Shortness of Breath (SoB): Times They Are A Changin’, isn’t it?

Come gather ‘round people
Wherever you roam
And admit that the waters
Around you have grown
And accept it that soon
You’ll be drenched to the bone.
If your time to you
Is worth savin’
Then you better start swimmin’
Or you’ll sink like a stone
For the times they are a-changin’.

[Bob Dylan]

Shortness of breath (SoB) is a common symptom in respiratory medicine, but it is also an expression of concern and worrying. Shortness of Breath (SoB) is a new online journal aimed first of all to be read. Favorite readers will be physicians, respiratory and critical care ones, but not only them, with the ambition to be timely for the readers, but also moving to the next future.

Bob Dylan sang the song "Times they are a changin’" just on the night President JF Kennedy was killed, and it immediately became the song of a new generation which accompanied the hopes and the changes of the following years. At the beginning, the journal will privilege mini-reviews on scientific and daily practice topics, and clinical cases. Quarterly SoB will cover respiratory medicine, with emphasis on clinical medical practice, but also translational medicine, innovation in respiratory and critical care. We are deeply convinced that medicine is a rapidly changing multidisciplinary field of knowledge based on Life Sciences. Current medical care could not exist without a constant referral to knowledge area just few decades ago not involved into traditional references of pathology and clinics, such as biotechnology, molecular biology (the "omics" and beyond), bioinformatics, GRID computing, nanotechnology, economics, safety and quality evaluation, and so on. Systems biology is giving its aid to medicine moving from a reductionist to a personalized approach to the patient. A major paradigm of changing point of view in medicine is the dominant role of Internet not only for training and learning, but also for medical practice (e.g. ‘googling’ for diagnosis) and patient-physician relationship. Even if medicine is even more science of life than a physician centred discipline, relationship among humans remains the core of medicine, attention will be also paid to "medical humanities", a section of the journal hosting non-medical papers concerning the complexity of human factor in health and illness status. In this first issue of the journal we have the privilege to host the contribution of the famous writer and newspaper columnist Claudio Magris. The Italian-French artist Marco Ceruti will help the journal to stay young and pleasing by means of cartoons and paintings in the New Yorker’s magazine style.

We claim for contributions from physicians (pneumologists, critical care physicians, but not only them), and scientists. Each contribution will be peer reviewed in an attempt to ensure that articles meet the journal’s standards of quality, and scientific validity. The journal SoB is coming out in changing times, characterized by the global economic crisis, climate change, social and religious conflicts: it should be easier to follow the "Zeitgeist", the spirit of the times, and to be worried and concerned. Nevertheless, we will collect in a section of SoB called “Land of hope and dreams” any news from the scientific literature that may carry hope for positive changes of patient care in a next future’. Respiratory medicine and science of life are for the progress and wellness of human being, so they have a bet on better times, anyway. Hoping this spirit of SoB will be shared by Authors and readers too.

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COPD and metabolic disorders: role of adiponectin

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Summary

Metabolic disorders are common conditions associated to chronic obstructive pulmonary disease (COPD) contributing to lung function impairment and mortality. Evidence suggests that systemic inflammation may be the link between COPD and metabolic alterations, but this issue is still poorly investigated. This review focuses on the adipocyte-derived cytokine adiponectin which has been shown to have a role in the airway patho-physiology and therefore represents an attractive marker to link COPD and metabolic disorders.

KEY WORDS: COPD; adiponectin; metabolic disorders; inflammation.

Background

Chronic obstructive pulmonary disease (COPD) is a complex inflammatory disorder characterized by progressive airflow limitation (1). There is a growing awareness that COPD is a lung disease with heterogeneous systemic inflammatory consequences and extrapulmonary comorbidities. Like other complex diseases, COPD is due to a variety of processes that contribute to the onset and progression of the disease including immune response, influence of hormones and environmental factors that represent both initiators and causative agents. Extrapulmonary comorbidities are common and significantly impact disease severity and mortality. Cardiovascular disease, hypertension, musculoskeletal disorders, lung cancer, diabetes mellitus II, and metabolic disorders are among the most prevalent and relevant, although the molecular mechanisms linking COPD and its comorbidities are still poorly understood (2).

Unexplained weight loss, changes in body composition as well as alterations in caloric intake, basal metabolic rate and intermediate metabolism are commonly reported in COPD. In parallel, a consistent number of COPD patients experience overweight and obesity, although the nature of this association remains to be clarified (3).

A close association between metabolic syndrome biomarkers and impairment of respiratory function as been recently reported, suggesting a key role for systemic inflammation in development of both metabolic disorders and lung function impairment. In this regard, scientific interest has been recently focused on adipocyte-derived cytokines including adiponectin whose receptors have been identified on lung tissue.

Airway epithelium, environmental factors and inflammation

Airway epithelium represents a critical site for the mechanisms involved in the complex interaction between environmental triggers, airway inflammation (4-6) and specific metabolic pathways. In addition to environmental air pollution, smoking habit is the most relevant risk factor not only for COPD but also for many other chronic diseases. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree and pathological changes characteristic of COPD are found in the proximal large airways, peripheral small airways, lung parenchyma and pulmonary vasculature. Evidence indicates that airway inflammatory cell trafficking at epithelium level is mainly coordinated by adhesion molecules expression (7-10). The cellular pattern is quite heterogeneous, involving macrophages, neutrophils, T and B lymphocytes and mast cells. Beside these local effects, smoking may significantly contribute...
to systemic inflammation, acting on the stimulation of the hematopoietic system and the consequent release of polymorphonuclear leukocytes and generation of systemic oxidative stress. These systemic effects of smoking could explain why patients with COPD often concomitantly suffer from other chronic diseases such as cardiovascular diseases or metabolic disorders with or without other risk factors such as arterial hypertension, hyperlipidemia and obesity (2). The chronicity of the inflammatory state in COPD is sustained by an increased production of several pro-inflammatory cytokines at both serum and airway levels. Indeed, C-reactive protein (CRP), fibrinogen, IL-1, TNF-α, MCP-1, IL-8, IL-6 have been associated with disease progression and exacerbation (11, 12), whilst an inverse correlation between anti-inflammatory cytokine IL-10 and COPD has been demonstrated.

Inflammation and metabolic disorders

Around 50% of patients with severe COPD and chronic respiratory failure and 10 to 15% of patients with mild to moderate disease experience unexplained weight loss (13, 4).

It has been suggested that the potential causative factors of cachexia are energy imbalance, disuse atrophy of the muscles, arterial hypoxiaemia and hormonal insufficiency (14). In addition, it has been reported that COPD patients present an increased basal metabolism leading to protein catabolism, resistance to anabolic hormones (insulin) and to increased levels of catabolic molecules (cortisol, glucagon and catecholamines) (15). This so called “Hypercatabolic syndrome” (HS) has the consequence of skeletal and cardiac muscle protein breakdown (16-18) and loss of fat mass contributing to a lesser extent, although body composition alterations can occur also in the absence of clinically significant weight loss (13).

Systemic inflammation has become the primary focus to link COPD and cachexia (13, 19, 20, 14) and to explain the development of COPD as a syndrome in susceptible subjects (2). Several inflammatory markers, such as TNF-α, PCR, IL-6, IL-8, Fas, Fas-L, Lipopolysaccharide Binding Protein have receiving great attention for their role in increased metabolism, weight loss and asthenia (21), although there is still no direct evidence for a cause-and-effect relationship between them (14).

Whilst weightloss has been the traditional nutritional concern in patients with COPD, a great number of COPD patients is affected by overweight and obesity, but the nature of this association remains to be clarified (3).

Clinical evidence indicates that in any given individual obesity decreases chest wall and lung compliance, reduces the diaphragm motility and increases work and oxygen cost of breathing (22, 23).

On the other side, COPD patients are at increased risk of developing obesity because of reduced level of physical activities in daily life and the repeated courses of systemic glucocorticosteroids, which cause truncal obesity as a result of glucocorticoid mediated redistribution of stored energy. (24). However, the pathophysiological interactions that occur when both COPD and obesity coexist in the same individual are still poorly understood.

It has been recently shown that the metabolic syndrome can precede reductions in lung function. The results by Naaved et al. indicate that dyslipidemia, elevated heart rate, elevated insulin resistance and leptin levels were independent risk factors of subsequent FEV1 decline within six months of World Trade Center irritant exposure (13). However, evidence also indicates a possible protective role of obesity in COPD mortality. In mild and moderate COPD patient, the low-grade systemic inflammation associated with visceral fat accumulation contributes to develop cardiovascular complications and type 2 diabetes and may contribute to mortality; in contrast, in severe COPD obese patients mortality risk is reduced: this condition is described as “Obesity Paradox” (24, 25).

Systemic inflammation may represent a common background for abnormal adipose tissue function and lung function impairment and may provide new insights into the pathogenesis and reversibility of systemic involvement of COPD (28).

Recent studies have provided evidence for a link between adipose tissue and circulating concentrations of TNF-α, IL-6, leptin and adiponectin that play a part in metabolic changes associated with COPD and reduced/impaired lung function (17).

Adiponectin as a potential target for COPD-related metabolic disorders

In physiologic condition, adipose tissue synthesizes and secretes a variety of proteins known as “adipokines” involved in several biological functions as immunity, insulin resistance, lipid and glucose metabolism, inflammation. Among the adipokines, adiponectin is a protein hormone that structurally belongs to the complement 1q family and is found at high concentrations (~0.01% of the total protein) in serum of healthy individuals (25). Adiponectin is synthesized and secreted by adipose tissue as a 30 KDa monomer that, due to post-translational modifications, forms characteristic homomers. A peculiar structural feature of adiponectin is its ability to assemble into several characteristic oligomeric multimers including trimers known ad low molecular weight (LMW), hexamers known medium molecular weight (MMW), and higher-molecular weight (HMW) multimeric complexes. Growing evidences associate the oligomerization process with multiple biological activities of adiponectin.

In humans, the gene encoding adiponectin (ACDC) is located on chromosome 3q27; single-nucleotide polymorphisms (SNPs) and haplotypes in ACDC gene have been associated with obesity as well as with metabolic syndrome (MS) and CAD (26-28). Adiponectin acts through binding and activation of two receptors, AdipoR1 and AdipoR2 that are ubiquitously expressed in several organs, tissues and cell lines (29-31). In particular, it is reported that AdipoR1 is mainly implicated in the metabolic functions of adiponectin, whereas AdipoR2 is more involved in anti-inflammatory and anti-stress-oxidative activities (32, 33). Downstream of these two receptors, the biological effects of adiponectin are mediated by different signal pathways involving the following molecules: AMPK, ERK, AKT and P38 (34).
Adiponectin plays an important role in energy homeostasis, regulating both glucose and lipid metabolism. In humans, down regulation of adiponectin and its receptors are associated with obesity, metabolic syndrome, insulin resistance, hyperinsulinaemia, and type 2 diabetes, as well as with cardiovascular diseases (25, 35, 36). Moreover, adiponectin seems implicated in the development and progression of several local and systemic inflammatory processes. In fact, it has been recently outlined that adiponectin could play an important role in anti-inflammatory responses in several tissues and cell cultures such as pancreatic beta cells and endothelial cells (37, 38). Mouse models of adiponectin deficiency develop lung function impairment and systemic inflammation. In fact, Summer et al. reported a protective role of adiponectin in lung through inhibition of alveolar macrophage function and vascular homeostasis regulation (39, 40). On the other hand, it was also reported that adiponectin plays an important pro-inflammatory role in experimental tobacco smoke-induced COPD (29). All these in vitro and in vivo evidences support the idea of an anti-inflammatory role of adiponectin. Furthermore, in several pathological conditions, adiponectin serum levels have been found elevated: osteoarthritis, rheumatoid arthritis, lupus erythematosus, Crohn’s disease, cystic fibrosis, pulmonary emphysema, myotonic distrophy and COPD (41, 42). In all these diseases, adiponectin levels correlated with increased inflammatory cytokines (TNF-β, IL-6, IL-1) and CRP suggesting that adiponectin attenuates or modulates inflammation. Additionally, while the role of adiponectin in energy metabolism has been studied in several tissues, organs and cells, little is known about its role in inflammatory lung diseases.

