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SPECIAL ISSUE

Alterations in vasomotor control of coronary resistance vessels in remodelled myocardium of swine with a recent myocardial infarction

Dirk J. Duncker · Vincent J. de Beer · Daphne Merkus

Abstract The mechanism underlying the progressive deterioration of left ventricular (LV) dysfunction after myocardial infarction (MI) towards overt heart failure remains incompletely understood, but may involve impairments in coronary blood flow regulation within remodelled myocardium leading to intermittent myocardial ischemia. Blood flow to the remodelled myocardium is hampered as the coronary vasculature does not grow commensurate with the increase in LV mass and because extravascular compression of the coronary vasculature is increased. In addition to these factors, an increase in coronary vasomotor tone, secondary to neurohumoral activation and endothelial dysfunction, could also contribute to the impaired myocardial oxygen supply. Consequently, we explored, in a series of studies, the alterations in regulation of coronary resistance vessel tone in remodelled myocardium of swine with a 2 to 3-week-old MI. These studies indicate that myocardial oxygen balance is perturbed in remodelled myocardium, thereby forcing the myocardium to increase its oxygen extraction. These perturbations do not appear to be the result of blunted β-adrenergic or endothelial NO-mediated coronary vasodilator influences, and are opposed by an increased vasodilator influence through opening of K_{ATP} channels. Unexpectedly, we observed that despite increased circulating levels of noradrenaline, angiotensin II and endothelin-1, α-adrenergic tone remained negligible, while the coronary vasoconstrictor influences of endogenous endothelin and angiotensin II were virtually abolished. We conclude that, early after MI, perturbations in myocardial oxygen balance are observed in remodelled myocardium. However, adaptive alterations in coronary resistance vessel control, consisting of increased vasodilator influences in conjunction with blunted vasoconstrictor influences, act to minimize the impairments of myocardial oxygen balance.

Keywords Myocardial infarction · Swine · Coronary blood flow · Myocardial oxygen balance · Exercise

1 Introduction

Heart failure constitutes a major cardiovascular disorder of which the incidence and prevalence are increasing, principally due to an increased survival of acute myocardial infarction (MI) in conjunction with an ageing population. The mechanism underlying the progressive deterioration of left ventricular (LV) dysfunction towards overt heart failure remains incompletely understood, but may involve (1) loss of cardiomyocytes through apoptosis [75], (2) a primary reduction in contractile function of the surviving myocardium [97], and/or (3) alterations in extracellular matrix leading to progressive LV dilation [87]. In addition, myocardial blood flow (MBF) abnormalities, resulting in impaired myocardial O_2 delivery to the non-infarcted regions (leading to secondary contractile dysfunction and/ or enhanced apoptosis), have been suggested to contribute to the progression of LV dysfunction after MI [99]. For example, in vivo studies in rats [54, 55] and swine [108] indicate a reduction in MBF reserve of up to 35% in the surviving remodelled LV myocardium, 3–8 weeks after infarction. Furthermore, in patients with overt heart failure

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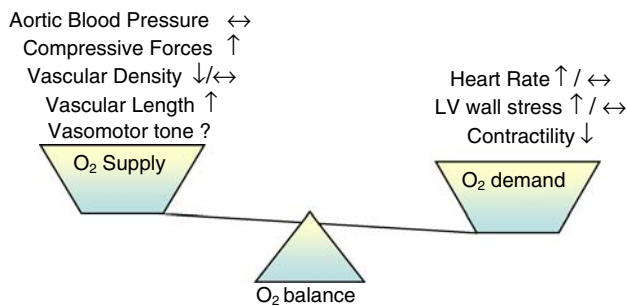e-mail: d.duncker@erasmusmc.nl

Aortic Blood Pressure ↔
Compressive Forces ↑
Vascular Density ↓/↔
Vascular Length ↑
Vasomotor tone ?

O₂ Supply

Heart Rate ↑ / ↔
LV wall stress ↑ / ↔
Contractility ↓

O₂ demand

O₂ balance

Fig. 1 Alterations in determinants of oxygen supply and demand in remodelled myocardium in swine with a 3-week-old myocardial infarction (*MI*). The net effect of these alterations is a decrease in oxygen supply/demand ratio

[94], but also in patients with only asymptomatic LV dysfunction [95], flow reserve is reduced in the non-stenotic myocardial regions. In line with these clinical observations, we observed in a porcine model of post-infarct remodelling that during increased O_2-demand induced by exercise, the increase in coronary blood flow (CBF) is impaired resulting in perturbations in oxygen delivery [43, 70]. The reduction in flow reserve and the perturbed oxygen delivery during exercise are caused, at least in part, by insufficient growth of the coronary vasculature to maintain flow capacity commensurate with myocardial hypertrophy, in conjunction with a decrease in diastolic pressure time index resulting from the elevated heart rate and particularly elevated LV diastolic pressures [43]. In addition, coronary vasomotor tone may also be increased secondary to neurohumoral activation and endothelial dysfunction, further adding to the perturbations in CBF. However, little is known about the alterations in vasomotor control in coronary resistance vessels within remodelled myocardium (Fig. 1). For this reason we undertook a series of studies to determine whether neurohumoral (autonomic nervous system and renin-angiotensin system), local metabolic, and endothelial control mechanisms of coronary resistance vessel tone are altered in swine with remodelled myocardium produced by a recent MI.

2 Characteristics of LV remodelling and dysfunction after MI in swine

Left ventricular remodelling was produced by permanent ligation of the left circumflex coronary artery. This ligation results in a circumscribed transmural infarction of the lateral LV wall, comprising 20–25% of the total LV [82, 96]. LV dysfunction in awake resting MI swine is characterised by 20–30% decreases in cardiac output, stroke volume and LVdP/dt_{max} and a tripling of LV filling

pressure. This difference between LVdP/dt_{max}, cardiac output and stroke volume in normal and MI swine remained constant between ~ 10 and ~ 32 days, indicating that the degree of LV dysfunction and the circulatory adaptations in MI were stable during this observation period [43]. Similarly, we observed that already during the first week after infarction significant LV remodelling occurs, consisting of LV dilation and hypertrophy that remain fairly stable between 1 and 6 weeks after infarction [98]. During exercise, cardiac output, LV systolic pressure and LVdP/dt_{max} increased almost in parallel in MI and normal animals up to 3 km/h, after which curves diverged (Fig. 2); 4 km/h was also the maximally attainable exercise level for most MI swine.

