Endothelial dysfunction and renal fibrosis in sepsis-induced acute kidney injury: possible role of LPS binding protein

G Castellano[1], A Stasi[1], AM Di Palma[1], M Gigante[1], GS Netti[2], C Curci[3], A Intini[1], C Divella[1], C Prattichizzo[2], E Fiaccadori[4], G Pertosa[1], G Grandaliano[2] and L Gesualdo[1]

[1]Department of Emergency and Organ Transplantation, Univ. of Bari, Bari, Italy; [2]Department of Medical and Surgical Sciences, Univ. of Foggia, Italy; [3] Consorzio Carso, Valenzano (Ba), Italy; [4]Department of Clinical and Experimental Medicine, Univ. of Parma, Italy

Background: The pathophysiology of sepsis-induced acute kidney injury (AKI) is characterized by a complex activation of the host immune system and renal resident cells by pathogen derived pro-inflammatory products. The occurrence of renal fibrosis in this setting has been poorly investigated and is usually associated with later development of chronic kidney disease. **Aim:** to investigate the possible association between EC dysfunction and acute development of tissue fibrosis in a swine model of LPS-induced AKI. Moreover we highlight the beneficial effects of coupled plasma filtration adsorption (CPFA) by plasma clearance of LPS-Binding Protein (LBP), a key mediator of LPS signaling. **Methods:** After 3 h from LPS infusion, 8 pigs were treated with CPFA for 6 h; 8 control pigs receive no treatment. Renal biopsies were performed before (T0) and 9 hours (T9) after LPS infusion. LBP levels were quantified in sera by ELISA. Endothelial cells (ECs) were cultured in presence of 1% different swine sera for 12h and were analyzed by FACS.