While the role of adiponectin in energy metabolism has been widely studied, little is known about its role in inflammatory processes of lung (25). Different studies indicate that adiponectin can exert pro-inflammatory rather than anti-inflammatory lung properties. Recent data have revealed an anti-inflammatory role in the lung; mice lacking adiponectin spontaneously develops a COPD-like phenotype with extrapulmonary effects, including systemic inflammation, body weight loss and osteoporosis. This finding highlights the key role of adiponectin in lung pathologies and the novel link between COPD and metabolic disorders (43, 44). In humans, adiponectin serum levels are elevated in COPD patients but the biological effects of adiponectin on human lung and even less in lung diseases are not fully clear (42). In fact, it is known that low levels of total adiponectin are present in smokers without COPD, while high levels are observed in COPD patients (45-47). Recently, different studies showed that total serum levels of adiponectin represent a significant diagnostic and prognostic marker of COPD. Recently, it has been demonstrated that the oligomerization pattern of adiponectin is altered in COPD; in particular the higher levels of adiponectin are associated with a specific increase of HMW, the most biologically active isoforms (42). Protective anti-inflammatory role of HMW oligomers has been demonstrated both in vivo and in vitro studies (48). Pajavani reported that HMW oligomers improve insulin sensitivity, suppress apoptosis in endothelial cells, and their levels are inversely correlated to cardiovascular events and to the severity of coronary artery disease (49). Furthermore, in vitro evidences indicate that HMW oligomers are also involved in TNF-β suppression. Daniele et al. found no detectable TNF-β values in normal subjects and in COPD patients suggesting that the high levels of adiponectin and HMW could be involved in reducing the increase of circulating levels of this pro-inflammatory cytokine. As COPD is a disease characterized by inflammatory process and impairment of endothelial functions, the high levels of HMW found in this study may exert a protective role on both pathogenic mechanisms. These observations suggest that total levels of adiponectin and HMW oligomers can be considered useful complementary criteria to improve prognostic and therapeutic strategies for lung diseases (42).

The specific biological role of adiponectin in lung functions derives also from the observation that both AdipoRs are expressed in COPD and tumour lung (29, 50). Petridou et al. reported the presence of AdipoR1 and AdipoR2 in cancerous lungs and the association of AdipoR2 expression with the progression of lung cancer, while Miller et al. showed that only AdipoR1 was expressed in healthy and COPD lungs (29, 50). A recent study demonstrated the expression of AdipoR1 and AdipoR2 at mRNA level as well as at protein level in lung tissues from COPD and from non small cell lung cancer (NSCLC) with a AdipoR1 expression higher than AdipoR2 in COPD suggesting a specific signaling pathway of adiponectin in this disease (42). The downregulation of AdipoR2 could be responsible for the worsening of inflammation state in COPD and related to lung NSCLC cancer. Accordingly, it was reported that AdipoR2 signaling pathway is mainly involved in adiponectin inhibition effects on inflammation and oxidative stress (32). Furthermore, epidemiologic as well as in vitro studies have associated adiponectin and AdipoRs with several malignancies (51). In fact, adiponectin has been shown to suppress tumor growth in mice and cell growth in various cell lines (52, 53). In contrast, adiponectin stimulated colonic epithelial cell proliferation and breast carcinoma cell lines (54, 55). Besides, because serum adiponectin is not significantly influenced by smoking status, it is a very promising biomarker of cardiovascular outcomes in COPD (56).

The adiponectin concentration and oligomeric isoform distribution, and the modulation of receptors add complexity to adiponectin system.

Conclusions

New insight into mechanisms underlying systemic inflammatory consequences and extrapulmonary comorbidities in COPD will contribute to identification of potential targets for new diagnostic and therapeutic approaches. Adiponectin appears to be an attractive biomarker in COPD and represents a promising disease indicator with implications for the treatment of COPD.

In humans, adiponectin serum levels are elevated in COPD patients but the biological effects of adiponectin on human lung are not yet fully clarified.
COPD and metabolic disorders: role of adiponectin

References


Mini-review

Measuring respiratory mechanics in ARDS

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Summary
Mechanical ventilation is necessary in most patients affected by the acute respiratory distress syndrome (ARDS). Unfortunately, mechanical ventilation itself can cause lung damage as a result of ventilator-induced lung injury (VILI). The cyclical recruitment and de-recruitment of atelectatic lung regions (atelectrauma), lung overdistension (volutrauma) and de-novo inflammation caused by a combination of the two (biotrauma) are likely participants in the development of VILI. Increasing experimental evidence suggests that the risk of VILI may be decreased by careful titration of ventilator support guided by monitoring pulmonary mechanics. Airway pressure (Paw) is the simplest signal available to monitor mechanics in ARDS. In combination with measurements of lung volume, Paw allows to plot volume-pressure curves (VP curves) and to record end-expiratory pressure and end-inspiratory pressure during zero flow (Pplat). In the past it was assumed that VP curves could give accurate information on lung recruitment and overdistension. Those assumptions, however, have been proven incorrect. Similarly, it is incorrect to consider Pplat an accurate index of overdistension. In this review we will examine some of the available tools to monitor pulmonary mechanics in ARDS. The critical interpretation of the data recorded with these tools, their limitations and the potentials use of these data in setting the ventilator will be discussed as well.

KEY WORDS: Acute Respiratory Distress Syndrome; monitoring; respiratory mechanics; Ventilator-Induced Lung Injury.

Introduction
The acute respiratory distress syndrome (ARDS) is a form of noncardiogenic pulmonary edema that results from acute damage to the alveoli (1). Most patients with this syndrome will die if they do not receive supplemental oxygen and mechanical ventilation (2, 3). By reversing life-threatening hypoxemia and alleviating the work of breathing, mechanical ventilation buys time for the lungs to heal (3). Mechanical ventilation can also cause lung damage by several mechanisms, including alveolar rupture and alveolar hemorrhage, especially when high airway pressures are used for ventilation (4, 5). In these patients, the damage to the lungs caused by mechanical ventilation is known as ventilator-induced lung injury (VILI) (5). Mounting experimental evidence suggests that the risk of VILI may be decreased by a careful titration of ventilator support guided by monitoring pulmonary mechanics in ARDS (5-8).

Pressure Volume curves in ARDS
A useful first step in understanding the impact of monitoring pulmonary mechanics in ARDS is to examine the pressure-volume relationship of the respiratory system in these patients. As shown in Figure 1, the pressure-volume curve in patients with ARDS can have a sigmoid shape with two discrete bends (9). The lower bend is called lower inflection point (LIP) and the upper bend is called upper inflection point (UIP) (9). In the past the LIP was thought to be the critical pressure needed to reopen most of previously collapsed airways and alveoli. The UIP was thought to be the critical pressure beyond which alveolar overdistension occurs. That meant that tidal ventilation was thought to be safe as long as it was delivered within these two points. We now know that these are oversimplifications because recruitment of collapsed lung units continues above LIP (10) and above UIP (11).
Ventilation that continues beyond the UIP can cause lung injury (5). This type of lung injury is known as “baro-trauma” or lung trauma caused by excessive pressure applied to the lungs (5). Some investigators, however, prefer the term “volutrauma” (lung trauma caused by excessive distension of the lungs) because – they note – it is not the pressure at the airway opening that causes lung injury but the disention of the lung (12). Ventilation that starts below the LIP is associated with cyclical collapse and reopening of lung units. This cyclical collapse and reopening causes a type of lung damage known as “atelectrauma” (13). In addition to biophysical injury (volutrauma and atelectrauma), investigators now posit that injurious ventilatory strategies associated with overdistension of the lung and with repeated recruitment and de-recruitment of collapsed lung units can also lead to the release of inflammatory mediators, including TNF-α, interleukin-6, prostaglandins, leukotrienes and reactive oxygen species (13). According to those investigators, these inflammatory mediators cause a biochemical injury termed “bio-trauma” (13). At a local level inflammatory mediators can lead to recruitment of a number of cells, including neutrophils (14). In addition, inflammatory mediators can translocate from the lung into the systemic circulation and this may lead to distal organ dysfunction and death (4, 13).

At one time, investigators advocated obtaining pressure-volume curves to properly select ventilator settings in patients with ARDS (15). Unfortunately, pressure-volume curves are difficult to generate because they require heavy sedation and paralysis (16). In addition they can cause hypoxemia at low lung volumes, derecruitment at low levels of positive end-expiratory pressure (PEEP) and hemodynamic compromise (decrease of venous return) (16). Pressure volume curves are also difficult to interpret due to many confounders. These confounders include expiratory flow limitation (17), abnormal chest-wall mechanics (18), continuous recruitment of collapsed lung units above LIP (10) and above UIP (11) and focal vs. non-focal distribution of ARDS (6, 19). Not surprisingly, most experts around the world use pressure-volume curves only for research purposes but not in clinical practice (Figure 2).

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How often do you obtain PV curves in your clinical practice when treating patients with ARDS?

Slutsky never
Tobin never
Natanson never
Barbas never
Mancebo never
Brochard never
Pesenti ~10%
Ranieri never
Bersten very seldom

Figure 1 - Schematic representation of a pressure-volume curve of the respiratory system in a patient with ARDS. In these patients, the pressure-volume curve can have a sigmoid shape with two discrete bends above functional residual capacity. The lower bend is called lower inflection point and an upper bend is called upper inflection point. In 1995, Roupie et al. (AJRCCM 1995;152:121) reported that using conventional tidal volumes (9-12 mL/kg), and a mean PEEP of 10 cm H2O, more than 70% of patients with ARDS had an end-inspiratory plateau airway pressure exceeding upper inflection point. Reducing tidal volumes to 6 mL/kg brought the end-inspiratory plateau airway pressure below upper inflection point. This was the first study to demonstrate the relevance of reduction in tidal volume for lung protection.

Figure 2 - Pressure volume curves are difficult to generate and to interpret. This is why most international experts do not use them in their daily clinical practice (Franco Laghi, personal communication, November 2010).
Monitoring pulmonary mechanics to limit overdistension (Volutrauma)

Following the seminal study of Amato et al. (15), the ARDS Network published the result of a large multicenter trial of 861 patients with ARDS (20). In the study, one group of patients was randomized to mechanical ventilation with small tidal volumes (6 ml/kg of ideal body weight or IBW) and a plateau airway pressure (Pplat) recorded following an inspiratory pause of 0.5 seconds of 30 cm H\textsubscript{2}O or less. A second group of patients was randomized to traditional tidal volumes (12 ml/kg IBW) and a Pplat of 50 cm H\textsubscript{2}O or less (20). The trial was stopped when an interim analysis revealed that lowering tidal volume and Pplat decreased mortality by 22%. In a subsequent metaanalysis, Eichacker et al. (21) concluded that the most important aspect in setting the tidal volume in ARDS is to use tidal volumes that produce a Pplat between 28 and 32 cm H\textsubscript{2}O.