Left ventricular dysfunction produced by MI results in neurohumoral activation, characterized by a trend towards elevated plasma levels of catecholamines, but normal circulating levels of renin, angiotensin II and aldosterone at rest. The latter may have been due to the increments in atrial natriuretic peptide (ANP) and endothelin, which can suppress renin and aldosterone release [83]. In resting MI swine, ANP doubled within 24 h, recovered to 50% above normal values within 2 weeks and remained stable between 2 and 6 weeks after infarction, while renin and norepinephrine levels remained normal under resting conditions [98]. In contrast to the discrete neurohumoral activation in resting swine with MI, exercise resulted in exaggerated increases in catecholamines and ANP and increases in endothelin, angiotensin II, and aldosterone (Fig. 3). While resting circulating levels of norepinephrine were still normal and the relative sympathetic drive in response to exercise was preserved in MI, the cardiac responsiveness to exercise (both heart rate and LVdP/dt_{max}) was already blunted 3 weeks after infarction [43], likely due to β-adrenoceptor desensitization and/or downregulation [100].

3 Myocardial O₂ balance in remodelled myocardium

Marked decreases in myocardial perfusion occur in pacing-induced severe heart failure in swine [88] and dogs [85, 90], especially in the more vulnerable subendocardial layers. Although one study in dogs indicated that the lower MBF is principally the result of a lower myocardial O_2 consumption (MVO_2) [90], studies in swine suggest that the impaired perfusion is, at least in part, responsible for the deterioration of LV function because the interstitial edema and disruption of collagen fibers in the subendocardium resemble the ultrastuctural changes that occur with recurrent ischemia [49, 89]. In animal models of severe pressure-overload induced LV hypertrophy, selective underperfusion of the subendocardium can produce myocardial

Fig. 2 Cardiovascular responses to exercise in normal swine and swine with a ~3-week-old MI. 0_L = lying, 0_S = standing. Data are mean ± SEM; *$P < 0.05$ versus 0_L, †$P < 0.05$ MI versus normal a corresponding exercise level. Data are from Haitsma et al. [43]
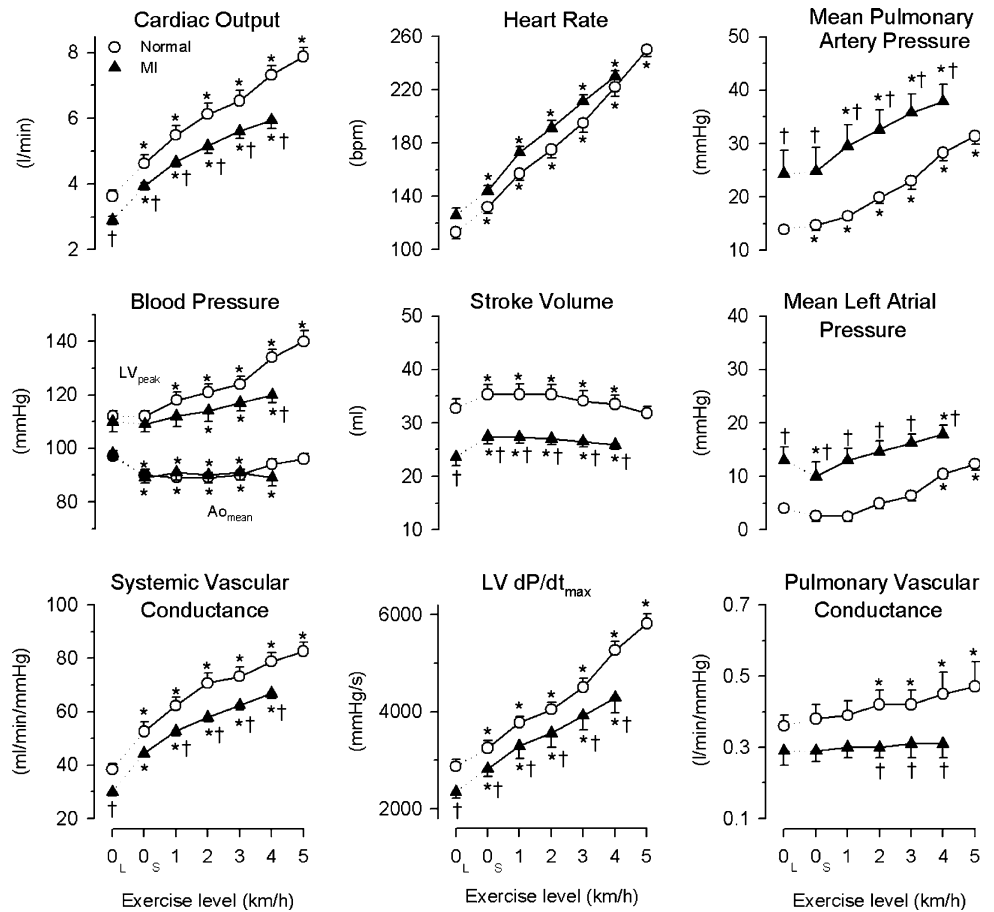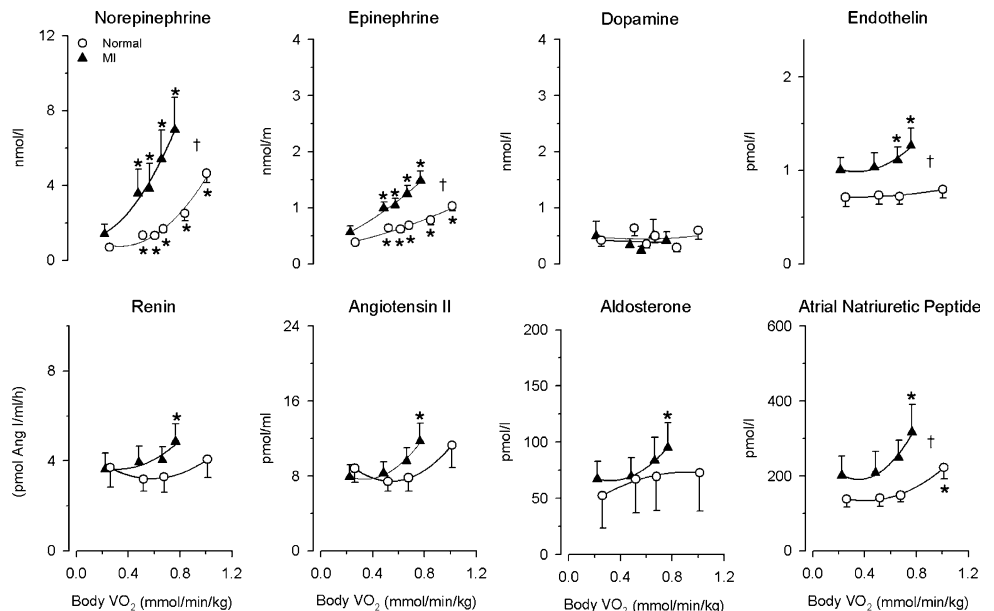

