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EDITORIAL

Questions relating to premenstrual asthma

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Abstract

The study of asthma in fertile women needs to consider its potentially recurrent exacerbation in a specific phase of the menstrual cycle. Premenstrual asthma (PMA) refers to the deterioration of asthma in some women of fertile age during the premenstrual phase. Prevalence varies considerably according to studies (11%-47.44%) mainly because there is no standardized definition of the illness. There is a possible link between PMA and premenstrual syndrome, which is a set of physical and psychic manifestations that occur in some fertile women during the same premenstrual phase. This relation has been widely studied but there are still several unknowns. PMA etiopathogeny is not known. It involves possible causes such as hormonal variations in the premenstrual phase, the coexistence of atopy, variations during the cycle in substances related to inflammation, like LTC4 leukotrienes, catecholamines, E2 and F2α prostaglandins and certain cytokines. Also considered are psychological factors related to this phase of the menstrual cycle, a high susceptibility to infection or increased bronchial hyperreactivity prior to menstruation. Yet no factor fully explains its etiology, consequently no specific treatment exists. Researchers have investigated hormones, anti-leukotrienes, prostaglandin synthesis inhibitors, diuretics, phytoestrogens and alternative therapies, but none has been shown to be effective.

Key words: Premenstrual asthma; Definition; Etiology; Risk factors; Treatment

Core tip: Premenstrual asthma (PMA) refers to the exacerbation of asthma in women of fertile age during the premenstrual phase. Whether or not it is an asthma phenotype, its definition, etiopathogeny and treatment are issues still to be resolved. PMA seems to be a female asthma phenotype despite contradictory results. It can occur at any level of asthma severity and it is usually associated with poorer disease control. Its etiology is not well known, and there is no specific widely recognized treatment. We need new well-designed studies to compare asthmatic women with or without PMA, and good quality clinical trials.

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INTRODUCTION

Unfortunately, there are illnesses or phenotypes of illnesses whose etiopathogeny remains unknown and for which specific treatment is still not available. One such is premenstrual asthma (PMA).

Bronchial asthma in women of fertile age has several specific connotations that include factors such as female sexual hormones and the variations they undergo in the menstrual cycle, women's psychology and metabolism, aspects related to reproduction and the influence of external factors on certain genetic characteristics, among others.

Several authors have investigated the cyclical exacerbation of asthma in fertile women in a specific phase of menstrual cycle. Deterioration has been described in the periovulatory phase[1,2], in the middle of the preovulatory or luteal phase[3,4] and more frequently in the premenstrual phase, an entity defined as premenstrual asthma[5-9].

As well as PMA, other exacerbations in the premenstrual phase have been described, in acne, psoriasis, porphyria, epilepsy, nasal symptoms[10], multiple sclerosis, migraine, urticarial, Behçet syndrome and myasthenia gravis, among others[11].

All this seems to indicate that there are still more questions than answers concerning the possible influence of the menstrual cycle on women and their health, especially in terms of bronchial asthma.

QUESTIONS RELATING TO PREMENSTRUAL ASTHMA

A definition

The classic definition of PMA continues to be the cyclical deterioration of asthma in some women of fertile age during the premenstrual phase and/or the first days of menstruation[6,7]. Although it can occur at any level of asthma severity according to the Global Initiative for Asthma classification[12], it is usually associated with poorer disease control.

Definition of deterioration

Deterioration refers to the worsening of the symptoms of asthma, lung function and inflammation markers, or all of these factors together. As a result, the definition of premenstrual asthma varies in the studies of this entity. Early research[7,9,13,14] defined PMA merely on the basis of a "Yes" answer by a female asthma sufferer to the question, "Does your asthma get worse during the premenstrual phase?" This definition is clearly subjective, referring to the patient's own perception of her asthmatic symptoms in this phase. Authors such as Balzano *et al*[15] comment in their conclusions that it is not clear whether the asthma exacerbation occurring in many women during the premenstrual period is due to an objectively measurable intensification of the disease or to an increased perception of symptoms caused by the particular psychological state occurring shortly before menstruation. Our research group[1] defines this as "PMA from a subjective perspective".

Later authors sought a definition by formulating a methodology that gathered data on the symptoms and then subjected them to a structured analysis in order to consider whether a patient's condition conformed to PMA criteria[8,16]. These definitions still retained a subjective component since they asked women about their personal "perception" of asthmatic symptoms. Our research group[17] defines this as "semi-objective PMA".

Other researchers applied criteria that were more obviously objective. These included the observation of a premenstrual exacerbation in lung function through peak flow[17-19] or spirometry[20] (a reduction in lung volume and flow, or lung diffusing capacity, bronchial hyperreactivity[21] to methacholine or to physical exercise), an increase in inflammation markers such as Nitric Oxide (NOx)[22] or eosinophils in the sputum in the premenstrual phase[23]. There is also some controversy over the level of exacerbation that needs to occur in the premenstrual as opposed to the preovulatory phase. Some authors[16] require more than 20% in the objective parameters while for others it must be 40%[19].

Our research group[16] has categorized these three possible definitions of PMA as "PMA from a subjective perspective", "semi-objective PMA" and "PMA defined by objective criteria", and analyzed the relation between all three. We found that the biggest differences between the preovulatory and premenstrual phases in asthmatic females occurred within the semi-objective PMA category. On the other hand, there is a greater correlation between the semi-objective exacerbation of the symptoms and perception of the exacerbation of the asthma before menstruation when considering one single menstrual cycle than requiring semi-objective exacerbation in two consecutive cycles. We believe it is too stringent to require that semi-objective criteria apply in two consecutive cycles. Objective criteria, which demand a peak flow variation of 20%, are much more restrictive. Our results lead us to think that the definition by semi-objective criteria in a menstrual cycle is what best defines the problem of PMA.

These disparate definitions are seen in the variation in figures for PMA prevalence that appear in studies (from 11% to 47%) and highlight the need to standardize criteria.

Another aspect that further confuses the issue is the relation between subjective, semi-objective and objective criteria. Pauli *et al*[24] found that 11 asthmatic women who had stated that their asthma did not

deteriorate prior to menstruation (non-compliance with subjective criteria) in fact had more symptoms before menstruation when these same symptoms were later analyzed (semi-objective criteria); they also experienced deterioration in premenstrual peak flow (objective criteria according to peak flow). However, there was no deterioration in spirometry or in bronchial hyperreactivity (objective criteria according to other parameters different from peak flow).

How many cycles?

While some authors only require that deterioration occurs in a single cycle[17,25,26], others believe that exacerbation of symptoms must be present in several consecutive cycles[14], the question being whether women with PMA fulfill PMA criteria in all menstrual cycles. With this in mind, Agarwal *et al*[9] studied a group of women over four consecutive menstrual cycles and found that 61% of those with PMA showed deterioration in almost every cycle, 39% had worsening once every 2-3 cycles while one patient had an increase in symptoms every 3-4 cycles. These data question how many cycles are required for PMA criteria to be satisfied. They also make us think about whether PMA sufferers vary in their symptoms during different cycles in the same year or whether these symptoms can change over several years. We consider the semi-objective criteria in a complete menstrual cycle as the most valid approximation to real PMA[16].

At which point in the cycle?

Why do some women experience deterioration in some pre-existing illnesses during the premenstrual phase and others do not? Why do some women suffer this exacerbation in other phases of the menstrual cycle? Such questions remain to be answered convincingly.

Questions on the relation between premenstrual asthma and premenstrual syndrome

Premenstrual syndrome is the cyclical recurrence of a set of physical and psychic symptoms that occur in some women of fertile age following ovulation, in the luteal phase of the menstrual cycle and, in particular, before menstruation, and which is resolved at the beginning of the next menstrual cycle[27,28].

More than 150 clinical manifestations of the syndrome have been described[14,29,30], with congestive and edematous symptoms being predominant in the physical aspect, and mood changes in the psychic aspect. These premenstrual symptoms are relatively frequent in fertile women although their intensity and possible repercussion on quality of life vary significantly (80% experience a slight exacerbation and 3% a severe exacerbation)[31-33]. Their true etiology and physiopathology are unknown[34-36], although the alterations in the balance between sexual hormones and neurotransmitters are noteworthy[37].

Several works have found links between PMA and premenstrual syndrome[17,38]. Our research group[39] has shown a clear connection between PMA and premenstrual syndrome. A detailed analysis of the various symptoms related to premenstrual syndrome reveals that the relation is particularly intense in psychic and edematous symptoms such as abdominal and mammary tension. This could be due to the fact that the generalized nature of the edema in women also occurs in nasal and bronchial mucosa[10] leading to a deterioration of nasal and asthmatic symptoms, and lung function in this premenstrual phase.

Although we believe there exists a relation between PMA and the symptoms related to premenstrual syndrome, the etiology and physiopathology of both is unknown, and not all women with PMA necessarily present with premenstrual syndrome and vice versa.

Questions relating to the etiology of premenstrual asthma

Premenstrual asthma's true etiology is still in doubt. Some authors stress the influence of hormonal factors (premenstrual decline in estrogens or progesterone, or variations in the estrogen/progesterone relation in the premenstrual phase[25,40-46], LH[41], FSH[41]), atopy[47-51], variations during the menstrual cycle of inflammation-related substances [leukotrienes (LTC) 4[19,52], the E2 and F2α[53] prostaglandins and cytokines[54]], psychological factors, diminished resistance to infections or increased bronchial hyperreactivity (Table 1)[8,55,56]. The results of studies that have analyzed the possible factors vary and are occasionally contradictory.

For the possible genetic factors involved, Gorovenko *et al*[57] studied aspects related to asthma genetics and found that women with PMA showed a greater frequency of functioning alleles in Glutathione transferase T1. This genetic polymorphism (in terms of inactive GSTM1 alleles) relates to the metabolism of prostaglandins (PG), LTC and the sexual hormones. The genetic component associated to the atopy could also influence the relation found in some studies between levels of total IgE and premenstrual asthma[47].

Other factors such as sensibility to aspirin (ASS)[48], use of aspirin or non-steroidal anti-inflammatory drugs[58] or body mass index (BMI)[48] have been related to premenstrual asthma. No clear link has been found between ASS and PMA, and although Rao *et al*[48] found higher BMI scores in asthmatics with PMA, other authors found no link between obesity and premenstrual asthma[59].

