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REVIEW

Near-fatal asthma

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ABSTRACT: The prevalence of patients with acute severe asthma appears to be increasing in many countries. In the present review, we summarize data in the literature relating to the prevention and treatment of fatality-prone asthmatics. The underlying assumption is that increased understanding of near-fatal asthma will increase our understanding of the pathophysiology of severe asthma, and lead to interventions that could reduce the mortality rate from asthma.

Recognition of acute life-threatening asthma attacks by any physician is mandatory, since lack of such diagnosis and appropriate treatment has been shown to have devastating consequences. The characteristics that allow identification of asthmatics prone to die in ambulatory settings (*i.e.* previous admissions, type of therapy, *etc.*) as well as the principal precipitating factors of acute near-fatal and fatal attacks of asthma are reviewed. Predisposing factors, such as lack of appropriate treatment, lack of compliance or poor preventive measures are debated.

Finally, we discuss current therapeutic approaches in emergency facilities, based on the major pathophysiological findings in near-fatal asthma.
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Despite our increased understanding of the pathogenesis of asthma and the development of new therapeutic modalities, asthma morbidity and mortality rates remain disturbingly high. One of the difficulties in attempting to reduce mortality from asthma is the paucity of data regarding the pathophysiology of fatal asthma attacks. Since the majority of asthma-related deaths are preceded by rapid and severe deterioration, and many occur outside the hospital setting, such a fundamental question as whether deaths from asthma are due to cardiac arrhythmias, or other factors remains controversial. As a surrogate measure, a number of investigators have examined near-fatal asthma episodes, with the underlying assumption that the pathophysiological mechanisms in patients who die from asthma are similar to those of patients who have near-fatal events. Although there are clearly major limitations with this approach, it provides physiological and biochemical data which can provide clues to the pathophysiology of asthma deaths.

This article will examine a number of issues related to near-fatal asthma, including identification of fatality-prone asthmatics, precipitating factors, pathophysiology and some aspects of treatment.

Definition and incidence

The variable definition of asthma has created difficulties in estimating the overall prevalence of this condition [1], as well as the incidence of well defined near-fatal asthma episodes [2]. RUFFIN *et al.* [3] and SEARS *et al.* [4] defined near-fatal asthma as either respiratory arrest due to acute asthma, or acute asthma with an arterial carbon dioxide tension ($Paco_2$) greater than 6.7 kPa (50 mmHg) and/or an altered state of consciousness. CROMPTON [5] has defined the "catastrophic asthmatic" as that subject who develops a sudden, severe, asthma attack despite receiving treatment which controls symptoms in most other patients. Emphasis is put on the observation that many asthmatics of this type have a rapid decline in ventilatory function before the onset of the catastrophic attack. MOLFINO *et al.* [6] described near-fatal asthma as those episodes in which the asthmatic patient presented with respiratory arrest. In these patients the mean (±SD) $Paco_2$ at the time of the first arterial blood gas analysis was 12.9±4.1 kPa (97.1±31.1 mmHg).

The number of episodes of acute, near-fatal asthma [7], as well as the number of asthma admissions [1], have increased more in recent years than asthma mortality rates [8]. Although a British survey [9] of Emergency Room deaths from medical conditions has pointed out the importance of proper recognition and assessment of life-threatening asthma, the prevalence of this type of episode is largely unknown [1].

The reasons for the increased incidence of severe asthma, despite apparently better management and drugs, are unknown. WEISS [10] has demonstrated that during the period 1982–1986 the admission rates in the United States on a yearly basis, paralleled the mortality rates, but there was a discrepancy in the timing of admissions and deaths.

Table 1. – Recognition of near-fatal asthma

Potentially life-threatening features
(any of the following indicates a severe asthma attack)
Increasing wheeze and breathlessness. Patient unable to complete sentences in one breath or unable to get up from a chair or bed
Respiratory rate≥25 breaths·min^{-1}
Heart rate persistently ≥110 beats·min^{-1}
Peak expiratory flow <40% of predicted or best obtained <200 *l*·min^{-1}
Pulsus paradoxus ≥10 mmHg
Imminently life-threatening features
(any of the following indicates a very severe asthma attack)
Silent chest on auscultation
Cyanosis
Bradycardia
Exhaustion, confusion or unconsciousness

(From [13]).

