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The relationship between plasma lipid peroxidation products and primary graft dysfunction after lung transplantation is modified by donor smoking and reperfusion hyperoxia

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BACKGROUND: Donor smoking history and higher fraction of inspired oxygen (F_{IO_2}) at reperfusion are associated with primary graft dysfunction (PGD) after lung transplantation. We hypothesized that oxidative injury biomarkers would be elevated in PGD, with higher levels associated with donor exposure to cigarette smoke and recipient hyperoxia at reperfusion.

METHODS: We performed a nested case-control study of 72 lung transplant recipients from the Lung Transplant Outcomes Group cohort. Using mass spectroscopy, F_2-isoprostanes and isofurans were measured in plasma collected after transplantation. Cases were defined in 2 ways: grade 3 PGD present at day 2 or day 3 after reperfusion (severe PGD) or any grade 3 PGD (any PGD).

RESULTS: There were 31 severe PGD cases with 41 controls and 35 any PGD cases with 37 controls. Plasma F_2-isoprostane levels were higher in severe PGD cases compared with controls (28.6 pg/ml vs 19.8 pg/ml, $p = 0.03$). Plasma F_2-isoprostane levels were higher in severe PGD cases compared with controls (29.6 pg/ml vs 19.0 pg/ml, $p = 0.03$) among patients reperfused with F_{IO_2} >40%. Among recipients of lungs from donors with smoke exposure, plasma F_2-isoprostane (38.2 pg/ml vs 22.5 pg/ml, $p = 0.046$) and isofuran (66.9 pg/ml vs 34.6 pg/ml, $p = 0.046$) levels were higher in severe PGD compared with control subjects.

CONCLUSIONS: Plasma levels of lipid peroxidation products are higher in patients with severe PGD, in recipients of lungs from donors with smoke exposure, and in recipients exposed to higher F_{IO_2} at reperfusion. Oxidative injury is an important mechanism of PGD and may be magnified by donor exposure to cigarette smoke and hyperoxia at reperfusion.

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Primary graft dysfunction (PGD) is a form of acute lung injury predominantly resulting from severe ischemia reperfusion injury in the allograft in the setting of lung transplantation.[1–3] We previously reported that receipt of a lung from a donor with smoking exposure history and higher fraction of inspired oxygen (F_{IO_2}) at the time of organ reperfusion are independent risk factors for the development of PGD.[4] The mechanisms leading to these associations are unclear.

Exposure to cigarette smoke and hyperoxia can induce oxidative injury in the lung.[5,6] Although the role of reactive oxygen species in signaling and lung homeostasis is complex, during lung transplantation there may be an excess of reactive oxygen species production, leading to lipid peroxidation.[7] F_2-isoprostanes are a group of prostaglandin-like compounds formed via non-enzymatic free radical–induced peroxidation of arachidonic acid that serve as robust markers of oxidative lipid peroxidation.[8] Some of these compounds have other physiologic effects in the lung, including vasoconstriction of the pulmonary vasculature.[9] F_2-isoprostane levels are higher in smokers compared with non-smokers and decrease in response to smoking cessation and anti-oxidant therapy.[10,11] In animal models of ischemia and reperfusion of the heart and liver, F_2-isoprostanes are released in response to reperfusion.[12–14] In rabbit lungs, hyperoxia and anoxia induced release of F_2-isoprostanes.[15] Plasma F_2-isoprostane levels have also been associated with organ dysfunction in patients with severe sepsis.[16]

Isofurans are also formed as a result of lipid peroxidation of arachidonic acid but differ from F_2-isoprostanes by the presence of a tetrahydrofuran ring.[17] Isofurans and F_2-isoprostanes share an intermediate step in formation that is dependent on oxygen concentration. In the presence of high oxygen tension, isofuran formation is favored.[18,19] Thus, isofurans may play a role in hyperoxia-induced oxidant injury.[18]

Because oxidant injury and lipid peroxidation may be important mechanistic pathways in PGD, we hypothesized that higher systemic F_2-isoprostane and isofuran concentrations would be associated with PGD. Furthermore, based on the association of F_2-isoprostanes and isofurans with hyperoxia and cigarette smoke exposure, we hypothesized that the association of F_2-isoprostanes and isofurans with PGD would be affected by donor smoking history and higher F_{IO_2} at reperfusion.

Methods

Subject selection and study design

The institutional review boards at all participating centers approved the study. A nested case-control study was chosen for efficiency based on the cost of performing the bioassays of lipid peroxidation. Subjects were selected from lung transplant recipients enrolled in the prospective multicenter Lung Transplant Outcomes Group cohort during the period 2002–2012.[4,20] PGD cases were defined using the International Society for Heart and Lung Transplantation (ISHLT) guidelines in 2 ways: (1) grade 3 PGD present at day 2 or day 3 after reperfusion (severe PGD); (2) any grade 3 PGD in the first 72 hours after allograft reperfusion (any PGD).[2,4,21–24] The severe PGD definition is thought to represent a more severe phenotype, associated with worse mortality, and was used in previous studies.[4] Cases and controls were selected to ensure inclusion of subjects who had received allografts from donors with and without a history of cigarette smoke exposure as well as a broad range of F_{IO_2} values at the time of allograft reperfusion. Donor smoke exposure was defined as any reported current or former history of donor cigarette use, collected prospectively from multiple sources at the time of transplant, including data from the United Network for Organ Sharing database UNet. F_{IO_2} at