Pplat is used to estimate transpulmonary pressure (lung stretching). A high Pplat signifies excessive lung stretching, and a low Pplat signifies less lung stretching. Unfortunately, the value of Pplat is determined not only by the stiffness of the lung but is also determined by the stiffness of the chest wall. In some patients, including those who are obese, pregnant or who have tense ascites, the stiffness of the chest wall can be significant. In these patients, Pplat may be very high without this signifying that the lungs are truly overdistended (volutrauma). That is, in patients with a chest wall that is stiffer than normal the simple measurement of Pplat will cause physicians to grossly overestimate lung stretching. In these patients it may necessary to measure transpulmonary pressure using esophageal pressure tracings (see below).

Transpulmonary pressure is calculated by subtracting alveolar pressure from pleural pressure (Figure 3). In clinical practice, it is unrealistic to perform direct measurements of alveolar pressure and direct measurements of pleural pressure. Instead, airway pressure is used as a substitute of alveolar pressure and esophageal pressure substitutes pleural pressure.

Figure 3 - Transpulmonary pressure or P\textsubscript{L} (lung stretching) is calculated by subtracting alveolar pressure (PA) from pleural pressure (Ppl). In clinical practice, airway pressure (Paw) substitutes alveolar pressure and esophageal pressure substitutes pleural pressure.

Monitoring pulmonary mechanics to limit cyclical recruitment-derecruitment (Atelectrauma)

The central question here is “what aspects of pulmonary mechanics should we monitor to avoid atelectrauma?”. Stated differently the question is “what aspects of pulmonary mechanics should we monitor to set PEEP in ARDS?”. This is a difficult question that can be answered only tentatively.

The various strategies used to set PEEP in ARDS include:

1. Monitoring oxygenation and using a sliding-scale (table) developed by a panel of experts to adjust PEEP and Fi\textsubscript{O}\textsubscript{2}, in discrete steps to maintain adequate arterial oxygenhemoglobin saturation (24, 25).

2. Monitoring respiratory system compliance while titrating PEEP (optimal PEEP defined as the PEEP associated with maximal compliance) (26, 27).
1. End-inspiratory strain: according to continuum mechanics, a branch of classic mechanics that deals with solids and fluids, the transformation of a body relative to a reference configuration to a current configuration is called deformation. This is quantified as the displacement between particles in the body relative to a reference length or strain. In the case of the lungs undergoing mechanical ventilation, the change in lung volume relative to the resting volume is measured as the end-inspiratory strain of the lung. The magnitude of the end-inspiratory strain can be calculated as the difference between the end-inspiratory volume and the resting volume, divided by the resting volume. It is important to note that the end-inspiratory strain is dependent on the mechanical characteristics of the individual patient and the ventilator settings. Investigators have reported encouraging results (tendency to improve survival) in patients with ARDS ventilated with high PEEP associated with total pulmonary pressure at end-exhalation while keeping transpulmonary pressure in the physiologic range of <25 cm H$_2$O. This observation implies the presence of inhomogeneous distribution of local end-inspiratory strain.

2. Driving pressure: this pressure is calculated as the difference between Pplat and PEEP. This means that one of the determinants of driving pressure is end-inspiratory lung strain: the greater the strain the greater the driving pressure. Post-hoc analysis of several clinical investigations suggests that driving pressures above 15-20 cm H$_2$O are conducive to increased mortality in ARDS. It would be tempting to speculate that the excess mortality in those studies was due at least in part to excessive strain and biotrauma. For several reasons such speculation cannot be either accepted or refuted. First, the link between strain and biotrauma is indirect. Second, the value of Pplat required to calculate driving pressure is not only a function of lung mechanics but it is also a function of chest wall mechanics (see section on volutrauma). Third, no study has prospectively determined the impact of different driving pressures on ARDS outcome. Fourth, ventilator settings (such ventilator mode, as PEEP, respiratory rate, Fio$_2$) in the investigations summarized in Figure 4 varied from study to study. It is important to bear in mind that such threshold is based on conjecture, biological plausibility and post hoc analysis of studies not designed to identify the ideal driving pressure to use in patients with ARDS.

3. Monitoring the shape of the airway pressure signal during lung inflation with constant airflow (optimal PEEP defined as the PEEP associated with a linear rise in airway pressure or “stress insensitivity”) (24, 25).

4. Monitoring Pplat while titrating PEEP (optimal PEEP defined as the highest PEEP associated Pplat of 20-30 cm H$_2$O) (28).

5. Monitoring an estimate of transpulmonary pressure measured with an esophageal balloon (optimal PEEP defined as the PEEP associated with positive transpulmonary pressure at end-exhalation while keeping transpulmonary pressure in the physiologic range of <25 cm H$_2$O) (7).

Except for the first strategy listed above, all the other strategies are based on two ideas, first, to monitor the mechanical characteristics of the individual patient with ARDS and, second, set PEEP accordingly. Investigators have reported encouraging results (tendency to improve survival) in patients with ARDS ventilated with tidal volume of 8 ml/kg IBW in whom PEEP was titrated according to the mechanical characteristics of each individual patient (7, 28). In contrast, titrating PEEP using a sliding-scale (table) designed to adjust PEEP according to driving pressures on ARDS outcome. Fourth, ventilator settings (such ventilator mode, as PEEP, respiratory rate, Fio$_2$) in the investigations summarized in Figure 4 varied from study to study (4, 7, 15, 20, 24, 25, 28, 36-40). It would be tempting to speculate that the excess mortality in those studies was due at least in part to excessive strain and biotrauma. For several reasons such speculation cannot be either accepted or refuted. First, the link between strain and biotrauma is indirect. Second, the value of Pplat required to calculate driving pressure is not only a function of lung mechanics but it is also a function of chest wall mechanics (see section on volutrauma). Third, no study has prospectively determined the impact of different driving pressures on ARDS outcome. Fourth, ventilator settings (such ventilator mode, as PEEP, respiratory rate, Fio$_2$) in the investigations summarized in Figure 4 varied from study to study. It is important to bear in mind that such threshold is based on conjecture, biological plausibility and post hoc analysis of studies not designed to identify the ideal driving pressure to use in patients with ARDS.

Monitoring pulmonary mechanics to limit biotrauma

To posit that monitoring a particular aspect of pulmonary mechanics can give an insight to the risk of developing biotrauma implies the existence of a not yet well identified link between pulmonary mechanics and biotrauma. Monitoring tools that have triggered interest in this regard include the quantification of the end-inspiratory strain of the lung and the computation of the so-called driving pressure (31).

1. End-inspiratory strain: according to continuum mechanics, a branch of classic mechanics that deals with solids and fluids, the transformation of a body from a reference configuration to a current configuration is called deformation. This is quantified as the displacement between particles in the body relative to a reference length or strain. In the case of the lungs undergoing mechanical ventilation, the change in lung volume relative to the resting volume is measured as the end-inspiratory strain of the lung. The magnitude of the end-inspiratory strain can be calculated as the difference between the end-inspiratory volume and the resting volume, divided by the resting volume. It is important to note that the end-inspiratory strain is dependent on the mechanical characteristics of the individual patient and the ventilator settings. Investigators have reported encouraging results (tendency to improve survival) in patients with ARDS ventilated with high PEEP associated with total pulmonary pressure at end-exhalation while keeping transpulmonary pressure in the physiologic range of <25 cm H$_2$O. This observation implies the presence of inhomogeneous distribution of local end-inspiratory strain.

2. Driving pressure: this pressure is calculated as the difference between Pplat and PEEP. This means that one of the determinants of driving pressure is end-inspiratory lung strain: the greater the strain the greater the driving pressure. Post-hoc analysis of several clinical investigations suggests that driving pressures above 15-20 cm H$_2$O are conducive to increased mortality in ARDS. It would be tempting to speculate that the excess mortality in those studies was due at least in part to excessive strain and biotrauma. For several reasons such speculation cannot be either accepted or refuted. First, the link between strain and biotrauma is indirect. Second, the value of Pplat required to calculate driving pressure is not only a function of lung mechanics but it is also a function of chest wall mechanics (see section on volutrauma). Third, no study has prospectively determined the impact of different driving pressures on ARDS outcome. Fourth, ventilator settings (such ventilator mode, as PEEP, respiratory rate, Fio$_2$) in the investigations summarized in Figure 4 varied from study to study. It is important to bear in mind that such threshold is based on conjecture, biological plausibility and post hoc analysis of studies not designed to identify the ideal driving pressure to use in patients with ARDS.

Conclusion

In patients with ARDS mechanical ventilation can be life-saving yet it can also exacerbate lung injury (VILI). Current knowledge suggests that preventing VILI during mechanical ventilation requires avoidance of cyclical opening and closing of unstable lung units and avoidance of excessive stretching of lung parenchyma. Growing experimental evidence suggests that these goals may be
achieved by a careful titration of ventilator support guided by monitoring pulmonary mechanics (5-8).

Acknowledgements and disclosures

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References


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Mini-review

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Summary

Sleep breathing disorders (SBD) are commonly divided in three syndromes: obstructive sleep apnoea syndrome (OSA), central sleep apnoea-hypopnoea syndrome (CSA) and Cheyne-Stokes breathing syndrome (CSR), the latter two both characterized by cyclic non-obstructive breathing patterns. Because the prevalence of CSA-CSR in chronic heart failure (CHF) population has been reported from 40% to 60%, CSA-CSR is the more frequent respiratory consequence of such cardiovascular illness. CSA-CSR has been associated with increased mortality in heart failure patients, but a causal role for CSA-CSR in the morbidity and mortality of heart failure awaits more definitive evidence.

In fact, it is not yet known whether CSA-CSR is an epiphenomenon in the setting of heart failure or whether it may itself lead to increased risk or progression of heart failure. CPAP is the most studied form of treatment for CSA-CSR. However, in randomized trials of long term duration, several forms of non-invasive positive airway pressure, including CPAP, bi-level, adaptive pressure support ventilation and nocturnal oxygen therapy, have been shown to alleviate CSA-CSR in heart failure patients. Nevertheless, at present, none therapeutic approach was ideal with respect to both efficacy and tolerance, nor has any available therapy been demonstrated to improve survival. In CHF patients with CSA-CSR, standard employment of CPAP cannot be recommended at present, though the post hoc analysis of the CANPAP study is intriguing and suggests that CPAP responders may benefit prognostically. Furthermore, the results of the CANPAP study should not be extrapolated to heart failure patients with OSA, which is much more effectively suppressed by CPAP. Finally, there is a need to examine novel treatment options for CSA-CSR in patients with CHF, as these patients appear to have the worst prognosis and therefore the most to gain if successful treatment of CSA-CSR improves survival.

KEY WORDS: Cheyne-Stokes; Central Sleep Apnea; Heart Failure.

Introduction

One of the most recent and intriguing developments in the field of cardiovascular medicine originated from the observations that some sleep disorders, such as obstructive sleep apnoea-hypopnoea syndrome (OSA), may cause or worsen cardiac disease and, in turn, that certain cardiac diseases, like chronic heart failure (CHF), may bring on sleep disorders such as central sleep apnoea-hypopnoea syndrome (CSA) and Cheyne-Stokes breathing syndrome (CSR). This review will mainly focus on the current treatment options of CSR-CSA in CHF. First we will explore the physiopathology and clinical significance of CSA-CSA in CHF and then we will examine the up-to-date knowledge on the effects of treatment of central sleep disordered breathing in patients with CHF.