Whilst admissions reached a maximum in November, deaths were maximum around February. This "uncoupling" of such curves strongly suggests that, at least in the United States, different environmental factors may be involved in the determination of admissions and fatalities from asthma. Whether this is also true in other countries experiencing an increase in asthma morbidity and mortality is not known, but seasonal trends in near-fatal asthma have been identified in other regions of the world [11]. For example ROUX *et al*. [11] found that children with fatality prone characteristics represented a "seasonal" group, lending support to other reports [12] of seasonal, near-fatal attacks of asthma.

An asthma crisis can be easily recognized as life-threatening. Patients at presentation either suffer from respiratory arrest or exhibit severe dyspnoea, difficulty in speaking, use of accessory muscles of respiration and silent chest on auscultation [6]. The findings that indicate a potentially or an imminently life-threatening asthma attack have recently been listed [13–l5], and are presented in table 1. However, near-fatal or fatal attacks can occur in patients who do not have these characteristics. HETZEL *et al*. [16] studied the incidence of episodes of unexpected ventilatory arrest, some of which led to sudden death, in 1,169 consecutive hospital admissions for asthma. Accepted clinical criteria of a severe attack were not present in some of the episodes, which appeared to be mild. In this study [16], and one of our studies [6], the risk of sudden death in some patients could not always be related to the severity of the attack. However, it does correlate with the presence of excessive diurnal variation in peak expiratory flow rates (PEFR) [17]. A number of other studies examining near-fatal asthma, or life threatening asthma [5, 18] clearly demonstrated that these episodes were associated with more severe or more rapid deterioration than that seen in non-life-threatening attacks. This suggests that the time elapsed until the patient receives appropriate medical help may be critical in averting fatal asthma [19, 20] since the severity of the obstruction, albeit not initially present, can worsen suddenly. This rapid deterioration can also occur after the patient is admitted to hospital [16, 21] and sometimes following discharge, even with a forced expiratory volume in one second (FEV_1) >70% [6].

Identification of the fatality-prone asthmatic

A group of asthmatic patients in whom severe and life-threatening asthma attacks do occur frequently was described initially as "brittle asthma" by TURNER-WARWICK [17]. These patients have sudden asthma attacks and often, but not always, have large oscillations in PEFR that respond to bronchodilators. A number of years after this initial description, STRUNK [22] reported the characteristics of patients who have an increased risk of dying from asthma: those suffering from sudden severe overwhelming deterioration of airway function (brittle asthma) and patients who are chronic asthmatics with long-standing episodes of acute asthma. However, there are patients that do not have any of these criteria.

WASSERFALLEN *et al*. [18] obtained similar data reporting that asthmatic patients who suffer from acute severe deterioration and go on to receive mechanical ventilation have similar characteristics to those described by STRUNK [22]. The features in the asthmatic patients that developed sudden asphyxia were different from those in subjects who developed gradual worsening, suggesting different pathophysiological mechanisms leading to these near-fatal events. The similarities in the subjects described by all these authors [5, 17, 18, 22] lend support to the epidemiological studies of asthma deaths [4, 23, 24] which have reported that patients dying from asthma were those who did not reach hospital expeditiously, but also indicate that some deaths appeared to be unavoidable.

The principal characteristics that help to identify fatality-prone asthmatics are summarized in table 2 [14, 15]. Of these, previous occurrence of life-threatening events and hospitalization within the last year are the most specific. Many patients require multiple drugs, have large

Table 2. – Risk and precipitating factors of near-fatal asthma attacks

Risk factors [14]
Age
Ethnicity
Previous life-threatening exacerbation
Hospital admission within the last year
Inadequate general management
Psychological and psychosocial problems
Lack of access to medical care
Precipitating factors
Allergens [12, 18, 25]
Infections [18]
Lack of appropriate assessment or treatment [21, 22, 26]
Air pollution [27–30]
Weather changes [10, 31]*
Emotional upsets [18]
Drugs [32]

*: acute asthma deterioration reported but not near-fatal asthma or fatal asthma attacks.

variations in lung function or associated psychological disorders, but never experience respiratory failure. Furthermore, many asthmatic patients use the Emergency Room as the primary source of care, and have frequent visits to these facilities without this being a major risk factor. Finally, some risk factors, such as ethnicity, may be indicative of socio-economic barriers to adequate medical care. Lack of appropriate control of symptoms and treatment has been shown to be another important factor in worsening asthma leading to death [19, 20, 22, 33]. In this respect, it is possible that an expanding group of patients who do not respond completely (or comply) to conventional therapy represent a great proportion of near-fatal and fatal asthma attacks [20].

