Myocardial Salvage, AT₁-Receptor Blockade, AT₂-Receptor Activation and Coronary Collaterals

The article by Jalowy et al. (1) supports the hypothesis that the cardioprotective effect of AT₁-receptor blockade involves angiotensin II-induced AT₁-receptor activation, bradykinin and prostaglandins. This vascular mechanism (AT₁-receptor activation mediates proliferation and vasoconstriction, and AT₂-receptor activation opposes these) might be especially important in patients with heart failure where AT₂-receptors are dominant (2). The authors insightfully highlighted the conflicting results of AT₁-blockade in different experimental models (1). Unfortunately, they confused AT₁- and AT₂-receptors (page 1787, second column, second paragraph, lines 3 to 11; page 1792, first column, line 7) and made erroneous statements about AT₁- and AT₂-receptor activation and blockade. Thus, on page 1787, AT₂-receptor activation (not AT₁) increases kinin formation in isolated dog coronary arteries; attenuation of left ventricular dilatation after myocardial infarction in rats by AT₁-receptor blockade is abolished by AT₂-receptor blockade (not AT₁); a kinin-mediated mechanism secondary to activation of the AT₂-receptor may contribute to cardioprotection achieved by AT₁-receptor blockade (not AT₂).

The finding of a dramatic reduction in infarct size after only 30 min of pretreatment with intravenous candesartan (an AT₁-receptor antagonist) in an in vivo, anesthetized minipig model of 90-min “low-flow ischemia” and 120-min reperfusion (1) also confirms reports of in vitro evidence of cardioprotection after chronic pretreatment (>30 min) with AT₁-receptor antagonists. However, patient groups in whom benefits of pretreatment might be applicable need to be identified and studied. One such group is the hypertensive patient who is prone to heart failure where AT₂-receptors are dominant (2). The authors (1) did not mention that dramatic myocardial salvage and limitation of early remodeling with the AT₁-receptor antagonist L-158,809, given intravenously for 48 h (0.1 mg/kg bolus and 0.6 mg/kg/min infusions) after anterior myocardial infarction in the in vivo dog model, has already been reported (3). However, Jalowy et al. (1) elegantly produced coronary hyperfusion in the minipig by adjusting a roller pump to reduce systolic transmural flow (radioactive microspheres) in samples from the site of the crystals, their finding of decreased infarct size (albeit using the TTC [triphenyl tetrazolium chloride] technique) (1) underscores the cardioprotective effect of AT₁-receptor blockade in models of low-flow ischemia (in dogs). It is pertinent that a pig heart has poorly developed collaterals (resembling patients without longstanding coronary disease or ischemia) so that acute coronary occlusion results in no reflow ischemia (4). In contrast, a dog heart has a rich collateral supply (resembling patients with longstanding coronary disease and ischemia) so that acute coronary occlusion results in low-flow ischemia (5). The argument that low-flow allowed the drugs (PD 123,319 i.c., HOE-140 i.c. and indomethacin i.v. given before and during ischemia) to reach the ischemic zone in their modified minipig model (1) is therefore probably valid. However, because Jalowy et al. (1) only report transmural flow after 90-min ischemia but not flow (or hemodynamics) after 120 min of reperfusion, one cannot be certain of “reflow” or “no-reflow” in their model.

The demonstration of a decrease in slope of the relation between flow after 5 min of ischemia and subsequent infarct size (as percent of risk region) with candesartan (1) is interesting. However, a similar effect between flow after 90-min ischemia and 120-min reperfusion (when infarct size was measured) would have been more convincing. Demonstration of a reduction of the slope of the relation between infarct size (after ischemia and reperfusion) and the risk region (6) would have provided definitive evidence of myocardial salvage with candesartan.

Jalowy et al. also hinted on the converse hypothesis (page 1792, first column) whereby AT₂-receptor blockade might redistribute AngII toward AT₁-receptors and cause their activation (1). However, AT₂-receptor blockade with PD 123,319 did not increase infarct size, but rather, suggested a slight reduction that was not statistically significant (1). They acknowledged that acute AT₂-receptor blockade is cardioprotective in the in vitro isolated working heart model, where AT₁-receptor blockade has a deleterious effect on recovery of contractile function (1,7). They recognized that an AT₁-receptor-mediated positive inotropic effect on the myocardium is the most likely mechanism for this previously reported improvement of contractile function with AT₂-receptor blockade after ischemia-reperfusion (7). This AT₁-receptor-mediated, nonvascular, second mechanism of cardioprotection might be important and requires further study.

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REFERENCES