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The Obesity ARDS Paradox: "A Pre-Conditioning Cloud"

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Medical paradoxes arise when a surprising finding contradicts the expected logical conventional wisdom. The most famous example is the French paradox that forces one to struggle to rationalize the unsettling contradiction between the fat rich diet of the French and their reduced cardiovascular mortality [1]. A more recent example is the Obesity ARDS paradox---a new apparent contradiction that presents new challenges and concepts for understanding the relationship of obesity and the Acute Respiratory Distress Syndrome (ARDS).

The obesity ARDS paradox centers on the perplexing idea that obesity, which chronically heightens inflammation and oxidative stress [2-4] and contributes to serious pulmonary, cardiovascular and other medical consequences [5], does not increase susceptibility or the severity of the ARDS, also characterized by increased inflammation and oxidative stress. For some reason, the enhanced pro-inflammatory state of obesity does not seem to augment the inflammatory response that contributes to ARDS. Obesity is also the primary risk factor for obstructive sleep apnea---another pro-inflammatory pro-oxidant condition and considered by some as the respiratory sign of metabolic syndrome [6,7]. Although it is totally reasonable that the pro-inflammatory state created by obesity would increase the incidence and severity of ARDS, it does not. Interestingly, despite assuming the challenges of multiple associated comorbidities, and along with other clinical outcomes such as Chronic Obstructive Pulmonary Disease (COPD) outcomes [8], need for or the duration of mechanical ventilation [9,10], the length of hospital stay or ICU mortality [11,12], obesity may actually confer some protection against ARDS [13-18].

Why do obese patients not have an obvious greater share of ARDS? Our theory is that the obesity-induced low-grade inflammation acts as a "pre-conditioning cloud" that protects the lung against a subsequent insult. This pre-conditioning cloud represents a combination of obesity-triggered anti-inflammatory, antioxidant and other endogenous protective mechanisms that attempt to control the inflammatory propensity created by obesity. Inadvertently, this pre-conditioning response then blunts the excessive inflammatory reaction that is characteristic and contributing to ARDS. This pre-conditioning adaptation may be effective against either the "first hit" or the "second hit" causation of ARDS---a phenomena well known to occur in animals [19,20]. When obesity is combined with other pro-inflammatory conditions, such as diabetes and hypertension as part of the metabolic syndrome, the worsening of clinical outcomes becomes more clear [21-23]. Since the timing and intensity of the pre-conditioning insult is critical, the presence of too many simultaneous "hits" or pro-inflammatory conditions (obesity plus hypertension plus diabetes, etc) likely overwhelms the pre-conditioning cloud and abolishes the obesity-related protection.

Several recent findings support this pre-conditioning cloud concept that is schematically depicted in Figure 1. First, obesity is associated with impaired neutrophil chemotaxis and decreased lung injury [24]. In the study by Kordonowy et al. [24], the neutrophil surface expression of chemokine receptor CXCR2 (also known as IL-8 receptor β) was significantly reduced in obese compared to lean mice---an observation that may constitute a novel explanation for why neutrophils are less prone recruiting into the lung during obesity.

Macrophage activation phenotypes may also be impacted by

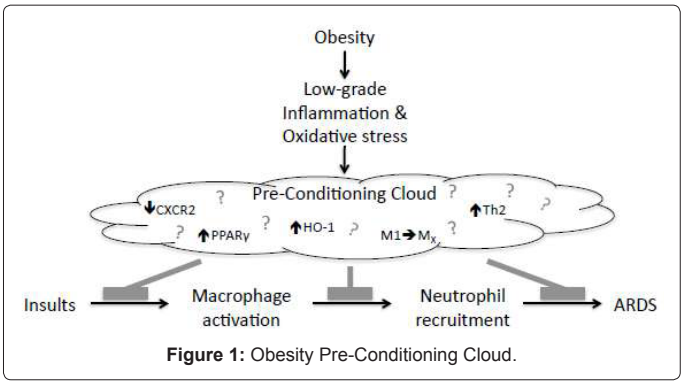

Figure 1: Obesity Pre-Conditioning Cloud.

the obesity pre-conditioning cloud. New macrophage activation phenotypes are being characterized other than the classic/M1 versus alternative/M2 activation pathways [25,26], and adipose tissue macrophages are no exemption [4]. These macrophage phenotypes may play a more definitive role than previously thought in deciding the direction and intensity of the overall inflammatory response. Possibly some features of obesity-related low-grade inflammation may be contributing to producing a more anti-injury and/or pro-healing macrophage phenotype. This type of new balance might resemble the pre-conditioning process that decreases ischemia/reperfusion damage [27]. The unknown macrophage phenotypes (M_X) could potentially protect against additional insults, systemically and in the lung and in the process underlie the Obesity ARDS Paradox.