Monitoring peak expiratory flow rates on a regular basis [17, 34] has allowed determination of at least two groups of patients who are at risk of near-fatal asthma, by apparently different pathophysiological mechanisms: 1) The first group are patients with severe airflow limitation, who have abnormal physiological responses to their airway narrowing [35, 36]. Among these, one subgroup of patients have a blunted hypoxic ventilatory drive and do not respond to the development of bronchial narrowing and hypoxia with hyperventilation during acute attacks [35]. These patients may present with hypercapnia, even during moderate airways obstruction. A second subgroup of patients do not perceive that they are developing worsening airways obstruction and, thus, may be relatively symptom-free even with severe obstruction [36]. Although these conditions are rare, it is important to identify these groups using appropriate pulmonary function testing, because when they do report symptoms, albeit minimal, they may be at much greater risk of death than other asthmatics.

2) The second group are patients who have marked diurnal variations in peak flow rate [17]. These are patients who may have normal peak flow rates on intermittent testing, but who have large fluctuations in flow, and may develop sudden catastrophic attacks of asthma.

Use of peak flow recording is highly desirable in all patients with moderate and severe asthma, and should be mandatory in all those admitted to hospital in the preceding year, or in whom life-threatening attacks have occurred. Usually, peak flow rates will change prior to the development of symptoms, and detection of these changes can lead to a modification of therapy to attenuate or prevent sudden attacks [2].

Precipitating factors

There are no unique precipitating factors that have been identified as common to near-fatal episodes in all patients [2], but a careful interview of the patient or relatives can usually pinpoint a predominant cause for that particular episode [18]. The prolonged duration of the attack and the time frame over which symptoms develop can give an indication of the development of airflow inflammation, whilst a rapid deterioration suggests predominant airway smooth muscle contraction.

ARNOLD *et al*. [37] prospectively evaluated 261 episodes of acute asthma, and found that 46% began within the 24 h prior to presentation, whereas 13% occurred less than an hour prior to presentation. This period may vary depending on a number of different factors, but clearly these data identify a group of patients in whom rapid and overwhelming deterioration of asthma can exist [5, 6, 18].

Life-threatening asthma is more common in young people [18] but can occur at any age and without gender distribution [5, 6, 14, 22] and, although there are seasonal variations [10], these episodes can occur at any time of the day or any day of the week [6]. However, recently, WEISS [10] has reported that death rates from asthma in the United States are higher during weekends; however, there is no clear explanation for this finding. Possible mechanisms include, more time spent outdoors, reduced patient compliance with therapy, and/or reduced efficacy of Emergency Departments.

Factors that are known to precipitate near-fatal episodes (table 2) are being increasingly recognized [2]. WASSERFALLEN *et al*. [18] found that those asthmatic patients who developed sudden asphyxia had a massive exposure to allergens (3 out of 10), or emotional upsets (4 out of 10), as precipitating factors. By contrast, the majority of patients (15 out of 24) who required mechanical ventilation after gradual impairment of their respiratory function had a respiratory infection as the precipitating factor [18].

The importance of allergens as triggering factors for near-fatal and fatal asthma has been shown, more recently, by O'HOLLAREN *et al*. [12]. These authors have reported that all respiratory arrests due to asthma in their study developed during the Alternaria season, and that these patients had markers of atopy that were significantly higher than the control group (asthmatics without respiratory arrest). These findings lend support to a previous British Thoracic Society study [38], which found that death from asthma was more frequent in atopic than in nonatopic patients, as well as to the results of POLART *et al*. [25] showing that emergency visits for acute asthma occurred more frequently in atopic asthmatics.

Some drugs, such as beta-blockers, aspirin and/or nonsteroidal anti-inflammatories, can also precipitate near-fatal or fatal asthma. PICADO *et al*. [32] reviewed 92 asthmatics who required mechanical ventilation due to asthma, and found that aspirin had been the precipitating factor in 8% of the cases. There are more than 200 compounds that contain aspirin and, in addition, cross reaction with nonsteroideal anti-inflammatories has been reported. These adverse reactions are apparently linked with the ability of such compounds to block the cyclooxygenase pathway, with a shift towards the production of leukotrienes. The exact mechanism(s), however, remain unclear [39]. Unfortunately, even hydrocortisone can provoke severe asthma, requiring intubation, in aspirin sensitive patients [40]. Beta-blockers are well-known to trigger asthma decompensation [41] and have been reported to cause exacerbations that persist for prolonged periods after the withdrawal of the drug, and occasionally to cause death in patients with a known history of reversible bronchospasm.