A priori, the varying behaviors of the sexual hormones in the premenstrual phase compared to the preovulatory phase would seem to be the best explanation of the mechanism by which to describe why some women with bronchial asthma have PMA and others do not. However, the studies have found no difference between the blood levels of the different hormones between women with and without PMA[40]. Researchers have always explored this relation *via* hormone levels in the blood but perhaps this relation is more complex, and is found in intermediary mechanisms such as the cyclical variations

Table 1 Etiological factors in premenstrual asthma

Group	Factor	Ref.	Design	Level of factor in PMA	Level of factor in non PMA	*P* vaule	Evidence level[1]
Hormones	Estrogen	Pasaoglu *et al*[41]	Pre-post study	PM: 89.3 pg/mL	PM: 72 pg/mL	N/A	4
	Estrogen	Pereira *et al*[40]	Cross-sectional study	PO: 111.49 pg/mL PM: 95.9 pg/mL	PO: 131.31 pg/mL PM: 123.83	(for change) 0.845	4
	Progesterone	Pasaoglu *et al*[41]	Pre-post study	PM: 7.3 pg/mL	PM: 9.2 pg/mL	N/A	4
	Progesterone	Pereira *et al*[40]	Cross-sectional study	PO: 0.83 pg/mL PM: 6.82 pg/mL	PO: 1.39 pg/mL PM: 6.31	(for change) 0.225	4
	Estrogen/ Progesterone	Pereira *et al*[40]	Cross-sectional study	PO: 219.26 pg/mL PM: 35.53 pg/mL	PO: 356.6 PM: 355.22	0.865 0.371	4
	LH	Pasaoglu *et al*[41]	Pre-post study	PM: 3.5 mU/mL	PM: 4.9 mU/mL	N/A	4
	FSH	Pasaoglu *et al*[41]	Pre-post study	PM: 13.3 mIU/mL	PM: 3.3 mIU/mL	N/A	4
Inflammation	LTC4	Nakasato *et al*[19]	Pre-post study	PO: 24.0 pg/mL PM: 69.0 pg/mL	PO: NA[1] PM: NA[1]	NA	4
	LTC4	Pereira *et al*[52]	Cross-sectional study	PO: 1.5 ng/mL PM: 1.31 pg/mL	PO: 1.4 ng/mL PM: 1.29	NS	4
	Prostaglandin F2α	Eliasson *et al*[53]	Cross-sectional study	Early cycle: 143 pg/0.1 mL Late cycle: 15.9 pg/0.1 mL	169.3 pg/0.1 mL 9.5 pg/0.1 mL	NS[1] NS[1]	4
Atopy	Total IgE (geometric mean)	Pereira *et al*[47]	Cross-sectional study	206.31	87.99	0.01	4
	Total IgE (% > 100 kU/L)	Pereira *et al*[47]	Cross-sectional study	84	43	0.001	4
	Total IgE (mean)	Rao *et al*[48]	Cross-sectional study	208.4	292.2	0.06	4
	Phadiatop (% +)	Pereira *et al*[47]	Cross-sectional study	68	50	0.17	4
	Skin prick test +	Rao *et al*[48]	Cross-sectional study	60 (76%)	297 (88%)	0.01	4
Others	Aspirin sensitivity	Rao[48]	Cross-sectional study	23 (39%)	36 (10%)	< 0.0001	4
	Use of aspirin or non-steroidal anti-inflammatory drugs	Forbes[58]	Cross-sectional study	14/38 (36.8%)	172/421 (40.9%)	NS	4

[1]Oxford Centre for Evidence-based Medicine-Levels of Evidence (March 2009, http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). N/A: Not available; PMA: Premenstrual asthma; NS: Not significant; LTC: Leukotrienes.

of substances like cytokines (CK) or LTC, among others, which are, in turn, influenced by hormone variations.

In short, despite the studies carried out so far and the reviews published on the subject[60-65], the research results are inconclusive and the causal factors of this entity remain unknown.

Questions related to treatment

Some women with PMA experience a slight worsening of their asthmatic symptoms before menstruation, which is resolved by increasing the dosage of base medication. However, other women suffer severe exacerbation that require frequent visits to hospital emergency rooms or even hospitalization[48,66]. The latter cases would be those most urgently requiring a treatment specific to the patient's condition[40,52,67]. Various specific treatments for PMA have been analyzed (Table 2) without agreement as to which is the most effective. Study results continue to be contradictory. The most attractive hypothesis to explain the cause of PMA is hormonal variations in the premenstrual phase, and the proposed treatments involve oral or intramuscular[68] progesterone, estrogens[25,69] and oral contraceptives[18,44,70]. Other treatments tested include gonadotropin analogues[71], which can cause uncomfortable side effects such as amenorrhea or osteoporosis, leukotrienes antagonists[19,41] and sodium meclofenomate[72] among others.

Our research group is currently carrying out a randomized double-blind placebo-controlled clinical trial to analyze the possible benefits of phytoestrogens (Genistein) in cases of premenstrual asthma[73]. Phytoestrogens are natural estrogens that present fewer side effects than human estrogens. They can have an agonistic or antagonistic effect according to the tissue on which they act[74]. It is shown to be useful in treating postmenopausal symptoms[75], premenstrual syndrome[76] and asthma[77,78]. Our study is based on the relation that we have found between PMA and symptoms related to premenstrual syndrome, and it is boosted by the fact that the side effects of these substances are few. The results have not been published yet.

So we can say that due to the absence of a definitive PMA etiology, and despite the various therapeutic interventions proposed[19,25,41,42,70,71], the best approach for this entity remains unknown. Treating this condition requires well-designed randomized double-blind placebo-

Table 2 Specific treatments used in premenstrual asthma

Group	Treatment	Ref.	Design	patients	Outcome	Results	*P* vaule	Evidence level
Hormonal	Oral or intramuscular progesterone	Beynon *et al*[68]	Case-series	3	Premenstrual dips in peak flow	3 eliminated premenstrual dips in peak flow	NS	4
	Estrogen	Ensom *et al*[25]	Cross-over trial	12 (mild severity)	Asthma Quality of Life Questionnaire, FEV1	No differences	NS	1b
		Ensom *et al*[69]	Case report	1 (severe asthma)	Symptoms, pulmonary function, peak flow	Improved	N/A	4
	OC	Murphy *et al*[18]	Case-series	28 (16 with PMA)	OC use (%)	5.42% in Non PMA 6.38% in PMA	NS	4
		Tan *et al*[44]	Cross-sectional study	18 (9 taking OC)	Changes between follicular and luteal phases in airway reactivity and peak flow	Changes in patients not taking OC; No changes in patients taking OC	0.03 NS	4
		Derimanov *et al*[70]	Case report	1	Deterioration of asthma, decline of pulmonary function tests	After discontinuing the contraceptives, her condition returned to baseline	N/A	4
	Gonadotropin analogues	Murray *et al*[71]	Case report	1	Respiratory symptoms, PEFR dips premenstrual and prednisolone dosage and hospital admissions	Improvement	N/A	4
Anti-inflamma-tory	Anti-leukotrienes: pranlukast	Nakasato *et al*[19]	Pre-post study	5	Respiratory symptoms, PEFR	Improved asthma symptom scores, inhibited maximal decreases in PEFR	< 0.05 < 0.01	4
	Anti-leukotrienes: montelukast	Pasaoglu *et al*[41]	Pre-post study	24 mild asthma-tics (11 with PMA)	PEFR and symptom scores	Improvement in PEFR variability and symptom scores in women with PMA. No differences in women without PMA	0.005 0.002	4
	Prostaglandin synthesis inhibitors: sodium meclofenomate	Shimoda *et al*[72]	Cross-over trial	17 PMA	Peak flow, symptoms score	Improvement in peak flow during the early premenstrual period. No effect on the exacerbation of asthma during the late premenstrual period and early menstruation	0.025 NS	2
Others	Phytoestrogens soy genistein	Bime *et al*[77]	Case series	300 poorly controlled asthma	FEV1 and asthma control	Participants with little or no genistein intake had a lower baseline FEV1 and poorer asthma control than those with a moderate or high intake	0.01 0.001	4
	Phytoestrogens soy isoflavone	Smith *et al*[78]	Clinical trial	386 poorly controlled asthma	FEV1 at 24 wk symptoms, episodes of poor asthma control, asthma control test score	Not result in improved lung function or clinical outcomes	NS	1b

N/A: Not available; NS: Not significant; PEFR: Peak expiratory flow rate; PMA: Premenstrual asthma; OC: Oral contraceptives.

controlled clinical trials.

CONCLUSION

Definition

The definition used in studies needs to be clarified in order for results to be compared.

Relation between premenstrual asthma and premenstrual syndrome

Although a relation between both events seems to exist, there are still doubts about the type of premenstrual

syndrome-related symptoms that can be clearly linked to PMA; and doubts persist as to the etiology of both phenomena.

Etiology of premenstrual asthma

The type of relation that exists between hormonal changes throughout the cycle and PMA has yet to be established; this relation would be the most likely hypothesis. Investigators have searched for this link in hormone levels of the blood but the relation seems to be more complex. There are still doubts about PMA etiology, and like Skoczynsky *et al*[23], we believe that close collaboration between medical specialities such as pneumology, gynaecology and endocrinology, among others, could shed light on this issue.

Specific treatment for premenstrual asthma

Although there are several works published on the subject, there is currently no treatment specifically designed for PMA. More studies are needed in this area.

Final conclusion

Although the results are contradictory, it seems that PMA can be considered a phenotype specific to asthma in women. Although it can occur at any level of asthma severity classification[16] it is usually associated with poorer disease control[50,79,80]. We still do not know its etiology entirely and no specific treatment exists that has been widely accepted. All this requires new studies to compare groups of asthmatic women with or without premenstrual asthma, with clear criteria regarding definition of the entity.

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MINIREVIEWS

Reducing acute respiratory distress syndrome occurrence using mechanical ventilation

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Abstract

The standard treatment for acute respiratory distress syndrome (ARDS) is supportive in the form of low tidal volume ventilation applied after significant lung injury has already developed. Nevertheless, ARDS mortality remains unacceptably high (> 40%). Indeed, once ARDS is established it becomes refractory to treatment, and therefore avoidance is key. However, preventive techniques and therapeutics to reduce the incidence of ARDS in patients at high-risk have not been validated clinically. This review discusses the current data suggesting that preemptive application of the properly adjusted mechanical breath can block progressive acute lung injury and significantly reduce the occurrence of ARDS.

Key words: Acute respiratory distress syndrome; Ventilator induced lung injury; Early acute lung injury; Mechanical ventilation; Acute respiratory distress syndrome incidence; Airway pressure release ventilation; Acute respiratory distress syndrome pathophysiology

Core tip: In all patients at risk of developing acute lung injury or acute respiratory distress syndrome (ARDS), protective mechanical ventilation should be applied immediately upon intubation. However, the optimally protective breath to block progressive acute lung injury is not known. Recent clinical studies have shown that preemptive low tidal volume can both reduce and increase mortality. Application of preemptive airway pressure release ventilation has shown a great deal of promise at reducing ARDS occurrence in both animal and clinical studies.

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INTRODUCTION

The standard treatment for acute respiratory distress syndrome (ARDS) is supportive in the form of low tidal volume (Vt) ventilation applied after significant lung injury has already developed[1]. Nevertheless, ARDS mortality remains unacceptably high (> 40%)[2]. Indeed, once ARDS is established it becomes refractory to treatment[3,4], and therefore avoidance is key. However, preventive techniques and therapeutics to reduce the incidence of ARDS in patients at high-risk have not been validated clinically. This review discusses the current data suggesting that preemptive application of the properly adjusted mechanical breath can block progressive acute lung injury and significantly reduce the occurrence of ARDS.

Currently the concept of ARDS is binary; either a patient has ARDS or they do not. However, it is now recognized that ARDS begins sub-clinically as early acute lung injury (EALI), which is developing long before (hours to days) the patient is even intubated[5]. Over time EALI becomes clinically apparent and the patient is intubated and placed on mechanical ventilation. Non-protective mechanical ventilation (N-P_{MV}) during this EALI stage works synergistically with the initiating event (*i.e.,* systemic inflammatory response syndrome-SIRS) to amplify lung injury by a mechanism of increased alveolar and alveolar duct mirco(μ)-strain and if unchecked will culminate in ARDS (Figure 1). This concept is supported by recent studies showing that application of mechanical ventilation with Vt during EALI significantly reduced the incidence of ARDS[6-14]. In addition, early application of a novel ventilator strategy using an extended time at inspiration and minimal time at expiration delivered using the airway pressure release ventilation (APRV) mode, dramatically reduced the incidence of ARDS in patients at high risk secondary to major trauma[15]. It has been shown that N-P_{MV} exacerbates alveolar and alveolar duct μ-strain[16,17] causing extensive damage to the pulmonary parenchyma and deactivating surfactant, both of which are established mechanisms driving EALI to ARDS (Figure 1). Thus it has been shown that the combination of the parameters that comprise the MB_P (*i.e.,* airway pressures, volumes, flows, rates and most importantly the time that these parameters are exposed to the lung during each breath) can either exacerbate or block progressive acute lung injury. Therefore a key research goal is to identify the optimal mechanical breath necessary to protect the lung and reduce ARDS incidence.

