Acute lung injury following lung resection: is one lung anaesthesia to blame?

Significant developments in the multiple disciplines of anaesthesia, pharmacology, radiology, and cardiorespiratory physiology have established the foundations for the practice of modern thoracic surgery. The introduction of endobronchial intubation and one lung anaesthesia for thoracic surgery in the 1930s by Gale and Waters\(^1\) in the USA and Magill\(^2\) in the UK enabled the lung on the operated side to be excluded from tidal ventilation, thereby preventing contamination of the contralateral lung by secretions and diminishing the amount of surgical manipulation during the procedure. Together with the introduction of muscle relaxants and techniques of controlled ventilation, facilitated by the advent of double lumen endotracheal tubes, the hazards previously associated with spontaneous ventilation in an open hemithorax were virtually eliminated. At the turn of the century the main indications for thoracic surgery were empyema and tuberculosis. In the post-war period the development of antituberculous chemotherapy, together with the discovery of penicillin in 1945, revolutionised the treatment of infective lung disease and, coupled with the increase in cigarette consumption, infective pathology was superseded by malignancy as the main indication for pulmonary resection.

**Complications of contemporary thoracic surgery**

In current practice, preoperative preparation by formal evaluation of pulmonary function\(^3\) and intensive postoperative care (particularly physiotherapy) are vital in minimising the most frequent postoperative respiratory complications of atelectasis and pneumonia\(^4\) which may be life threatening in this setting. However, conventional parameters used in preoperative assessment have not been shown to be of predictive value in identifying those patients at risk of developing the potentially fatal complication of – what is termed in the North American literature – “postpneumonectomy pulmonary edema” (PPE).\(^6\)

PPE is uncommon and the literature describing its incidence and outcome is sparse. Typically, it presents clinically as acute lung injury following lung resection. Apart from acute respiratory distress, physical examination and signs may be unremarkable in the early stages. The most striking feature is rapidly progressive and refractory arterial hypoxaemia. Radiological changes often lag behind the frequently devastating clinical decline and range from diffuse interstitial infiltration to florid alveolar oedema. To differentiate between PPE and hydrostatic oedema, guidelines suggest that a pulmonary artery occlusion pressure of less than 18 mm Hg is required. However, the pulmonary artery occlusion pressure may be falsely low following pneumonectomy\(^7\) and not accurately representative of pulmonary capillary hydrostatic pressure. Distinguishing PPE from postoperative pneumonia may be difficult as a low grade pyrexia may be apparent in both. An absence of positive blood and sputum cultures favours PPE but is not exclusive and the two may coexist.

The overall incidence of PPE is estimated to be 4–5%\(^8\) although most reports have been isolated cases or small studies. Thus, out of a yearly total of 3315 lung resections for malignancy in the UK (pneumonectomy and lobectomy only), PPE might complicate about 160 cases.\(^9\)

The associated mortality is extremely high and exceeds 80% in most series.\(^11\) Statistically significant risk factors such as right sided pneumonectomy and intravenous fluid overload were identified in early studies\(^12\) but have received conflicting support in more recent reviews.\(^8\)

In its extreme form PPE follows a clinical and histological course indistinguishable from the acute respiratory distress syndrome (ARDS),\(^13\) representing one of its many and diverse aetiologies. The diagnosis of ARDS remains one of exclusion, and therapeutic intervention is largely supportive. The pulmonary pathology of ARDS is characterised by increased permeability of the alveolar capillary membrane resulting from diffuse damage to the alveolar capillary unit. Many patients who do not meet the recently defined diagnostic criteria for ARDS may meet those specified simultaneously as defining acute lung injury (ALI).\(^15\)

Of the conditions associated with ALI/ARDS and the many individuals at risk,\(^16\) only a few develop the full blown syndrome. Far more patients suffer from a lesser degree of lung injury, but recent evidence suggests that even these and those individuals at risk of developing ARDS display signs of a loss of endothelial integrity.\(^17\) Altered pulmonary endothelial permeability has therefore emerged as the characteristic hallmark of all forms of ALI/ARDS.