Recently, concern has been raised regarding the effects of certain foods provoking rare episodes of near-fatal and fatal asthma in children [42]. SAMPSON *et al*. [42] identified six children and adolescents who died of anaphylactic reactions to foods, and seven others who nearly died and required intubation. Of the 13 children and adolescents, 12 had asthma that was well-controlled. The reactions were to peanuts (four patients), nuts (six patients), eggs (one patient), and milk (two patients), all of which were contained in foods such as candy, cookies, and pastry. The six patients who died had symptoms within 3–30 min of the ingestion of the allergen, but only two received epinephrine in the first hour. All patients who survived had symptoms within 5 min of allergen ingestion, and all but one received epinephrine within 30 min.

The role of air pollution in precipitating near-fatal asthma is not yet clear. It is unlikely that relatively low levels of pollutants alone would be able to precipitate an acute severe asthma attack, but thermal inversions with massive accumulation of pollutants are said to be precipitating factors [2, 31, 34]. Thus, pollution might act as an adjuvant factor in certain circumstances. In this regard, MOLFINO *et al*. [27] have recently reported potentiation of the allergic bronchial response when resting asthmatics were exposed to a relatively low level of ozone (0.12 ppm) for one hour prior to the allergen challenge. Notably, these levels of ozone are lower than levels commonly observed in large urban centres in the summer months. Whether these results can be extrapolated to episodes of near-fatal and fatal asthma is not yet known, but reducing the magnitude of the stimulus is an obvious goal, and all known precipitating factors should be minimized or eliminated in an effort to reduce both airway inflammation and responsiveness.

The role of airway hyperresponsiveness in determining the risk of near-fatal and fatal asthma is controversial. In a group of patients who survived respiratory arrests [6, 20] we found increased airway responsiveness to methacholine within the range described as very severe [43] *i.e*. provocative concentration producing a 20% fall in FEV_1 (PC_{20}) <0.1 $mg \cdot ml^{-1}$ when the patients were challenged 8–16 weeks after discharge (table 3). This is in accord with data from WOOLCOCK *et al*. [43] who examined histamine challenges 3–10 weeks after the near-fatal event. However, these results differ from those reported by RUFFIN *et al*. [3] in their longitudinal study of near-fatal asthma. In their patients, the geometric mean histamine PC_{20} of 0.23 $mg \cdot ml^{-1}$ (n=45) obtained after the near-fatal event increased to 0.83 $mg \cdot ml^{-1}$ after appropriate therapy. Although it has been suggested that reducing bronchial hyperresponsiveness to methacholine or histamine may be beneficial in all patients with asthma [2, 43], the importance of this approach in decreasing the likelihood of a fatal or near-fatal asthma attack has not been proved. Nonetheless, recent epidemiological evidence suggests that use of inhaled steroids seems to decrease the risk of near-fatal and fatal attacks of asthma [45].

Table 3. – PC_{20} Methacholine in asthmatics survivors from near-fatal attacks

Patient No.	Visits to ER after discharge	PC_{20} Mch† $mg \cdot ml^{-1}$	Ambulatory treatment
1	4	0.07	T-S-B-P
2	2	0.80	T-S-B
3	1	0.31	T-S-B
4	4	0.04	T-F-P
5	4	0.08	T-F-B-P
6	1	0.04	T-S-B-P
7	0	NSS	S-B-P

ER: Emergency Room; T: theophylline; S: salbutamol; B: beclomethasone; P: prednisone (20–40 $mg \cdot day^{-1}$); F: fenoterol; †PC_{20} methacholine was measured 2–4 months after discharge from hospital (by the method described by COCKCROFT *et al*. [44], using a Puritan Bennet nebulizer that maintained an output of 0.13 $ml \cdot min^{-1}$) and following a period of at least 8 weeks of asthma quiescence. NSS: drop of FEV_1 >20% with nebulized normal saline solution; FEV_1: forced expiratory volume in one second; PC_{20}: provocative concentration producing a 20% fall in FEV_1. (Adapted from [20]).

