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LETTER TO THE EDITOR

Cyclosporine A at Reperfusion Reduces Infarct Size in Pigs

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Timely reperfusion is mandatory for salvage of ischemic myocardium from irreversible damage. However, reperfusion induces damage per se, i.e. reperfusion injury contributes to final infarct size [1]. Ischemic postconditioning, i.e. brief episodes of intermittent coronary re-occlusion during early reperfusion, reduces infarct size. This protective effect was confirmed in all species tested so far [2], including humans [3], but common co-morbidities of ischemic heart disease may interfere with cardioprotective mechanisms including ischemic postconditioning [4].

The signal transduction of ischemic postconditioning is still unclear in detail [5]. Activation of "reperfusion injury salvage kinases" (RISK) is causal for ischemic postconditioning's protection in rodents [6]. In pigs, in which coronary anatomy and the spatial and temporal development of myocardial infarction are closer to that of humans, RISK activation is not mandatory for protection [7].

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The mitochondrial permeability transition pore (mPTP) is a potential end-effector of myocardial protection at reperfusion [8–10]. Cyclosporine A binds to cyclophilin D, inhibits mPTP opening and reduces infarct size [9, 11]. Apart from experiments in rodents, cyclosporine A when given at reperfusion reduced infarct size in a proof-of-concept study in patients with acute myocardial infarction [12].

Protection by cyclosporine A at reperfusion was now tested in pigs. Enflurane-anesthetized Göttinger minipigs (20–40 kg body weight) of either sex were subjected to 90 min controlled hypoperfusion of the left anterior descending coronary artery and 120 min reperfusion [7]. In four pigs cyclosporine A (5 mg/kg i.v.) was infused 5 min before reperfusion; in four pigs, ischemic postconditioning was induced with six cycles of 20 s re-occlusion/reperfusion each; four pigs with immediate full reperfusion served as controls. Systemic hemodynamics (Table 1) and subendocardial blood flow during ischemia (microspheres) were matched between groups (Fig. 1). Both, cyclosporine A at reperfusion and ischemic postconditioning reduced infarct size (TTC staining) to a similar extent compared to controls (Fig. 1).

Whereas pigs differ from rodents with respect to the causal role of RISK in ischemic postconditioning, they share with both rodents and importantly also humans protection by cyclosporine A at reperfusion, suggesting an important role for mitochondrial permeability transition pore opening across all species.

Table 1 Systemic hemodynamics

		HR [1/min]	LVP_{max} [mmHg]	$dPdt_{max}$ [mmHg/s]	CAP_{mean} [mmHg]	CBF_{mean} [ml/min]
Cyclosporine A	Baseline	99±7	94±7	1330±68	112±5	22.5±2.8
	Isch5	100±6	79±3	959±55	20±3*	1.9±0.1*
	Isch85	97±5	77±6*	925±45	20±2*	1.9±0.1*
	Rep10	91±4	68±7*	796±108	102±4	66.1±8.9*
	Rep30	108±7	72±8*	1060±203	105±1	61.4±10.9*
	Rep60	115±7	70±6*	946±117	105±3	54.8±7.2*
	Rep120	119±10	65±7*	946±111	103±5	54.1±7.7*
Postconditioning	Baseline	100±9	96±3	1446±36	122±6	24.6±3.1
	Isch5	112±11	77±7*	997±59	22±2*	2.9±0.6*
	Isch85	105±9	77±3*	1112±46	24±2*	2.9±0.6*
	Rep10	109±8	76±5*	1383±103	109±6	74.2±9.3*
	Rep30	113±8	76±3*	1377±79	111±4	66.1±8.0*
	Rep60	113±11	69±12*	1380±416	122±4#	65.8±10.9*
	Rep120	125±12	69±5*	1364±259	115±7	59.1±14.7*
Immediate full reperfusion	Baseline	93±6	103±2	1294±52	122±5	24.3±2.6
	Isch5	98±10	82±2*	1039±87	23±2*	2.8±0.4*
	Isch85	94±7	85±4*	1178±45	23±1*	2.8±0.4*
	Rep10	95±7	76±5*	1101±173	111±7	57.6±9.0*
	Rep30	103±12	72±6*	1278±183	106±4*	53.5±7.9*
	Rep60	118±16	73±2*	1432±111	110±1	55.1±9.4*
	Rep120	116±15	61±3*	1222±174	118±9#	67.1±16.8*

Isch5/85: 5/85 min ischemia; Rep10/30/60/120: 10/30/60/120 min reperfusion; HR: heart rate; LVP_{max}: maximal left ventricular pressure; $dPdt_{max}$: maximum in the first derivative of LVP; CAP_{mean}: mean coronary arterial pressure; CBF_{mean}: mean coronary blood flow; means±SEM; *$p<0.05$ vs. Baseline; # $p<0.05$ vs. Cyclosporine A; two-way-ANOVA with Fisher's LSD post-hoc tests.

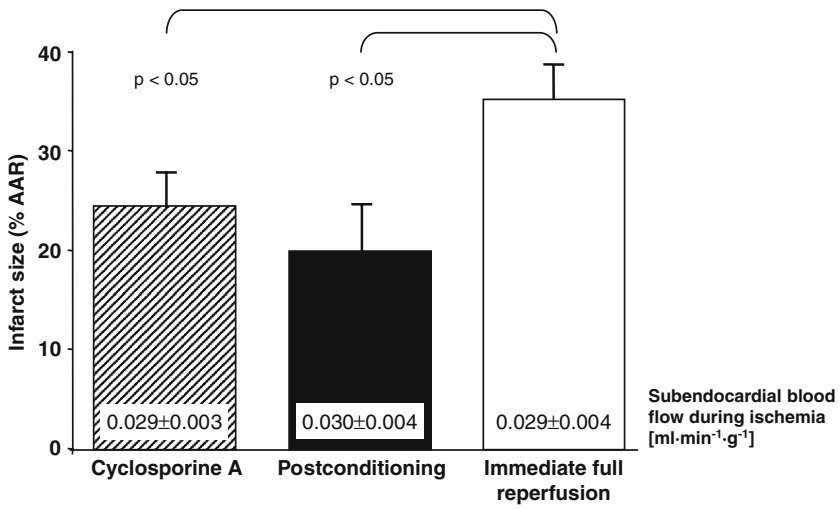

Fig. 1 Infarct size with cyclosporine A given at reperfusion, postconditioning, and immediate full reperfusion; means±SEM; AAR: area at risk; ANOVA with Fisher's LSD post-hoc tests

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