Fig. 3 Neurohumoral responses in exercising swine with a ~3-week-old MI. In the norepinephrine, epinephrine and dopamine panels, data shown for N represent 0_L, 1, 2, 3, 4 and 5 km/h and data for MI represent 0_L, 1, 2, 3 and 4 km/h. In all other panels, data shown for N represent 0_L, 1, 3 and 5 km/h and data for MI represent 0_L, 1, 3 and 4 km/h. Mean data points were fitted with second order curves. VO_2 = O_2-consumption. Data are mean ± SEM; *$P < 0.05$ vs 0_L, †$P < 0.05$ MI versus Normal. Data are from Haitsma et al [43]

ischemia during exercise and result in post-exercise myocardial stunning [2, 102]. The contribution of perfusion abnormalities in the remote surviving myocardium to LV dysfunction after a MI remains unclear. Studies in rats

demonstrated a 25–40% reduction in coronary flow reserve in the surviving myocardium at four [55] and eight [54] weeks after MI. Similarly, maximum subendocardial blood flow was blunted by 40% in anesthetized swine with heart

failure 3 weeks after a MI [108]. We hypothesized that the decreased flow reserve could limit the increase in MBF to the hypertrophied myocardium during exercise when hemodynamic abnormalities and neurohumoral activation are exacerbated, thereby impairing myocardial O_2-supply.

Three weeks after infarction, blood flow per gram of myocardium in the (remote) LV anterior wall of resting swine with MI was similar to that in normal animals (Fig. 4), confirming previous studies in rats and swine [54, 55, 108]. Interestingly, we observed a trend towards slightly higher blood flows in the outer two layers ($P = 0.09$), suggesting that despite hypertrophy of the surviving myocardium, metabolic demand in the outer, but not the inner, layers was still slightly elevated, 3 weeks after infarction [43]. During exercise, MBF increased but was redistributed in favor of the subepicardium in MI compared to normal swine. These perturbations were most likely due to increased extravascular compressive forces, resulting from a reduction in diastolic time fraction (secondary to impaired relaxation and increased heart rate) and elevated LV filling pressures [43, 97], that impede MBF, particularly in the subendocardial layers. The decreased MBF necessitated a small increase in O_2 extraction that

resulted in a slightly lower coronary venous O_2 tension (Fig. 4), which actually may have been underestimated as the lower myocardial capillary density in swine with MI possibly prevented a greater increase in O_2 extraction [43, 70]. The observation that O_2 extraction was forced to increase indicates that increases in extravascular forces are not fully compensated by a concomitant lowering of coronary vasomotor tone in remodelled myocardium during exercise. These observations prompted us to further investigate the control of coronary vasomotor tone in remodelled myocardium during exercise.

4 Vasomotor control of the coronary microcirculation in remodelled myocardium

4.1 Neurohumoral control

Cardiac dysfunction is accompanied by a hemodynamic defense reaction consisting of salt and water retention, peripheral vasoconstriction and cardiac stimulation, which serves to partially restore cardiac output and to increase systemic vascular resistance in order to maintain arterial pressure [56]. An integral part of this defense reaction involves alterations in autonomic balance, consisting of an increase in sympathetic activity and a decrease in parasympathetic activity [56].

4.1.1 Sympathetic control

In patients with advanced heart failure plasma noradrenaline levels are already increased under resting conditions [11, 36]. These increased levels result principally from increased sympathetic nerve activity although impaired reuptake may also contribute [56]. Prolonged exposure to elevated noradrenaline levels results in desensitization and downregulation of the β-adrenergic receptors [8, 32, 101]. During exercise, the increases in catecholamine levels are exaggerated in patients with heart failure as compared to healthy controls [35], which is aimed at maintaining chronotropic and inotropic responses to exercise [34].

Also in swine with LV dysfunction produced by a 2–3-week-old MI, we observed exaggerated increases in arterial and coronary venous catecholamine levels during treadmill exercise [23, 43], at a time when resting catecholamine levels were still in the normal range [43, 98]. The exaggerated exercise-induced increases in catecholamine levels reflect increased sympathetic activity, which acts to maintain the chronotropic and inotropic responses to acute exercise. This concept is supported by the observation that β-adrenoceptor blockade produced slightly greater decreases in the chronotropic response during exercise in
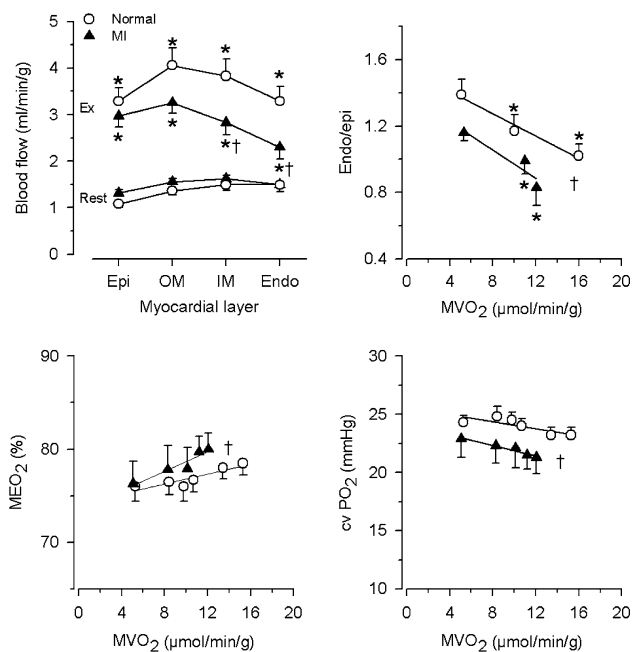

Fig. 4 Myocardial blood flow and O_2-balance in the left ventricular anterior wall of N and MI ∼3 weeks after myocardial infarction. *Epi* subepicardial, *OM* outer mid; *IM* inner mid; *Endo* subendocardial. MVO_2 = myocardial O_2-consumption; MEO_2 = myocardial O_2 extraction; $CVPO_2$ = coronary venous O_2 tension In the top left panel data myocardial blood flow data are shown for resting (Rest, lying) conditions, and during maximum exercise (Ex, 5 km/h in N and 4 km/h in MI). Data are mean ± SEM; *$P < 0.05$ versus 0_L, † $P < 0.05$ MI versus Normal. Data are from Haitsma et al [43]

MI as compared to normal swine. In contrast, β-adrenoceptor blockade in MI swine resulted in a smaller decrease in global LV contractility compared to normal swine, in particular during exercise. The latter findings are consistent with a reduced left ventricular myocardial β-adrenoceptor responsiveness [100].