Ineffective ARDS treatments

There are no drugs currently available to reduce the occurrence of ARDS in patients at high-risk[18]. Thus clinicians must attempt to treat the syndrome once it has fully developed[3]. Although many treatment strategies have been tested in clinical trials almost all have failed[3,19-21] and mortality of ARDS remains higher than 40%[2]. In addition ARDS survivors often develop chronic pulmonary[22] and brain[23] lesions. Mechanical ventilation is essential in patients with respiratory failure[1] but, if not adjusted properly, it can cause additional lung damage, termed ventilator induced lung injury (VILI) (Figure 1)[24]. Injurious mechanical ventilation has not only been shown to damage the lung but to also injure distant organs, and thus VILI is a potential mechanism for the development of multiple organ dysfunction syndrome with an even higher mortality than ARDS[25].

McIntyre *et al*[3] rated multiple ARDS treatment strategies from "A" (highly effective) to "E'" (no effect above placebo). Most treatments either received a "D" or "E" except for Low tidal volume and Open Lung protective ventilation strategies, which received a Recommendation of "B" (no treatments received "A"). Brower *et al*[4] published a similar report demonstrating the difficulty of treating established-ARDS. Thus, it appears that there is no effective treatment of established-ARDS and thus reducing the incidence of ARDS would have a remarkable benefit in reducing ARDS mortality. Therefore, if ARDS morbidity and mortality are going to be reduced, a pre-emptive treatment strategy will have to be employed to prevent the syndrome before it develops.

Ventilator-induced ARDS pathogenesis

It is well established that ARDS pathogenesis is due to an increased vascular permeability, which causes a high permeability pulmonary edema and sequentially deactivates pulmonary surfactant, resulting in alveolar instability (Figure 1)[26]. However, the current binary concept that the lungs are "sick" only after ARDS criteria are met perpetuates less than optimal treatment strategies, which are implemented only after established-ARDS has already developed. We postulate that in the EALI phase the identical pathologic mechanisms are at work, but lung injury is not identified because in this early stage only a relatively small percentage of the lung is damaged[27]. With progressive alveolar flooding, which deactivates more and more surfactant, there is an alteration in alveolar mechanics (*i.e.,* the dynamic change in alveolar size and shape during tidal ventilation) leading to alveolar instability and induced tissue damage at the cellular level (*i.e.,* μ-strain) (Figure 1). Because of the limited volume of lung initially involved, the ability of hypoxic pulmonary vasoconstriction[28] to match ventilation with perfusion, and rapid transit time of hemoglobin saturation[29,30], there are minimal clinical signs or symptoms of EALI; nevertheless, over time a larger and larger portion of these patient's lungs become abnormal despite normal blood gases. Thus, in the studies demonstrating that VILI occurs in "normal" lungs before the development of acute lung injury (ALI)[6,7,31], we postulate that these lungs were not normal but rather a significant portion of lung was already edematous with unstable alveoli (EALI).

We also postulate that the systemic inflammatory

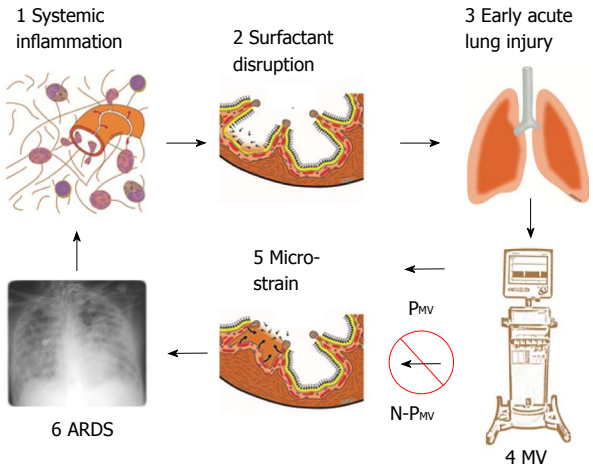

Figure 1 Pathogenesis of acute respiratory distress syndrome. 1: Systemic inflammation, also know as the systemic inflammatory response syndrome (SIRS) activates white blood cells and increases vascular permeability (red arrows); 2: Surfactant disruption occurs if increased permeability result in alveolar edema (tan color) forces surfactant molecules off of the alveolar surface into the lumen of the alveolus; 3: Early acute lung injury (EALI) pathology is associated with moderate surfactant deactivation and pulmonary edema with limited clinical symptoms; 4: Mechanical ventilation (MV) if non-protective (N-P_{MV}) will cause a ventilator induced lung injury, which greatly exacerbates progressive acute lung damage; 5: Micro-strain on the alveolar walls occurs as alveoli with limited surfactant function collapse and reopen during each breath. N-P_{MV} greatly accelerates and expands micro-strain injury and is one of the primary VILI mechanisms. However, if a protective mechanical breath (P_{MV}) is applied immediately upon intubation alveolar micro-strain is avoided; 6: Acute respiratory distress syndrome (ARDS) is caused by a combination of systemic inflammation-induced pulmonary edema, deactivation of surfactant and N-P_{MV}, resulting in alveolar micro-strain. If micro-strain is prevented by applying P_{MV}, VILI will be avoided and ARDS incidence reduced. P_{MV}: Protective mechanical ventilation; VILI: Ventilator induced lung injury.

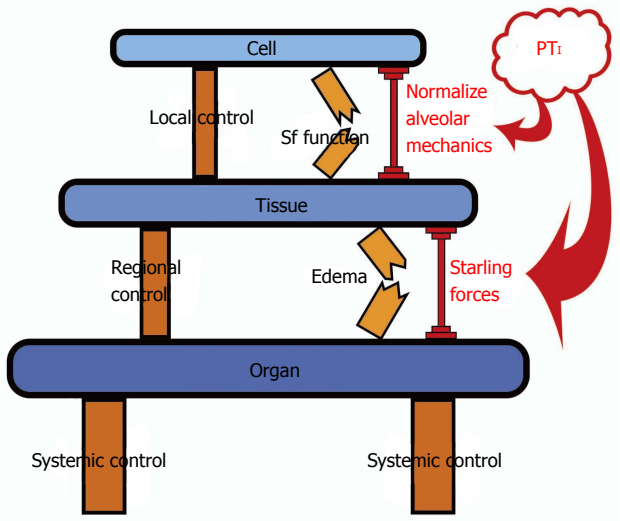

Figure 2 Appropriate mechanical breath settings prevent 'tipping point' cascade and acute respiratory distress syndrome. Control mechanisms at the Local (Cell), Regional (Tissue) and Systemic (Organ) level attempt to balance insults/perturbations such as loss of surfactant (Sf) function and pulmonary edema formation but can fail without additional support. The control systems can be overwhelmed, leading to a cascading effect that culminates in dysfunction at the next higher biologic level (Cell→Tissue→Organ). Current therapies for acute lung injury are applied too late, after the health state has cascaded all the way down to the Organ Level (*i.e.*, development of established-ARDS). We propose that mechanical ventilation modulation strategies with an appropriate pressure time integral (PT_I) directed at lower level control structures (*i.e.*, Sf function by normalizing alveolar mechanics and edema prevention by altering the Starling fluid flux forces) early in the failure sequence, prior to complete loss of containment and tipping to the organ level, may help reset the underlying control mechanisms, limit spill-over effects and bolster maintenance of compartmental containment. Application of a preemptive mechanical breath with the proper PT_I can assist the endogenous control mechanisms and "shore up" the insults/perturbations to prevent the development of established-ARDS. ARDS: Acute respiratory distress syndrome; PT_I: Pressure/time integral.

response syndrome (SIRS) and VILI often work additively or synergistically in a progressive manner until a "tipping point" in lung pathology is reached (Figure 2) resulting in the clinical manifestation of ARDS (Figure 1); however if preemptive mechanical ventilation with an appropriate airway mechanical breath is applied before this "tipping point", ARDS can be prevented (Figure 1).

Our preemptive ventilator strategy

ARDS is rarely present at the time of hospital admission but develops over a period of hours to days[32], providing an opportunity for intervention. We postulate that not only airway pressure, but the time that this pressure is applied to the lung during each breath, is important to lung protection. Andrews *et al*[15] placed all intubated patients arriving in the Multitrauma Critical Care (MTCC) unit on APRV with an extended time at inspiration and minimal time at expiration and showed ARDS rates were reduced (1.4%) by an order of magnitude as compared to the incidence of 15 other SICUs (14%). In addition, Roy *et al*[33] showed a direct correlation between an elevated pressure/time integral (PT_I - an integral of airway pressure over the time from peak inspiration to end expiration) and reduced ARDS incidence using the identical APRV strategy used by Andrews *et al*[15]. APRV has the ability to precisely regulate the time spent during the plateau pressure as well as the time spent in the release phase. This allows precise control of the variables of pressure and time thus, controlling the breath profile that directly impacts the lung. However, the APRV acronym is a nebulous term for ventilation with an extended time (T_{high}) at peak airway pressure (P_{high}) and with a short time (T_{low}) at end expiratory pressure (P_{low}). Any combination of these times and pressures would be defined as APRV, yet, only a specific combination of these settings, developed by our group, is effective at reducing the incidence of ARDS[15-17,27,33-36]. Our work shows that a specific protocol of T_{high}, P_{high} and T_{low} settings must be precisely followed in order for this airway PT_I to be effective at preventing ARDS.

To summarize, trauma/sepsis/hemorrhage induced SIRS initiates a heterogeneous lung injury caused by edema-induced surfactant deactivation, resulting in unstable alveoli. As the disease progresses and overwhelms more and more lung, the patient is intubated and placed on ventilation often with relatively high Vt. Ventilation with a N-P_{MV} strategy using an inappropriate PT_I exacerbates alveolar instability causing VILI (Figure 1). SIRS plus

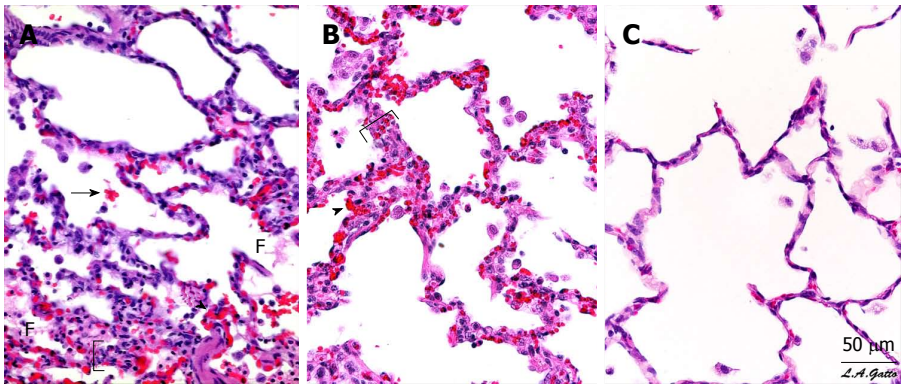

Figure 3 Pulmonary Histopathology - Photomicrographs of representative lung sections of specimens from each treatment group at 40 x magnification. A: Sham- animals received 48 h of mechanical ventilation without peritoneal sepsis + gut ischemia/reperfusion (PS + I/R) injury. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, and thickened alveolar walls; B: LTV- animals received PS + I/R injury and LTV ventilation after onset of ALI. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, leukocyte infiltration, and thickened alveolar walls; C: APRV- Animals received APRV one hour following PS + I/R injury. Specimen shows normal pulmonary architecture, alveoli are well expanded, thin walled and there are no exudates. APRV applied early in animals with severe septic shock protected the lung superior to Sham animals with conventional mechanical ventilation without septic shock. (with permission)[33]. F: Fibrinous deposit in the air compartment; Arrow: Blood in alveolus; Arrowhead: Congested alveolar capillary; Bracket: Thickened alveolar wall; APRV: Airway pressure release ventilation.

