THE NEW ARMENIAN MEDICAL JOURNAL
Vol.9 (2015), No 1 p.75-82

MODULATORY ROLE OF BLOOD CYTOKINES IN PREVENTION OF ADRENALINE-INDUCED ACUTE LUNG AND MYOCARDIAL INJURY BY INDOMETHACIN AND MECHANICAL VENTILATION

Semerjyan A.B.[1], Krasnikov N.F.[1], Misakyan A.E.[1], Davtyan A.R.[2], Mkhitaryan A.G.[3],

[1] Yerevan State Medical University, Department of Medical Biology, Yerevan, Armenia
[2] Yerevan Outpatient Clinic N16, Yerevan, Armenia
[3] "Muratsan" Hospital Complex of the Yerevan State Medical University, Yerevan, Armenia

Received 3/19/2014; accepted for printing 02/28/2015

Abstract

Objective: the objective of this study is to investigate the role of some cytokines in adrenaline-induced pulmonary and myocardial injury, as well as prevention by treatment with indomethacin and mechanical lung ventilation in rats.

Materials and Methods: experiments were performed in albino male rats divided into: group 1 – control group, group 2 – animals treated with IV adrenaline, group 3 – animals treated with IM indomethacin 30 min prior to adrenaline injection, and group 4 – animals exposed to mechanical lung ventilation (positive end-expiration pressure) 10 min prior to adrenaline injection.

Lung and myocardial tissue sections were stained by Hematoxylin-Eosin. Blood cytokines (IL-1β, IL-6, IL-8, IL-10 and TNF-a) were detected by ELISA method. Statistical analysis was run by Student's t-test in Excel 2007.

Results: showed hemorrhages, inflammation and edema in lungs and neutrophil retention in myocardial sections of adrenaline-treated animals. Pretreatment with indomethacin and mechanical lung ventilation led to almost no pathological alterations in either of the tissues. Blood cytokine analysis in adrenaline-injected group resulted in increase of IL-1β, IL-6, IL-10 and TNF-a and slight suppression of IL-8. Pretreatment with indomethacin or mechanical lung ventilation led to even higher values of IL-1β and IL-6, and reduction of IL-10 and TNF-a compared to adrenaline group; IL-8 was significantly elevated in indomethacin-pretreated rats and normalized in animals exposed to mechanical lung ventilation.

Conclusion: indomethacin and mechanical lung ventilation can prevent adrenaline-induced injury of lungs and myocardium presumably via modulation of inflammatory and anti-inflammatory blood cytokines. This may have impact on the course of stress-related diseases.

Keywords: *adrenaline, acute lung and myocardial injury, cytokines, indomethacin, lung ventilation.*

Introduction

As previously known, a major cause of cardiac mortality is the myocardial infarction. Stressful conditions are associated with hypersecretion of catecholamines (CA) which may induce tachycardia, coronary vasoconstriction, splitting of oxygen supply and consumption resulting in hypoxia, diffuse necrosis of cardiomyocytes, and ventricular fibrillation [*Adameova A et al., 2009*].

Address for Correspondence:
Yerevan State Medical University, Department of Medical Biology,
2 Koryun St., Yerevan 0025, Armenia
Tel.: (+374) 94 449493
E-mail: annasemerjian@hotmail.com

The role of pulmonary ventilation and progression of generalized hypoxia (hypoxemia) in pathogenesis of myocardial infarction is suggested by us as a new hypothesis opposing the well-established concept of myocardial affection under primary influence of CA. High CA levels lead to systemic and pulmonary vasoconstriction resultant in elevated pulmonary capillary resistance followed by increase of capillary permeability, pulmonary inflammation and lung edema, for example, in pheochromocytoma [*Sukoh N et al., 2004*] and experimental CA-stimulation [*Rassler B et al., 2012*]. Activation of phospholipases by CA exerts stimulatory effects on pro-inflammatory cytokines and also affect number and function of inflammatory cells, the neutrophils in particular [*Rassler B. 2007*].

Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) is a complex clinical syndrome involving acute inflammation, microvascular damage and increased pulmonary vascular and epithelial permeability, frequently resulting in acute respiratory failure [*Allen TC, Kurdowska A, 2014*]. According to Wheeler and Bernard, the ALI (also called non-cardiogenic pulmonary edema) is characterized by the abrupt onset of significant hypoxemia and diffuse pulmonary infiltrates in the absence of cardiac failure [*Wheeler AP, Bernard GR, 2007*].