The possible increased risk of death from asthma due to chronic use of β_2-agonists has been debated in the last few years. There is evidence that suggests that β_2-agonists should be used on demand rather than on a regular basis [46, 47]. The mechanisms by which β_2-agonists would cause asthma deterioration remains speculative, and whether this deleterious effect applies to all β_2-agonists [46, 47], particularly those with long-lasting action such as formoterol and salmeterol, is not yet known. Following the evidence gathered in New Zealand by case-control studies [48–50] a hypothesis was put forward by PAGE [51] who proposed a paradoxical deterioration of asthma with greater use of inhaled β_2-agonists. A study from SEARS *et al*. [46], showing poorer asthma control with regular use of fenoterol, and a study by SPITZER *et al*. [47] supported the "asthma paradox" hypothesis. Although inhaled heparin can block exercise-induced bronchospasm [52], how reducing heparin [51] would cause deterioration of asthma in unclear.

More recently, COCKCROFT *et al*. [53] confirmed that the regular use of salbutamol for two weeks increased the bronchial response to inhaled allergens by unknown mechanism(s). At least in lung or bronchial tissue, down-regulation of β_2-adrenoreceptors due to chronic use of β_2-agonists seems unlikely [54–56] although uncoupling to G-proteins is possible after β_2-stimulation [57, 58]. Increased bronchial responsiveness following use of inhaled β_2-agonists [59, 60] has also been shown, and facilitation of mast cell degranulation has been suggested [53, 61] but the clinical significance and extrapolation to near-fatal or fatal asthma of these studies [51, 54–56, 59–62] awaits elucidation.

Some conclusions with regards to chronic treatment of asthma with inhaled β_2-agonists can be drawn from the evidence available: 1) the vast majority of patients presenting with near-fatal asthma are grossly undertreated with anti-inflammatories; 2) β_2-agonists should be used on demand, but probably not on a regular basis, to achieve asthma control; whether this applies to all asthmatic patients, particularly those who have suffered previous

near-fatal events requires clarification relatively quickly; 3) the apparent deleterious effect of inhaled β_2-agonists in asthma may or may not be true for all β_2-agonists (this also awaits elucidation); and 4) inhaled β_2-agonists are by far the best treatment in acute severe asthma, due to their potent bronchodilator effect.

Pathophysiology

Asphyxia and/or cardiac arrhythmias are thought to be the major pathophysiological events directly implicated in asthma fatalities. Unfortunately, as discussed above, there is a paucity of data in the literature examining the pathophysiology of asthmatic deaths. MOLFINO *et al*. [6] examined the mechanisms by which patients might die during acute exacerbations of asthma, by studying 10 patients who arrived at the hospital in respiratory arrest or in whom it developed within 20 min after admission. These patients had characteristics similar to those described previously for patients at high risk of death from asthma, including a long history of disease in young to middle age patients, previous life-threatening attacks or hospitalizations, delay in obtaining medical aid, and sudden onset of a rapidly progressive crisis [23, 24]. They were found to have marked hypercapnia (mean±SD 12.9±4.1 kPa (97.1± 31.1 mmHg)) and acidosis (pH=7.01±0.11) before mechanical ventilation was begun. In addition, 4 patients had hypokalaemia on admission, although the mean potassium was in the low normal range (3.4±0.3 $mmol \cdot l^{-1}$). Despite the marked severe respiratory acidosis, no patient had a serious cardiac arrhythmia during resuscitation manoeuvres or during hospitalization. Although one patient had atrial fibrillation and another had relative sinus bradycardia, both arrhythmias reverted to sinus rhythm after the initiation of ventilation with hyperoxic gas mixtures. Based on these findings, we conclude that, at least in this group of patients, the near-fatal nature of the exacerbations was the result of severe asphyxia rather than cardiac arrythmias. It is important to note, however, that the patients examined in this study may not be representative of patients who actually die from asthma. Nonetheless, given the severity of their clinical and biochemical data on admission, they certainly had potentially fatal attacks and probably survived because they were fortunate enough to reach a hospital for definitive treatment. Thus, they probably represent a subgroup of patients who die from asthma [21, 23]

Given the findings mentioned above, it is important to review the pathophysiology related to asphyxia, hypoxaemia, and their effect on cardiac arrhythmias. The most common findings in mild to moderate acute asthma are hypoxaemia, hypocapnia and respiratory alkalosis [63]. However, as the severity of the acute attack worsens, severe alterations in gas exchange with hypercapnia and respiratory acidosis with [64] or without metabolic acidosis [65] are generally found [6, 18, 63, 65–68]. The mechanisms by which asphyxia develops are probably multifactorial. MCFADDEN [2] has summarized them as the combination of a certain degree of airway lability, the severity of the pre-existing obstruction, the magnitude of the stimulus applied, and the patient's ability to respond to the alterations of the airway geometry.