In normal swine and dogs, β-adrenergic receptor activation contributes to coronary vasodilatation during exercise [27, 39]. The β-adrenergic coronary vasodilatation results in an increase in myocardial oxygen delivery that is commensurate with the increase in oxygen consumption, so that myocardial oxygen extraction and hence coronary venous O_2 tension remain constant (Fig. 5). In MI swine, the net β-adrenergic vasodilator influence on the coronary circulation is maintained. However, in view of the exaggerated increases in catecholamine levels during exercise, these findings suggest a diminished β-adrenergic responsiveness of the coronary resistance vessels after MI.

In dogs, α-adrenoceptor activation limits the exercise-induced increase in CBF, thereby necessitating an increase in myocardial O_2 extraction, which leads to a decrease in coronary venous O_2 tension [39, 51]. In contrast, α-adrenoceptors do not contribute to regulation of coronary blood flow in normal swine during exercise [27]. We found that, in accordance with our findings in normal swine, administration of the α-adrenoceptor blocker phentolamine had also no effect on coronary venous O_2 tension of MI swine (Fig. 5). These findings indicate that even in the presence of exaggerated increments in catecholamine levels in MI swine during exercise, α-adrenoceptors do not contribute to regulation of tone in porcine coronary resistance vessels [23].

4.1.2 Parasympathetic control

The shift in the sympathovagal balance, with an increased sympathetic activity [12, 33] and a blunted parasympathetic activity is reflected in reduced heart rate variability and reduced baroreceptor reflex sensitivity [6, 12, 30, 76] in patients with advanced heart failure. We observed that a maximal dose of the muscarinic receptor blocker atropine produced a similar increase in resting heart rate in swine with MI as compared to normal swine, suggesting preserved parasympathetic activity under resting conditions [23]. In contrast, the atropine-induced increase in heart rate during exercise (particularly at higher exercise levels) was blunted in MI swine, while the increase in LVdP/dt_{max} was abolished [23]. These results are consistent with the concept that gradual inhibition of parasympathetic influence on the heart during exercise was more pronounced in swine with MI compared to normal swine. Importantly, these
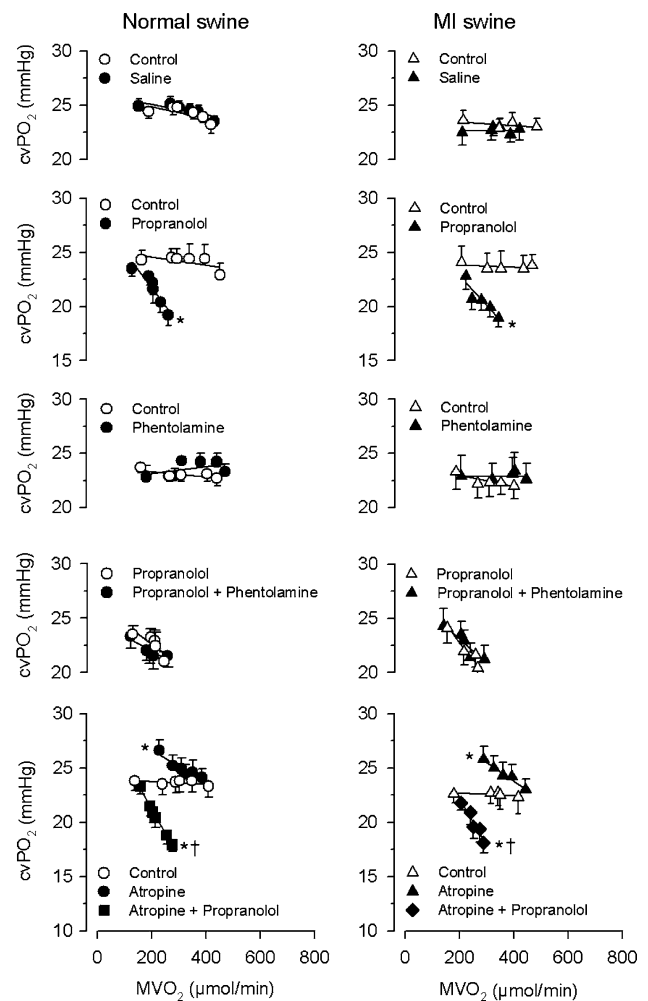

Fig. 5 Effect of saline, α-adrenoceptor blockade (phentolamine, 1 mg/kg iv) and/or β-adrenoceptor blockade (propranolol, 0.5 mg/kg iv) and of muscarinic receptor blockade (atropine, 30 µg/kg/min, iv) and/or β-adrenoceptor blockade (propranolol, 0.5 mg/kg iv) on the response of coronary venous O_2 tension (CVPO$_2$) plotted as a function of myocardial O_2 consumption (MVO$_2$) in seven normal and 7 MI swine. *$P < 0.05$ versus corresponding Control; †$P < 0.05$ Atropine + Propranolol versus corresponding Atropine or Phentolamine + Propranolol versus corresponding Phentolamine; Data are mean ± SEM. Data are from Duncker et al. [23]

findings suggest that after MI, at a time when parasympathetic tone under basal resting conditions is normal, a more pronounced inhibition of parasympathetic tone occurs with increasing exercise intensity. Since parasympathetic activity can presynaptically modulate sympathetic activity [1], it is likely that the greater degree of withdrawal of parasympathetic tone during exercise contributed to the exaggerated increase in sympathetic activity during exercise. This is also supported by the observation that in the presence of propranolol, the effects of atropine were no longer different between MI and normal swine [23].