Cheyne-Stokes Respiration/Central Sleep Apnoea in Heart Failure

Sleep breathing disorders (SBD) are commonly divided (1) in three syndromes: obstructive sleep apnoea syndrome, central sleep apnoea-hypopnoea syndrome and Cheyne-Stokes breathing syndrome, the latter two both characterized by cyclic non-obstructive breathing patterns.

Patients with heart failure and CSA-CRS have a significantly lower PaCO₂, while awake and asleep, when compared with patients with similar ejection fraction but no CSA-CSR.
with a *crescendo-decrescendo* pattern in the depth of respirations (Figure 1). Central sleep apnoea is a manifestation of respiratory instability and is particularly prone to occur during sleep when the respiratory system becomes critically dependent on the metabolic control system. One of the most well-known mathematical models proposes an explanation to CSA-CSR (2) based on three basic components: a controlling system, a controlled system and a feedback loop. The controlled variables are PaO\(_2\) and PaCO\(_2\). Prolonged circulation time, which is a hallmark of heart failure, promotes a delayed response that may promote respiratory instability. However, it is generally agreed that this mechanism may contribute to the generation of CSA-CSR, but is not alone sufficient (3). The high sensitivity of ventilatory chemoreceptors promotes a strong ventilatory response and blood gas instability. Increased controller gain is well-documented and it is thought to play a central role in the genesis of CSA-CSR in patients with heart failure (4, 5). Plant gain is dependent on lung gas stores, on body stores of oxygen and carbon dioxide, and on the metabolic rate (Figure 2). Reduction in lung volumes increases plant gain because smaller volumes are less effective at damping out changes in PaCO\(_2\) and PaO\(_2\), thus favouring instability (6), and that may explain the increased propensity to CSA-CSR in the supine position (7). Low PaCO\(_2\) levels play a central role in the genesis of apnoeas and hypopneas. Patients with heart failure and CSA-CRS have a significantly lower PaCO\(_2\), while awake and asleep, when compared with patients with similar ejection fraction but no CSA-CSR. It has been shown that the first apnoea is regularly preceded by hyperventilation (4), which caused PaCO\(_2\) to reach the value below the apnoeic threshold; this proved to be the key element in triggering central apnoea (8). Several mechanisms were proposed to explain why patients with heart failure tend to hyperventilate. PaCO\(_2\) levels correlate negatively with pulmonary capillary wedge in patients with HF submitted to cardiac catheterization (9). Therefore, the development of CSA-CSR by state of hyperventilation may be explained as a consequence of pulmonary congestion due to tonic stimulation of pulmonary vagal afferents (10). However, the observation of CSA-CSR in one patient submitted to lung transplantation (11), suggests that other mechanisms, such as cardiac vagal afferents, may also be important. Hyperventilation may be caused by an elevated sympathetic activity upon central and peripheral chemoreceptors (12). While OSA has been identified as a possible independent risk factor for the development of heart and vascular disease, CSA-CSR is a more frequent consequence of such cardiovascular illness. However it is not yet known whether CSA-CSR is an epiphenomenon in the setting of heart failure or whether it may itself lead to increased risk or progression of heart failure (13-16). Lanfranchi et al. (13), while studying a variety of baseline patient characteristics, including New York Heart Association class, left ventricular

![Figure 1 - Polysomnographic example of CSA-CSR (180 sec). On flow trace # 7, Cheyne-Stokes respiration with typical “waxing and waning” pattern and central apnoea with concomitant absent movements of chest (trace # 8) and abdomen (trace # 9). Arousal occurred at the top of “crescendo” flow.](image-url)
ejection fraction, and exercise capacity, found that the left atrial area and the apnoea/hypopnoea index (AHI) emerged as the two most potent predictors of mortality. Other studies suggested that the higher rates of death and cardiac transplantation seen in patients with heart failure, along with low diastolic BP and severe right ventricular dysfunction (17), were proportional to the frequency of central apnoeic events (15). Another issue that should be stressed is that central and obstructive events are not independent phenomena, in fact they often coexist in patients with heart failure, who may convert OSA to CSA during the course of a single night (18) and over a longer period of time (19).

Treatment of central sleep disordered breathing in chronic heart failure

CPAP is the most studied form of treatment for CSA-CSR. Nevertheless, in randomized trials of long term duration, several forms of non-invasive positive airway pressure, including CPAP, bi-level, and adaptive pressure support servo-ventilation, have been shown to alleviate CSA-CSR in heart failure patients (20-22). The mechanisms by which CPAP exerts the beneficial effects in HF without obstruction of the upper airways during sleep are not completely understood, but the primary effect may be on the cardiovascular system by reducing the preload and afterload (23). This may be due to the increase of the intrathoracic pressure and the decrease of the transmural pressure of the intrathoracic structures. CPAP also reduces the work of breathing in patients with HF (24). In randomized trials, nightly application of CPAP for three months increased left ventricular ejection fraction, reduced mitral regurgitation and nocturnal urinary and daytime plasma nor-epinephrine, and improved quality of life (24, 25). Sin et al. (16) studied patients with HF and CSA-CSR and reported a significant improvement in LVEF and transplant-free survival in those randomized to CPAP therapy, if they complied with treatment, compared to control with no CPAP. Bradley et al. (26) carried out the largest randomized prospective study on the use of nasal CPAP therapy in 258 HF patients with CSA-CSR (CANTAP study). They found no difference in 2-year survival or atrial natriuretic peptide plasma level despite significant improvements in LVEF, lower noradrenaline levels and increased mean 6-minute walk test distance in patients randomized to CPAP. The authors suggested that current medical therapies for HF (particularly beta-blockers) led to significant improvement in prognosis, with a fall in the mortality of both control and treatment groups which reduced the study’s power to detect a treatment difference. In addition, the mean reduction of AHI in the treatment arm was to a level above the inclusion AHI threshold of 15. Moreover, the issues of compliance and efficacy may be relevant. At one year, CPAP was used for 3.6 hours per night and attenuated AHI by 50%, indicating only a partial reduction in “apnoea burden”. A recent post hoc analysis of CANTAP study showed that responders to CPAP had a significant improvement in LVEF and transplant-free survival compared to non-responders or controls (27). Although
this was a post hoc analysis, it is hypothesis generating and provides directions for future research on CPAP in HF patients with CSA-CSN responsive to CPAP because better-tolerated and more effective treatment of CSA-CSN might have resulted in improved survival (27-29). Another point of interest regards the theoretical possibility that other forms of non-invasive ventilation able to abolish CSA-CSN may be effective in the treatment of the cardiovascular consequences associated with CSA-CSN. Because CPAP is not effective in reducing CSA-CSN in a significant number of patients, other forms of non-invasive ventilation, including bi-level positive airway pressure (BiPAP) and adaptive pressure support ventilation (ASV), have been proposed as alternative.

Bi-level positive airway pressure (BiPAP) is a ventilatory mode that delivers two pressure levels, a higher inspiratory pressure and a lower expiratory pressure. BiPAP has been postulated to be superior to CPAP in HF patients because the typically lower expiratory pressure may not impede stroke volume in patients with low cardiac filling pressures, as may occur with CPAP (30). Despite the general concern that these patients already hyperventilate, and further increasing ventilation may not necessarily be a good approach, possibly leading to hypocapnic alkalotic glotic closure, recently Khayat et al. (31), in moderate-severe HF patients randomly assigned to CPAP or BiPAP treatment, found that LVEF improved significantly in the BiPAP group but not the CPAP group. Previously, on the other hand, Kohnlein et al. (32) in a random, crossover study design concluded that both CPAP and BiPAP treatments equally and effectively improve Cheyne-Stokes respiration in HF patients. At any rate, it’s important to highlight the setting values of the bi-level devices employed in aforementioned studies (31, 32) because the very low span used (mean 3 cmH2O) between inspiratory and expiratory pressure really suggest a CPAP-like effect more than a pressure support ventilation. One interesting and relatively new format of treatment is the adaptive pressure support ventilation (ASV). This is a novel form of bi-level PAP in which the flow generator provides a fixed end expiratory pressure that should be titrated to abolish upper airway obstructive events. The inspiratory pressure support level then varies in accordance to an algorithm that aims at stabilizing ventilation at an approximate 80% of the baseline minute ventilation. Adaptive pressure support ventilation results in acute suppression of CSA-CSN (21) that is more effective than CPAP and may result in better compliance and a greater improvement in heart function (22).

A prospective study used a randomized parallel design in treating 26 CSA-CSN in heart failure patients, comparing one month of therapeutic and sub therapeutic ASV (33). Active treatment attenuated daytime sleepiness (primary end point), plasma brain natriuretic peptide and urine non-adrenaline (secondary end points). Despite these promising results, further studies are needed to clarify the optimal ventilation strategy for patients with CSA-CSN and HF. As an alternative approach nocturnal oxygen therapy has been reported to improve CSA in patients with systolic heart failure (34-36). Hanly et al. (35) should be credited for the first randomized, placebo controlled study. In nine subjects with systolic heart failure, the authors showed that the administration of nasal oxygen for one night (when compared to nasal air) improved CSA-CSN, sleep architecture (i.e. decreased arousals and shifted sleep to deep stages), and arterial oxyhaemoglobin desaturation. Two studies of Andreas et al. (37) and Staniforth (38) et al. indicated that in systolic heart failure, oxygen decreases sympathetic activity due to CSA. Another study of Sasayama (39) showed that supplemental nocturnal oxygen therapy for three months, compared to control, significantly improved CSA-CSN, LVEF and quality of life in patients with HF and central sleep breathing disorders.

Oxygen administration decreased periodic breathing with the most significant effect on CSA. While the patients were receiving oxygen, desaturation was virtually eliminated. Unfortunately not all patients with heart failure and CSA-CSN have a complete reversal of sleep apnoea with oxygen. It was noted (40) that in patients fully responsive to oxygen therapy the PaCO2 values of the subjects were within the normocapnic at the apnoeic threshold, the suppression of ventilatory response to hypercapnia, and an increase in the body stores of oxygen. Taken together, this should dampen the respiratory loop gain (change of ventilation for a given change of ventilation) (41) and decrease the likelihood of ventilatory instability promoting CSA-CSN. It was speculated (40) that subjects that resulted as only partial responders to oxygen therapy have such an intense non-chemical ventilatory stimuli that oxygen failed to raise their baseline PCO2 in the transition from wakefulness to sleep. Because oxygen decreases sympathetic activity and eliminates desaturation, long-term therapy may potentially decrease the morbidity and mortality of subjects with HF. Nevertheless, careful, randomized, placebo controlled, multicenter studies with mortality as the end point are required to prove nocturnal oxygen therapy as a long-term helpful treatment modalit in HF with CSA-CSN.

In accordance to point of view that CSA-CSN is a consequence of a failing heart, all therapies able to ameliorate heart function may be helpful in reducing CSA-CSN. In effect CSA-CSN was abolished in patients underwent to heart transplant for CHF (42). Some, but not all, studies indicate that beta-blockers and furosemide ameliorate CSA-CSN (43, 44). Also theophylline (45), acetazolamide (46), administration of carbon dioxide (47) and addition of dead space (48) can reduce CSA-CSN; however there is...
a general concern that to use drugs or devices with a strong stimulatory effect on respiratory drive in patients with CHF and CSA/CSR, already hyperventilate, may not to beneficial.