Hypoxaemia is closely related to the degree of airway obstruction but is rarely severe (arterial oxygen tension (Pa_{O_2}) <8 kPa (60 mmHg)), although occasionally it can be aggravated by administration of β_2-agonists [68]. Hypoxaemia is the result of severe ventilation-perfusion inequalities, and must be corrected immediately [63]. Respiratory acidosis always indicates a potentially life-threatening asthma attack requiring urgent intervention. It does not, however, necessarily mean that mechanical ventilation is required, since airway obstruction and hypercapnia can be reverted by conventional medical therapy. Given the potentially life-threatening nature of severe disturbances in arterial blood gases, it is also important to examine how much hypoxaemia, hypercapnia and acidosis humans can tolerate, and if present, the effect of anti-asthma therapy (specifically β_2-agonists) on arrhythmias.

A number of reports have suggested that healthy humans can tolerate extremely severe respiratory acidosis if they are adequately oxygenated. FRUMIN *et al*. [69] studied eight human subjects who were subjected to apnoeic oxygenation for periods ranging from 18–55 min during routine operative procedures. All patients maintained their oxygen saturations at greater than 98%. However, at the end of the apnoeic period, Pa_{CO_2} ranged from 17.3–33.3 kPa (130–250 mmHg) and pH ranged from 6.97–6.72. Despite these extremely severe derangements, 6 of the 8 patients maintained normal sinus rhythm, only 2 had occasional premature ventricular contractions, and all recovered without obvious sequelae. Similarly, CLOWES *et al*. [70] studied subjects who breathed gas mixtures containing high concentrations of carbon dioxide. Arterial pH decreased to values as low as 6.8; however, all subjects had uneventful recoveries. Thus, if hypoxaemia is avoided, severe respiratory acidosis seems to be well-tolerated. However, it is important to point out that patients outside the hospital setting who develop severe respiratory acidosis are likely to be hypoxaemic, since they are not breathing oxygen-enriched gas mixtures. Assuming a Pa_{CO_2} of 80 mmHg (10.6 kPa), a "best - case" scenario of an alveolar-arterial oxygen gradient ($(A\text{-}a)_{O_2}$) of only 10 mmHg (1.3 kPa) and a normal respiratory quotient of 0.8, based on the alveolar gas equation, the Pa_{O_2} would be 40 mmHg (5.3 kPa). This, along with the right-shift in the oxyhaemoglobin dissociation curve would be indicative of very severe hypoxaemia.

The effect of hypoxaemia on cardiac arrhythmias has been clearly demonstrated in dogs by COLLINS *et al*. [71] who showed that cardiac disturbances were induced by lower doses of isoprenaline if hypoxaemia was present. On the other hand, STEINHART *et al*. [72] have reported that severe hypercapnia (>53.3 kPa or 400 mmHg) in dogs resulted in heart failure, which could be reversed by administration of catecholamines or worsened by administration of beta-blockers. Taken together, these studies suggest that hypoxaemia is the principal alteration to be corrected.

In humans with acute severe asthma (not life-threatening), DOUGLAS *et al*. [73] did not report detectable

cardiac arrhythmias in the presence of mild hypoxaemia after administration of 1.25, 2.5 or 5 mg of salbutamol nebulized in air. Similar results were obtained by BREMNER *et al*. [74] in mildly hypoxic healthy volunteers treated with 800 μg of inhaled fenoterol. Cardiac arrhythmias may still occur despite adequate oxygenation, because of direct cardiotoxicity of the drugs or because of hypokalaemia [34, 75]. Hypokalaemia can be the result of anti-asthma therapy [76, 77] and can be associated with muscle weakness [78], but its role in acute severe asthma awaits elucidation.

Excess bronchial muscle shortening appears to be the cause of sudden decompensation and death in some cases of asthma. This is likely to be true in asthmatics who die of severe airway obstruction, in whom no mucous plugging or submucosal oedema of the airways is found postmortem [79]. BAI [54] has reported an increased maximal response to contractile agonists, such as histamine, electric field stimulation and acetylcholine, in airway smooth muscle obtained from patients who died from asthma attacks. In addition, this author reported a diminished relaxation response to β_2-agonists and theophylline in these tissues. Whether this is a result of a change in the smooth muscle activation, in the loading of the airway muscle, or in the smooth muscle shortening is not yet clear [79].