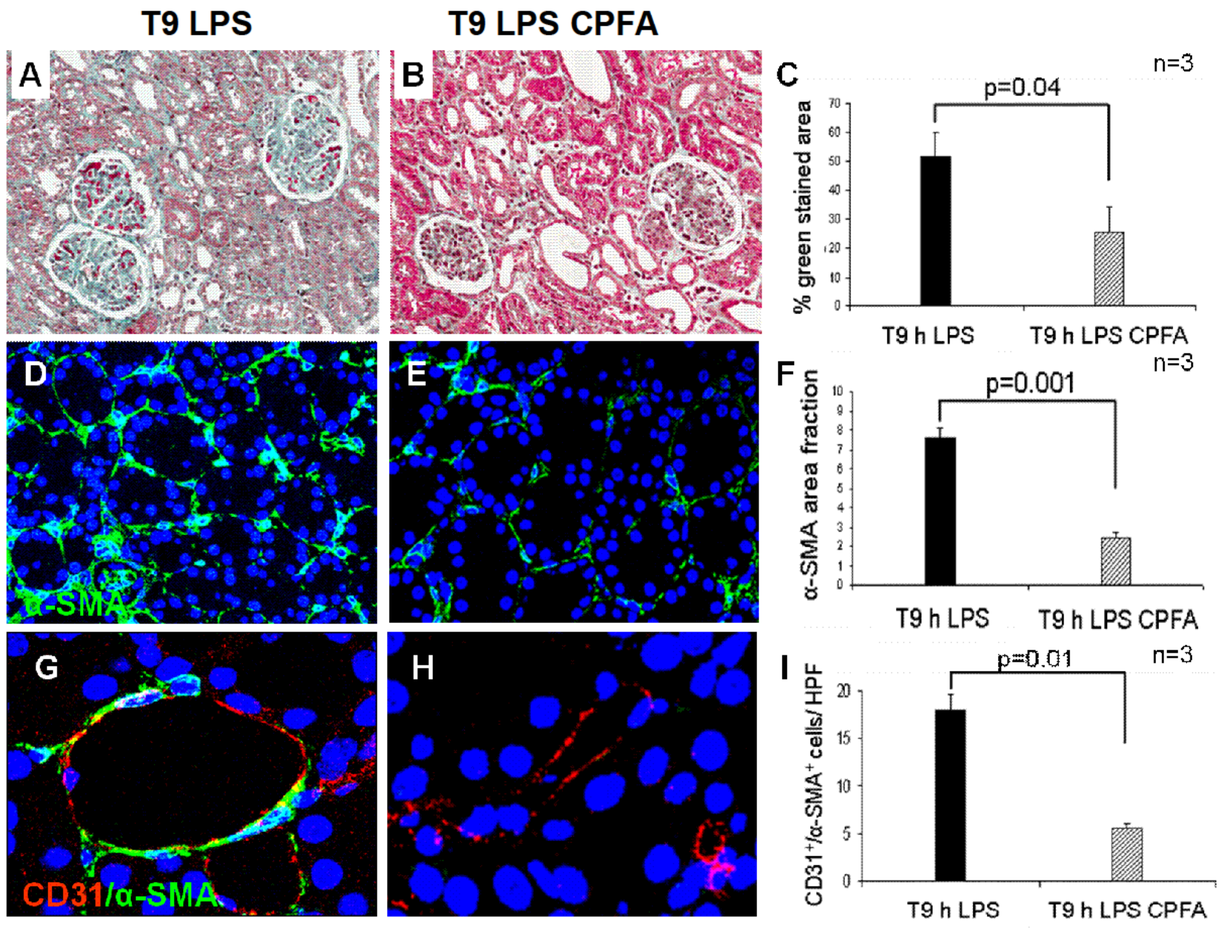

Fig3:Effects of CPFA treatment. CPFA treated pigs showed a significant reduction in collagen deposits and glomerular thrombi (B-C) compared to untreated animals(A). Overall, α-SMA expression (E-F), as well as endothelial dysfunction (H-I) were strongly reduced by CPFA treatment.

Results:

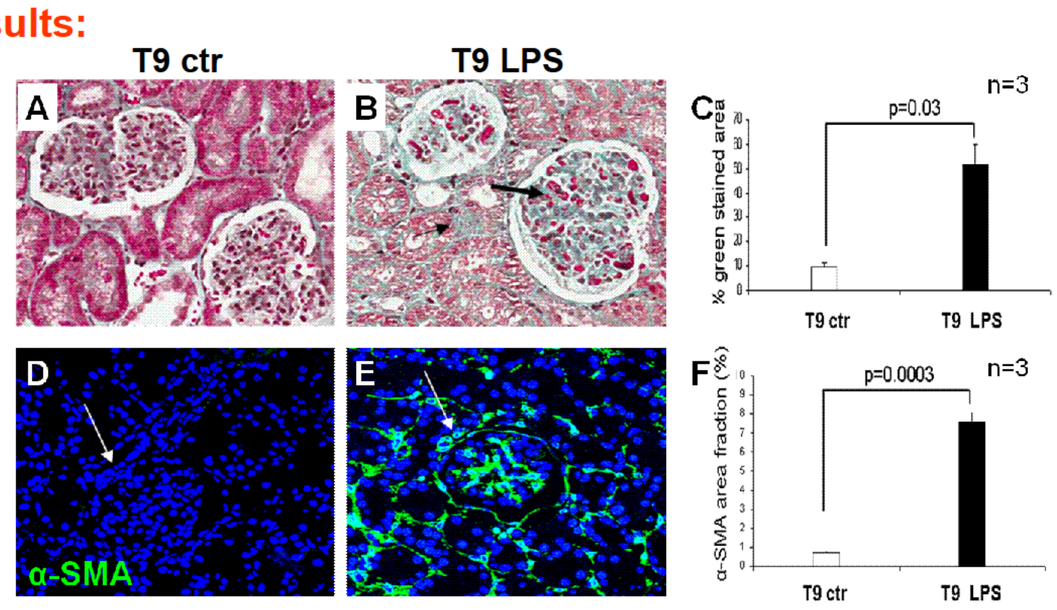

Fig1: Collagen deposits and α-SMA expression in Swine model of sepsis induced AKI. Masson's trichrome staining revealed an early fibrosis at the interstitial level and diffuse glomerular thrombi at T9 in septic pig (B-C) respect to control (A) An interstitial increase of the myofibroblast marker α-SMA was observed in septic pigs (E-F) compared to T9 ctr (D).