The contribution of epithelial injury to progression of ALI/ARDS has become increasingly obvious. Decreases in epithelial cell barrier function facilitate influx of protein rich fluid into alveolar space; furthermore, epithelial injury leads to impaired cell fluid transport and reduced production of surfactant [*Manicone AM, 2009*]. Neutrophils are an important component of the inflammatory response in ALI and demonstrate increased production of pro-inflammatory cytokines [*Gommes J, Soehnlein O, 2011; Williams AE, Chambers RC, 2014*].

Cytokines are small proteins secreted by immune system cells, thereby transmitting signals between them. After an acute insult there is systemic release of cytokines such as TNF, IL-1 and IL-6 that have diverse effects on endothelium, epithelium and on circulating as well as resident immune cells [*Manicone AM, 2009*], and in turn, stimulate release of other pro-inflammatory cytokines as IL-8, which is a potent neutrophil attractant and is produced in lung macrophages performing a crucial role in ALI [*Allen TC, Kurdowska A, 2014; Williams AE, Chambers RC, 2014*].

Among powerful anti-inflammatory mediators IL-10 provides degradation of transcription factors for inflammatory IL genes or activates transcription repression factors [*Murray PJ, 2005*], suppresses inflammatory mediators TNF-a, IL-1, IL-6 and IL-8 [*Yilma AN et al., 2012*].

Arachidonic acid metabolites (prostanoids) that have diverse physiological effects in lungs contribute also to ALI [*Park GY, Christman JW, 2006*] and cardiovascular pathology [*Smyth EM et al., 2009; Qiu H et al., 2012*], trigger acute ischemic tissue injury via activation of endotheliocytes and oxidative stress processes [*Feitoza CQ et al., 2008*].

Treatment of ALI is based on both ventilatory and non-ventilatory strategies. To date, the most significant advances in the supportive care of lung injury patients have been associated with improved ventilator management – positive end-expiration pressure (PEEP) [*Johnson ER, Matthay MAJ, 2010*]. Among non-ventilatory strategies the non-steroidal anti-inflammatory drugs (NSAID) are used to block inflammatory actions of prostanoids and interleukins, and also improve the functional state of the ischemic tissue [*Feitoza CQ et al., 2008*].

Indomethacin is a non-selective inhibitor of arachidonic acid metabolism enzymes cyclooxygenase (COX) 1 and COX 2, which has earlier been proved to prevent the adrenaline-induced life-threatening cardiac arrhythmias in rats [*Sisakian SH et al., 1987*]. Hence, anti-inflammatory agents are suggested as drugs of choice to prevent adrenaline-induced acute lung and heart injury. In addition, protective mode of mechanical lung ventilation (MLV) as a means improving lung ventilation is applied to prevent gas exchange imbalance in the same model of lung injury.

The objective of this study is to investigate the role of indomethacin (IND) and MLV in modulating blood cytokines and preventing adrenaline-induced injury of lung and heart.

MATERIALS AND METHODS

Experiments were performed in male albino rats (150-180 g.) divided into 4 groups: group 1 – control (intact) animals (n=11); group 2 – animals (n=12) treated with IV adrenaline (ADR) 0.09 *mg/kg* (adrenaline hydrotartrate solution 0.18%) under Nembutal anesthesia (40 *mg/kg*, IP); group 3 – animals (n=12) were administered indomethacin (50 *mg/kg*, IM) 30 min prior to adrenaline treatment (IND+ADR); group 4 – animals (n=12) were exposed to MLV through endotracheal intubation to TOPO™ Volume/Pressure Small Animal Ventilator "Kent Scientific, USA" (ventilation rate – 30*/min*, ventilation volume – 2.76 cm^3, inhaled oxygen concentration – 21%, PEEP ventilation mode) 10 *min* prior to ADR injection (MLV+ADR). Animals were sacrificed using Nembutal, 20 *min* following adrenaline injection.

Paraffin-embedded lung and myocardial tissues were stained by hematoxylin-eosin.