On the other hand, patients who suffer from status asthmaticus often have airways filled with mucous plugs. The problem in these cases of near-fatal and fatal asthma may be the excessive inflammatory process in the submucosa and lumen of the airways, that results in severe airway narrowing when coupled with normal or excessive airway smooth muscle contraction [79]. Recently, SUR *et al*. [80] reported that patients dying with crises of less than 1 h duration had significantly more neutrophils in the airway submucosa and less eosinophils, when compared to patients dying after crises of more than 2.5 h. These findings lend immunohistological support to mechanisms possibly related more to overwhelming airway smooth muscle contraction, than to excessive airway inflammation.

Hyperinflation is a constant finding in acute asthma, as a result of the prolonged time constant of the respiratory system leading to a positive alveolar pressure at the end of expiration, a phenomenon referred to as intrinsic PEEP (PEEPi) or auto-PEEP [81]. The magnitude of auto-PEEP and alveolar pressure is directly related to the minute ventilation, the mechanical time constant of the respiratory system, and is inversely related to expiratory time [81]. There is also regional hyperinflation due to inhomogeneity in the time constants of various alveolar regions. These factors increase the risk of barotrauma and haemodynamic deterioration and have important implications regarding mechanical ventilation of asthmatic patients, as will be described below. In addition, hyperinflation has been shown to be an important factor producing respiratory muscle impairment in asthma [82, 83]. Although it appears that muscle fatigue does not play an important role by itself during acute bronchospasm [82], one of the beneficial effects of beta-agonists in acute asthma may be related to the reduction of lung volume, which in turns improves diaphragmatic function and endurance [83].

Treatment

Although the initial therapeutic measures to treat acute asthma may vary from one country to another, [13–15], all of them are aimed at avoiding mechanical ventilation by producing immediate bronchodilatation. Patients presenting with life-threatening asthma who are conscious must receive immediate continuous oxygen-impelled nebulizations with high doses of β_2-agonists, and intravenous steroids. The latter do not act immediately, and it is precisely for this reason that they should be administered as soon as possible.

The use of intravenous theophylline is controversial. Whilst the overall population of asthmatics may not benefit from this drug as much as from inhaled β_2-agonists, some individuals exhibit a degree of bronchodilatation that justifies its use to alleviate extremely severe bronchoconstriction and even to improve prognosis after the attack [84]. If it is used, the dose must be adjusted according to the maintenance dose of oral theophylline [13, 84]. Alternatively an intravenous β_2-agonist may be preferred in this circumstance [13]. Inhaled ipratropium is another additional therapy (to inhaled β_2-agonists and intravenous steroids) that is used in many countries to increase or accelerate the relief of airway obstruction. In this respect, inhaled ipratropium has been shown to offer a significant bronchodilatator effect, providing it is combined with inhaled β_2-agonists [85, 86].

Many patients with severe asthma respond satisfactorily to these measures in a few hours; however, no patient recovering from a life-threatening event should be discharged [6] before a monitoring period in hospital of at least 24 h. Home monitoring may be sufficient for most patients discharged from the emergency room [8, 87] but patients with life-threatening events can have sudden overwhelming fluctuations in pulmonary function and need close supervision in hospital [17]. Criteria for hospital admission of patients with acute severe asthma treated at the Emergency Department have recently been summarized [13–15].

Mechanical ventilation

Occasionally, respiratory arrest and/or unconsciousness [6], or development of confusion and agitation in addition to a rising Pa_{CO_2} despite aggressive conventional therapy, are indications for endotracheal intubation and mechanical ventilation.

Because of the considerations described previously with respect to barotrauma, in the last few years there has been a change in the approach to ventilating these patients, based on the concept of controlled mechanical hypoventilation [88]. The aim of this technique is to restore normal oxygenation, whilst minimizing dynamic hyperinflation, and alveolar pressures. The approach consists of

