Selective pressure-regulated retroinfusion of coronary veins. Selective retroinfusion of coronary veins has been shown to protect against acute myocardial ischemia in patients and in in vivo experiments.\textsuperscript{1,2} The efficacy of retroinfusion is clearly dependent on two factors. First, selective catheterization of the vein draining the ischemic myocardium is necessary to facilitate and target retrograde delivery to the ischemic myocardium without affecting antegrade blood flow to non-ischemic tissue at the same time.\textsuperscript{1} Access to different myocardial regions is possible through the coronary veins (Figure 1), as has been demonstrated in high-risk patients undergoing retroinfusion-supported stent implantation.\textsuperscript{2}

Second, pressure regulation of retrograde flow (Figure 2) is a prerequisite to optimize efficacy by avoiding under- or over-perfusion of the ischemic myocardium. Myocardial protection was found to be dependent from the individual venous anatomy, reflecting different venous capacities and the existence of arteriovenous and venovenous shunts as well as thebesian’s veins. Furthermore, efficacy of retroinfusion was dependent on coronary venous pressure in studies with non-pulsatile and pulsatile retrograde flow (Figure 3).\textsuperscript{1} As a consequence, retrograde blood flow has been adapted to the individual coronary venous system by using a pressure-regulated device for selective retroinfusion. The clinical safety and efficacy of this device have been demonstrated in patients undergoing high-risk percutaneous transluminal coronary angioplasty (PTCA) of an unprotected main stem or a main stem equivalent stenosis.\textsuperscript{2,3}

Targeting of regional drug delivery to ischemic myocardium by selective retroinfusion. Regional drug delivery by selective pressure-regulated retroinfusion relies on the concept that tissue binding and myocardial concentrations of a drug can be substantially increased by prolonging contact time of the drug with the myocardium as a consequence of the delivery through the coronary veins. Indeed, angiographic studies in pigs and humans showed that pressure-regulated retroinfusion is able to prolong passage time of contrast agent by about 10-fold compared to antegrade delivery.\textsuperscript{6} Selective retroinfusion of coronary veins enhances myocardial concentrations of β-blockers and calcium antagonists in ischemic myocardium, as has been shown by other groups.\textsuperscript{3,4} In addition, we could demonstrate that pressure-regulated retroinfusion was able to target dobutamine selectively to the ischemic myocardium without systemic effects.\textsuperscript{10} Similar results were obtained in patients undergoing retroinfusion-supported high-risk PTCA showing inotropic effects of dobutamine in the targeted left anterior descending coronary artery (LAD) region during ischemia.\textsuperscript{3} Furthermore, regional delivery of an ACE-inhibitor during ischemia was well tolerated and attenuated regional leukocyte activation as determined by MAC-1 expression.\textsuperscript{11} From these observations, we infer that selective pressure-regulated retroinfusion is able to target and enhance drug delivery to ischemic myocardium which is of increasing interest for gene transfer and therapeutic angiogenesis.

Gene transfer to ischemic myocardium by selective retroinfusion. Following the concept of regional drug delivery by selective retroinfusion, the efficacy and selectivity of percutaneous retrograde transluminal gene
delivery (PTRGD) using continuous pressure-regulated retroinfusion (Figure 2) was studied in pigs.6 Adenoviral-mediated reporter gene transfer could be substantially increased by retrograde delivery through the coronary veins compared to antegrade delivery into the coronary artery (Figure 4). After two retrograde treatments of 10 minutes, a fairly homogeneous distribution of gene transfer was observed showing no difference between proximal and distal probes of the targeted LAD region (Figure 5). Gene transfer to the endocardial probes was somewhat less pronounced, but still at considerable levels of expression. Of note, gene transfer was targeted exclusively to the LAD region and no adenoviral transfection was detected in the nontargeted circumflex region [by polymerase chain reaction (PCR) technique]. However, systemic contamination during PTRGD cannot be excluded due to the presence of venovenous and venoarterial shunts, although no transfection of noncardiac tissues was detected in this study.

**Implications for therapeutic angiogenesis.** Therapeutic angiogenesis is an emerging option for the treatment of patients with severe symptomatic coronary artery disease who do not respond to conventional therapy such as balloon angioplasty and bypass surgery. Selective catheterization of the coronary veins (Figure 1) provides a unique intravascular access to the ischemic myocardium, which cannot be reached through severely diseased or occluded coronary arteries. Pressure-regulated retroinfusion may target regional delivery of recombinant growth factors, DNA-carrying liposomes or viral gene vectors encoding for angiogenic proteins.

With regard to recombinant angiogenic growth factors, selective pressure-regulated retroinfusion may enhance and prolong tissue binding to the ischemic myocardium. Indeed, we were able to show that tissue binding of radioactively labeled basic fibroblast growth factor (bFGF) was substantially increased after retrograde delivery in a chronic pig model.10 Moreover, functionally relevant arteriogenesis and angiogenesis in the targeted LAD region were observed three weeks after a 30-minute retrograde delivery of bFGF. Delivery of recombinant growth factors into the coronary arteries is certainly
limited by systemic contamination and associated side effects. In contrast, retrograde delivery into coronary veins may be extended to several hours as a consequence of more selective delivery of growth factors into ischemic myocardium. Prolonged treatment of patients with acute myocardial infarction and cardiogenic shock has been accomplished safely using the Myoprotect™ system (PTC, Austria).

Catheter-based retrograde DNA delivery using liposomes has been studied in a chronic pig model of ischemia and reperfusion injury.13 Targeted delivery of NFκB decoy oligonucleotides into ischemic myocardium attempted to inhibit subacute endothelial activation. Selective retroinfusion of NFκB decoy oligonucleotide immediately before reperfusion resulted in a subsequent downregulation of

Figure 3. Pressure-dependent efficacy of selective retroinfusion. Regional myocardial function (subendocardial segment shortening in the ischemic region) during balloon occlusion of the left anterior descending coronary artery supported by selective pressure-regulated retroinfusion using different pre-set pressures in a randomized protocol. SSR = selective suction and retroinfusion; SCVOP = systolic coronary venous occlusion pressure. ‘p < 0.001 vs. control.

Figure 4. Reporter gene expression seven days after adenoviral gene transfer of 2.5 x 10⁹ pfu Ad.rsv-Luc using antegrade or retrograde delivery during 10 minutes of ischemia. LAD = left anterior descending artery; CX = circumflex artery; n.s. = nonsignificant; p = p-value. Modified from reference 6.

Figure 5. Distribution of reporter gene expression in the targeted left anterior descending coronary artery region 7 days after retrograde delivery during 2 x 10 minutes of ischemia. Modified from reference 6.
NFκB activation as a key regulator of subacute endothelial activation. This inhibition of NFκB activation was associated with a decrease in infarct size and a preservation of regional myocardial function 7 days after ischemia. Thus, liposome-mediated DNA delivery by selective retroinfusion was shown to be feasible and functionally relevant. Therefore, this strategy may also be used for delivery of angiogenic growth factors.

Whether sustained production of growth factors can be induced by adenoviral-mediated PTRGD is currently under investigation using a third-generation adenovirus, which should reduce immunoresponse. As long as sufficient transfection and gene delivery into ischemic myocardium can be provided by PTRGD, this approach may overcome some of the present limitations of adenoviral gene transfer for angiogenesis.

REFERENCES