Cardiac resynchronization therapy also appears to improve CSA-CSR in HF, but only in those patients whose cardiac function improved with the resynchronization therapy (24), suggesting that improved cardiac function may have reduced the severity of CSA-CSR. Changes in CSA-CSR sleep CPAP-to be associated with CRT-induced changes in mitral regurgitation but further studies are required to confirm these early results, to determine the exact mechanisms by which CRT might improve CSA-CSR, and to identify which CSA-CSR patients with heart failure would benefit from such interventions.

Conclusions

Although CSA-CSR has been associated with increased mortality in CHF patients, a causal role for CSA-CSR in the morbidity and mortality of heart failure awaits more definitive evidence. A number of treatment strategies for CSA have been tested, but presently none is ideal with respect to both efficacy and tolerance, nor has any available therapy been demonstrated to improve survival. For CSA-CSR, use of CPAP cannot be recommended at present, though the post hoc analysis of the CANPAP study (27) is intriguing and suggests that CPAP responders may benefit prognostically. Furthermore, the results of the CANPAP study should not be extrapolated to heart failure patients with OSA, which is much more effectively sup- pressed by CPAP. Finally, examined novel treatment options for CSA-CSR in patients with HF, as these patients appear to have the worst prognosis and therefore the most to gain if successful treatment of CSA-CSR improves survival.

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References


Lymphomatoid granulomatosis: a poorly-recognized lymphoproliferative disorder of the lung

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Summary

Lymphomatoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder predominantly involving the lungs, but poorly-recognized among clinicians and pathologists. It is an Epstein-Barr virus (EBV)-driven disease mimicking several other diseases on clinical and radiological grounds, generally showing multiple, bilateral nodules tending to coalescence and/or cavitation. LYG often affects middle-aged males with an underlying immunodeficiency and commonly involves skin and central nervous system during disease progression. Diagnosis requires a generous biopsy and a careful histologic examination with immunohistochemical stains and molecular demonstration of EBV genome in large atypical B-cells. LYG is graded from I to III based on the rate of EBV-positive large B-cells and grade II/III are now considered as a peculiar variant of T-cell rich diffuse large B-cell lymphoma.

This brief report, the main clinico-radiologic and pathologic features of LYG are reviewed in order to highlight the most helpful diagnostic features to be kept in mind in routine practice when dealing with this controversial and difficult entity.

Methods

Clinical features

LYG has a predilection for men in a 2:1 ratio and may affect children and elderly, with a prevalence in the forth and fifth decades of life. The disease more commonly occurs in patients with immunodeficiency or predisposing conditions, as Wiskott-Aldrich syndrome, human immunodeficiency virus infection (HIV), allogenic organ transplantation, common variable immunodeficiency, X-linked hypo- or agammaglobulinemia, rheumatoid arthritis, previous history of solid or hematologic neoplasms, and chronic treatment with methotrexate. It is a common view that LYG may derive from a deficit of CD8 T lymphocytes that cannot control EBV-specific immunity. LYG may be localized to the lungs or rather presents as a systemic disease involving skin, central nervous system and less commonly kidneys. LYG is graded from I to III, with grade I being the least aggressive and grade III the most aggressive.

It is important to keep in mind that LYG may present with symptoms similar to other diseases, such as Wegener’s granulomatosis, sarcoidosis, and Castleman’s disease. Diagnosis is often delayed due to the nonspecific presentation and lack of awareness among clinicians and pathologists.

Diagnosis

Diagnosis of LYG is challenging and requires a high index of suspicion. The disease is characterized by a polymorphic lymphoproliferative process with a predominant T-cell rich infiltrate obscuring large lymphomatous B-cells. Demonstration of EBV RNA genome is the crucial point for the correct diagnosis. LYG is graded from I to III based on the rate of EBV-positive large B-cells, with grade I being the least aggressive and grade III the most aggressive.

In this brief report, the main clinico-radiologic and pathologic features of LYG are reviewed in order to highlight the most helpful diagnostic features to be kept in mind in routine practice when dealing with this controversial and difficult entity.
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Cutaneous involvement often occur in the arms and legs with a very heterogeneous manifestation, ranging from an erythematous maculopapular eruption to subcutaneous nodules with non confluent rash (11-16, 28-30). Neurologic presentation may present as an isolated peripheral or cranial neuropathy, as a central mass lesion, or with seizures (11-16, 28-30).

Predictors of poor prognosis are central nervous system involvement, high grade, young age at diagnosis (less than 25 years), leukocytosis and hepatomegaly (11-16, 28-30).

**Imaging studies**

The most common radiographic feature is multiple lung nodules, occurring in approximately 80% of the cases, predominantly involving the lung bases (15-21). The lesions can progress rapidly, coalesce and commonly cavitate, therefore mimicking Wegener’s granulomatosis or metastases (Figure 1) (15-21, 26). Dee et al. (18) described two distinct radiographic manifestations of LYG. In their series of five patients, diffuse reticulonodular opacities correlated microscopically with angiocentric granulomatous infiltration without pulmonary infarction, whereas larger mass-like opacities corresponded to biopsy-proven pulmonary infarcts (18). There is a wide range in the number (5-60) and diameter of the nodules (up to 6.5 cm) but generally they measure 1 cm and tend to be located along the bronchovascular bundles and interlobular septa (15-21). Less common radiological appearances include coarse linear opacities along the bronchovascular bundles and thin-walled cysts (15, 18). Nodules can disappear or migrate spontaneously, and may display central ground-glass opacity surrounded by denser consolidation at least 2 mm thick – the so called “reversed halo sign” (20). However, this is a non-specific sign, most commonly seen in organising pneumonia. Differential diagnosis at imaging presentation may be very challenging and includes several other, more common diseases, including metastases, lymphocytic interstitial pneumonia (LIP), sarcoidosis, Wegener’s granulomatosis, and cryptogenic organizing pneumonia (Table 2) (15-21). In contrast with other lymphomas involving the thoracic region, mediastinal lymphadenopathy is very uncommon in LYG (15-21).

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**Table 1 - Conditions associated with lymphomatoid granulomatosis.**

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**Table 2 - Differential diagnosis of lymphomatoid granulomatosis.**

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<td>Psoriasis</td>
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<td>Dermatitis herpetiformis</td>
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The disease more commonly occurs in patients with immunodeficiency, e.g. CD8+ lymphocytopenia that cannot control EBV-specific immunity.
Histology, immunohistochemistry and molecular analysis

Histology is characterized by poorly-defined pulmonary nodules (Figure 2, A) along the bronchovascular bundles and interstitial inflammatory infiltrates consisting of lymphocytes, plasma cells, histiocytes and intermediate-to-large centroblast-like lymphoid cells (Figure 2, B, C) (1-8, 22, 23). Vascular and bronchiolar involvement by lymphoid infiltrates is frequently noted. In fact, venous and arterial vessels tend to be infiltrated by a mixture of small sized and large atypical lymphocytes justifying the peculiar angiocentric involvement (Figure 2, D) (1-8, 22, 23). At the periphery of lymphoid proliferation, lung parenchyma commonly shows an acute lung injury with fibrin and interaline membranes (Figure 2, E) (14, 27). At immunohistochemistry, there is a background of small T-lymphocytes (CD3+) predominantly with helper phenotype (CD4+) (Figure 3, A) and CD68+ histiocytes intermingled by a population of large B-cells (CD20+, PAX5+, CD79a+) (Figure 3, B, C) with high proliferative index by Ki67/MIB-1 (Figure 3, D) (3-8, 22, 23). In-situ hybridization for EBV-encoded RNA (EBER) reveals a consistent number of EBV-positive large B-cells (Figure 3, E), while molecular analyses generally demonstrate B-cell clonality by immunoglobulin heavy chain gene rearrangement (3-8, 10-13, 16, 22, 23).

Despite the misnomer, no granulomas or multinucleated giant cells are observed in LYG. According to the WHO classification criteria based on the number of EBV-positive large atypical B-cells, 3 grades are recognized in LYG. Grade I is very rare and shows a polymorphous infiltrate with minimal angiocentric lesions and fewer than 5 EBV-positive atypical B-cells x high-power field (hpf) (3, 8, 22, 23). Grade II had more than 5 and fewer than 20 EBV-positive atypical B-cells x hpf, while grade III LYG contains aggregates of EBV positive large B-cells (more than 20 x hpf), prominent angiocentric lesions and necrosis (3, 8, 22, 23).

Treatment and prognosis

No standard therapy has been so far established, and treatment is controversial and problematic, basically depending on disease grade (7, 9, 10-13, 30-37). Several regimens have been considered in the past, from observation to cyclophosphamide plus prednisone or combination chemotherapy with different agents with variable success (10).

Table 2 - Main pathologic conditions mimicking LYG in the lungs.

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<th>Neoplasms</th>
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<td>Primary lung carcinomas</td>
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<td>Metastatic tumors</td>
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<td>Lymphoproliferative disease (i.e., leukaemia)</td>
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<th>Infections</th>
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<th>Autoimmune diseases</th>
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<td>Churg-Strauss syndrome</td>
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<td>Microscopic polyangitis</td>
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<td>COP</td>
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<td>Pneumoconioses</td>
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| Abbreviations: LYG, lymphomatoid granulomatosis; LIP, lymphocytic interstitial pneumonia; COP, cryptogenic organizing pneumonia. |

Demonstration of EBV RNA genome is the crucial point for the correct diagnosis and LYG.

Figure 2 - Histology showing surgical lung specimens with several “blue” nodules (A). Higher magnification shows a polymorphous mononuclear infiltrate (B, C) with vascular involvement (D) and areas of diffuse alveolar damage (E).
However, the outcome is poor and most patients with LYG succumb to the disease after a short period of time. In addition, patients often respond initially, but relapse is very common and the immunosuppressive effects of therapy may actually worsen the condition. During therapy, a close follow-up for possible superimposed infections is required.

Since this is an EBV-driven process, grade I LYG is often treated with interferon alpha (starting dose of 7.5 million units subcutaneously administered 3 times per week, then dose-escalation to best response or complete remission and therapy continued at that dose for a year beyond) (7, 10-13). By contrast, grade II and III should be considered high-grade lymphomas, requiring a more aggressive treatment including cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combined with the anti-CD20 monoclonal antibody rituximab (R-CHOP). Etoposide, prednisone, vincristine, cyclophosphamide doxorubicin and rituximab (DAEPOCH-R) was also considered an effective treatment strategy in grade III LYG (7, 10-13, 30-37). Of note, patients with grade I LYG can relapse with grade II or grade III disease, but this is sampling-dependent due to the presence of discordant disease at different sites. Re-biopsy should then be highly recommended in patients who are progressing on therapy in order to switch in treatment strategy. At a median follow-up time of 5 years, the progression-free survival (PFS) of patients with grade I LYG was 56% with a median time to remission of 9 months (7, 10-13). Almost all deaths are recorded in the first 36 months after diagnosis. Grade II-III disease at diagnosis treated with immunochemotherapy, PFS was 40% with a median follow-up of 28 months (7, 10-13).