Concentration of blood cytokines (IL-1β, IL-6, IL-8, IL-10 and TNF-a) was detected by immune-enzyme analysis method (ELISA) on immune analyzers StatFax-3200 (Awareness Technologies Inc., USA) and Elecsys cobas 2010 (Roche, Germany) in the laboratory of N1 Clinical Hospital of Yerevan State Medical University.

Statistical analysis was performed by Student's *t*-test (2 sided, $\alpha < 0.05$) in Excel 2007. All data are presented as mean ± SD.

Results

Histopathology of the heart following adrenaline injection revealed cardiomyocytes contractures, most of the cardiac muscle cells performed wavy outlines (Fig. 1b) compared to the control group (Fig. 1a). Interrupted intercalated disks leading to cardiomyocytes dyscomplexity were often found, intercellular capillaries were anemic, the myocardial stroma showed neutrophil accumulations (Fig. 1b). The lung specimens of the same animals exhibited pulmonary edema with interstitial and intra-alveolar components (Fig. 2b) in contrast to a control specimen (Fig. 2a). Eosinophilic liquid within bronchi and alveoli as well as thickening of interalveolar septa (due to hyperemia, focal erythrodiapedesis and diffuse inflammatory infiltration presenting recruitment of neutrophils) were observed (Fig. 2b).

Pretreatment with indomethacin led to almost complete restoration of normal cardiac morphology, with minor stromal edema left (Fig. 1c); lung sections performed no hemorrhages, though minor inflammatory reaction was preserved (Fig. 2c). Lung ventilation preventive strategy restored almost normal histomorphological pattern of myocardial sections (Fig. 1d), the lungs showed emphysematous dilations due to certain mechanical stretch (Fig. 2d).

The results of the blood cytokines study showed 2.4 fold increase of IL-1β and IL-6, minor depres-