Interestingly, Heme-oxygenase-1 (HO-1) has been linked to anti-inflammatory macrophage markers. For example, increased expression of HO-1 in monocyte/macrophages increases arginase activity (M2 phenotype marker), phagocytic ability, and IL-10 production while decreasing Macrophage Inhibitory Factor (MIF), TLR4, IL-33 and iNOS activity via p38 MAPK [28-31]. HO-1 is increased in the lungs of ARDS patients [32] and its induction (macrophage-located or otherwise) has anti-inflammatory and antioxidant effects in a variety of inflammatory diseases including not only ARDS [30,33,34] but also obesity [35,36]. For unknown reasons, HO-1 is increased in the adipose macrophages of obese humans compared to lean subjects [37]. Thus, obesity-initiated macrophage HO-1 increases could possibly induce long a protective pre-conditioning adaptation in the lung and be responsible for the Obesity ARDS paradox. Aging dampens stress-induced HO-1 responses in alveolar macrophages---a finding that could partially

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explain the higher susceptibility and severity of ARDS in the aging population.

Similarly, the peroxisomal proliferator-activated receptor-γ (PPAR-γ), a nuclear ligand-activated transcription factor of the nuclear receptor superfamily, has dual pulmonary and metabolic effects. PPAR-γ is mostly found in intestine and adipose tissue but also vascular endothelium and macrophages [38]. In monocyte/macrophages, PPAR-γ stabilizes HO-1 mRNA [39] and decreases IFN-β expression [39]. Macrophage-specific PPAR-γ has a critical role in M2 phenotype polarization and improves insulin resistance [40]. In the lung, PPAR-γ agonist troglitazone decreases TNF-α and protects alveolar type II epithelial cells from LPS-induced apoptosis in vitro [41]. In other models of lung injury (chronic alcohol ingestion), PPAR-γ activation reduced the expression of eNOS and production of reactive oxidative species [42]. PPAR-γ is down regulated by increased leptin levels (an indicator of insulin resistance [43]), and this promotes pro-inflammatory and fibroproliferative changes in a bleomycin-induced murine lung fibrosis model and in human lung fibroblasts [44]. Plasma levels of leptin, secreted by adipocytes, are directly proportional to the amount of adipose tissue and have the physiological purpose of centrally maintaining the energy intake-expenditure balance. However, in obese patients, increased leptin fails to achieve this goal by a so-called "leptin resistance" or desensitization or other mechanisms [45,46]. Not surprisingly, the findings of Jain and colleagues suggest that this "leptin resistance" in diabetic patients could also be involved in their paradoxical protection against ARDS.

Independently of the HO-1 upstream regulation (PPAR-γ, NrF2, NOS, etc), the anti-inflammatory effect of HO-1 down-regulates neutrophil migration [47], involving the down-regulation of Iκ-B and IFN-β [39,48]. The pro-inflammatory TNF-α, one of first cytokines in the NF-κB cascade, is associated with alveolar neutrophil recruitment, increased insulin resistance, type 2 diabetes and obesity [49,50]. It is well known that obesity causes increased Th1-derived cytokines, but recent findings suggest a skewing in CD4+ T cells towards a Th2 profile (more anti-inflammatory) in the peripheral blood of morbidly obese subjects [51].

In conclusion, the mechanistic link(s) between obesity and ARDS, both pro-inflammatory and pro-oxidant conditions with high prevalence in our society, are a rich area for not only deciphering the Obesity ARDS Paradox but also learning about both obesity and ARDS in an unexpected way. Learning from the obesity-activated endogenous anti-inflammatory pathways--the obesity pre-conditioning cloud--could provide interesting insight and may lead to novel therapeutical approaches for ARDS.

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