VILI (*i.e.,* N-P_{MV}) combine to progress the lung from EALI into established-ARDS (Figure 1). The fact that acute lung injury develops slowly in stages while the patient is in the hospital, suggests the possibility that mechanical ventilation can be used as a therapeutic tool and if applied before a certain pathophysiological "tipping point" can prevent or reduce the development of established-ARDS (Figure 2)[32]. Our preliminary data has shown that the early application of the proper mechanical breath reduced the incidence of ARDS to 1.4%[15], as compared to the Nation Wide average of 13.5% ± 2.2%, in severely injured trauma patients[37-45] and in a high fidelity translational animal model[33]. The mechanisms of lung protection involve limiting vascular permeability and pulmonary edema, and preservation of surfactant function[27,33]. The Andrews study[15], combined with our animal data[27,33], strongly supports our hypothesis that the ventilator can reduce ARDS occurrence. Indeed, Villar and Slutsky[46] recently suggested that it makes much more sense to prevent rather than treat ARDS once it fully develops.

"Tipping point" theory

Our group has been analyzing sepsis-induced ARDS pathogenesis using mathematical modeling[47-49]. We found that sepsis pathogenesis does not progress in a linear fashion, but rather proceeds at a given scale until it exceeds a "tipping point" (*i.e.,* conversion from EALI to established-ARDS). Below this tipping point, mechanical stress/strain-induced tissue damage and inflammation is contained and manageable; when this threshold is crossed, mechanical damage and inflammation escalates, and dysfunction propagates to a higher biological scale (*e.g.,* progressing from cellular, to tissue/organ, to multiple organs, to the organism; Figure 2)[47-49]. We hypothesize that for as long as tissue injury and inflammation remain effectively controlled and confined to a given scale or compartment the process will affect only the physiology characteristic of that scale. If the perturbation can be reversed within that scale, before a critical "tipping point" is reached, it will limit the possibility of impacting higher scales (Figure 2)[47-49]. A global system-level insult, such as severe injury and hemorrhagic shock, can lead to SIRS. This containment failure leads to the presence of inflammatory mediators throughout the circulation that when combined with injurious mechanical ventilation will cause progressive lung injury and if untreated will develop into ARDS (Figure 1)[47-49].

We clearly recognize that inappropriate ventilation therapies themselves carry detrimental potential (*i.e.,* ventilator-associated injury - VILI). However, if ventilation therapies with appropriate mechanical breath are applied at an early ARDS stage, the initial tipping from cellular to the tissue level may be prevented without any negative side effects (*i.e.,* VILI). We postulate that preemptive application of our APRV protocol arrests lung pathogenesis before the "tipping point" is reached, thus preventing the damage from jumping scales, therefore preventing damage at the organ level (Figure 3)[47-49].

Starling forces: Although vascular permeability is critical in edema formation it is only one component in the Starling equation for fluid flux[50,51]. Capillary filtration rate (Jv) is governed by the balance between capillary hydrostatic pressure (Pc) and plasma colloid osmotic pressure (πp), interstitial hydrostatic pressure (Pi) and colloid osmotic pressure (πi), the hydraulic conductivity (Lp), the surface area available for filtration (PS) and the vascular permeability expressed as a reflection coefficient (σ) (Equation 1):

$$Jv = LpPS [(Pc - Pi) - \sigma(\pi p - \pi i)] \quad \text{(Equation 1)}$$

It is our hypothesis that ventilation with the appropriate mechanical breath can shift the balance of the Starling equation from high capillary filtration to a significantly reduced filtration rate, even in the presence of increased σ,

by increasing Pi. Alternatively, an appropriate mechanical breath may prevent stretch induced increases in σ by stabilizing alveoli[52,53].

VENTILATOR AS A THERAPEUTIC TOOL TO PREVENT ARDS

We hypothesize that ARDS can be prevented if mechanical ventilation with the appropriate mechanical breath is applied during the EALI stage, before a "tipping point" of no return is reached. We tested this hypothesis initially in our clinically applicable porcine model of peritoneal sepsis (PS) and gut ischemia/reperfusion (I/R) ARDS model[54]. This is a highly sophisticated model that treats the animal as a trauma or septic patient would be treated in the ICU. Animals are ventilated with a critical care grade ventilator, receive fluid resuscitation according to surviving sepsis criteria[55], are given scheduled doses of wide spectrum antibiotics, vasopressors to maintain arterial pressure and urine output and, in spite of this treatment 100% of the animals develop ARDS over a 48hr period without additional protection. All of the main pathologic features required in a clinically applicable animal ARDS model including: (1) histological evidence of tissue injury; (2) alteration of alveolar capillary barrier; (3) an inflammatory response; and (4) evidence of physiological dysfunction[56], are also present in our porcine model[27,33]. Since so many features of our model match those seen in the clinical practice, the model has been described as "good evidence" in that whatever treatment proves successful in this model will also be successful in a clinical trial[57].

Animal experiment reducing ARDS incidence

We chose to use the APRV mode to test our first mechanical breath because APRV allows precise control of the time during which airway pressure and volume are applied to the lung with each breath and hypothesized that the T_{High} at plateau pressure would keep the pulmonary interstitial pressure sustained for the majority of each breath, which would reduce transvascular fluid transduction by elevating Pi (Equation 1) and thus reduce edema. In addition we postulated that T_{Low} at expiratory pressure would prevent alveolar collapse and instability and that this combination would prevent ARDS development. We tested our hypothesis in our PS + I/R porcine ARDS model. In this study animals were on conventional mechanical ventilation (CMV) during the surgery and injury (*i.e.,* PS + I/R) period and then either remained on CMV or were converted to APRV 1 h into the 48 h experiment.

APRV settings

There are 4 basic APRV adjustments that can be made: (1) time at high pressure (T_{high}); (2) the magnitude of high pressure (P_{High}); (3) time at low pressure (T_{Low}); and (4) the magnitude of low pressure (P_{low}). In our studies the T_{high} was set at 90% of each breath. P_{High} was set to be similar to the plateau pressure with CMV. T_{Low} was very brief and is calculated as 75% of the peak expiratory flow rate (PEFR) thus, it is adjusted in response to changes in lung physiology (*i.e.,* the rate of lung collapse) in a closed loop fashion[34]. P_{low} was always set at zero to maximize the bulk gas flow movement during exhalation. However, P_{Low} never reached zero since T_{Low} is so short, the lung does not have sufficient time to totally deflate and thus P_{low} is always positive. Unpublished observations suggest that the P_{Low} is approximately 33%-50% of P_{High} with a T_{Low} set to 75% of the PEFR. We postulate that the combined effects of our P_{High}, T_{High} and T_{Low} strategy will create a mechanical breath that can block the ARDS progressive pathogenesis and prevent the development of ARDS (Figure 1).

Experiments in our laboratory

In our initial study we compared two groups of animals[27]: Group 1: Non-protective ventilation (NPV) - animals were ventilated with volume cycled ventilation [Tidal volume (Vt) = 10 cc/kg] with 5 cmH_2O of PEEP. Group Ⅱ animals were converted to our APRV ventilation protocol with the settings described above, immediately following PS + I/R and remained on APRV for the entire 48 h experiment. The results of the study were very definitive; APRV completely protected the lung from injury[27]. Lung injury was assessed at many levels including organ function, histologic and molecular. Lung function was assessed by oxygenation using the PaO_2/FiO_2 (P/F) ratio. Oxygenation was clearly maintained throughout the 48 h experiment in the APRV group, whereas in the CMV group P/F fell below 200[27], which is the Berlin definitions of ARDS[58]. This was due to almost complete protection at the tissue level. APRV also protected the lung at the molecular level. There was a significant reduction in total protein and interleukin-6 (IL-6) in bronchoalveolar lavage fluid (BALF)[27]. This suggests that APRV prevents the increase in pulmonary microvascular permeability and reduces lung inflammation. In addition, APRV preserved surfactant protein B (SP-B) concentration, which is known to play a critical role in surfactant function, thus, maintaining normal levels of SP-B would prevent alveolar instability[27]. All of these physiologic, cellular and molecular improvements translated into a significant reduction in pulmonary edema[27].

More recently we compared preemptive application of APRV with the current standard of care low tidal volume ventilation (LVt). LVt was adjusted using the ARDSnet strategy and was applied similarity to current clinical practice once the patient's P/F fell below > 300. Additional adjustments were made using the ARDSnet protocol following the high PEEP scale, as well as the protocol guidelines(*i.e.,* SaO_2 < 88%)[1]. APRV kept the lung fully inflated preventing the severe atelectasis associated with ARDS. In addition, APRV significantly reduced interstitial and airway edema as compared with the LVt group, with significantly less histopathologic injury (Figure 3). These improvements in lung function and pathology were coupled with preservation of

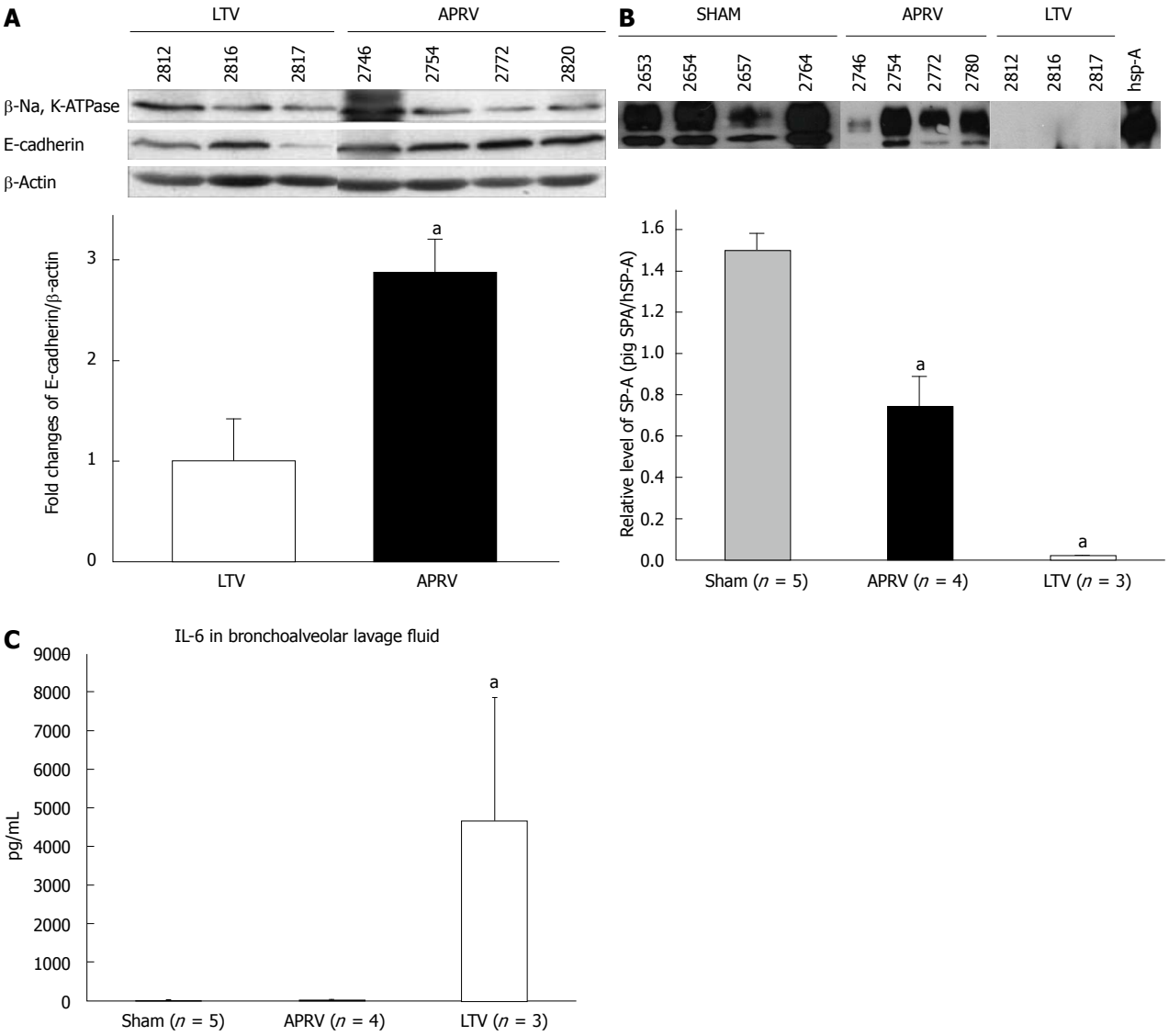

Figure 4 Bronchoalveolar lavage and lung tissue analysis. A: Epithelial Cadherin in Lung tissue showing APRV had significantly greater E-Cadherin abundance in lung tissue than LTV ($^aP < 0.05$); B: Surfactant protein A in BALF showing APRV had significantly higher SP-A abundance in BALF than LTV ($^aP < 0.05$); C: Interleukin-6 (IL-6) in BALF showing APRV had significantly lower IL-6 in BALF than LTV ($^aP < 0.05$)[33]. APRV: Airway pressure release ventilation; BALF: Bronchoalveolar lavage fluid (with permission)[33].