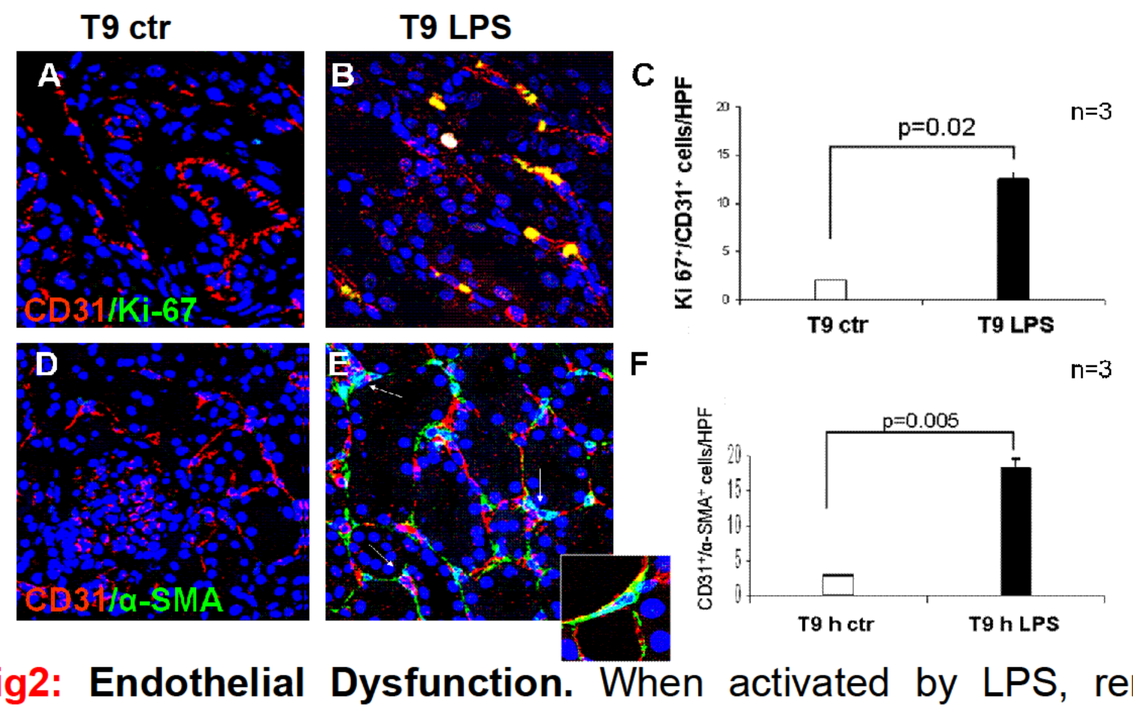

Fig2: Endothelial Dysfunction. When activated by LPS, renal **CD31+** EC proliferated (**Ki-67+**, B-C) and acquired several markers of myofibroblasts (**α-SMA**, E-F).

