Thus the effects of MCT-induced pulmonary hypertension on responsiveness of pulmonary artery to vasodilator drugs with different mechanisms of action varied. The loss in potency of the nitrovasodilator, NP, is unlikely to be due to a reduced relaxant effect of cyclic GMP because there was no loss in potency for AP (which also acts through cyclic GMP albeit via membrane rather than soluble guanylate cyclase). It is not yet known whether the increase in vasodilator potency seen for PIN in this model of pulmonary hypertension will be shared by other potassium channel opening drugs. It was not seen for NIC, a drug which like pinacidil can open membrane potassium channels but this may be because any increase in potency associated with this mechanism could be overridden by a decrease in potency associated with its additional properties resembling those of the nitrovasodilators.

The PA/AO selectivity seen for PIN in vessels from rats with pulmonary hypertension induced by MCT but not in controls, suggests that it may be worthwhile to investigate pinacidil, and possibly other potassium channel opening drugs, in patients with pulmonary hypertension where other drugs have proved inadequate.

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The central and regional cardiovascular responses to intravenous administration of the potassium channel opener EMD 52692

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The present study was conducted to investigate the systemic and regional haemodynamic effects of the newly synthesized potassium channel opener EMD 52692 (n = 7) or its solvent (n = 7) after intravenous administration in anaesthetized pigs. Infusion of the solvent did not affect systemic haemodynamics (baseline values for heart rate, mean arterial blood pressure, cardiac output, systemic vascular resistance, left ventricular end diastolic blood pressure and left ventricular dP/dt_{max} were 99 ± 6 beats min^{-1}, 89 ± 5 mmHg, 2.8 ± 0.2 l min^{-1}, 34 ± 4 mmHg.min l^{-1}, 6 ± 1 mmHg and 2670 ± 170 mmHg s^{-1}, respectively). Consecutive 10 min intravenous infusions of EMD 52692 (0.15, 0.30, 0.60, 1.20 $\mu g\ kg^{-1}\ min^{-1}$) caused a dose-dependent decrease in mean arterial blood pressure from 90 ± 3 to 44 ± 4 mmHg. This was entirely due to peripheral vasodilatation (decrease in systemic vascular resistance from 31 ± 3

Table 1

Effect of intravenous infusions of EMD 52692 ($\mu g\ kg^{-1}\ min^{-1}$, E) or equal volumes of its solvent (S) on regional vascular conductances (ml min 100 g^{-1} $mmHg^{-1}$).

	Baseline		0.15	0.30	0.60	1.2
Subepicardium	S	162 ±33	169 ±38	156 ±16	151 ±11	158 ± 9
	E	173 ±17	185 ±15	248 ±19 *	369 ±37 *	450 ±40 *
Subendocardium	S	203 ±35	198 ±38	196 ±17	196 ±15	194 ±16
	E	209 ±36	406 ±20	507 ±47	523 ±47 *	412 ±44 *
Total brain	S	37 ± 5	41 ± 3	36 ± 3	36 ± 3	35 ± 3
	E	37 ± 2	42 ± 3	67 ± 6 *	129 ± 7 *	163 ±12 *
M. pectoralis	S	2.5± 0.7	2.3± 0.7	2.2± 0.4	1.7± 0.2	1.8± 0.3
	E	2.2± 0.2	2.1± 0.3	2.7± 0.3	3.4± 0.4 *	4.8± 0.8 *
Kidneys	S	289 ±31	314 ±25	295 ±34	279 ±31	267 ±17
	E	278 ±23	274 ±17	335 ±33	388 ±33	319 ±34
Adrenals	S	153 ±22	172 ±14	164 ±11	160 ±14	167 ±19
	E	204 ±32	270 ±30	516 ±36 *	583 ±42 *	545 ±44 *
Skin	S	2.2± 0.7	2.2± 1.2	1.8± 0.5	2.3± 0.8	2.8± 1.3
	E	2.7± 0.5	3.3± 0.7	3.6± 0.9	5.1± 0.7 *	5.8± 0.6 *

data are means ± sem; * EMD 52692-induced changes versus baseline are significantly different from solvent-induced changes

mmHg.min l^{-1} to 15 ± 2 mmHg.min l^{-1}), since cardiac output (baseline 3.0 ± 0.2 l min^{-1}) did not change. The EM 52692-induced increase in heart rate from 103 ± 7 beats min^{-1} to 151 ± 13 beats min^{-1} may be due to reflex activation of the sympathetic nervous system. Left ventricular end diastolic pressure dose-dependently decreased from 6 ± 1 mmHg to 3 ± 1 mmHg causing a fall in stroke volume from 30 ± 2 ml to 21 ± 2 ml ($P < 0.05$). Table 1 shows that vasodilatation was not the same for all organs and that in particular the vascular conductance of the cerebral vessels increased. In spite of the 20% decrease in myocardial oxygen consumption there was an increase in left ventricular blood flow, which was however only confined to the subepicardial layers. It is concluded that EM 52692 is a very potent vasodilator, especially of the cerebral vasculature.

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Dual mechanisms of relaxation by nicorandil through cyclic GMP and membrane hyperpolarization

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In addition to previous results from our laboratory showing that nicorandil relaxed vascular smooth muscle by increasing cyclic GMP (cGMP) levels, it was found that it also activated K-channels, an effect which also leads to relaxation. In the present study it was attempted to differentiate quantitatively between these two effects in isolated bovine coronary arterial strips with simultaneous isotonic measurement of length and RIA-determination of cGMP. When the strips were contracted by the thromboxan analogue U 46619 (1 μM) in the presence of 10 μM methylene blue nicorandil produced 30-50% relaxation without significant changes in cGMP.

When in U 46619 contracted strips the hyperpolarizing effect of nicorandil was suppressed by raising extracellular K^+ to the 30-fold control value (80 mM), or by addition of 10 mM Ba^{++}, nicorandil only caused 52% and 40% relaxation, respectively, whereas cGMP-rises were not significantly suppressed.

Quantitative separation of both mechanisms of relaxation by nicorandil was further achieved through calculation of the cGMP mediated component from a correlation between rises in cGMP and percent relaxation as produced by nicorandil under conditions of inhibited hyperpolarization, i.e. in strips contracted with 1 μM U 46619 or $10 \times K^+$ and exposed to either 30-fold K^+ (80 mM) or 10 mM Ba^{++}. Under both conditions similar correlations between cGMP and relaxation were obtained.

The cGMP mediated part was 20% at low concentrations of 40-100 μM to 40% at high concentrations of 0.47-1.4 mM of the total relaxation produced by nicorandil in U 46619 contracted strips. Since U 46619 in addition to its contractile effect antagonized the relaxation by nicorandil to some extent without changing cGMP, the correlation when corrected for this effect yielded a participation of cGMP in the overall relaxant response of 40% at low concentrations to 85% at high concentrations of nicorandil.

The existence of two independent effects was also demonstrated by calculating the dose response curves for independent and for additive effects of the cGMP-activators nitroglycerin, nitroprusside-Na, nitrosoglutathion and SIN-1 in the presence of one concentration of 20 or 50 μM nicorandil. In all of these cases the independence of the effect of added nicorandil from the effect of the respective nitrocompound could be demonstrated.

These results indicate that nicorandil at low concentrations mainly relaxes by hyperpolarization whereas higher concentrations mainly relax through cGMP.