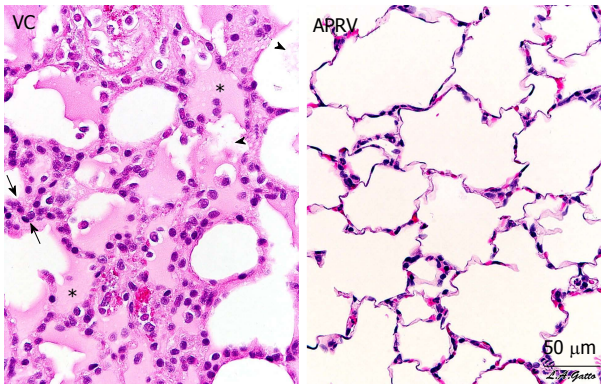

Figure 5 Histological comparison of a rat receiving early airway pressure release ventilation with a rat receiving volume cycled ventilation. The VC animal exhibits hallmarks of acute respiratory distress syndrome, including alveolar flooding (stars), fibrinous deposits in the air compartment (arrowheads) and high cellularity (between arrows). The APRV animal shows patent alveoli with notable preservation of nearly normal histology (with permission)[35]. APRV: Airway pressure release ventilation; VC: Volume cycled ventilation.

E-Cadherin (reduced vascular permeability), surfactant protein-A (improved surfactant function) and IL-6 (reduced inflammation) (Figure 4)[33]. Combined, these studies clearly show that preemptive mechanical ventilation applied early in the disease processes can block ARDS pathogenesis, significantly reducing ARDS incidence.

Clinical studies reducing ARDS incidence

We have conducted a statistical review comparing the incidence and mortality of ARDS in patients with APRV applied immediately upon intubation, against the standard of care ventilation in severely injured trauma patients. Even though our Injury Severity Score was in the upper quartile, our ARDS incidence (14% *vs* 1.3%) and mortality (14.1% *vs* 3.9%) were both below the lower quartile. Although this study was a retrospective meta-analysis and not a prospective clinical trial, the order of magnitude differences in ARDS incidence and mortality strongly suggest that early

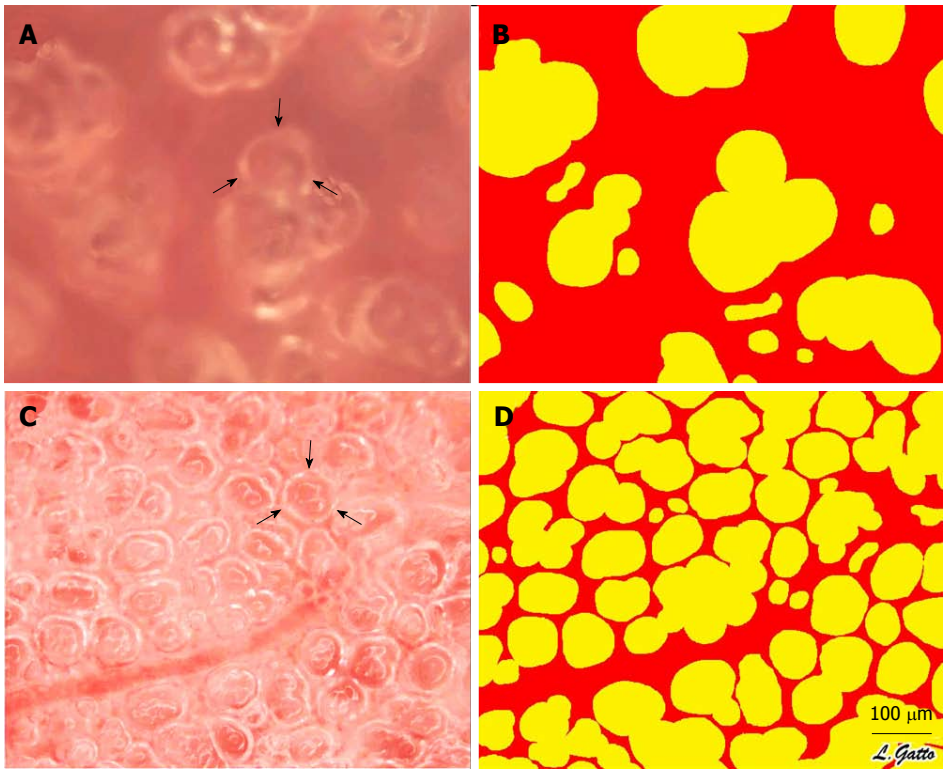

Figure 6 ***In vivo*** **photomicrographs and image analysis of inflated subpleural alveoli in the volume cycled ventilation (A, B) and airway pressure release ventilation (C, D) groups.** Measurement of the % Air Space was accomplished by circling the inflated alveoli using computer image analysis. All inflated alveoli were then assigned the color yellow and noninflated areas were assigned the color red generating a sharp contrast for the image analysis software to identify and measure the % of inflated alveoli/microscopic field. Arrows (A, C) identify a single alveolus (with permission)[35]. VC: Volume cycled ventilation.

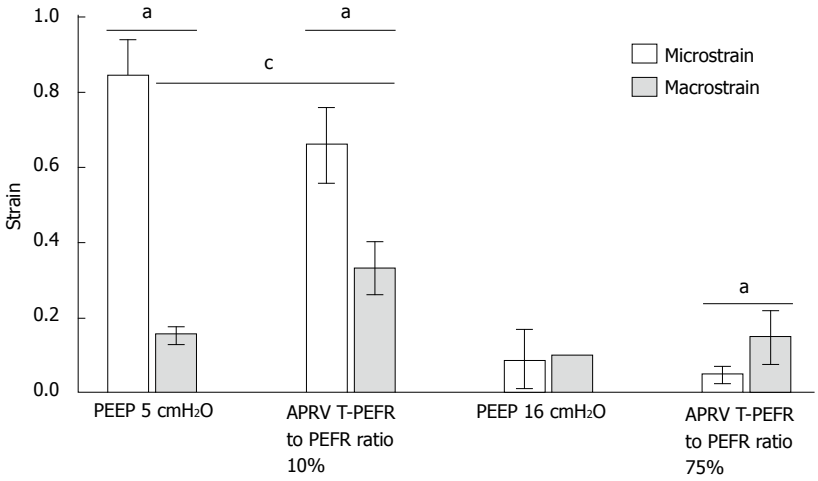

Figure 7 Macro-strain *vs* micro-strain. Macro-strain was that calculated for the entire lung and Micro-strain calculated for individual alveoli in the same lung under the identical conditions. Low PEEP (5 cmH_2O) with a conventional breath and an extended time at low pressure (10%) with APRV showed the largest difference between Macro- and Micro-strain. High PEEP (16 cmH_2O) and a brief time at low pressure with APRV (75%) minimized the differences between Macro- and Micro-strain. See text for description of APRV settings. $^{a}P < 0.05$ between Macro- and Micro-strain; $^{c}P < 0.05$ between PEEP 5 and APRV 10 (with permission)[17]. APRV: Airway pressure release ventilation.

application of protective mechanical ventilation, in the form of properly adjusted APRV, can reduce both ARDS incidence and mortality[15].

MECHANISM OF MECHANICAL BREATH PROTECTION

Although these studies offer proof-of-concept that preemptive APRV can reduce ARDS incidence[27,33], we need to better understand the mechanisms by which APRV protects the lung from progressive acute lung injury. To this end we have developed a rat trauma/hemorrhagic shock (T/HS) model with clinically applicable fluid resuscitation and mechanical ventilation protocols[35]. This model initiates a systemic inflammatory injury that results in progressive acute lung injury culminating in the development of ARDS over a 6 h period. This model gives an opportunity to study progressive acute lung injury that if unblocked will lead to ARDS. Our hypothesis was that early application of APRV immediately following HS, when the lungs were still normal, would block progressive lung damage and reduce ARDS incidence.

In our preliminary experiments we studied two groups

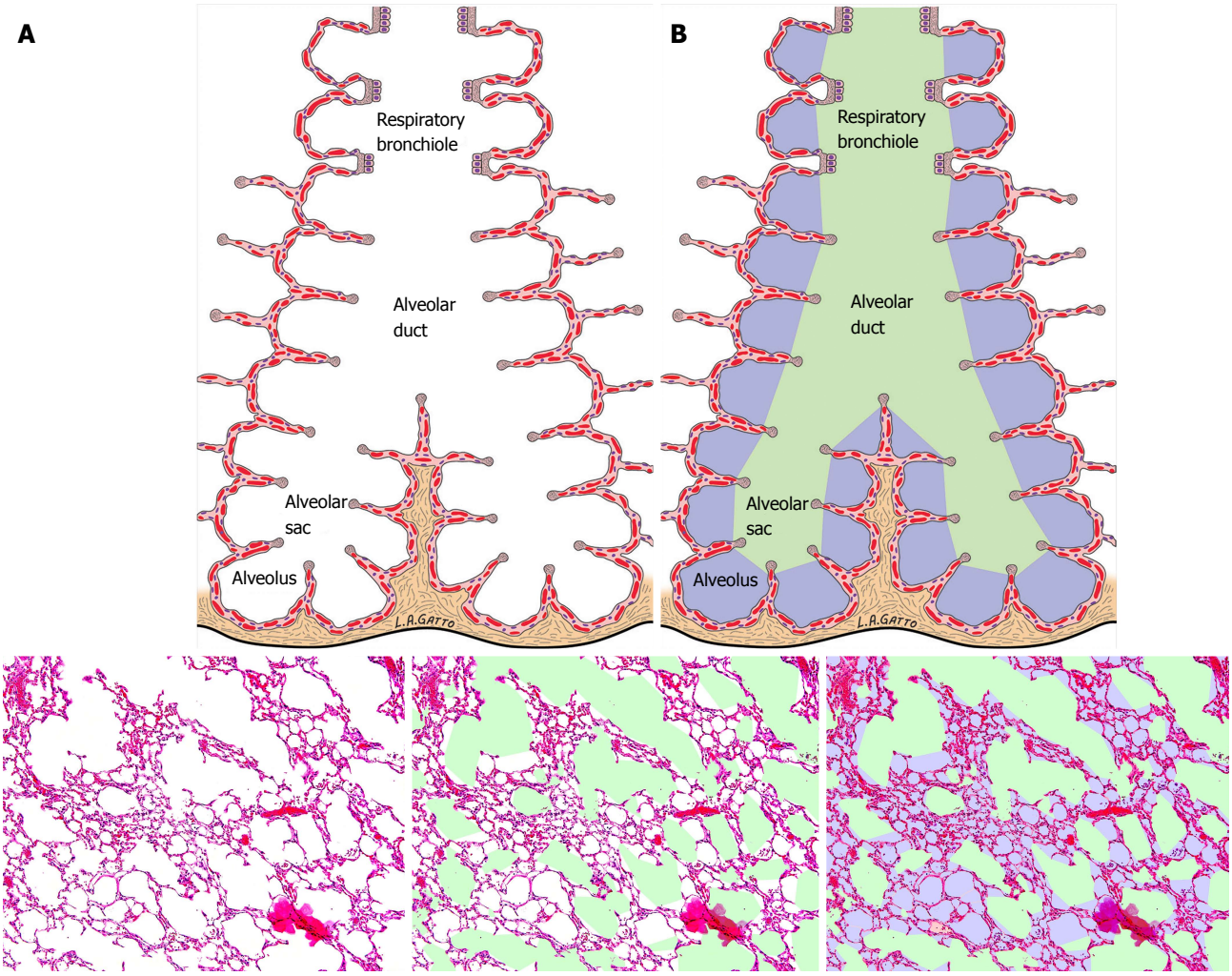

Figure 8 Impact of multiple ventilation strategies on the terminal airways. A: Schematic of the terminal airway before and after color demarcation; B: A standard hematoxylin-eosin staining of the lung is first analyzed for conducting airway air spaces and demarcated in green. The alveoli are demarcated in lilac while the remaining interstitium, blood vessels and lymphatics are colored in magenta (with permission)[16].