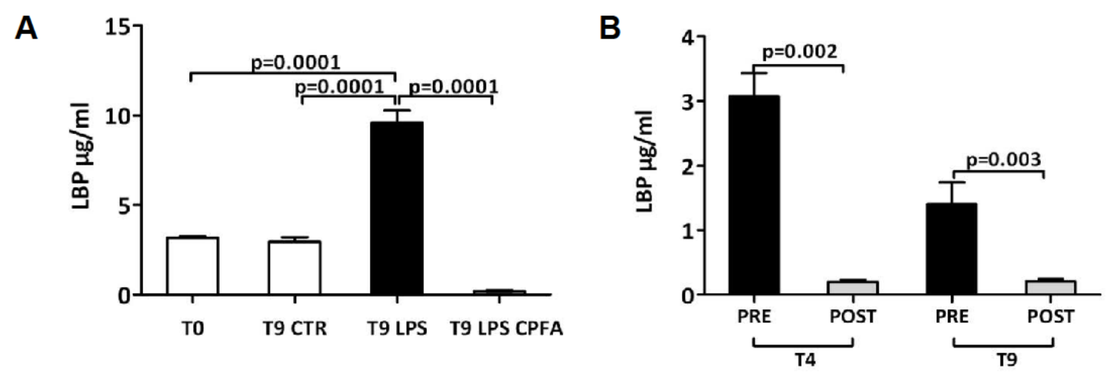

Fig4: Removal of LBP by CPFA treatment. (A) ELISA revealed the increased level of LBP in sera of septic pigs at T9. A considerable reduction was found after 6h of treatment. (B) Plasma samples drawn from CPFA circuit were also analyzed. A significant decrease of LBP was found in the plasma filtrate effluent from the sorbent cartridge 1h (T4 post) and 6h (T4 post) after circuit installation.

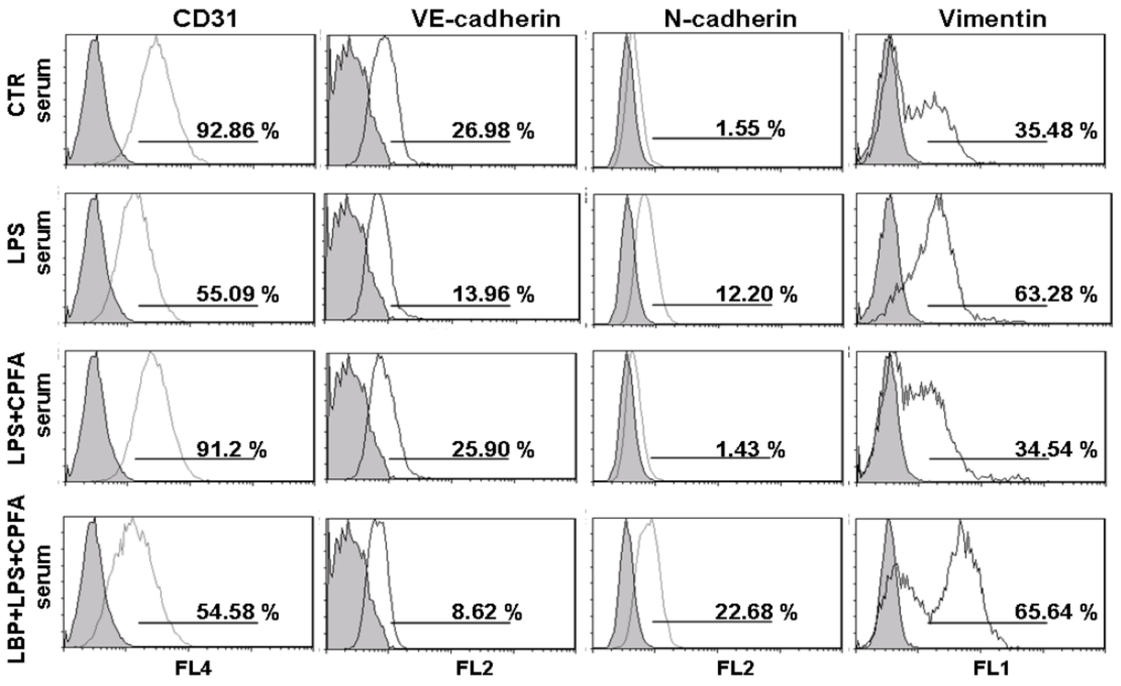

Fig5:LBP is pivotal in LPS-mediated endothelial dysfunction. FACs showed phenotypic changes of EC after 12h of LPS sera incubation. In the presence of LPS CPFA sera, EC preserved their phenotypes. After LBP addition in LPS CPFA sera, EC showed phenotypic changes (LBP+LPS CPFA).

Conclusion: Our data demonstrated the occurrence of endothelial dysfunction, tubular apoptosis and renal fibrosis in sepsis-induced AKI. CPFA treatment might be pivotal to counteract the detrimental effects of LPS on renal tissue.

References:

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G) Acute Renal Failure. G1) Experimental models.

Giuseppe Castellano

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