ventilation with small tidal volumes, low respiratory rates, and relatively high inspiratory flow rates [89]. Sedation and paralysis of the patient are required, and the initial ventilatory settings are adjusted as needed to maintain an inspiratory peak airway pressure of less than 35 cmH_2O and a Pa_{O_2} of more than 10.6 kPa (80 mmHg). This approach is probably the reason for the decrease in mortality in mechanically-ventilated asthmatics in the last decade [6, 88] and, indeed, in some studies the mortality rate of ventilated patients has been zero [6, 18, 88, 90]. This technique implies the acceptance of temporary hypercapnia and does not appear to prolong the duration of mechanical ventilation [18, 88, 90]. Recently, WILLIAMS *et al*. [91] examined the factors associated with hypotension, pulmonary barotrauma and cardiac arrhythmias in all patients admitted to their Intensive Care Unit (ICU) with severe asthma. They found that hypotension and barotrauma occurred at a much higher rate in patients who had greater dynamic hyperinflation, as quantified by the end-inspiration lung volume (V_{EI}) above functional residual capacity (FRC) [91]. These issues have recently been addressed in a Consensus Committee document on mechanical ventilation [92].

Follow-up and preventative measures

Once patients suffering from life-threatening asthma attacks are discharged, they should be enrolled in a special follow-up programme. Both rapid admission to specialized services [93] and compliance to this type of control appear to reduce mortality [20]. When the outcome of patients surviving near-fatal attacks [6] was tracked [20], we found that those subjects who complied with regular follow-up had a better survival rate than the ones who did not comply with such control. The study comprised 18 months of monthly follow-up visits in 12 patients who had been discharged following admission with near-fatal asthma attacks [20]. Only 7 of the 12 subjects consented to a tight monthly follow-up. Whereas 2 of the non-compliant group died within 18 months of discharge, none from the compliant group died within that period. Although the latter group was clearly a biased one, consisting of patients who did not agree to close follow-up, and thus may not have sought timely medical help or take their medications properly, this study lends support to previous reports regarding the benefits of intensive follow-up of these patients [93]. Moreover, at the present time, it appears that the most reasonable approach to use in patients discharged after near-fatal events is to provide adequate doses of inhaled anti-inflammatory therapy, regular peak flow monitoring [94, 95] and good communication with the physician or specialized service during the follow-up [2, 20, 93]. This general approach has been shown to be extremely efficacious in the self-admission centre in Edinburgh [93]. Measures to be taken by the patient during an acute attack of asthma and *en route* to hospital, as well as well-defined action plans, have recently been published following international consensus [15]. Patients and carers must be educated regarding these action plans.

Conclusions and recommendations

Near-fatal asthma is the penultimate step in patients with catastrophic asthma [6]. Identification of fatality-prone subjects and recognition of life-threatening features with understanding of its pathophysiology, may lead to further reduction of these episodes [80]. The predominant pathophysiological findings are the result of severe airway obstruction with severe alterations in acid-base status [6]. Respiratory arrest and coma upon admission, or severe dyspnoea with silent chest on auscultation and use of accessory muscles of respiration constitute the basic clinical picture [13]. Respiratory acidosis associated with hypoxaemia and metabolic acidosis are the result of gross ventilation-perfusion alterations, and hypoxaemia is the principal factor that must be immediately corrected. Cardiac arrhythmias are rarely present [6]. Albeit difficult [6, 17], every effort must be made by the physicians to identify the principal inciter(s) of a life-threatening attack of asthma. Airway inflammation is not always the predominant finding in acute onset near-fatal and fatal asthma [80].

Conventional treatment of acute attacks with high doses of inhaled β_2-agonists, oxygen and intravenous steroids are the first therapeutic measures in any severe asthma attack. Physicians should be aggressive under these circumstances, since severe asphyxia as the result of massive airway obstruction seems to be the important determinant of death during these episodes [6]. Mechanical ventilation is occasionally required as a last resort and, if instituted, it should be controlled to avoid barotrauma [92].

Objective measurement of pulmonary function (PEFR or FEV_1) must be obtained to monitor treatment in hospital as soon as the patient's condition allows. Admission or in-hospital supervision for at least 24 h is desirable in these patients in whom relapses can be fatal. Upon discharge, patient education, close patient-physician communication, anti-inflammatory drugs, inhaled β_2-agonists on demand, and regular peak flow monitoring are mandatory.

It has been determined that the inability by the patient or the physician to recognize asthma severity is a major factor in near-fatal and fatal asthma attacks [96]. However, since admission rates from asthma have increased more dramatically than death rates, one can speculate that patients are not dying because they are correctly diagnosed and admitted. Clearly, further studies are required to elucidate the multitude of poorly understood factors that seem to be playing a role in the increasing asthma morbidity and mortality rates [7, 10, 27, 47, 51, 53].

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