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P1451 Multiple pre-conditioning stimuli attenuate protection against the infarct size in rabbits

E.K. Iliodromitis, C. Papadopoulos, D. Katrakis, Z.S. Kyriakides, E. Bofilis, D.T. Kremastinos. *2nd Dept. of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece*

The aim of the study was to determine if the repeated periods of 5 min ischemia and 10 min reperfusion (5 isc/10 rep) are protective against the infarct size in a collateral deficient model.

Methods: Forty-one rabbits were divided into 7 groups. Group (Gp) A (n = 5) was subjected to one cycle of 5 isc/10 rep, GpB (n = 5) was subjected to two 5 isc/10 rep, GpC (n = 7) to four 5 isc/10 rep, GpD (n = 7) to six 5 isc/10 rep, GpE (n = 7) and GpF (n = 5) to eight 5 isc/10 rep while GpG (n = 5) served as control. After the initial interventions all the Gps (except GpF) were subjected to 45 min regional ischemia and 2 hours reperfusion. The elapsed time from the first preconditioning stimulus to the final 45 min ischemic insult was 15, 30, 60, 90 and 120 mins, respectively for the Gps A, B, C, D and E. infarct size (I) and risk zones (R) were delineated with the aid of tetrazolium staining and fluorescent particles. I/R ratio was expressed in percent (% I/R).

Groups	A	B	C	D	E	F	G
%I/R	2.2 ± 2.5*	19.5 ± 4.1*	23.3 ± 3.4*	41.8 ± 6.9#†	47.1 ± 7.6#	0 ± 0	59.8 ± 4

*p < 0.001 vs G, #p < 0.05 vs A, B, C, †p < 0.05 vs G

Conclusion: These results indicate that protection against infarct size diminishes after multiple and repetitive preconditioning stimuli in rabbits.

P1452 Reperfusion damage is mediated by a stable long-lasting cardiac metabolite which is probably not a protein

V. Stangl, S.B. Felix, T. Frank, O. Rödiger, T. Berndt, G. Baumann. *Medizinische Klinik I, Charité, Humboldt-Universität Berlin, Germany*

We have previously reported that after global ischemia (IS) of an isolated heart cardiodepressant agents are released during reperfusion (R) which induced a pronounced but reversible decrease in contractility in a serially perfused non ischemic second heart (H2) (double heart model). This effect was not attributable to changes in pH or concentration of electrolytes of the coronary effluent and the metabolites do probably not derive from coronary endothelium. In order to further characterize the chemical structure of these mediators we investigated whether storage of the coronary effluent for several hours or days, heating to 56°C for 30 min or protease treatment influence the negative inotropic effect.

Two isolated guinea pig hearts were perfused separately at constant flow (10 ml/min) with a modified Krebs-Henseleit-solution oxygenated with 95% O₂ and 5% CO₂. This was followed by serial perfusion without (group 1, n = 5) and with (group 2, n = 5) preceding IS (10 min) of the first heart (H1). In group 1 no significant changes of the left ventricular contractile parameters of H2 were observed during serial perfusion. In group 2, after a global 10-min IS of H1 left ventricular (LV) systolic pressure of H2 (basal 76.3 ± 3.5 mmHg, SEM) immediately decreased by 16%, +LVdP/dt_{max} (1491.9 ± 112.4 mmHg/s by 22%, -LVdP/dt_{max} (1261.3 ± 56.8 mmHg/s) by 30% when R was started. Coronary perfusion pressure (77.1 ± 3.4 cmH₂O) decreased by 26%. These parameters returned to baseline within 10 min. Heart rate did not change significantly. The cardiodepressant effect of the coronary effluent was not destroyed by protease treatment (chymotrypsine 0.005 U) or by heating the coronary effluent to 56°C for 30 min. Coronary effluent kept at room temperature for 24 hours before delivery to H2 also retained its activity.

These data suggest the release of a stable, long-lasting cardiodepressant agent from myocardial tissue after global IS during R. The resistance against protease treatment and heating suggests that the mediator is not a protein.

P1453 Production of interleukin-6 triggers an enhanced acute phase response after percutaneous coronary angioplasty in patients with unstable angina

G. Liuzzo, A. Buffon, A. Vitelli¹, G. Ciliberto¹, G. Calligiuri, G. Quaranta, C. Monaco, F. Crea, L.M. Biasucci, A. Maseri. *UCSC; ¹ IRBM Rome, Italy*

C-reactive protein (CRP) levels are predictors of prognosis in unstable angina (UA) and increase further after coronary angioplasty (PTCA). As interleukin-6 (IL-6) is the major inducer of the acute phase proteins production, we have measured IL-6 and CRP levels in 32 UA pts, undergoing single-vessel PTCA. Venous blood samples were taken immediately before PTCA and 6-24-48-72 h after the end of the procedure. **Results** (median and range): Before PTCA, elevated levels of CRP (>3 mg/l) were observed in 23/32 pts (72%, G1) and normal levels in 9/23 pts (28%, G2). Detectable levels of IL-6 (undetectable in normals) were found in 13/23 (57%) G1 pts, but in none G2 pts. After PTCA, in G1 pts CRP levels increased from 9.8 (3.2-29) mg/l to a peak value of 21 (4.4-174) mg/l 24 h after the end of the procedure (p < 0.001 vs baseline). This increase was preceded by a significant increase of IL-6 at 6 h [from 2