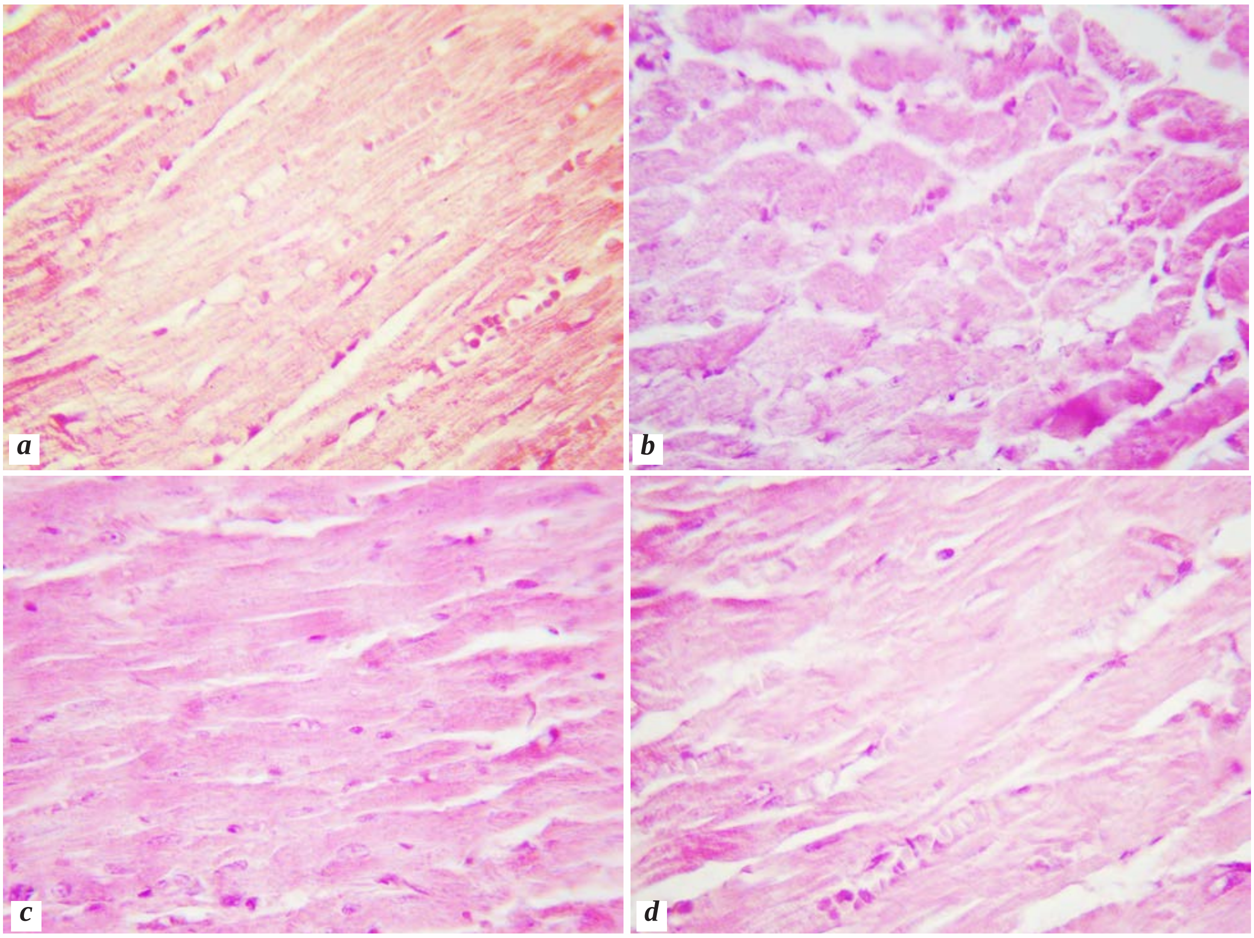

Figure 1. Myocardium sections stained by hematoxylin-eosin, ob. 40, oc. 10. ***a)*** *control group,* ***b)*** *adrenaline injection group,* ***c)*** *indomethacin-pretreated group,* ***d)*** *mechanically ventilated animals group.*

