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Blood-dependent Redox Activity During Extracorporeal Circulation in Health and Disease

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LETTER TO THE EDITOR

The increased protein tyrosine nitration and lipid peroxidation under ischemic heart disease (IHD) condition is now firmly established and represents a shift from the signal-transducing physiological actions of free radicals to oxidative and potentially pathogenic actions.[1] In addition, inflammatory response initiated by ROS is known to be initiated via the activation of redox-sensitive transcription nuclear factor kappa- B (NF-?B) and may promote the progression of disease process.[1,2]

However, the precise nature of the interplay between ROS and intermediates responsible for oxidative stress in human blood is still controversial. For instance, peroxynitrite ($ONOO^-$) is known to nitrate tyrosine residues in vitro, however its role *in vivo* has been questioned and alternative pathways, involving peroxidases, nitrites, superoxide (O_2^-), hydroxyl radicals (OH^-) and transition metal-dependent mechanisms have been proposed as the cause of cell dysfunction via oxidizing proteins, lipids and DNA.[2]

Little is known about the exact role of ROS in blood and how this is related to the pathophyisiology of IHD. ROS appears to have a critical role in the inflammatory process and as such there is a considerable interest in studying the enzyme systems involved in their generation. Here we studied the role of Ischemic Heart Disease (IHD) patients in relation with free radicals production and antioxidant capacity (AOC).

50 mL of blood from IHD patients with stable angina before surgery and sex-age matched healthy controls (n=15/group) were recirculated at normothermia (37^0C) in an *ex vivo* model of extracorporeal circulation[3] for 4h. Blood samples were collected at different time points: before the start of the circulation (time 0) and at 4h. For the detection of $ONOO^-$, blood was treated with dihydrorhodamine-123 (100 ìM) and the fluorescence intensities quantified (excitation at 488 nm and emission at 515 nm) in leukocytes and plasma. O_2^- were measured using an enhanced lucigenin chemiluminescent assay whereas AOC was measured using the total peroxyl radical trapping antioxidant parameter (TRAP) assay. The changes of each parameter with time were plotted and analysed by comparison of the areas under the curve (AUC) using a one-way ANOVA. We observed that the overall production of O_2^- and $ONOO^-$ were significantly greater in blood obtained from IHD patients (Fig. 1 a,b). This increase in O_2^- and $ONOO^-$ production was associated with a substantial depletion in AOC in IHD patients (Fig. 1c).

This may suggest that the levels of ROS produced completely overwhelms antioxidant mechanisms and probably alter the function of enzymes such as SOD, glutathione peroxidase and catalase.[4] This may also be a reflection of the existence of a state of upregulation of pro-oxidant enzymes genes leading to an increased production of ROS. Indeed this hypothesis is supported by evidence from the literature, that has shown that there is a differential response of the cardiac isoforms Nox-2 and Nox-4 in the upregulation of gp91phox present in the NADH/NADPH pathway of superoxide production within the cardiac myocytes and the mitochondrial membrane.[4] The reduced ROS production may be as a result of release of antioxidant molecules from erythrocytes or an upregulation of activities of antioxidant enzymes.[5]

Results obtained from these studies suggest that there is a differential response to stress by blood from healthy subjects compared with IHD patients, which may directly reflect upon the induction of a proinflammatory state. This mechanism may involve chemical modification of redox-sensitive transcription factors an effect that is strongly related to the concentration of $ONOO^-$[6,2] Specifically, the complexity of $ONOO^-$ reactivity within the cells is clearly of scientific interest and warrants further research to elucidate its role on membrane associated enzymes that are involved in the development of oxidative stress In disease and healthy states (Fig. 1d).

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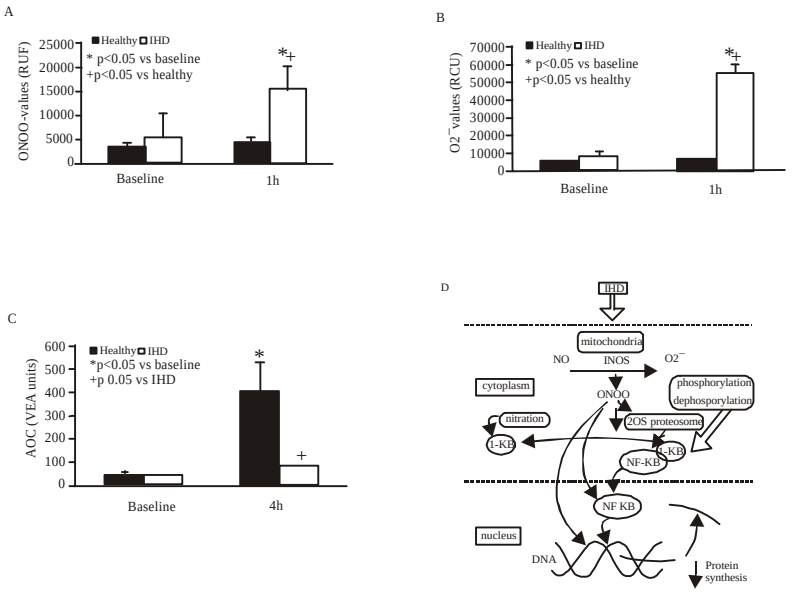

Fig. 1: Redox activity

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