In resting dogs, parasympathetic activity exerts a direct vasodilator influence on coronary resistance vessels that is

mediated via nitric oxide [109]. In contrast, in resting swine parasympathetic activity exerts an indirect vasoconstrictor effect on the coronary resistance vessels (which wanes at increasing exercise intensity) that is mediated via inhibition of β-adrenergic vasodilatation [27]. In contrast to the loss of the inhibitory influence of the parasympathetic system on β-adrenoceptor mediated cardiostimulation, we observed that its effects on the coronary circulation were maintained in MI compared to normal swine (Fig. 5) [23]. These findings indicate that at this stage of LV dysfunction, parasympathetic control of β-adrenoceptor-mediated coronary vasodilatation is unimpaired.

4.1.3 Angiotensin II

The renin-angiotensin system plays an important role in cardiovascular homeostasis by contributing to the regulation of blood volume, blood pressure and vascular tone. Angiotensin II (ANG-II) exerts its effects on vascular tone through binding to the AT_1-receptor, resulting in vasoconstriction, as well as binding to the AT_2-receptor, evoking vasodilation [14]. Both receptor subtypes have been identified in the coronary microcirculation [4, 107], suggesting that endogenous ANG-II may contribute to the regulation of coronary vascular tone and to the regulation of myocardial perfusion. Under pathological circumstances, i.e. after MI, the renin-angiotensin system is activated, resulting in increased plasma levels of ANG-II, particularly during exercise [34, 43]. Moreover, there is evidence that AT_1-receptor density in the viable region of the myocardium is increased early after MI [62, 98], suggesting that its vasoconstrictor influence on the coronary vasculature could be increased, which may limit myocardial perfusion thereby exacerbating LV dysfunction.

Contrary to our hypothesis, we observed a loss of ANG-II induced vasoconstrictor influence, reflected by the lack of increase in coronary venous O_2 tension (Fig. 6), despite increased plasma ANG-II levels and maintained AT_1 receptor densities in coronary arterioles isolated from remodelled myocardium of MI swine [68]. It is unlikely that a generalized loss of vasodilator capacity in the remote myocardium contributed to the blunted vasodilator response to the AT_1 receptor blocker irbesartan, as we have previously shown that vasodilation produced by nitroprusside is unperturbed [44]. Although an increased AT_2-receptor expression could have acted to limit ANG-II induced vasoconstriction [84] this is unlikely as AT_2-mRNA was not altered in coronary arteries from patients with ischemic heart disease [103]. Moreover, the dramatic increases in ANG-II levels that we observed after irbesartan did not result in enhanced, but rather blunted, coronary vasodilation [68]. Therefore, the observation of a reduced
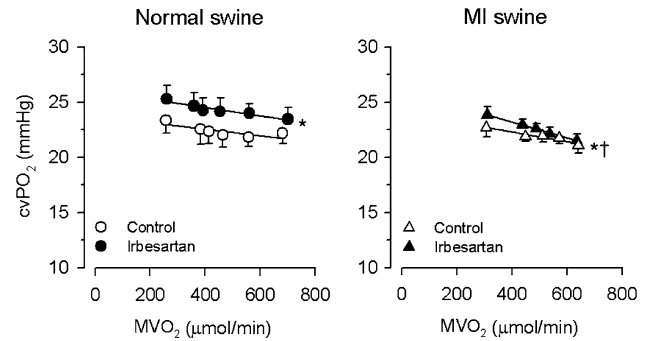

Fig. 6 Effect of AT_1-receptor blockade with irbesartan (1 mg/kg iv) on the relation between myocardial O_2 consumption (MVO_2) and coronary venous O_2 tension ($CVPO_2$) in normal swine and swine with a 2–3-week-old myocardial infarction. Data are means ± SE; *$P < 0.05$ versus corresponding control relation, $^{†}P < 0.05$ effect of irbesartan different in MI versus Normal animals. Data are from Merkus et al. [68]

vasoconstrictor influence of endogenous ANG-II is best explained by AT_1-receptor-desensitization, which is in accordance with studies in dogs with pacing-induced heart failure [78], in rats with pressure-overload LV hypertrophy [63], and in rats with LV remodeling after MI [84], that demonstrated blunted vasoconstrictor responses to exogenous ANG-II.

4.2 Local metabolic control

4.2.1 Adenosine

Adenosine has been proposed to be a metabolic messenger that regulates coronary resistance vessel tone in response to changes in metabolic needs of the myocardium [5]. However, adenosine receptor blockade with 8PT and/or augmenting adenosine catabolism with intracoronary adenosine deaminase had either no effect [3] or produced a small decrease [28, 67, 93] in basal coronary venous O_2 tension (reflecting vasoconstriction), but did not interfere with the normal exercise-induced increase in CBF and O_2 delivery [3, 28, 67, 93], indicating that adenosine is not critical for the exercise-induced coronary vasodilation or that loss of adenosine-mediated vasodilation can be compensated for by increased contribution of other vasodilator pathways to maintain adequate metabolic vasodilation.

In contrast to the lack of evidence for an essential role of adenosine in regulation of CBF under physiological conditions, endogenously released adenosine does contribute to coronary vasodilation when there is insufficient supply of O_2 [61]. Similarly, adenosine production could be increased in the remodelled myocardium after MI as a result of the perturbations in the myocardial O_2 balance [43, 70, 108].

However, we found no evidence for an increased contribution of adenosine to regulation of coronary resistance vessel tone in remodelled myocardium of swine with a recent MI [71], as adenosine receptor blockade with 8PT caused a similar decrease in coronary venous O_2 tension in post-infarct remodelled hearts and normal hearts both at rest and during exercise (Fig. 7). These findings are in agreement with observations in dogs with pressure-overload LV hypertrophy, in which adenosine receptor blockade did not affect CBF either at rest or during exercise [65].

Several reasons could be forwarded for the failure to observe a larger contribution of adenosine to regulation of coronary resistance vessel tone. First, it is possible that the perturbations in the myocardial O_2 balance were too mild to increase adenosine production. Second, the activity of enzymes that regulate tissue adenosine levels may have been altered [16, 17]. For example, the activity of

adenosine deaminase, the enzyme responsible for breakdown of adenosine to inosine, was found to be elevated in LV hypertrophy [10, 13, 15]. Furthermore, there is evidence that the activity of cytosolic 5′ nucleotidase, which converts 5′AMP to adenosine, is lower in certain models of pressure-overload [13] and volume-overload [10] induced LV hypertrophy, which could be related to intermittent hypoperfusion of the hypertrophic myocardium [41]. Together these enzymatic alterations, which act to decrease myocardial levels of adenosine may have prevented a significant increase in myocardial adenosine levels in the post MI remodelled hearts.