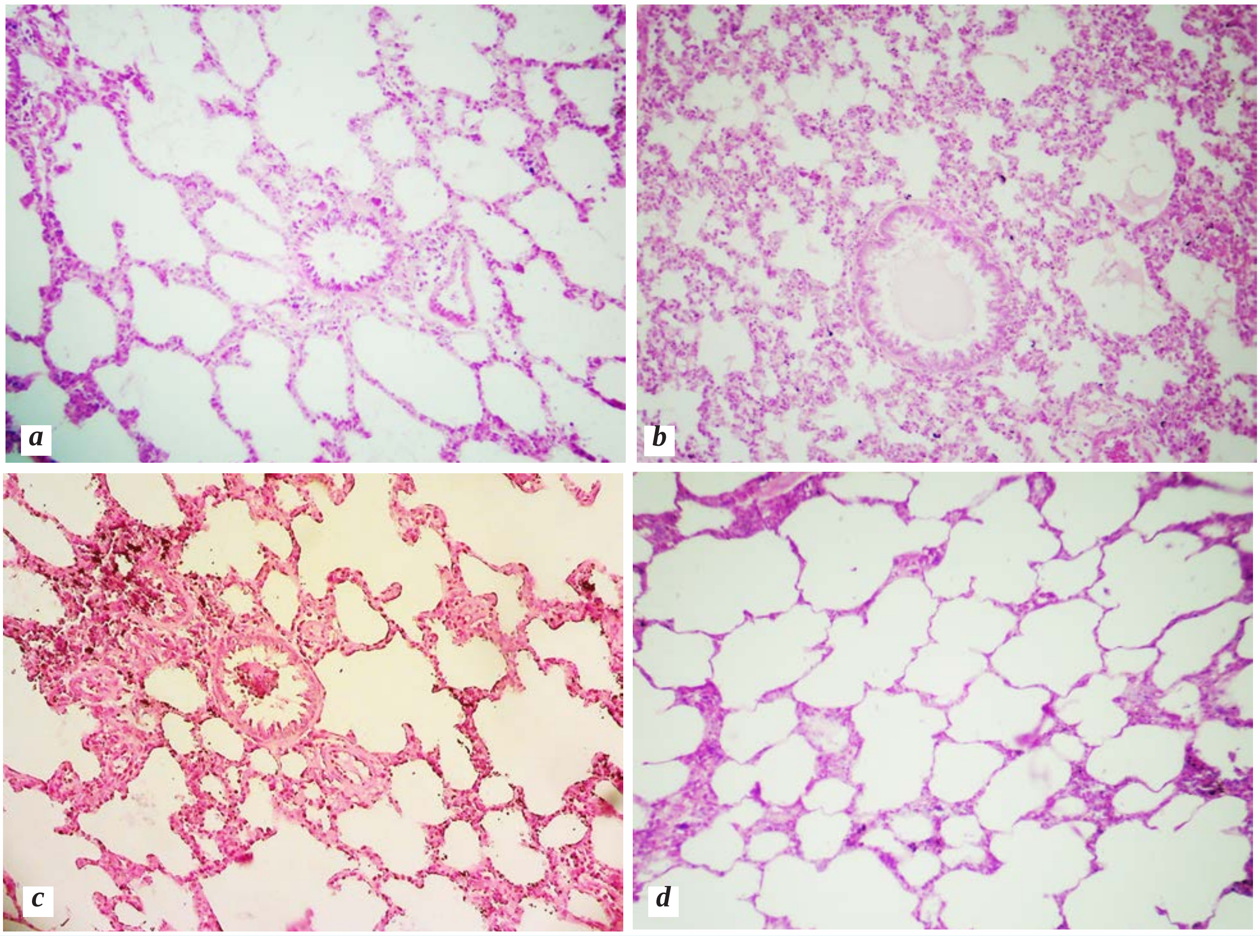

FIGURE 2. Lung sections stained by hematoxylin-eosin, ob. 10, oc. 10: a) control group, b) adrenaline injection group, c) indomethacin pretreated group, d) mechanically ventilated animals group.

sion of IL-8 (by 10%, p<0.05), 3.8-fold elevation of TNF-a and 43.7% increase of IL-10 in contrast to ADR group animals (Tab.). Indomethacin and protective mode MLV pretreatment animals developed more expressed elevation of IL-1β and IL-6 vs. ADR group, IL-8 was substantially increased (3.1-fold, p<0.001) in IND+ADR animals and was normalized in ventilatory correction. Inverse shift was recorded for IL-10 and TNF-a following NSAID injection before adrenaline exposure and MLV+ADR groups (in IND+ADR group decrease by 64.2% and 60% (p<0.001), respectively, and in ventilated rats – by 37.8% and 48%, p<0.001, respectively).

TABLE

Blood cytokine data (M±SD)

Cytokine measurements	Control	ADR	IND+ADR	MLV+ADR
IL-1β, (*pg/ml*)	8.92±0.71	20.98±0.96*	43.56±3.64†	51.5±2.85#
IL-6, (*ng/ml*)	21.12±2.82	51.26±2.39*	81.54±5.42†	84.65±3.07#
IL-8, (*pg/ml*)	43.84±11.81	38.56±3.68**	123.56±4.76†	42.6±3.11
IL-10, (*pg/ml*)	102.86±2.88	147.9±6.84*	53.02±3.21†	92±5.69#
TNF-α, (*pg/ml*)	7.69±0.61	29.12±5.99*	11.66±2.22†	15.15±1.67#

*NOTE: * - p<0.001, ** - p<0.05, significance of differences between ADR and control groups; † - p<0.001, significance of differences between IND+ADR and ADR groups; # - p<0.001, significance of differences between MLV+ADR and ADR groups.*

DISCUSSIONS

No studies to date, to the best of our knowledge, have investigated the inflammatory changes in lungs, alterations of blood cytokines influenced by high-dose adrenaline during acute lung injury followed by cardiac affection.

Our study investigated the mechanisms involved in the preventive effects of indomethacin and MLV in experimental ADR-induced model of ALI leading to myocardial affection. We observed the effects of high-dose adrenaline, mechanical ventilation and indomethacin on histomorphological status of lungs and myocardium, the modulation of blood cytokine activity.

As stated in the report of "Acute Lung Injury in Animals Study Group", an animal model of ALI should ideally capture one or more features of human ALI, including rapid onset (hours) after an inciting stimulus, evidence of pulmonary physiological dysfunction (e.g., abnormalities of gas exchange), histological evidence of injury to the lung parenchyma (inflammatory response) and evidence of increased permeability of the alveolocapillary membrane [*Matute-Bello G et al., 2011*]. It is noteworthy that, based on more precise definitions, in regard to the recent classification (Berlin 2012) the term "Acute lung injury" is replaced by "Acute respiratory distress syndrome", despite using the same basic pathogenetic principles [*Ranieri VM et al., 2012*]. This term ALI considered in our studies still to apply the term of ALI. With that in mind we used the term ALI in our studies.