of rats: Group 1 - volume cycled ventilation (VC) with 0.5 cmH_2O PEEP and Group 2 - APRV with our standard settings (see APRV Settings above). Our model uniformly causes ARDS between 4 and 6 h after HS when ventilated with VC. Lung function declined gradually over time in the VC group and all animals either died due to pulmonary edema, which was so severe that they could not be ventilated or the P/F ratio was below 200 at the end of the experiment[35]. Pulmonary edema was confirmed histologically (Figure 5). Pulmonary edema-induced surfactant deactivation resulted in alveolar instability (Figure 6). Preemptive application of APRV maintained P/F in the normal range and prevented lung damage (Figure 5) and alveolar instability (Figure 6). Thus, early application of APRV protects the lung and prevents progressive lung injury by reducing pulmonary edema (see Starling forces above) and by stabilizing alveoli, which prevents mechanical damage caused by shear-stress during alveolar collapse and reopening.

More recently we have begun to explore the impact of any mechanical breath on the pulmonary micro-environment (*i.e.,* alveoli and alveolar ducts). Gattinoni's group has shown that excessive whole lung stress and strain, caused by injurious mechanical breath, are the mechanical mechanism of VILI[59]. Our group has taken the whole lung stress/strain concept one step further and has analyzed the impact of ventilator-induced stress and strain in the microenvironment, or the alveoli and alveolar ducts[16,17]. We used an *in vivo* microscopic technique to analyze the μ-strain on individual alveoli in a rat ARDS model using 4 different mechanical breath settings: (CMV - Vt 6 cc/kg + PEEP 5 and 16 cmH_2O and APRV T_{High} 90% + T_{Low} 10% and 75%)[16]. ARDS was caused using Tween-20 lavage and subpleural alveoli were photographed at peak inspiration and end-expiration using all 4 mechanical breath settings. Appropriately set APRV with a T_{High} of 90%, regardless of the T_{Low} setting (10% or 75%), caused significantly more alveolar recruitment than did CMV at any PEEP level. However, APRV with an inappropriately set T_{Low} of 10% allowed a large derecruitment of alveoli, which was prevented by setting T_{Low} appropriately at 75%. The fully recruited

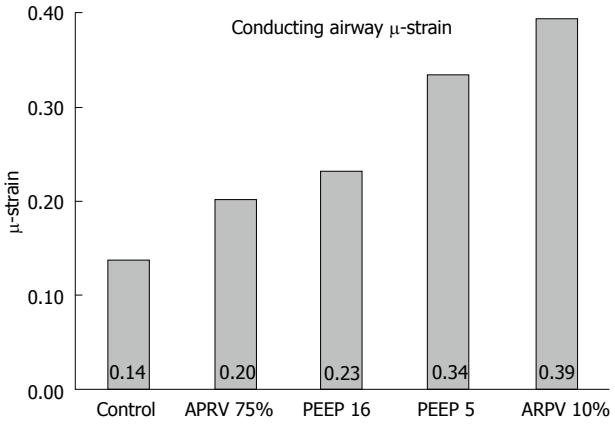

Figure 9 Airway duct μ-strain, was calculated from conducting airway perimeters at inspiration and expiration in all 4 mechanical breath strategies (CMV with PEEP 5 and 10; APRV with T_{Low} at 10% and 75%) tested, plus a Control group with normal lung under mechanical ventilation. (with permission)[16]. CMV: Conventional mechanical ventilation; APRV: Airway pressure release ventilation.

alveoli at peak inspiration, followed by collapse at end-expiration, caused a large μ-strain on the alveoli being ventilated with inappropriately set APRV T_{Low} 10% (Figure 7). Conversely, APRV with an appropriately set T_{Low} set at 75% PEFR had the least μ-strain, demonstrating the importance of all the parameters that make up the mechanical breath (see APRV Settings). Also important is the large difference between macro- and μ-strain (Figure 7). CMV with PEEP 5 caused a very small macro-strain, although it was the largest μ-strain of all the mechanical breaths tested. Thus, if a clinician used a protective ventilator strategy set to minimize the macro-strain, it would not be protective unless the μ-strain was also reduced. This highlights the importance of understanding how any mechanical breath impacts the strain on alveoli and alveolar ducts.

Although *in vivo* microscopy is a highly effective tool with which to measure dynamic alveolar μ-strain, we could not directly observe the impact of the mechanical breath on the alveolar ducts. We therefore developed a technique using lung tissue fixed at peak inspiration and end-expiration to analyze the μ-strain on both alveoli and alveolar ducts (Figure 8)[17]. We color coded alveoli blue and alveolar ducts green and measured the change in alveolar and alveolar duct size using computer image analysis. Using the same four mechanical breath settings that we used in our previous study[16], we demonstrated that APRV with a T_{Low} set at 75% PEFR caused the least μ-strain on the alveolar duct, whereas APRV with an inappropriately T_{Low} set at 10% PEFR, effected the largest μ-strain (Figure 9).

CONCLUSION

To our knowledge we are the only group that is conducting experiments investigating the optimal mechanical breath necessary to reduce the incidence of ARDS in animals models of secondary ARDS (*i.e.*, hemorrhagic shock and sepsis). Our work clearly shows that preemptive APRV using the settings developed by our group will reduce ARDS incidence in a rat trauma/hemorrhagic shock model and in a high fidelity, clinically applicable porcine ARDS model[27,35]. Because our animal model so closely represents the clinical progression from injury (*i.e.*, hemorrhagic shock and sepsis) to established-ARDS, it is considered "good evidence" that any treatment shown efficacious in this model will be successful in a clinical trial[57]. In addition, we have shown that part of the protective mechanism of preemptive APRV is minimizing μ-strain in the alveolus and alveolar ducts, highlighting the importance of understanding the impact of any given PT_I on the microenvironment[16,17]. The meta-analysis on severely injured trauma patients showed an order of magnitude reduction in ARDS incidence and mortality with preemptive application of APRV strongly suggesting that a prospective clinical trail is warranted. In conclusion, the optimal method of protecting a patients lung with established-ARDS, as described by Dr. Lachmann[60] in 1992, is to "Open the Lung and Keep it Open" and likewise, the goal of preemptive mechanical ventilation to reduce ARDS incidence is to "Never let the Lung Collapse".

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β2-adrenoceptor in obstructive airway diseases: Agonism, antagonism or both?

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Abstract

Obstructive airway disease is a complex disease entity including several maladies characterized by bronchoconstriction and abnormal airway inflammation. Reversing bronchoconstriction leads to symptomatic relief and improvement in quality of life, both in reversible (bronchial asthma) and partially reversible (chronic obstructive airway disease) obstructive airway diseases. β2-adrenoceptor expressed in human airway is the main β-receptor subtype, and its activation in airway smooth muscle cells leads to bronchodilatation. Drugs targeting β-adrenoceptors have been around for many years, for which agonists of the receptors are used in bronchodilation while antagonists are used in cardiovascular diseases. This review article summarizes the effect and usage of β2-agonist in obstructive airway disease, addressing the benefits and potential risks of β2-agonist. The article also looks at the safety of β-blocker usage for cardiovascular disease in patients with obstructive airway disease. There is also emerging evidence that non-selective β-blockers with inverse agonism ironically can have long-term beneficial effects in obstructive airway disease that is beyond cardiovascular protection. Further trials are urgently needed in this area as it might lead to a dramatic turnaround in clinical practice for obstructive airway diseases as has already been seen in the usage of β-blockers for heart failure.

Key words: β-adrenoceptors; β2-agonist; β-blocker; Inverse agonist; Heart failure; β-arrestin

Core tip: This review summarizes the effect and usage

of β_2-agonist in obstructive airway disease, addressing the benefits and potential risks of β_2-agonist. The review also looks at the safety of β-blocker for cardiovascular disease in patients with obstructive airway disease. There is also emerging evidence that non-selective β-blockers with inverse agonism ironically can have long-term beneficial effects in obstructive airway disease beyond cardiovascular protection. Further trials are urgently needed in this field as it might lead to a dramatic turnaround in clinical practice for obstructive airway diseases as has already been seen in the usage of β-blockers for heart failure.

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INTRODUCTION

According to the 2015 reports from Global initiative for Asthma and Global initiative for chronic obstructive lung disease, the prevalence of asthma ranges from 1% to 18% worldwide, while prevalence of chronic obstructive pulmonary disease (COPD) is about 6%[1,2]. Obstructive airway diseases, both asthma and COPD, are characterized by abnormal inflammation and bronchoconstriction. Bronchospasm is contributed by both airway smooth muscle contraction and mucus production by the epithelial cells. Pathogenesis of obstructive airway disease is therefore a complex interaction among inflammatory cells, epithelial cells of the bronchial airway, smooth muscle cells and fibroblasts. While the role of inflammation is emphasized in the pathogenesis and treatment of airway diseases, especially asthma, the role of airway smooth muscle cells beyond inflammation has been gaining increased recognition. This has led to the development of new β_2-agonists, especially the long-acting β_2-agonists since the 1990s. Their introduction into clinical practice however has generated some controversy. Recently, there was a paradigm shift in the understanding of obstructive airway disease and increasing evidence points to the role of β-blockers, especially those with inverse agonist action (or negative intrinsic efficacy), in the management of obstructive airway diseases.

Adrenoceptors in the airways

Adrenoceptors (AR) belong to the G protein-coupled receptor family and are activated by endogenous hormone adrenaline and neurotransmitter noradrenaline. Receptor activation stimulates the heterotrimeric G proteins (Gα and G$\beta\gamma$ subunits) and, in turn, the Gα subunit activates effector molecule (*e.g.*, adenylyl cyclase, phospholipase Cβ, and transducin) for signal transduction. Various subtypes of Gα protein have been described, including Gαq, Gαt, Gαs and Gαi proteins.

There are two main groups of AR which have been classified as α- and β-subtypes, and are encoded by at least nine unique genes (α_{1A}, α_{1B}, α_{1D}, $\alpha_{2A/D}$, α_{2B}, α_{2C}, β_1, β_2 and β_3)[3]. α_1-AR typically induce vascular smooth muscle contraction *via* a Gαq protein. α_2-AR are mainly expressed in presynaptic terminals and regulate release of neurotransmitters. Despite evidence for α-AR distribution in the lung, neither receptor subtype has a clear role in regulating human airway smooth muscle tone or plays a significant role in the pathogenesis of asthma or COPD[4]. In contrast, β-AR activate adenylyl cyclase *via* the Gαs protein to produce cyclic adenosine monophosphate (cAMP), which promotes airway smooth muscle relaxation (Figure 1).