Finally, it is possible that an increased role of adenosine in hypertrophied myocardium is masked by an increased contribution of other vasodilator systems during adenosine receptor blockade, as the process of metabolic vasodilation is thought to be mediated through multiple parallel or redundant pathways. Thus, K_{ATP} channel activity may have increased in response to adenosine receptor blockade to compensate for the loss of adenosine-mediated vasodilation. Hence, we evaluated the interactions between these vasodilator pathways.

4.2.2 K_{ATP} channels

In addition to the role of K_{ATP} channels in the regulation of CBF under physiological conditions [24, 25, 31], there is evidence for an increased K_{ATP} channel activity in the coronary circulation of remodelled hearts. For example, in anesthetized dogs with pacing-induced severe heart failure [106], the K_{ATP} channel blocker glibenclamide resulted in an exaggerated vasoconstrictor response as compared to normal dogs. Interestingly, in dogs subjected to only 1 week of pacing (when LV function was still normal), K_{ATP} channel activity was not different from normal dogs [106], suggesting that K_{ATP} channel activity in the basal resting state was only enhanced in the presence of overt heart failure. Similarly, in awake dogs with compensated pressure-overload induced LV hypertrophy, the reduction in CBF produced by glibenclamide was similar to that in normal dogs [65]. During exercise, however, glibenclamide produced a greater reduction in CBF in hypertrophied hearts, indicating increased K_{ATP}-channel contribution to coronary vasodilation when O_2 requirements of the hypertrophied heart were augmented [65].

In swine with MI-induced moderate LV remodeling and dysfunction, glibenclamide caused a marked decrease in coronary venous O_2 tension in remodelled left ventricle under resting conditions, that was similar to the decrease in coronary venous O_2 tension in normal hearts (Fig. 7; [71]). Although the vasoconstriction under resting conditions in response to K_{ATP} channel blockade was similar in normal
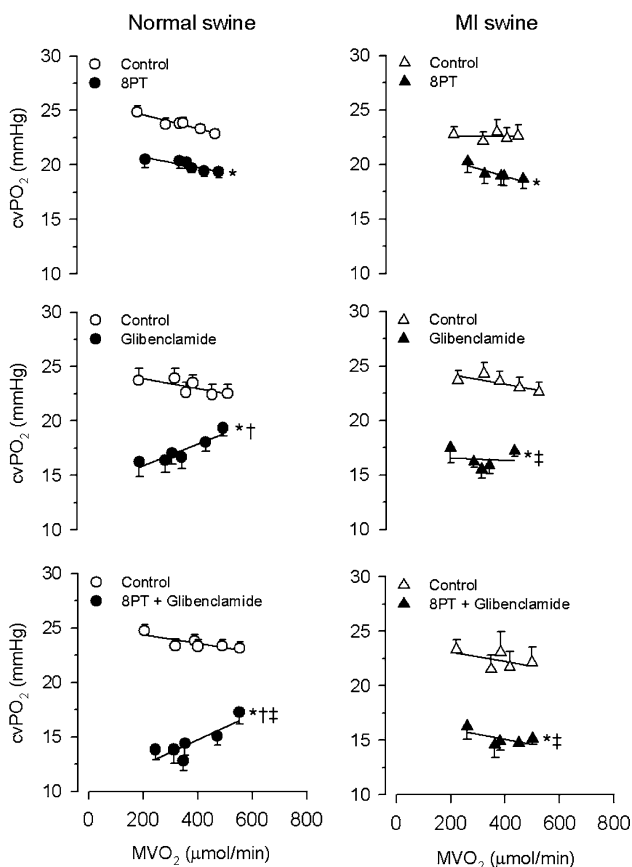

Fig. 7 Effect of the adenosine receptor antagonist 8-phenyltheophylline (*8PT*, 5 mg/kg iv), the K_{ATP} channel blocker glibenclamide (Glib, 3 mg/kg iv) or their combination on myocardial O_2 balance in the LV anterior free wall of normal swine and swine with a recent MI. MVO_2 = myocardial O_2 consumption; $CVPO_2$ = coronary venous O_2 tension; Data are mean ± SEM; Data are mean ± SEM; *$P \leq 0.05$ versus corresponding control; †$P \leq 0.05$ effect of Glib was blunted at higher MVO_2 levels (Glib × MVO_2); ‡$P \leq 0.05$ effect of Glib different after MI (Glib × MVO_2 × MI). Data are from Merkus et al. [71]

and post-MI remodelled hearts, the responses to exercise were different. Thus in normal swine, the effects of K_{ATP} channel blockade waned during exercise, suggesting that other vasodilator systems compensated for the loss of K_{ATP} channels during exercise. In contrast, in the post-MI remodelled hearts the effects of K_{ATP} channel blockade were maintained during exercise. Our findings, which are consistent with the observations in dogs [65], support the hypothesis that K_{ATP} channel opening is of greater importance in resistance vessel dilation during exercise in hypertrophied than in normal hearts. It is likely that with the progression from LV dysfunction to overt heart failure, increased K_{ATP} channel activity may also become important under resting conditions [106].

4.2.3 Interaction between K_{ATP} channels and adenosine

In contrast to the canine heart in which adenosine can act as a back-up system [29, 81], adenosine and K_{ATP} channels appear to exert additive vasodilator influences on coronary vasomotor tone in the normal porcine heart [67]. Thus, the coronary vasoconstriction that occurs in response to combined adenosine receptor blockade and K_{ATP} channel blockade equalled the sum of the vasoconstriction induced by blockade of the individual pathways. Adenosine mediates its vasodilator effect on porcine coronary resistance vessels via K_{ATP}, K_{Ca} and K_v channels [9, 46–48] It is therefore possible that following K_{ATP} channel blockade adenosine maintained its vasodilator influence via K_{Ca} and/or K_v channels.