Our results showed several evidences for ALI, including histological alterations, inflammatory response, and physiological dysfunction. In particular, high doses of adrenaline resulted in extravasation of neutrophils, erythrocytes in lungs, interstitial and intra-alveolar edema, and diffuse alveolar damage.

The research of Rassler and coauthors showed that infusion of CA (norepinephrine, phenylephrine, isoproterenol) over 72*h* may induce pulmonary remodeling (fibrosis and vascular hypertrophy) in rats. They have concluded that mainly α-adrenergic but also β-adrenergic mechanisms contribute to these processes. In addition, cardiac hypertrophy also developed and was predominantly mediated by β-adrenergic stimulation. Noteworthy, cardiac hypertrophy was considered to be a direct adrenergic effect rather than a consequence of pulmonary fibrosis [*Rassler B et al., 2012*]. Meanwhile, our suggestion to elucidate CA-induced ALI followed by acute myocardial damage is that cardiac affection is secondary to pulmonary gas exchange imbalance. The CA used in our studies was adrenaline in single injection and high doses.

According to Castro et al, the acute exposure of mice to cigarette smoke led to cellular activation of transcription factor NF-kB and p38 mitogen activated protein kinase (regulatory factor in translocation of NF-kB to the nucleus implicated in intracellular signaling during inflammatory stimuli) resulting in neutrophil recruitment into the lungs and oxidative damage. They showed that these effects can be blocked by treatment with indomethacin (10 *mg/kg*, IP), administered during 4 days, 1h before cigarette smoke exposure [*Castro P et al., 2009*]. Treatment with both NSAID inhibited the augmentation of PGE2 in bronchoalveolar lavage fluid. This suggests that COX independent mechanisms are at least as important as COX-dependent ones to the anti-inflammatory effect of indomethacin.

In the last years, growing evidence demonstrated a broad molecular modulation of NSAID by interacting with different intracellular pathways other than COX inhibition, suggesting a new therapeutic potential of these drugs. Particularly, indomethacin has been further described to have an effect on cellular apoptosis and inflammatory cell migration via a COX-independent mechanism [*Standiford TJ et al., 2005*]. Several reports have shown that NSAID can inhibit acute experimental lung inflammation induced by different agents. For example, pretreatment of rabbits with indomethacin under partial lung microvascular recruitment, protects against phorbol myristate acetate-induced pulmonary endothelial enzyme dysfunction, perhaps by diverting flow to the lung tissue previously unperfused, unexposed to phorbol myristate acetate, and hence metabolically healthy vessels [*Chen X et al., 1992*].

An acknowledged way of treatment of ALI in patients is the mechanical lung ventilation, which improves the alveolar gas exchange in turn improving survival and reducing the duration of mechanical ventilation with a lung-protective ventilation strategy [*Johnson ER, Matthay MAJ, 2010*]. In our research we suggest it as a means of prevention rather than treatment of experimental ALI which further leads to cardiac affection and death in rats. As shown previously in our recent experiments, the mechanical ventilation prior to adrenaline injection prevents the life-threatening cardiac arrhythmias [*Sisakyan SH et al., 2008*].

Blood cytokine analysis in ADR group resulted in increase of IL-1β, IL-6, IL-10, TNF-a, and suppression of IL-8. Bergmann and Sautner demonstrated that activation of particularly TNF-a and IL-1b can be stimulated by alfa-adrenergic effect [*Bergmann M, Sautner T, 2002*]. In the study of DeRijk and coauthors it was revealed that adrenaline, given subcutaneously and IV infusion, increased plasma levels of IL-6, which could be blocked by the beta-adrenergic receptor antagonist propranolol [*DeRijk RH et al., 1994*]. As shown in a number of literature sources, IL-6 was considered as a pro-inflammatory cytokine. Meanwhile, number of researchers referred it as an anti-inflammatory IL in regard to its ability to down-regulate the synthesis of IL-1 and TNF-a [*Xing Z et al., 1998*].

A dynamic balance exists between pro-inflammatory cytokines and anti-inflammatory components of the immune system, and almost all the anti-inflammatory cytokines have at least some pro-inflammatory properties as well [*Opal SM, DePalo VA, 2000*]. Specifically, the lung injury is caused by an imbalance of pro- and anti-inflammatory mediators; and the transcription factor NF-κB has emerged as a likely candidate shifting the balance in favor of a pro-inflammatory state [*Ware LB, 2006*].