Discussion

LYG is an angiocentric large B-cell lymphoproliferative disorder due to a defective immune response to EBV and characterized by a mixed polymorphic mononuclear infiltrate with small and large lymphocytes, plasma cells and histiocytes arranged in ill-defined nodules with transmural angiocentric infiltration leading to an angiodestructive process (7, 10-13, 22, 23). The disease generally occurs in middle-aged patients (mean, 40-50 years; range, 2-85 years) with systemic symptoms (fever, malaise, arthralgia, weight loss) mimicking infections (especially tuberculosis and acute histoplasmosis), vasculitides (Wegener’s granulomatosis) or malignancies (7, 10-13, 16, 22, 23). Given the rarity of LYG and the non-specific symptoms, correct diagnosis is frequently delayed, requiring a mean time of 8 months from disease onset (14, 30). When LYG is restricted to lungs, fever is the main and often unique symptom, followed by general malaise, weight loss, arthralgia, but clinical manifestations are mainly organ-related (skin, central nervous system, kidney) (7, 10-13). Lungs are almost always involved by LYG, but respiratory symptoms may be absent in 20% of cases, while imaging studies invariably show parenchymal nodules, opacities or poorly-defined masses with a peculiar tropism for bronchoalveolar bundles and interlobular septa without mediastinal lymphadenopathy (15-21). Otherwise, LYG may appear as pulmonary cystic disease, pleural-based mass or prominent interstitial process (15, 18). Patients with LYG should be investigated for alterations of cytotoxic T-cell function, since a significant association between LYG and immunodeficiencies has been well-demonstrated (i.e., AIDS, Wiskott-Aldrich, post-transplantation, collagen-vascular diseases treated with methotrexate, sarcoidosis, hematologic and solid malignancies, chronic liver and cutaneous diseases, medications) (3, 7, 8, 10-13, 24, 25, 27). Interestingly, recent observations by Yamashita et al. (38) suggested that some cases of EBV-negative grade I LYG are indistinguishable from pulmonary IgG4-related sclerosing disease, an autoimmune disorder affecting several organs and characterized by elevated serum IgG4 titer, increased IgG4-positive plasma cells in tissues with vascular involvement and dramatic clinical response to steroids.

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Lymphomatoid granulomatosis

Diagnosis of LYG obligatorily requires an accurate histopathologic examination on generous biopsies. Bronchoalveolar lavage cytology does not permit a confident diagnosis, basically evidencing a non-specific mixed inflammatory infiltrate. Transbronchial or transthoracic CT-guided biopsies may be diagnostic when sampling a large amount of pathologic tissue and in the hands of expert pathologists. By the way, in the majority of cases diagnosis is performed on surgical specimens and tissue sampled should be entirely analyzed, since correct diagnosis mainly depends on a careful examination of various areas of the pathologic process coupled to adequate immuno histochemical stains and molecular analysis (22, 23). In other words, LYG may actually show grade I and grade III disease in different pathologic areas of the same case. Based on the number of EBV-positive large B-cell counted x high-power-field, LYG is subdivided in III grades (7, 8). According to recent observations by Katzenstein et al. (22) and Colby (23), grade I LYG is a formidable challenge diagnosis and probably represent a early or poorly sampled lymphoma. Grade II/III LYG likely raise the suspicion of a malignant lymphoproliferative disease even in the hands of general pathologist. Sharing these complicated cases with more expert colleagues and performing EBER-EBV analysis on multiple sections or blocks is very helpful in discriminating LYG from other mimicking processes.

Differential diagnosis at histology includes other lymphoproliferative (primary or secondary) and inflammatory diseases (22, 23). Knowledge of a previous diagnosis of lymphoma (Hodgkin or large B-cell lymphomas) is mandatory before performing a diagnosis of LYG. Since post-transplant lymphoproliferative disorder and iatrogenic immunodeficiency-associated lymphoproliferative disorder are quite similar to LYG, such a diagnosis should be posed with caution in patients receiving organ transplant or those heavily treated with methotrexate or other immunosuppressive agents (7, 22).

The main differentials is with Wegener’s granulomatosis (WG). However, WG shows a true granulomatous inflammation with scattered multinucleated giant cells, dirty “blue” necrosis and/or granulocytic microabscesses. Neutrophils, plasma cells and eosinophils represent the major cellular components in the necrotic background (1, 2, 22, 23). Vascular infiltration of WG takes the form of an inflammatory necrotizing vasculitis with a mixture of granulocytes and mononuclear cells with or without giant cells leading to at least segmental vessel wall necrosis (1, 2, 22, 23). Special stains for mycobacteria and fungi should be performed in all cases before considering a diagnosis of LYG.

Spontaneous remission or waxing-and-waning course has been reported in grade I LYG, while grade II and III LYG are basically a unique variant of “T-cell-rich diffuse large B-cell lymphoma”, mortality ranging from 50% to 90% with an overall median survival of 14 months (3, 7, 8, 10-13, 22, 23). No standard therapies are available at now for patients with LYG. Monotherapy using steroids, rituximab or interferon-alpha has been adopted mainly in grade I LYG (10). Combined chemotherapy with CHOP ± rituximab in patients with grade II-III LYG seems to represent the best therapeutic option at now (3, 10-14, 29, 30, 32, 34).

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Lymphomatoid granulomatosis


Measuring respiratory mechanics in ARDS

Introduction

The acute respiratory distress syndrome (ARDS) is a form of noncardiogenic pulmonary edema that results from acute damage to the alveoli (1). Most patients with this syndrome will die if they do not receive supplemental oxygen and mechanical ventilation (2, 3). By reversing life-threatening hypoxemia and alleviating the work of breathing, mechanical ventilation buys time for the lungs to heal (3). Mechanical ventilation can also cause lung damage by several mechanisms, including alveolar rupture and alveolar hemorrhage, especially when high airway pressures are used for ventilation (4, 5). In these patients, the damage to the lungs caused by mechanical ventilation is known as ventilator-induced lung injury (VILI) (5). Mounting experimental evidence suggests that the risk of VILI may be decreased by a careful titration of ventilator support guided by monitoring pulmonary mechanics in ARDS (5-8).

Pressure Volume curves in ARDS

A useful first step in understanding the impact of monitoring pulmonary mechanics in ARDS is to examine the pressure-volume relationship of the respiratory system in these patients. As shown in Figure 1, the pressure-volume curve in patients with ARDS can have a sigmoid shape with two discrete bends (9). The lower bend is called lower inflection point (LIP) and the upper bend is called upper inflection point (UIP) (9). In the past it was assumed that VP curves could give accurate information on lung recruitment and overdistension. Those assumptions, however, have been proven incorrect. Similarly, it is incorrect to consider Pplat an accurate index of overdistension. In this review we will examine some of the available tools to monitor pulmonary mechanics in ARDS. The critical interpretation of the data recorded with these tools, their limitations and the potentials use of these data in setting the ventilator will be discussed as well.

KEY WORDS: Acute Respiratory Distress Syndrome; monitoring; respiratory mechanics; Ventilator-Induced Lung Injury.
Ventilation that continues beyond the UIP can cause lung injury (5). This type of lung injury is known as "baro-trauma" or lung trauma caused by excessive pressure applied to the lungs (5). Some investigators, however, prefer the term "volutrauma" (lung trauma caused by excessive distension of the lungs) because— they note— it is not the pressure at the airway opening that causes lung injury but the distention of the lung (12).

Ventilation that starts below the LIP is associated with cyclical collapse and reopening of lung units. This cyclical collapse and reopening causes a type of lung damage known as "atelectrauma" (13). In addition to biophysical injury (volutrauma and atelectrauma), investigators now posit that injurious ventilatory strategies associated with overdistension of the lung and with repeated recruitment and derecruitment of collapsed lung units can also lead to the release of inflammatory mediators, including TNF-α, interleukin-6, prostaglandins, leukotrienes and reactive oxygen species (13). According to those investigators, these inflammatory mediators cause a biochemical injury termed "bio-trauma" (13). At a local level inflammatory mediators can lead to recruitment of a number of cells, including neutrophils (14). In addition, inflammatory mediators can translocate from the lung into the systemic circulation and this may lead to distal organ dysfunction and death (4, 13).

At one time, investigators advocated obtaining pressure-volume curves to properly select ventilator settings in patients with ARDS (15). Unfortunately, pressure-volume curves are difficult to generate because they require heavy sedation and paralysis (16). In addition they can cause hypoxemia at low lung volumes, derecruitment at low levels of positive end-expiratory pressure (PEEP) and hemodynamic compromise (decrease of venous return) (16). Pressure volume curves are also difficult to interpret due to many confounders. These confounders include expiratory flow limitation (17), abnormal chest-wall mechanics (18), continuous recruitment of collapsed lung units above LIP (10) and above UIP (11) and focal vs. non-focal distribution of ARDS (6, 19). Not surprisingly, most experts around the world use pressure-volume curves only for research purposes but not in clinical practice (Figure 2).

![Pressure Volume Curve](image)

**Figure 1** - Schematic representation of a pressure-volume curve of the respiratory system in a patient with ARDS. In these patients, the pressure-volume curve can have a sigmoid shape with two discrete bends above functional residual capacity. The lower bend is called lower inflection point and an upper bend is called upper inflection point. In 1995, Roupie et al. (AJRCCM 1995;152:121) reported that using conventional tidal volumes (9-12 mL/kg), and a mean PEEP of 10 cm H₂O, more than 70% of patients with ARDS had an end-inspiratory plateau airway pressure exceeding upper inflection point. Reducing tidal volumes to 6 mL/kg brought the end-inspiratory plateau airway pressure below upper inflection point. This was the first study to demonstrate the relevance of reduction in tidal volume for lung protection.

**Figure 2** - Pressure volume curves are difficult to generate and to interpret. This is why most international experts do not use them in their daily clinical practice (Franco Laghi, personal communication, November 2010).
Monitoring pulmonary mechanics to limit overdistension (Volutrauma)

Following the seminal study of Amato et al. (15), the ARDS Network published the result of a large multicenter trial of 861 patients with ARDS (20). In the study, one group of patients was randomized to mechanical ventilation with small tidal volumes (6 ml/kg of ideal body weight or IBW) and a plateau airway pressure (Pplat) recorded following an inspiratory pause of 0.5 seconds of 30 cm H2O or less. A second group of patients was randomized to traditional tidal volumes (12 ml/kg IBW) and a Pplat of 50 cm H2O or less. The trial was stopped when an interim analysis revealed that lowering tidal volume and Pplat decreased mortality by 22%. In a subsequent meta-analysis, Eichacker et al. (21) concluded that the most important aspect in setting the tidal volume in ARDS is to use tidal volumes that produce a Pplat between 28 and 32 cm H2O.

Pplat is used to estimate transpulmonary pressure (lung stretching). In some patients a higher stiffness of the chest wall may cause grossly overestimation of lung stretching. Eichacker et al. (21) concluded that the most important aspect in setting the tidal volume in ARDS is to use tidal volumes that produce a Pplat between 28 and 32 cm H2O. Pplat is used to estimate transpulmonary pressure (lung stretching). A high Pplat signifies excessive lung stretching, and a low Pplat signifies less lung stretching. Unfortunately, the value of Pplat is determined not only by the stiffness of the lung but is also determined by the stiffness of the chest wall. In some patients, including those who are obese, pregnant or who have tense ascites, the stiffness of the chest wall can be significant. In these patients, Pplat may be very high without this signifying that the lungs are truly overdistended (volutrauma). That is, in patients with a chest wall that is stiffer than normal the simple measurement of Pplat will cause physicians to grossly overestimate lung stretching. In these patients it may necessary to measure transpulmonary pressure using esophageal pressure (see below).