In contrast to the normal porcine heart, the magnitude of the constriction induced in remodelled hearts by combined blockade of adenosine receptors and K_{ATP} channels was virtually identical to that produced by blockade of K_{ATP} channels alone [71]. These findings could be interpreted to suggest that in remodelled myocardium the vasodilator influence of endogenous adenosine was entirely mediated through opening of K_{ATP} channels, observations that are corroborated by findings in pressure-overload hypertrophied canine hearts [65]. Taken together these observations in the porcine and canine coronary circulations suggest that, although the magnitude of the vasodilator influence exerted by endogenous adenosine was similar in normal and remodelled hearts, its effector pathway was different.

4.3 Endothelial control

Several studies have indicated that endothelial dysfunction, in particular a decreased production of NO and an increased production of endothelin, could aggravate LV dysfunction due to the peripheral vasoconstriction-induced

increase in LV afterload, coronary vasoconstriction, and increased myocardial O_2 consumption [26, 59, 80, 105].

4.3.1 Nitric oxide

Clinical studies indicate that chronic heart failure is accompanied by blunted vasodilator responses to endothelium-dependent receptor mediated vasodilators (particularly acetylcholine) in the microcirculation of the LV myocardium [92], leg [45, 57], and forearm [19, 52, 57, 64]. In the canine model of pacing-induced end-stage congestive heart failure, attenuated vasodilator responses of resistance vessels to acetylcholine in vivo have also been observed in the microvasculature of the hindleg circulation [22, 64] and the coronary circulation [105]. In swine with a 2–3-week-old MI, we observed reduced vasodilator responses in the systemic and coronary microvasculature to ATP, in doses which we have previously shown to be completely abolished by pretreatment with the eNOS-inhibitor NLA [26]. The findings of a blunted ATP-induced vasodilation are in agreement with the hypothesis that agonist-induced eNOS-mediated NO production is blunted 2–3 weeks after MI.

A loss of NO-mediated vasodilation could enhance the progression of LV dysfunction to heart failure. This is supported by studies in dogs with pacing-induced dilated cardiomyopathy, in which the loss of basal NO production in the LV myocardium coincides with the progression from LV dysfunction to overt heart failure [80, 105]. However, in swine with a 2–3-week-old MI, we did not find any evidence of a reduced coronary vasodilator influence of endogenous NO as decreases in coronary venous O_2 tension produced by NLA in resting and exercising MI swine were similar to those of normal swine (Fig. 8). In heart failure patients, studies on the contribution of NO to basal
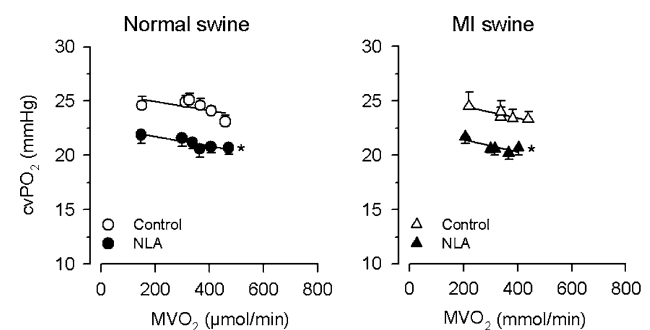

Fig. 8 Effect of inhibition of NO synthase by NLA (20 mg/kg iv) on myocardial O_2 extraction and coronary venous PO_2 at rest (lying) and during treadmill exercise in MI and N. Data are mean ± SEM. *$P < 0.05$ NLA versus corresponding Control; there were no significant differences in the responses to NLA between MI and N either at rest or during exercise. Data are from Haitsma et al. [44]

microvascular tone in the forearm, leg, or total systemic bed have yielded equivocal results with responses varying from blunted [45, 58, 64], to maintained [60], and even enhanced [20, 42] increases in vascular tone following NO synthase inhibition. It is possible that a maintained or increased NO production as observed in some studies, was the result of increased iNOS expression [21, 79], as part of a generalized inflammatory response in end-stage heart failure, that occurred in the presence of either a decreased [21, 86] or increased [37, 50] eNOS expression. Since NLA can block all three isoforms of NOS [7], we performed additional experiments, in which we blocked iNOS with aminoguanidine, to determine whether an upregulation of iNOS-mediated NO production masked a reduction in eNOS activity. iNOS blockade had no effect on coronary vasomotor tone, demonstrating that NO production via iNOS does not contribute significantly to vascular tone in MI swine, and, consequently, that basal and exercise-induced endothelial NO production is maintained early after MI [44].

The reason for the maintained basal and exercise-induced NO production in the presence of a blunted vasodilator response to ATP is unclear. However, Traverse et al. [91] have shown that the amount of NO, produced after stimulation with an agonist is larger than the amount of NO produced during moderate exercise (60% increase in heart rate). Hence, the maximal capacity of NO production may be reduced, whereas the capacity of eNOS is sufficient to maintain basal and exercise-induced NO production. This explanation is unlikely since agonist-induced dilation is already affected at the lowest dose of administered ATP (which probably releases less NO than strenuous exercise). Moreover, higher doses of ATP still produce more dilation. Another explanation for the divergent results between ATP and exercise-induced increases in NO-production may be that ATP activates eNOS through a different mechanism than shear stress. ATP-induced activation of eNOS is mediated through a calcium-calmodulin dependent pathway [74] whereas shear stress activates eNOS through Akt-mediated phosphorylation [18], resulting in calcium-independent activation of eNOS. Hence, it is possible that perturbations in the calcium homeostasis of endothelial cells contributed to the selective impairment of ATP-induced vasodilation in swine with MI.

4.3.2 Endothelin

Despite the increased plasma levels of endogenous ET in swine with a 2–3 week old MI, its vasoconstrictor influence on the coronary circulation was reduced (Fig. 9 [69, 70]). To determine whether this was the result of blunted receptor responsiveness or reduced local ET-production, we studied
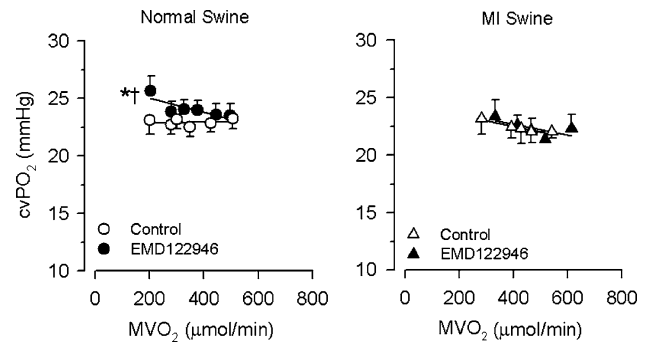