β-AR are subdivided into at least three distinct groups: β_1, β_2, and β_3. In mouse or guinea pig trachea, airway bronchial tissues have twice the density of β_2-AR compared to β_1, and the density of β_3 is much less[5]. In humans, however, quantitative autoradiographic analyses of human isolated bronchus have shown that β-AR of airway smooth muscle are entirely of the β_2-receptor subtype. Similarly, β-AR of airway epithelium are also entirely of the β_2-receptor subtype. Only in bronchial sub-mucosal glands was β_1-AR found[6]. As such, β_2-AR play a more important role than β_1-AR in the pathogenesis of obstructive airway diseases.

Role of β_2-AR in obstructive airway disease

Studies using non-selective β-blockers with inverse agonism or β_2-AR$^{-/-}$ knockout mice demonstrated that β_2-AR signaling is required for the full asthma phenotypic development in mice[7].

Smooth muscle relaxation in the airways is one of the most critical targets of drug therapy during acute exacerbation of bronchial asthma. It is believed that β_2 agonist action is primarily mediated by cAMP-dependent protein kinase A (PKA). Activated PKA will phosphorylate myosin light chain kinase, reducing its ability to activate myosin light chain which is essential for airway smooth muscle contraction, hence, leading to the bronchodilatory effect[3]. Another biologically important action of β_2-AR agonist is to induce membrane hyperpolarization *via* activation of the K^+ channels in the plasma membrane by PKA, which counteracts the electrical excitation and subsequent Ca^{2+} influx contributing to contraction[8]. Cyclic AMP has also been shown to cross-talk with the mitogen-activated protein kinase (MAPK) pathway through the inhibition of Ras-dependent activation of Raf, resulting in inhibition of this proliferative pathway. β_2-agonist usage may prevent smooth muscle remodeling as well as contraction[9].

β_2-AR are also found on the surface of bronchial epithelial cells. A study in transgenic mice shows that an over-expression of β_2-AR on the epithelial cells of bronchial airway could prevent bronchoconstriction and hyperresponsiveness to methacholine. β-AR activation could lead to increase ciliary beat frequency and increase alveolar fluid clearance in animal and human lung

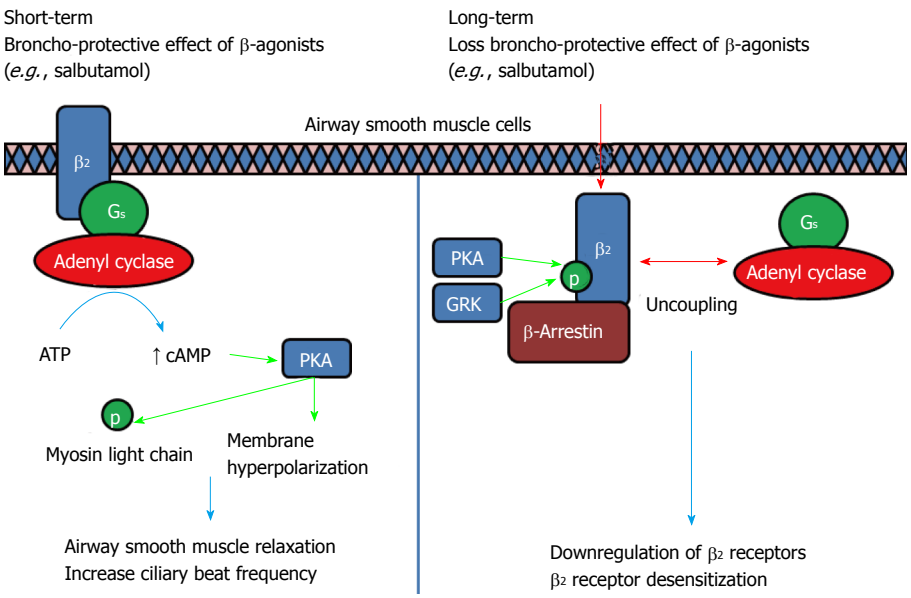

Figure 1 Long-term usage of β-agonists will result in a loss of Broncho-Protective Effect where β-adrenoceptors desensitization occurs. Broncho-Protective Effect is conferred when β-agonist binds to β_2-AR, activating adenyl cyclase through Gαs, leading to an increase in cAMP levels. The surge in cAMP in turn activates PKA which phosphorylates myosin light chain to inhibit contraction. PKA also activates K^+ channels, inducing membrane hyperpolarization which counteracts electrical excitation leading to contraction. Chronic use of β-agonist will lead to a loss of this Broncho-Protective Effect due to the uncoupling of Gαs from β_2-AR, phosphorylation by PKA/GRK and the binding of β-arrestin which leads to internalization, downregulation and desensitization towards β-agonist[15,27,28]. PKA: Protein kinase A; GRK: G-protein receptor kinases; AR: Adrenoceptors.

tissues. β_2-AR appear to be responsible for most of the β-receptor-sensitive alveolar active Na^+ transport which facilitates alveolar fluid removal[10]. Experimental data also suggest that β_2-agonist inhibits endothelial cell contraction and reduces intercellular gap, improving the endothelial barrier function. Human β_2-AR have been shown to regulate mucin production and increase mucous viscosity. In animals, usage of β_2-agonist is associated with increasing goblet cell hyperplasia[11], while the treatment with β-blockers in mouse epithelial cells significantly reduces the density of mucus-producing goblet cells[12].

The role of β_2-AR in inflammatory cells is more controversial. *In vitro* studies of long-acting β_2-agonists (LABA) formoterol and salmeterol show that activation of β_2 receptors inhibited neutrophil and eosinophil adhesion to tracheal venules, and interlukin (IL-1) and leukotriene B_4 secretion from human alveolar macrophages[13]. β_2-receptor activation inhibits the production of IL-6, IL-8, RANTES, eotaxin, granulocyte-macrophage colony stimulating factor, and monocyte chemotactic protein 1. However, some recent evidence has pointed towards the detrimental effects of LABA in promoting further inflammation in asthma. Loza *et al*[14] showed that β_2-agonist promoted IL-13^+ T-helper 2 cell survival by activation of the PKA pathway. An *in vitro* study by Oehme *et al*[15] demonstrated that prolonged treatment with β_2-agonists reduced β_2-receptor expression and stimulated IL-6 and IL-8 production in human bronchial epithelial cell line.

β$_2$*-agonist and its role in obstructive airway disease*

The Chinese have been inhaling herbs containing ephedrine for asthma from centuries ago. In 1698, John Foyer[16] understood that asthma treatment is "both in fit and out of it", suggesting early recognition of both acute treatment and maintenance therapy. Since the early 1900s, direct adrenergic bronchodilators were introduced in Western medicine for the treatment of asthmatic attacks[17], way before the usage of corticosteroids in the 1940s. During the 1960s and 1970s, relatively specific β_2-agonists were developed for inhalational use[18]. The introduction of LABA such as salmeterol and formoterol in the 1990s was considered a major advancement in asthma therapy with evidence of improved lung function and quality of life. In 2011, the once daily β_2-agonist indacaterol is being used in COPD patients[19].

Drugs that act on β_2-AR are classified by their speed of onset, duration of action, affinity, intrinsic efficacy and potency. The duration of action and onset of action is influenced by lipophilicity and kinetics of binding. Among the agents currently used, salmeterol and formoterol sustain longer duration of action than salbutamol as their lipophilicity produces a depot effect at the cell membrane, allowing slow and sustained release of the drugs[20]. Formoterol has a shortened lipophilic side chain compared to salmeterol and hence while it's moderate lipophilicity allows it to enter and be retained in the plasmalemma, sufficient drugs are still available in the aqueous biophase to allow immediate interaction with the active site of the receptor, accounting for its rapid onset of action.

The affinity of a drug depends on its specific binding to the β_2-AR and is usually described in terms of dissociation constant between the agonist and the

receptors. The intrinsic efficacy of a β_2-AR agonist will depend on the ability of the drug to activate its receptor. Drugs that have high intrinsic efficacy are termed full agonist while drugs with lower intrinsic efficacy are termed partial agonist. The potency of a drug depends on both its affinity and intrinsic efficacy. Drugs that inhibit the β-AR (β-blockers) are either antagonists or inverse agonists. Antagonists are drugs that prevent the agonist from binding to the receptors, while inverse agonists are drugs that bind the receptor and inactivate constitutive downstream signaling. Many β-blockers in the market possess inverse agonist action on the β-AR, such as propranolol and nadolol, where they are able to inhibit constitutively active receptors[7].

Although the role of the β_2-adrenergic agonists had long been recognized, their long term usage has been controversial. Occasional epidemics of asthma-related deaths have been linked to the use of β_2-agonists such as fenoterol[21]. The Serevent National Survey (SNS)[22] study in the United Kingdom and the Salmeterol Multicenter Asthma Research Trial (SMART)[23] study in the United States raised the concern that regular usage of LABAs such as salmeterol may increase asthma-related mortality. This mortality is not seen when a LABA is used concomitantly with an inhaled corticosteroid[24]. The increased mortality is attributed to increased bronchial hyperresponsiveness, loss of protection against bronchoconstrictor stimuli and the development of tolerance[25].

It has long been appreciated that the ability of β_2-agonist to induce bronchodilatation weans over time[26]. This is termed as loss of Broncho-Protective Effect of β_2-agonist, which was initially attributed to desensitization and down-regulation of the β_2-AR (Figure 1). The mechanism for desensitization and down-regulation of β_2-AR is linked to receptor phosphorylation by PKA and by β-adrenergic receptor kinase (βARK), a member of the G-protein receptor kinases, leading to conformational change in the receptor and its consequent reduced coupling to G proteins, leading to desensitization[27,28]. βARK also promotes the binding of β-arrestin proteins to the receptor[29]. Arrestins act as scaffolding proteins that allow desensitized receptors to undergo endocytosis into the cells, lysis, and termination of further signaling process.

β_2-blocker or inverse agonist and their role in obstructive airway disease

Traditionally β-blockers have been contraindicated in various diseases including obstructive airways disease and congestive cardiac failure. A recently published study by Bellocchia *et al*[30], which recruited 229 patients, showed that 51% COPD and 30% asthmatic patients had cardiovascular disease. Congestive heart failure (CHF) in COPD patients range from 8% to 27% while coronary artery disease (CAD) in COPD patients range from 15% to 25%[31]. In a recent RHYTHMOS study, in a population of 280 CAD with COPD patients, only 52.8% were treated with β-blockers, where most were treated with sub-optimal dosages[32]. In another study by Puente-Maestu *et al*[31], only 58% of COPD patients with indication for CHF/CAD were prescribed with β-blockers, while 97% of non-COPD patients with indications were treated with β-blockers. Studies of using β-blockers in asthma and COPD have demonstrated decreased airway reversibility[33] and reduction in FEV_1[34,35]. A large retrospective electronic medical record database review of 11592 adult patients with asthma and COPD by Brooks *et al*[36] in 2007 revealed that patients with asthma with or without COPD who were taking selective or non-selective β-blockers had an increased risk of hospitalization and emergency department visits. All these added to the reluctance to use β-blockers in obstructive airway disease.

However, a recent single center randomized double-blind placebo-controlled trial with a sample size of 16 in the United Kingdom showed that 80 mg/d of propranolol given to patients with persistent asthma did not cause adverse effects[37,38]. Using an OVA-induced murine asthma model, nadolol, a non-selective β-blocker with inverse agonist action, was shown to reduce mucous metaplasia, BALF cellular infiltrates and airway hyperresponsiveness[7]. In a 4-mo rat model of smoking, it was shown that cigarette smoking leads to excessive sympathetic stimulation, resulting in down-regulation of β_2-AR[39]. Propranolol was found to be able to reduce inflammatory cell infiltration in lungs, mucus secretion, Tumor necrosis factor (TNF)-α and IL-8 levels[40]. It also reduced norepinephrine level in the serum and increased airway smooth muscle response to isoprenaline[41]. These studies highlight the feasibility of using β-blockers in obstructive airway disease (Figure 2).