Transpulmonary pressure is calculated by subtracting alveolar pressure and direct measurements of pleural pressure from airway pressure (Figure 3). In clinical practice, it is unrealistic to perform direct measurements of alveolar pressure and direct measurements of pleural pressure. Instead, airway pressure is used as a substitute of alveolar pressure, and esophageal pressure is used as a substitute of pleural pressure.

If a clinician wants to know the extent of lung stretching at end-inhalation he/she will have to record Pplat plus the corresponding esophageal pressure at end-inhalation. Of note, the value of Pplat already comprises any external PEEP applied to the patient and any intrinsic PEEP the patient may have. This means that it would be wrong to include in the calculation of transpulmonary pressure any correction for external PEEP or intrinsic PEEP. It has been reasoned that in patients with ARDS, tidal volume should be titrated to keep the transpulmonary pressure in the physiologic range – i.e., transpulmonary pressure <25 cm H2O while the patient is in the supine position (7, 22). The use of small tidal volumes in ARDS causes a reduction of CO2 clearance and a reduction in lung recruitment. These phenomena are responsible for an initial worsening in lung compliance and ventilation/perfusion matching when instituting low-tidal volume ventilation (20). In other words, permissive hypercapnia and permissive atelectasis/hypoxemia are the trade-offs we have to accept to improve the outcome of patients with ARDS (20). Of interest, new experimental evidence suggests that permissive hypercapnia may itself be lung-protective (22). Hypercapnia causes intracellular acidosis, which, in turn, has many potential protecting effects on injured alveolar cells. These potential protecting effects include the inhibition of xanthine oxidase (with consequent decrease in the production of free radicals), inhibition of the activity of NF-kB (with consequent decrease in cytokine production) and inhibition of caspase-3 that results in less apoptosis (23).

Monitoring pulmonary mechanics to limit cyclical recruitment-derecruitment (Atelectrauma)

The central question here is “what aspects of pulmonary mechanics should we monitor to avoid atelectrauma?”. Stated differently the question is “what aspects of pulmonary mechanics should we monitor to set PEEP in ARDS?”. This is a difficult question that can be answered only tentatively. The various strategies used to set PEEP in ARDS include:

1. Monitoring oxygenation and using a sliding-scale (table) developed by a panel of experts to adjust PEEP and FIO2 in discrete steps to maintain adequate arterial oxygen saturation (24, 25).

2. Monitoring respiratory system compliance while titrating PEEP (optimal PEEP defined as the PEEP associated with maximal compliance) (26, 27).
1. End-inspiratory strain: according to continuum mechanics, the deformation of a body from a reference configuration to a current configuration is called deformation. This is quantified as the displacement between particles in the body relative to a reference length or strain. In the case of the lungs undergoing mechanical ventilation end-inspiratory strain is defined as the change in lung volume relative to the resting volume (29, 30). This means that to calculate the end-inspiratory strain of the lung it is necessary to measure the end-expiratory lung volume and tidal volume (30). In mechanically ventilated patients, measurements of end-expiratory lung volume can be performed using the helium dilution technique, the nitrogen washout/washin technique and with spiral computed tomography (32, 33). (Whether strain should be calculated while patients are on PEEP or not remains controversial) (34). Cyclic end-inspiratory strain associated with inflation to total lung capacity is injurious to healthy lungs (29). This occurs when the resting lung volume (the baby lung in case of ARDS) is increased by two-fold to three-fold (29, 35). In patients with ARDS damage has been reported with end-inspiratory strains well below this upper limit (29). Such observation implies the presence of inhomogeneous distribution of local end-inspiratory strain (29).

2. Driving pressure: this pressure is calculated as the difference between Pplat and PEEP. This means that one of the determinants of driving pressure is end-inspiratory lung strain: the greater the strain the greater the driving pressure. Post-hoc analysis of several clinical investigations suggests that driving pressures above 15-20 cm H2O are conducive to increased mortality in ARDS (Figure 4) (4, 7, 15, 20, 24, 25, 28, 36-40). It would be tempting to speculate that the excess mortality in those studies was due, at least in part, to excessive strain and biotrauma. For several reasons such speculation cannot be either accepted or refuted. First, the link between strain and driving pressure is indirect. Second, the value of Pplat required to calculate driving pressure is not only a function of lung mechanics but it is also a function of chest wall mechanics (see section on volutrauma). Third, no study has prospectively determined the impact of different driving pressures on ARDS outcome. Fourth, ventilator settings (such ventilator mode, as PEEP, respiratory rate, FiO2) in the investigations summarized in Figure 4 varied from study to study (4, 7, 15, 20, 24, 25, 28, 36-40). This makes it impossible to disentangle the effect of driving pressure from other ventilator variables on patient outcome. In other words, while it would seem reasonable to aim for a driving pressure below 15-20 cm H2O (5, 15, 41) it is necessary to bear in mind that such threshold is based on conjecture, biological plausibility and post hoc analysis of studies not designed to identify the ideal driving pressure to use in patients with ARDS.

Conclusion

In patients with ARDS mechanical ventilation can be lifesaving yet it can also exacerbate lung injury (VILI). Current knowledge suggests that preventing VILI during mechanical ventilation requires avoidance of cyclical opening and closing of unstable lung units and avoidance of excessive stretching of lung parenchyma. Growing experimental evidence suggests that these goals may be...
Figure 4 - Mortality of patients with ARDS plotted against driving pressure in twelve clinical studies designed to compare some type of conventional ventilation against different lung-protective strategies (4, 7, 15, 20, 24, 25, 28, 36-40). For each study, the circle indicates the combination of mortality and driving pressure recorded with protective strategy and the star indicates the combination of mortality and driving pressure recorded with conventional ventilation. In blue are studies where there was no difference in mortality between protective strategy and conventional ventilation. In red are studies were the mortality with conventional ventilation was greater than with protective strategy. In most instances, mortality was the highest when driving pressure of the conventional ventilation group was more than 20 cm H$_2$O and it was the lowest when driving pressure of the lung-protective strategy group was less than 15 to 20 cm H$_2$O (Modified from Bugedo and Bruhn) (41).

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References


In mammals, enlargement of the heart during embryonic development is primarily dependent on the increase in cardiomyocyte numbers. Shortly after birth, however, cardiomyocytes stop proliferating and further growth of the myocardium occurs through hypertrophic enlargement of the existing myocytes. As a consequence of the minimal renewal of cardiomyocytes during adult life, repair of cardiac damage through myocardial regeneration is very limited. Here we show that the exogenous administration of selected microRNAs (miRNAs) markedly stimulates cardiomyocyte proliferation and promotes cardiac repair. We performed a high-content microscopy, high-throughput functional screening for human miRNAs that promoted neonatal cardiomyocyte proliferation using a whole-genome miRNA library. Forty miRNAs strongly increased both DNA synthesis and cytokinesis in neonatal mouse and rat cardiomyocytes. Two of these miRNAs (hsa-miR-590 and hsa-miR-199a) were further selected for testing and were shown to promote cell cycle re-entry of adult cardiomyocytes ex vivo and to promote cardiomyocyte proliferation in both neonatal and adult animals. After myocardial infarction in mice, these miRNAs stimulated marked cardiac regeneration and almost complete recovery of cardiac functional parameters. The miRNAs identified hold great promise for the treatment of cardiac pathologies consequent to cardiomyocyte loss.

2) IL-13–induced airway mucus production is attenuated by MAPK13 inhibition.

Alavy YG, Patel CA, Romero AG, Patel DA, Tucker J, Roswit WT, Miller CA, Heier RF, Byers DE, Brett TJ, Holtzman MJ

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Abstract

Increased mucus production is a common cause of morbidity and mortality in inflammatory airway diseases, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. However, the precise molecular mechanisms for pathogenic mucus production are largely undetermined. Accordingly, there are no specific and effective anti-mucus therapeutics. Here, we define a signaling pathway from chloride channel calcium-activated 1 (CLCA1) to MAPK13 that is responsible for IL-13–driven mucus production in human airway epithelial cells. The same pathway was also highly activated in the lungs of humans with excess mucus production due to COPD. We further validated the pathway by using structure-based drug design to develop a series of novel MAPK13 inhibitors with nanomolar potency that effectively reduced mucus production in human airway epithelial cells. These results uncover and validate a new pathway for regulating mucus production as well as a corresponding therapeutic approach to mucus overproduction in inflammatory airway diseases.

Land of hope and dreams
Selection of life science literature
by Marco Confalonieri

Two recent studies opened new exciting avenues of research, respectively in the field of regenerative medicine and new treatment for airways diseases. The first study (1) tested a method to stimulate organ tissue repair without complicated procedures. The second study (2) identified molecular pathways responsible for excess mucus production in airways suggesting new drugs that inhibit that pathway. Giacca’s team at Trieste’s International Centre for Genetic Engineering and Biology (ICGB) screened a library of human miRNAs to identify those inducing cardiomyocytes proliferation. They transfected rat neonatal cardiomyocytes in vitro with different 200 miRNAs and measured proliferation and cell division. Fluorescence microscopy showed that rat neonatal cardiomyocytes proliferated in response to miRNA injection, and 12 days after injection, mouse neonatal hearts were enlarged, but without showing signs of cell enlargement, indicating an increased number of cells in the organ. Importantly, hearts of adult rats administered the miRNAs immediately after induced heart attack showed reduced damage and preserved function compared to the hearts of rats that didn’t receive the therapy. Cardiac cells lose most of their capacity for proliferation and regeneration shortly after birth, making it difficult for hearts to recover from damage later in life. But researchers have identified four human microRNAs that can stimulate proliferation of adult rodent cardiac cells in culture and help protect against damage during heart attack in vivo, according to a study published in Nature. If the microRNAs work similarly in human cardiac cells, they may have potential as regenerative therapies after heart damage.

Holtzman et al. (2) have described the molecular pathway responsible for excess mucus in airway cells and have used that information to design a series of new drugs that inhibit that pathway. As part of the new research, the scientists discovered that a critical signaling molecule, CLCA1, has a special role in the mucus pathway. They showed that CLCA1 allows a protein known as IL-13 to inhibit that pathway. CLCA1 inhibits mucus production in human airway epithelial cells. The same researchers also showed that CLCA1 needs help from an enzyme called MAPK13. Although there were no existing drugs that acted against MAPK13, there were several that inhibit a similar enzyme known as MAPK14, which differs slightly in structure. MAPK13 inhibitor drugs may have a possible role in related conditions with excess mucus production, like COPD, asthma, cystic fibrosis and even the common cold.

1) Functional screening identifies miRNAs inducing cardiac regeneration.


