

222

MYOCARDIAL INFARCTION CAUSES INFLAMMATION AND LEUKOCYTE RECRUITMENT AT REMOTE SITES IN THE MYOCARDIUM AND IN THE RENAL GLOMERULUS

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doi:10.1136/heartjnl-2013-304019.222

Background Acute myocardial infarction (AMI) results in both systemic inflammation and recruitment of leukocytes to injured myocardium. Additionally, myocardium remote to the infarct zone, also becomes inflamed and is associated with adverse LV remodeling. Renal ischaemic syndromes have been associated with remote organ inflammation and impaired function. We therefore tested the hypothesis that AMI results in acute inflammation at remote sites which may contribute to organ dysfunction.

Methods Female C57BL/6J mice underwent AMI by surgical coronary artery ligation or sham procedure. At 24 hours, mice underwent transthoracic echocardiography prior to sacrifice (n=8/group). The inflammatory response in peripheral blood, injured and remote myocardium, and kidneys was studied.

Results At 24 hours, in comparison to sham operated mice, AMI resulted in increased circulating neutrophils and monocytes ($P<0.001$). Using quantitative RT-PCR, mRNA for inflammatory mediators increased in infarcted myocardium; IL6 by 11 ± 0.3 -fold ($P<0.01$), TNF- α by 32.9 ± 2.3 -fold ($P<0.01$), IL1RN by 5.4 ± 0.2 -fold ($P<0.05$), IL1R2 by 4.3 ± 0.9 -fold ($P<0.05$) and in remote myocardium; IL6 by 5.0 ± 0.7 -fold ($P<0.05$), TNF- α by 15.2 ± 4.2 -fold ($P<0.05$). VCAM-1 mRNA was significantly increased in both infarcted and remote myocardium. In kidneys of AMI

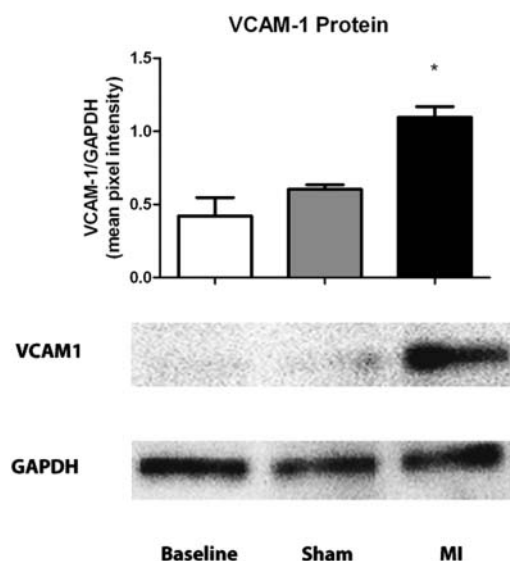


Figure 1

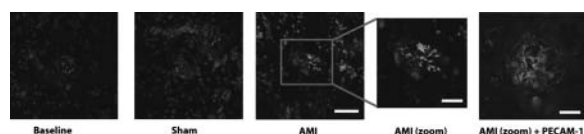


Figure 2

mice, VCAM-1 protein was increased by 2.6 ± 0.1 fold ($P < 0.01$) (Figure 1) and immunofluorescence revealed localisation of VCAM-1 to the same glomerular cells expressing PECAM-1 indicating endothelial expression of VCAM-1 (Figure 2, blue: DAPI, red: PECAM-1, green: VCAM-1). This was associated with leukocyte infiltration ($P < 0.01$) and increased inflammatory mRNA expression; IL6 by 2.9 ± 0.1 -fold ($P < 0.001$), TNF- α by 7.4 ± 1.8 -fold ($P < 0.01$), IL1RN by 3.9 ± 0.2 -fold ($P < 0.01$) and IL1R2 by 14.6 ± 4.9 -fold ($P < 0.01$). AMI did not affect plasma creatinine.

Conclusion (1) AMI induces a local inflammatory response, characterised by infiltration of leukocytes and increased expression of mRNA for inflammatory cytokines; (2) cytokines are upregulated in myocardium that is remote from the site of ischaemic injury; (3) AMI is associated with systemic inflammation, reflected in increased peripheral blood neutrophils and monocytes; (4) AMI is also associated with remote organ inflammation evidenced by (i) increased expression of mRNA for inflammatory cytokines, (ii) marked upregulation of VCAM-1 in renal glomeruli and (iii) by the recruitment and infiltration of leukocytes in the kidney.