**Functional significance of PPE**

Endothelial damage and loss of integrity has important functional implications since the endothelium is an important regulatory body in pulmonary and systemic vascular control.\(^18\)\(^19\) Endothelium-derived relaxing factor, recently identified as nitric oxide (NO),\(^20\) is released continuously under resting conditions and has been shown to be an important messenger molecule involved in the physiological regulation of basal vessel tone and tissue blood flow,\(^21\) ventilation/perfusion matching and airway relaxation,\(^22\) and the immune response. The endothelium has also been shown to modulate the phenomenon of hypoxic pulmonary vasoconstriction (HPV),\(^23\)\(^24\) a unique physiological control mechanism distinguishing the pulmonary from the systemic circulation (which dilates in response to hypoxia).\(^25\)\(^26\) HPV is an important adaptive mechanism that serves to divert blood away from hypoxic alveoli so that matching of ventilation and perfusion is improved and arterial hypoxaemia minimised. The complex mechanism underlying HPV may be mediated by a critical change in the balance of locally produced vasodilators, in particular NO, and vasoconstrictors such as endothelin.\(^27\) Significantly, HPV is lost in patients with ALI/ARDS, contributing to an increase in shunt fraction and resulting in refractory hypoxaemia.\(^28\) It is therefore likely that PPE represents the severe end of a spectrum of ALI, the effects of pulmonary endothelial damage ranging from mild respiratory impairment to the overwhelming pulmonary oedema that characterises ARDS. The incidence and long term significance of milder forms of PPE after thoracotomy are not known. At best, mild postoperative lung injury may necessitate a prolonged stay in an expensive critical care or high dependency facility. At worst, it could compromise maximal potential respiratory performance secondary to the effects of the inflammatory insult on
“healthy” lung tissue previously unaffected by the primary disease process.

The closest approximation to PPE recognised clinically is probably the lung injury that follows surgery involving cardiopulmonary bypass, which is detectable in all such patients and in those undergoing lung transplantation. The pathophysiology of these conditions bears close similarities to that of pulmonary resection, in that all these procedures involve collapse and subsequent re-expansion of the lung and therefore a period of relative ischaemia followed by reperfusion. It is probable that all patients undergoing lung resection may suffer a similar acute lung insult, further exacerbated by hyperfusion of residual lung tissue, a difference which may account for the less frequent and less fatal occurrence of a clinically recognisable disorder in the former situations. The lung injury attributable to ischaemia-reperfusion following lung resection may be manifest along a spectrum from low grade, transient, and clinically insignificant to one of frank ARDS/PPE with associated multisystem organ failure and attendant high mortality.

Pathophysiology of PPE

The pathophysiology of PPE is not fully understood and the underlying mechanisms have not been fully elucidated. The relative importance of increased pulmonary capillary hydrostatic pressure secondary to altered haemodynamics in a restricted pulmonary vascular bed and excessive fluid overload, balanced against a reduction in the compensatory mechanism of lymphatic drainage, is largely undetermined. Although all factors may contribute to some degree, recent experimental and clinical evidence suggest that altered alveolar capillary membrane permeability plays a much more significant part.

Although the exact mechanism of endothelial damage and altered permeability complicating pulmonary surgery is unknown, the phenomenon of ischaemia-reperfusion mediated by reactive oxygen species is implicated. Ischaemia-reperfusion injury is a complex phenomenon, the consequences of which may lead to both local and distant tissue damage. Interruption of the blood supply and therefore oxygenation of a tissue results in anaerobic metabolism and an increased lactic acid concentration causing acidosis and altered enzyme kinetics. Cellular homeostasis is altered resulting in reperfusion, interstitial oedema and, ultimately, cell destruction mediated by depletion of ATP and failure to maintain necessary ionic gradients across cell membranes. Although reperfusion and the restoration of the blood and oxygen supply is a prerequisite for tissue recovery in order to restore energy supply and remove toxic metabolites, paradoxically reperfusion can result in further local tissue injury and may mediate systemic effects through the return of toxic metabolites to the circulation. This paradoxical injury has been shown to be influenced by the interaction of endothelial-released factors, reactive oxygen species and neutrophils. Locally produced endothelial factors affect vascular reactivity, permeability, and neutrophil function. Activation and adhesion of neutrophils occurs with the release of granular proteases and reactive oxygen species and results in local tissue damage mediated by lipid peroxidation of the cell membrane. Evidence suggests that the initial inflammatory event during ischaemia-reperfusion is initiated by neutrocyte-derived reactive oxygen species resulting in subsequent adhesion and activation of neutrophils with alteration to the local microvascular permeability and amplification of reperfusion injury via granule depletion of reactive oxygen species and release of cytotoxic enzymes. In the isolated rat lung preparation ischaemia-reperfusion injury mediated by reactive oxygen species and their effects on the endothelium in arteriole of HPV and increased vascular permeability has been shown to occur. In the pulmonary reimplantation response to single lung transplantation there is evidence to suggest that the membrane permeability oedema that occurs is related to ischaemia-reperfusion injury to the graft.

In pulmonary surgery involving single lung ventilation ischaemia-reperfusion almost certainly occurs. During one lung anaesthesia relative ischaemia of the ipsilateral lung is followed by re-expansion and reperfusion of the remaining lung tissue following lobectomy, and by hyperperfusion of the contralateral lung following pneumonectomy. It is therefore likely that all patients undergoing pulmonary surgery involving single lung ventilation are subjected to conditions under which the risk of developing lung injury is increased. Factors that determine the degree of endothelial damage produced in any individual patient, and the subsequent effect on the release of endothelially released vaso-active factors, particularly NO, and their influence in modulating HPV, have yet to be determined. Whether NO plays a causative or protective part in the aetiology of lung injury is also not clear. At the molecular level NO may react with reactive oxygen species to produce other powerful and toxic oxidants; conversely, exogenous inhaled NO has been shown to be of therapeutic value in patients with lung injury by selectively dilating the pulmonary vasculature and improving ventilation/perfusion mismatch and oxygenation.