Nature doi:10.1038/nature11739

Abstract

In mammals, enlargement of the heart during embryonic development is primarily dependent on the increase in cardiomyocyte numbers. Shortly after birth, however, cardiomyocytes stop proliferating and further growth of the myocardium occurs through hypertrophic enlargement of the existing myocytes. As a consequence of the minimal renewal of cardiomyocytes during adult life, repair of cardiac damage through myocardial regeneration is very limited. Here we show that the exogenous administration of selected microRNAs (miRNAs) markedly stimulates cardiomyocyte proliferation and promotes cardiac repair. We performed a high-content microscopy, high-throughput functional screening for human miRNAs that promoted neonatal cardiomyocyte proliferation using a whole-genome miRNA library. Forty miRNAs strongly increased both DNA synthesis and cytokinesis in neonatal mouse and rat cardiomyocytes. Two of these miRNAs (hsa-miR-590 and hsa-miR-199a) were further selected for testing and were shown to promote cell cycle re-entry of adult cardiomyocytes ex vivo and to promote cardiomyocyte proliferation in both neonatal and adult animals. After myocardial infarction in mice, these miRNAs stimulated marked cardiac regeneration and almost complete recovery of cardiac functional parameters. The miRNAs identified hold great promise for the treatment of cardiac pathologies consequent to cardiomyocyte loss.
How, when and to what extent is it acceptable, essential or improper to tell the truth, a terrible truth, to a sick person who is unaware of how quickly his or her condition is deteriorating? This dilemma impacts deeply and painfully on the life and quality of life of many people. I speak from experience having had to cope with this painful dilemma personally; the life I shared with Marisa Madieri, my wife for thirty-two years, lead me to share also this ordeal with her. For five years, day after day – the experience of disease and of knowing the disease, the experience of truth when truth is so difficult to accept, and the liberating and devastating power of that truth. Every general problem – as, in this case, informing patients about their condition and the manner and method of delivering information involving the essence of their life and their death – is concretely endured by each person, by each family. That was our experience, too. I say “we” even if the protagonist of this story is Marisa, because it is she who was stricken by cancer, who coped with it, fought it and eventually lost her battle, although she made this victory an arduous one as she confronted and hit back at her enemy step by step, calmly, blow after blow. She is the protagonist, because she lived every aspect of her story with her unceasing need to know the truth and with her questions on how to ask for it, demand it and listen to it – while the others, those who were questioned by her, certainly wondered how they could or should tell such truth. I am just a witness to this story, one who escaped to tell it, as the Bible says. However, given the intensity of our relationship, I was directly involved, too, all the time, second by second, step by step in this problem of requesting and delivering the truth – in this case a harmful and evil truth – and in the way of requesting and providing this information. I can only describe what I lived through, without any claim to constructing a theory. Freud often quoted the Gospel’s phrase “The truth shall make you free”, in which he believed firmly, as I do. Without truth, there is no freedom, no intensity of life; the world cannot be crossed freely. Like any other instrument of salvation, truth is dangerous because it has to do with the essence of life; the great Spanish Jesuit and baroque writer Gracian said that nothing demands more caution than the truth: “tis the lancet of the heart”. If this operation is carried out hastily and driven by a rash albeit generous impulse, it could damage the aorta and kill the patient. It is one thing to love truth, it is quite another thing to be fanatical and obsessive about truth – an attitude against which the philosopher Benedetto Croce often warned. There are the right manners, forms, opportunities and times to tell the truth. If a person is ugly and ungainly, telling them outright is not love for truth. A humane act lies in how the truth is told, on how we care for the person to whom we are telling an unpleasant truth. In this case, too, we tell the truth not because we want to demonstrate our frankness (and that form of frankness that may take the disguise of scientific language); we should not be focused on ourselves, but on the other person. Moreover, we must be aware that given our finite condition, an exchange of absolute truth can never be achieved between two people, even within the closest of relationships. It is impossible to tell all the truth, to convey all its facets and possible shades; this is impossible due to the relative, imperfect and delimited nature of the human condition, and it would be wrong to believe that we can tell all the truth, that we can see everything clearly; as St. Paul maintains, we see “per speculum et in aenigmate”, through a mirror and in mystery, and it would be illusive to see ourselves as omniscient as God. Yet, we can tell almost all the truth, and this almost – if taken to its furthest possible extreme – is our all. When it comes to diseases (or news about diseases) that are serious, distressing and often fatal like cancer frequently is, there are people – Marisa, for example, or other people I was close to in similar circumstances now concluded, for the best or for the worst – who have by their intimate constitution a moral need, an existential, total, almost physical need to know and be told the truth, even a terrible truth about their condition. They need the truth to fight it, but they also need it to be able to live. Not knowing, ignoring, fearing to be deceived, even if for noble reasons, means to move in anguish through the mist, in an ambiguous darkness that erodes their life and destroys any opportunity for joy, pleasure, beneficial forgetfulness and abandonment that can be achieved in spite of the difficult or dramatic experience. However, there are other people – as I have personally seen with other friends stricken by the disease – who do not want to know the truth, who try to hide it in every possible way, who manage not to read and understand even the most evident signs, who misunderstand even the most clearly worded communication. I have seen rational people, even deeply religious people, who would normally analyze reality and try to grasp its meaning, choose to deceive themselves about their tumor even though they were experiencing the burden of the disease day by day, actually manage to deceive themselves until the end. In a situation like this, I think that physicians are faced with a terrible dilemma: telling the truth or not revealing it, hiding it, softening it. As I see it, there is no definite answer: of course, assuming that the protagonist is the patient, that his or her rights must be considered and not general principles and pre-defined behavioral models, and that the physician should pay attention to the patient’s requests, then it is (it should be) more appropriate to lie to a sick person who clearly asks for a lie, because this is what he or she wants and a doctor is there to serve the sick person, not to comply to a strict behavioral rule. It is a question for which I am not able to provide an answer, because a physician’s duty is not only to serve the sick person and
to meet his or her requests, but also to understand the innermost, real needs of the patient. If a person with liver cirrhosis asks for a bottle of whisky which he is really craving for, I do not think a doctor should give it to him, as a doctor knows better than his patient what the true needs of the person and of the patient as a whole are, from a psychological and physical point of view. And yet, there is a terrible implication (a necessary, but nonetheless terrible implication): that another person knows better than you what is best for your life, and has the power to make decisions for you according to his opinion.

As far as I am concerned, this attitude would be inconceivable; I need the truth, like Marisa did. Not because I am a brave person – Marisa was brave, much more than I am, and not only regarding diseases or death – but because truth is like a shield to me, the comfortable warmth of life against my fears or my weaknesses.

Marisa always wanted to be told the truth, and in fact she was always aware of the truth, all the truth, about her condition. I am sure of this, because at each visit I spoke at length with her doctors and I witnessed the conversations she had with them: I know what she asked them and what they replied. When, on a couple of occasions, we went to different hospitals from usual, even abroad, after every conversation with her doctor or doctors, Marisa would write a brief yet detailed and exhaustive description of her condition and of the state of her disease, and then show her report to the doctor to be sure that she had not written inaccuracies. And I can confirm that her report was perfectly in line with what her treating physicians wrote to describe her case to their colleagues. It is not without reason that she was a great writer, whose books are appreciated in many countries, and one of her characteristics was the clear-cut, accurate style, the ability to use the most appropriate words that reflect true poetry.

Throughout the five years of her illness – five years marked by alternating phases, with tumor exacerbations that were very hard to manage followed by long periods of good health and vitality – I have seen this continuing process of truth, as those years were characterized by frequent clinical tests, examinations, procedures, visits with doctors, questions and answers. I could see that this continuous “link”, as I call it, with Marisa’s own truth was an anti-anxiety factor for her, a sort of safety net (the little safety remaining under those circumstances), a sort of guarantee of normality.

Marisa managed, for herself and for the others who lived with her, to keep a “normal” atmosphere until the end; she did not allow the disease (which she fought strenuously) to control all her life, to become a nightmare or a fixed thought that would make her life a black hole. She devoted the necessary time and energy to her fight against the disease, but then she moved on to other things, and even if at times she certainly was scared and sad about her probable death, she never projected her anxiety onto the rest of her life; she did not become neurotic, did not lose her taste for life or interest in the personal and collective affairs of others; she kept her love for the sea and for all other pleasures or passions until the end. Not to mention her loving relationship with our two children, with her friends, and with me. I think that this knowledge of the truth, this gazing into the face of Medusa, this tearing off the mask of a terrible disease and looking it in the eye without fear or humble submission, allowed her to deprive the disease not of its destructive and ultimately triumphant
power, but of its dark nature. And it is darkness that more often and most of all scares us. This attitude was also made possible by the health professionals we were so lucky to encounter: humane people, who showed their wisdom and great ability in telling the truth. Not because they softened it, but because they placed it, frankly but very tactfully, within the general context of her condition, with an emphasis on all possible options available.

To be specific, I can quote the words of one of her doctors, Guido Tuveri. A month or two before the end, when her condition was rapidly worsening with the insurgence of an ascites, he described the likely fatal consequences to us – I was present with Marisa – without complacency, just the bare truth. Then he added “All this can happen an hour from now, in six months’ time or perhaps even never. It is unlikely, most unlikely, that it will never happen, but it is not to be excluded”.

He had told the truth, because he had yes given the bare facts of the new threat, but also because it was quite true that the devastating effect of the ascites could have occurred at any time or even, based on medical history, never – because not only in life itself, but also in those processes which threaten to destroy that life, or do destroy it, nothing can be absolutely certain. Of course, that ‘never’ was improbable compared to the other two possibilities; Dr. Tuveri did not hide the fact that these were more probable, but his tone when enumerating the three possibilities did convey the sense that after all ‘perhaps’ (perhaps never) was faint but not impossible. He was able to tell the unveiled truth in such a way that the dreadfulness of it was clear yet not totally damning.

I believe those words are an example of how a negative and destructive truth can and should be told to a patient; with no omissions but without brutality, with delicacy but without reserve. Perhaps, also, it is only right to clarify the truth, as it does not only regard the disease or the therapy or the psychotherapy, but existence itself; the truth in knowing that we die anyway – even without a fatal illness we are destined to die – but that we also live. Life is a deadly disease, but it is possible to live it happily, without dwelling too much on death, without letting the Grim Reaper cast too long a shadow.

That was how Marisa lived her life in those five difficult years, allowing those around her to live a better life too, and this, I believe, was due to her capacity and need for the truth but also to the ability of those who knew just how to impart that truth.

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Claudio Magris (born April 10, 1939, Trieste) is an Italian scholar, translator and writer. Magris graduated from the University of Turin, where he studied German studies, and has been a professor of modern German literature at the University of Trieste since 1978. He is an essayist and columnist for the Italian newspaper Corriere della Sera and for other European journals and newspapers. His numerous studies have helped to promote an awareness in Italy of Central European culture and of the literature of the Habsburg myth.

Magris is a member of several European academies and served as senator in the Italian Senate from 1994 to 1996. His first book on the Habsburg myth in modern Austrian literature rediscovered central European literature. His journalistic writings have been collected in “Behind Words”, 1978 and “Ithaca and Beyond”, 1982. He has written essays on E.T.A. Hoffmann, Henrik Ibsen, Italo Svevo, Robert Musil, Hermann Hesse and Jorge Luis Borges. His novels and theatre productions, many translated into several languages, include Inferences from a Sabre (1984), Danube: A Sentimental Journey from the Source to the Black Sea (1986), Stadelmann (1988), A different sea (1991), and Microcosms (1997).

His breakthrough was Danube (1986), which is a magnum opus. In this book (said by the author to be an “drowned novel”), Magris tracks the course of the Danube from its sources to the sea. The whole trip evolves into a colorful, rich canvas of the multicultural European history.

Magris won the Bagutta Prize in 1987 for Danube and the Strega Prize in 1997 for Microcosms. He was also awarded the Erasmus Prize in 2001 and a Prince of Asturias Award for Literature in 2004. On July 31, 2006 he won the Austrian State Prize for European Literature. On October 18, 2009 he received the Peace Prize of the German Book Trade during the Frankfurt Book Fair. He received in 2009 the Prix Européen de l’Essai Charles Veillon to honor his work.