Fig. 9 Effect of ET_A receptor blockade with EMD (3 mg/kg iv) on myocardial oxygen balance in normal swine and swine with a recent MI. Data are means ± SE; $*P < 0.05$ versus corresponding Control relation, $^{†}P < 0.05$ effect of EMD waned during exercise. Data are from Merkus et al. [70]

the vasoconstriction induced by exogenous ET. The coronary vasoconstrictor influence to exogenous ET-1 in vivo was reduced after MI, indicating a reduced coronary vascular responsiveness to ET. Paradoxically, a recent study showed that ischemic heart disease results in upregulation of ET_A and ET_B receptor mRNA in human coronary arteries [104]. This is in accordance with our measurements in isolated coronary arterioles obtained from sham-operated swine and swine with a MI, which showed that the ET responsiveness in vessels from animals with a MI was actually increased [70]. The discrepancy between the in vivo and the in vitro findings suggests that ET receptor sensitivity is modulated in vivo, and that this modulation is apparently lost in vitro. Possible modulators of ET-receptor sensitivity are adenosine and NO, which have been shown to desensitize ET-receptors on the coronary vasculature [72, 73], and which may have been lost in the in vitro set-up due to lack of surrounding myocardium and intravascular blood flow. However, since we observed similar vasoconstrictor responses to blockade of adenosine receptors and NO production in MI and normal swine, these vasodilators would seem unlikely explanations for the observed reduced ET receptor sensitivity in MI swine in vivo.

In conclusion, our observations suggest that when additional coronary vasodilation is required in the hypertrophied myocardium after MI, withdrawal of the ET-mediated vasoconstrictor influence contributes to a shift in vasomotor tone towards vasodilation. These findings may also explain in part why clinical trials of ET-receptor antagonists in heart failure have failed to show therapeutic value of these compounds [40, 77].

4.4 Conclusions and physiological relevance

Under physiological circumstances, the heart matches its blood supply to the demand of the myocardium by altering
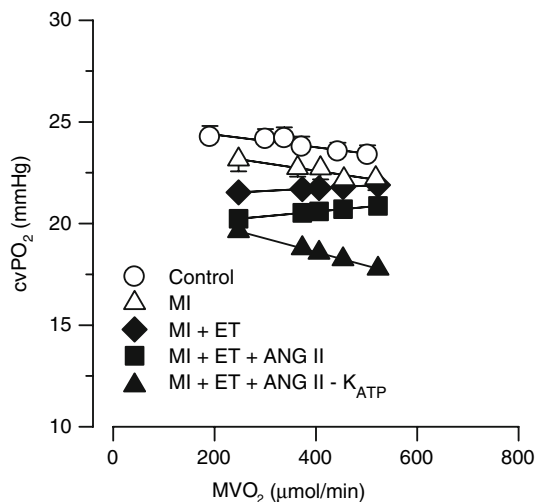
Fig. 10 Myocardial oxygen balance in normal and MI swine. Shown are the actual relations between MVO_2 and $CVPO_2$ in 30 normal swine (*open circles*) and 20 MI swine (*open triangles*) under control conditions. In addition, we have depicted the computed relations in MI swine if the ET (*solid diamonds*) and ANG II (*solid squares*) vasoconstrictor influences (which were both attenuated in MI swine) and the K_{ATP} (*solid triangles*) vasodilator influences (which were enhanced in MI swine) would have been identical to those in normal swine. The *graph* clearly illustrates that the adaptations in coronary vasomotor control act to blunt perturbations in oxygen balance in remodelled myocardium of swine with a recent MI
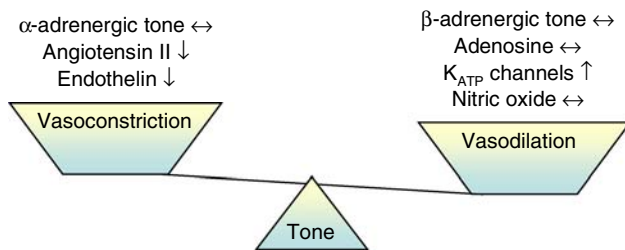

Fig. 11 Alterations in vasomotor balance in the coronary resistance vessels within remodelled myocardium in swine with a 2–3-week-old myocardial infarction

the balance of vasodilator and vasoconstrictor influences, i.e. an increase in myocardial O_2 demand results in an increased influence of vasodilators (opening of K_{ATP} channels, NO, adenosine [53], β-adrenergic vasodilation [27]) and a decreased influence of the potent vasoconstrictor endothelin-1 [66, 69]. Studies from our laboratory performed during the past 10 years have shown that following MI myocardial O_2 balance in the remodelled LV is perturbed, necessitating vasodilation and recruitment of coronary flow reserve, as evidenced by increased opening of K_{ATP} channels [71]. Importantly, however, not only an increased K_{ATP} channel vasodilator influence, but also blunting of the coronary vasoconstrictor influences of endogenous endothelin [70] and angiotensin II [68], aid in preventing a more significant impairment of oxygen supply

to the remodelled myocardium (Figs. 10, 11). Our studies suggest that generalized blunting of vasoconstrictor influences is one of the first adaptive mechanisms to reduce coronary resistance vessel tone and increase myocardial blood supply. This adaptation, which occurs in the healthy porcine heart during acute exercise, also appears operative in remodelled myocardium. Blunting of vasoconstrictor influences may be a physiologically favorable strategy, since it is more energy-efficient to blunt vasoconstrictor influences than to synthesize vasodilators.

Although the shift in coronary tone towards vasodilatation acts to blunt the flow perturbations in the remodelled heart, it does not appear to fully restore myocardial oxygen balance. This is also supported by the observation that K_{ATP} channel activation is increased, consistent with the presence of metabolic distress. Whether these perturbations in myocardial oxygen delivery blood are sufficiently severe to contribute to the progressive deterioration of contractile function of the remodelled left ventricle remains to be established, but it is of interest to note that we previously found that troponin I proteolysis occurred in remodelled myocardium, which was associated with a loss of myofilament force development [97]. Intermittent myocardial ischemia, as may occur in remodelled hearts during exercise or excitement, has been shown to be able to promote troponin I proteolysis [38] and could thereby mediate the flow perturbation-induced progressive deterioration of LV function after MI. Definitive proof of our hypothesis must await future studies demonstrating that prevention of such flow perturbations will indeed prevent progressive loss of contractile function of the remodelled porcine left ventricle.

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