASKI - London, UK

References: 1. Antman EM et al. *Circulation*. 2004;110:588-636. 2. Yellon DM, Hausenloy DJ. *N Engl J Med*. 2007;357:1121-1135. 3. Hausenloy DJ, Yellon DM. *N Engl J Med*. 2008;359:518-520. 4. Hausenloy DJ, Yellon DM. *J Mol Cell Cardiol*. 2003;35:339-341. 5. Hunter DR, Haworth RA. *Arch Biochem Biophys*. 1979;195:453-459. 6. Crompton M et al. *Biochem J*. 1988;255:357-360. 7. Piot C et al. *N Engl J Med*. 2008;359:473-481

All texts for *The European Cardiologist - Journal by Fax* are available on our website: www.servier.com

In the event of any questions, or if you wish to receive the referenced publications, please contact fax n° 01 55 72 75 02

Medical service from Serdia Pharmaceuticals
Makers of

COVERSYL[®]
PERINDOPRIL *Once daily*

NATRILIX *SR*
1 TABLET DAILY

FLAVEDON *MR*
2 tablets daily

SERDIA PHARMACEUTICALS (INDIA) PVT. LTD.

Serdia House, Off Dr. S.S. Rao Road, Parel, Mumbai 400 012.

Under Licence from: Les Laboratoires Servier, France. Visit us at: www.serdia-pharma.com