In a model of HCl-induced ALI IL-8 overproduction parallel with pulmonary hemorrhages was shown to occur in pigs [*Lampland AL et al., 2014*], and, along with TNF-a and IL-6 it increased following the ischemia-reperfusion lung injury caused by deep hypothermic circulatory arrest cardiopulmonary bypass in humans [*Dong LY et al., 2013*].

In accordance with several studies, stressor exposure significantly augments lipopolysaccharide (LPS)-induced IL-10 expression in mice, and our trials conclude that during sympathetic activation in stress-induced immune regulation, noradrenaline increases LPS-induced IL-10 via activation of beta-adrenoceptors [*Curtin NM et al., 2009*]. We can assume that IL-10 elevation in ALI is mediated by beta- rather than alfa-adrenoreceptor stimulation, and it is a feedback response to neutralize the detrimental effect of adrenaline.

Pretreatment with indomethacin or MLV led to even higher values of IL-1β and IL-6, and reduction of IL-10 and TNF-a compared to ADR group; IL-8 was significantly elevated in IND+ADR and normalized in MLV-treated animals. IND-mediated and MLV-induced suppression of IL-10 in our study can be considered as a feedback to reduced TNF-a activity. Sirota and coauthors showed that spontaneous secretion of IL-1b and TNF-a and LPS-induced production of TNF-a were substantially increased following incubation of adult PBMC with indomethacin, and only the spontaneous synthesis of TNF-a by cord blood monocytes of preterm newborns was suppressed by this drug [*Sirota L et al., 2000*]. Analogously, our findings reveal that indomethacin increased production of IL-1b, whereas TNF-a was reduced in peripheral blood along with elevation of IL-10 in IND+ADR group.

According to Zampronio et al., IL-8 induces fever in rats by a mechanism independent of the release of COX products, since indomethacin could not perform antipyretic effect following injection of IL-8 [*Zampronio AR et al., 1995*]. Interestingly, in our trials, IL-8 was not subject to substantial alterations, except IND+ADR group, where the mediator increased significantly along with IL-6 amount.

A lung-protective strategy of mechanical ventilation may reduce inflammatory response in patients with ARDS through decreasing concentrations of IL-6, soluble TNF-a receptors and IL-1 receptor antagonist [*Ranieri VM et al., 1999*]. The results of studies by Reis et al. showed that aerobic exercise plays an important role in protecting the lung from LPS-induced ALI [*Reis GCT et al., 2012*]. The beneficial effects of exercise are mainly mediated by the increased expression of anti-inflammatory cytokines and antioxidants and modulation of the inflammatory/anti-inflammatory and the oxidative/anti-oxidative balance in the early phase of ALI. These data can additionally support the idea of applying MLV as a method of prevention in our trials.

Petersen and Pedersen have concluded that muscle-derived IL-6 is mediating the health beneficial effects of regular exercise and can have important role in protection against diseases associated with cardiovascular disorders [*Petersen AMW, Pedersen BK, 2006; Pedersen BK, 2013*]. Here, it should be considered the classic signaling of IL-6, which stimulates physiological, regenerative, and anti-inflammatory responses, whereas IL-6 trans-signaling is used in pathophysiological states and is mainly pro-inflammatory [*Yamamoto K, Rose-John S, 2012*].

CONCLUSIONS

High doses of adrenaline induce ALI followed by myocardial injury manifested in recruitment of neutrophils, increase of capillary permeability, edema and damage of the lung and heart which are accompanied with increase of both inflammatory and anti-inflammatory blood cytokines.

MLV and indomethacin prevent adrenaline-induced experimental ALI and myocardial injury modulating the blood cytokine activity. It can be suggested that this may have an impact on stress-related disease processes. Presumably, the cardio- and lung-protective effects of non-selective NSAI drug indomethacin can be mediated by both COX-dependent (PGE_2 synthesis suppression) and COX-independent mechanisms, since it elevates the inflammatory cytokines, or else, certain pro-inflammatory interleukins (e.g., IL-6) can perform anti-inflammatory response in context of modulation of the rest of cytokines. Both indomethacin and mechanical lung ventilation share preventive mechanisms in suppressing TNF-a and IL-10 caused by adrenaline-induced injury of lungs and myocardium.

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