It has been shown that β-inverse agonists such as propranolol inhibit G protein-dependent signaling, but activate MAPK through β-arrestin in mouse embryonic fibroblasts and CHO cells[42,43]. β_2-AR have been studied intensively, and depending on the ligand binding site, it can induce differential stabilized conformation which in turn elicits a variety of selectivity toward G-protein-dependent and β-arrestin-dependent signaling[44,45]. It was further proposed that a secondary binding site may be exposed upon adequate conformational state, leading to a different signaling cascade[44]. However, a recent study reveals that chronic propranolol treatment reduced MAPK activation through β-arrestin-dependent signaling, leading to reduced MUC5AC expression and mucus hypersecretion induced by cigarette smoke[46]. The discrepancy could be due to a different models with acute *vs* chronic treatment with propranolol. It has been reported that acute treatment with nadolol led to an increase in airway resistance to methacholine in a murine asthma model, but chronic administration reduced it together with lower mucin content[47]. In addition, chronic treatment with nadolol in HEK293 cells led to reduced β_2-AR degradation and increased protein levels[47]. Therefore the beneficial effects of chronic treatment with β-inverse agonists are worthy

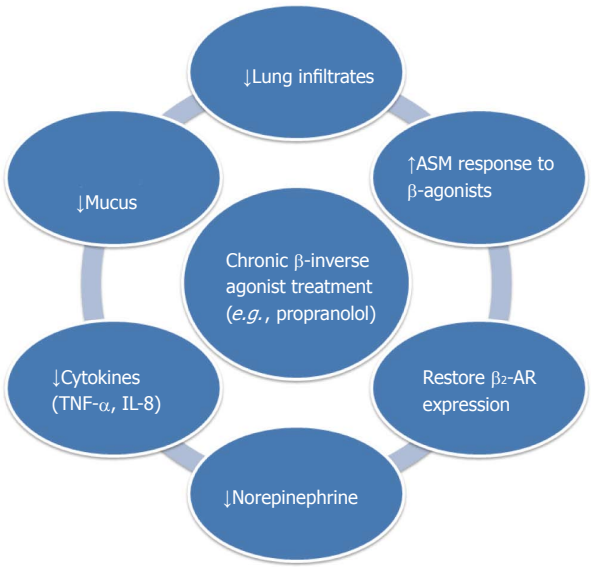

Figure 2 Potential therapeutic benefits by chronic β-blocker usage in obstructive airway diseases observed in animal and clinical studies[12,40,46,47,64,65]. AR: Adrenoceptors; TNF: Tumor necrosis factor; IL: Interlukin.

of further investigation (Figure 3).

Use of β-blocker for cardiovascular protective effects

In 1975, Waagstein *et al*[48] published the first positive results using a β-blocker to treat congestive cardiac failure (CHF), and this led to the FDA in approving the usage of β-blockers in CHF. Since then, β-blockers have been widely used in treating patients with ischemic heart disease (IHD) and impaired cardiac contractility. However, a significant proportion of patients with IHD also have risk factors for COPD. Reluctance on usage of β-blockers in patients with COPD and asthma has become a major cause of under usage of β-blockers in IHD. In one study, COPD patients had a nearly two-fold increase in cardiovascular disease (CVD) death rates compared to the general population[49]. In fact, impaired lung function seems to be an independent risk factor for arrhythmias, coronary events, and all-cause mortality[50]. Therefore, it seems crucial to explore the potential survival benefit of using β-blockers in obstructive airways disease.

A meta-analysis by Salpeter *et al*[51] (2005) examined all randomized, blinded and controlled trials from 1966 to 2005, on the effect of single dose or longer duration cardio-selective β-blockers on FEV_1 or symptoms in patients of COPD. This meta-analysis demonstrated that cardio-selective β-blockers do not affect the FEV_1 or respiratory symptoms compared to placebo. It is also a relief to see that the cardio-selective β-blockers do not blunt the effect of β_2-agonists on FEV_1[51]. Another recent meta-analysis of observational studies also concluded that non-selective β-blockers can reduce overall mortality risk and exacerbation risk[52]. Over the past decade, the are a plethora of observational trials suggesting that non-selective β-blockers in patients with COPD is not only safe but beneficial in terms of reducing mortality, hospitalization, health-care utilization, and even admissions for respiratory disease including COPD exacerbations[31,34,53-55]. The benefit was not only shown in a wide range of COPD patients with CVD like hypertension, acute myocardial infarction[56,57], congestive heart failure and patients that underwent major vascular surgery[58], but it was also shown in patients without any overt cardiovascular disease[59]. Recent heart failure guidelines published by the Heart Failure Society of America recommend that for the majority of patient with left ventricular systolic dysfunction, cardioselective β-blocker therapy is recommended even in the presence of concomitant COPD[60]. Nevertheless, caution must be exercised as the non-selective β-blockers were associated with an increase rate of hospitalization and emergency room visits in the study by Brook *et al*[36].

β-blockers beyond cardiovascular protective effects – the new frontier in asthma treatment

There is good evidence to suggest at least the usage of cardio-selective β-blockers in patients with obstructive airway disease with concomitant CVD. However their role beyond cardiovascular protection is still unknown, especially in asthma. Since the publication of the SMART and SNS studies documenting the potential side effects of β_2-agonist, several studies have now been undertaken to evaluate the role of chronic β-blocker usage in reducing the long term side effects of β_2-agonist, and in asthma control beyond the cardiovascular protection. This is a very bold and exciting development in the field of asthma pharmacotherapy and control.

The safety of β-blockers has also been demonstrated in asthmatic patients. A recent observational study in Scotland investigated the effect of non-selective β-blockers in 1527 asthmatic patients. The study did not find any significant increase in steroid rescue use in β-blocker treatment group[61]. Another meta-analysis study of randomized, blinded, and placebo-controlled trials reveals that acute single dosing with cardioselective β-blockers produced a slight but significant reduction in FEV_1 of 7.46% without affecting symptoms, while chronic dosing did not significantly reduce FEV_1. In addition, a significant increase in subsequent β_2-agonist response was seen upon chronic dosing, indicating that β_2-receptor up-regulation might have occurred[34].

In an experimental asthma model, acute administration of β_2-agonist salbutamol or alprenolol, a β-blocker without inverse agonist action, reduced airway resistance in mice, but upon chronic use, either drug did not affect the airway resistance response to antigen challenge. On the other hand, acute administration of β_2-AR inverse agonist nadolol or carvedilol did not affect airway responsiveness, but after 28 d of treatment, the inverse agonists markedly reduced airway responsiveness to antigen[62]. The beneficial effect may be contributed by an up-regulation β_2-AR expression in chronic usage of the β-inverse agonist, as demonstrated by the increased receptor staining in histological lung sections[63]. Furthermore, chronic β-blocker usage also reduces eosinophilic inflammation, cytokine production,

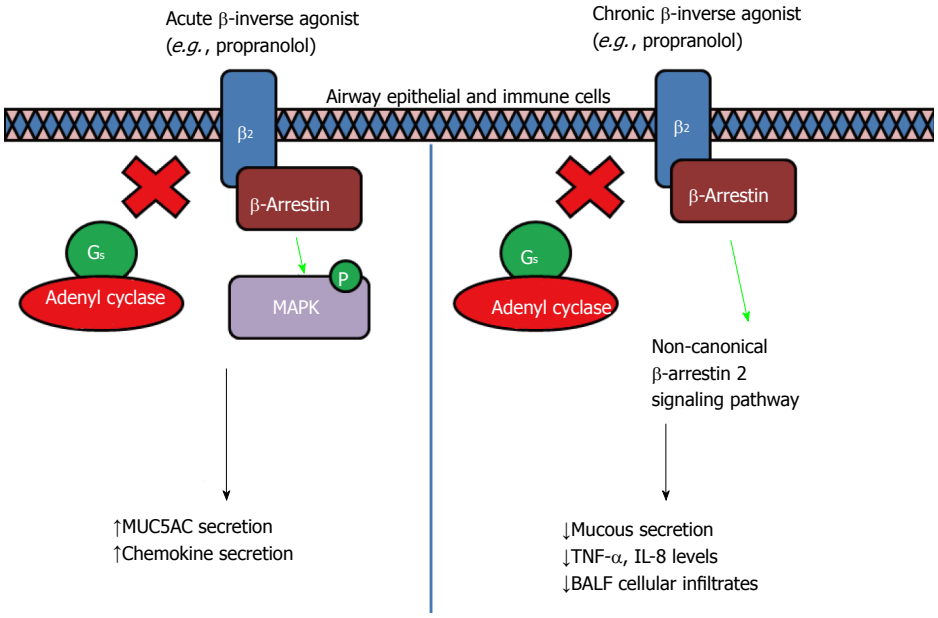

Figure 3 Acute and chronic inverse agonist treatment in obstructive airway diseases. It was shown in cell and animal models that acute treatment of β-blockers induced a partial agonist response that led to an increase in MUC5AC production *via* β-arrestin2 which serves as a multi-protein scaffold, activating ERK1/2 and p38 mitogen-activated protein kinase (MAPK), resulting in mucus hypersecretion and increased airway resistance response to methacholine. However, chronic treatment of β-blockers led to a reduction in mucus secretion, decreased airway hyperresponsiveness and reduced inflammation, through the non-canonical β-arrestin2-mediated signaling induced by inverse agonism of β2-adrenoceptors[46]. The differential response could be due to the binding of ligand to a shallower secondary binding site exposed only when an adequate conformational state is obtained as proposed by Soriano-Ursúa *et al*[44], however more work need to be done to validate the mechanism.

and mucin content in a chronic mouse asthma model[12].

These findings in murine models led to the first proof-of-concept open-label study by Hanania *et al*[64]. Ten patients with mild steroid-naive asthma (mean FEV_1 of 90%) were given incremental doses of nadolol from 10 to 40 mg for 9 wk. There was an initial decrease in FEV_1, but with chronic dosing this effect tended to ameliorate, and airway hyper-responsiveness to methacholine challenge significantly improved (amounting to 1.8 doubling doses in PC20, the provocative dose of methacholine that leads to a 20% fall in FEV_1)[64]. The effect of another β-blocker propranolol was further tested in a randomized control trial conducted by Short *et al*[65]. Although the primary outcome of the trial was not met, the trial demonstrated the safety of β-blocker in carefully selected steroid-treated stable patients with asthma. The usage of concomitant inhaled steroid may have caused the up-regulation of β2-AR hence reducing the effect of the β-blocker[65]. More trials are warranted in this exciting field.

CONCLUSION

It is projected that obstructive airway disease will become the third leading cause of death by the year 2020 by the World Health Organization. Obstructive airway disease is a spectrum of disease that ranges from reversible bronchial asthma to irreversible COPD with significant overlap. Both inflammatory cells and resident cells expressing β2-AR are vital in the pathogenesis of obstructive airway disease. Anti-inflammatory drugs and β2-agonists are the pillars of treatment for the disease. Acute usage of β2-agonist allows bronchodilatation and symptomatic relief. However the long term use of LABA monotherapy has been linked to reduced bronchoprotective effect of the drugs.

Emerging evidence shows that β2-blockers, particularly those with inverse agonist action and cardio-selective properties are safe in obstructive airway disease and should be used for its cardioprotective effect in at-risk patients. There is also evidence of benefit beyond the cardioprotective effects, particularly in reversible airway disease[64]. The risk of β2-AR blockade-mediated bronchoconstriction should be balanced against the long-term benefit of β-blocker usage in asthma. While early clinical studies of β-blocker in asthma shows exciting and promising results, further larger, more comprehensive studies are needed to address both the safety and long term benefit of β-blocker before changes to the treatment of obstructive airway disease can be justified.

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