(0-22) pg/ml to 6.2 (0-300) pg/ml, p = 0.002]. IL-6 remained high at 24 h [6.8 (3-148) pg/ml; p = 0.32 vs 6 h] and then returned to the baseline value by 48 h [2.5 (0-47) pg/ml; p = 0.97 vs baseline]. Conversely, CRP levels remained elevated at 48 h and decreased to baseline at 72 h, consistently with the plasma half life of CRP compared to that of IL-6. No changes in CRP and IL-6 levels were observed in G2 pts. There was a significant correlation between the peak values of IL-6 and CRP (r = 0.53, p = 0.01). The figure shows the median values of IL-6 (circles) and CRP (squares), in G1 pts. **Conclusion:** UA pts with elevated levels of CRP exhibit an enhanced production of IL-6 early after PTCA, followed by a large increase of CRP. In turn, IL-6 production may be triggered by powerful pro-inflammatory stimuli contained in the plaque core or may reflect a lower threshold for IL-6 synthesis in this subset of UA pts.

P1454 C-Reactive protein co-localizes with complement in human hearts during acute myocardial infarction

W.K. Lagrand¹, J.W.M. Niessen², G.J. Wolbink⁴, E.H. Jaspars², C.A. Visser¹, F.W.A. Verheugt¹, C.J.L.M. Meijer², C.E. Hack^{3,4}. *¹ Free University Hospital, Department of Cardiology; ² Department of Pathology; ³ Department of Internal Medicine; ⁴ Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands*

Plasma levels of C-reactive protein (CRP) correlate with clinical outcome in patients with myocardial ischemia and infarction. We hypothesized that these correlations might reflect active participation of CRP in the local inflammatory response ensuing in the jeopardized myocardium, since upon binding to a ligand CRP is able to activate the classical pathway of complement. In addition, complement activation has been shown to occur locally in human infarcted myocardium. To verify our hypothesis, we investigated immunohistochemical localization of CRP, in relation to deposition of complement, in tissue specimens of infarcted and normal heart tissues obtained from 17 patients, who had died following acute myocardial infarction (AMI). CRP was found to be deposited only in infarcted regions and not in normal appearing areas of human myocardium, being co-localized with depositions of C4- and C3-activation fragments of the complement system. Deposition of CRP and complement in infarcted myocardium appeared to be time-dependent since it was found in all infarctions except for one of very short duration (< 12 hours) and two of long duration (> 1 year). Thus, CRP may localize in infarcted human heart tissue. We suggest that this acute phase protein promotes local complement activation, and hence tissue damage in AMI.

P1455 Assessment of C-reactive protein levels after percutaneous transluminal coronary angioplasty and stent implantation

F. Versaci, F. Tomai, A. Gaspardone, A. De Fazio, M. Iamele, F. Benvissuto, F. Crea, P.A. Giofrè. *Divisione di Cardiologia, Università Tor Vergata, Rome, Italy*

In patients (pts) with acute coronary syndromes increased serum levels of C-reactive protein (CRP) are associated to a worse short-term outcome. The aim of this study was to establish whether coronary angioplasty (PTCA) or stent implantation (SI) have the potential to increase serum levels of CRP and whether the latter affects the short and long term prognosis. Ninety-nine pts (mean age 58 ± 7 years, 88 men) with stable angina and obstructive coronary atherosclerosis were randomised to PTCA (49 pts) or to SI (50 pts). There were no significant differences among the two groups with respect to baseline clinical characteristics (gender, previous myocardial infarctions, risk factors and therapy) and to angiographic characteristics before the procedures. Serum CRP levels were measured, by nephelometry, 24 hours before and 6 hours, 1 day, 2 days, 3 days and 4 days after the procedure. All pts were then followed-up for 6 months. Serum levels of CRP were obtained also at 3 and 6 months. Serum levels of CRP (mg/L) were as follows (mean ± SD values):

	PTCA	SI	P
Baseline	2.1 ± 0.6	2.0 ± 0.6	NS
6-hours	3.9 ± 3.6	3.9 ± 3.5	NS
1-day	4.6 ± 5.2	8.7 ± 6.8*	NS
2-days	8.2 ± 10*	21 ± 18*	p = 0.002
3-days	4.4 ± 5.0	10.8 ± 16*	p = 0.02
3-months	2.0 ± 0.7	2.4 ± 1.3	NS
6-months	2.7 ± 1.5	2.3 ± 1.0	NS

*p < 0.05 vs baseline value

The incidence of early complications and symptoms recurrence was similar after PTCA and SI (2 vs 2%, p = NS and 10 vs 16%, p = NS, respectively).

Conclusions: SI results in a much higher increase of CRP serum levels than that observed after PTCA; yet, the incidence of early complications and late outcomes is similar. Thus, a marked elevation of CRP caused by an inflammatory stimulus localized in an epicardial coronary vessel is not sufficient per se to trigger coronary instability.