Conclusion

Further examination of the parameters of oxidative stress, perioperative changes in the vasoregulatory mechanisms of the pulmonary circulation, and characterisation of the endothelial insult that probably occurs in all patients undergoing lung resection is necessary if the operative conditions under which lung surgery is carried out are to be optimised. Perhaps then, more insight might be gained into how to improve preservation of lungs for transplantation and how to protect the lung from significant injury following resection.

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LETTER TO THE EDITOR

Lung disease induced by drug addiction

In their editorial on the pulmonary consequences of illicit drug use (November 1995; 50:1125–7) Benson and Bentley draw attention to a complication of cocaine inhalation. Pneumothorax, pneumomediastinum, and pneumopericardium have also been described, however, in association with the use of marijuana,1 a drug that is more widely used in England and Australia than cocaine. The mechanism of injury is thought to be caused by coughing while breath-holding in inspiration, or by performance of a Valsalva manoeuvre. The latter has been recognised as a cause of spontaneous pneumomediastinum since the 17th century.2 We have found it rewarding to seek a history of illicit drug use in young adult patients presenting with spontaneous pneumothorax.

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The incidence of lung cancer has risen rapidly in recent years. The growing importance of the disease is illustrated by a great number of books on the topic. It is therefore not surprising to encounter a new book presenting state-of-the-art knowledge on lung cancer.

This book was written by an author with a 25-year library of knowledge and experience. The author is dedicated to providing a comprehensive and updated overview of the latest developments in lung cancer research. The book covers a wide range of topics, including epidemiology, genetics, pathology, diagnosis, and treatment. The writing style is clear and concise, making it easy to follow.

The book is divided into four parts, each covering a different aspect of lung cancer. The first part focuses on the epidemiology and genetics of lung cancer, providing an overview of risk factors and the biological mechanisms underlying the disease. The second part covers the diagnosis and staging of lung cancer, with chapters on imaging techniques, bronchoscopy, and biopsy. The third part delves into the treatment options, including surgery, chemotherapy, and radiation therapy. The final part discusses the psychosocial aspects of lung cancer, including coping strategies and support systems.

Overall, the book provides a comprehensive and up-to-date account of the current state of knowledge in lung cancer research. It is a valuable resource for professionals in the field, as well as for patients and their families. The detailed annotations and references included at the end of each chapter make it easy to follow the latest developments in the field.

At the end of the book, there is an extensive bibliography with over 1500 references, making it a valuable resource for further reading and research.

In conclusion, Lung Cancer is a well-written and comprehensive book that provides an in-depth overview of the latest developments in lung cancer research. It is a valuable resource for professionals in the field, as well as for patients and their families. The detailed annotations and references included at the end of each chapter make it easy to follow the latest developments in the field.

NOTICE

British Association for Lung Research

The Summer Meeting of the British Association for Lung Research will be held at the Biological Sciences Building (Boodle Building), University of Southampton on 19–20 September 1996. For further information contact Mrs Chris Vincent. Telephone: 01703 796891. Fax: 01703 701771.

CORRECTION

In the editorial entitled “Acute lung injury following lung resection: is it lung an-
anesthesia to blame?” by E A Williams, T W Evans and P Goldstraw which appeared on pages 114–6 of the February issue, the order of the authors should have been E A Williams, P Goldstraw and T W Evans. The publishers apologise for this error.

Asthma and Outdoor Air Pollution. Department of Health: Committee on the Medical Effects of Air Pollutants (Pp 195; £21.00). UK: HMSO Books, 1995. 0 11 321958 X.

Air pollution has been a hot topic in the media in the last few years and has been blamed for many respiratory problems. Doctors are often drawn into the debate by patients wishing to know whether they are victims of air pollution. It has been difficult for the doctor to find reliable evidence to reply to the patient. Help is now at hand in the form of this book which reports the extensive and considered deliberations of the Committee on Medical Effects of Air Pollutants and their relationship to asthma. The book contains a wealth of information and is ordered into sections addressing relevant questions such as whether (1) there are plausible mechanisms, (2) short term exposures can worsen asthma, (3) ambient air pollution induces asthma, (4) changes in asthma prevalence correspond to changes in air pollution, and others.

Each chapter comprises a critical discussion of all the studies that address the topic and assesses what can be deduced from those studies. Each section is fully referenced and there are many helpful tables and figures. Finally, the conclusions set out what can be inferred from the present knowledge.

The committee producing this work consisted of a mix of clinicians and basic scientists with strong academic credentials which are reflected in the logical approach to the subject, the considered analysis of the evidence, and the dispassionate conclusions they have reached. Although this book is not bedtime reading, it is not difficult to read and will enable doctors and other health professionals to answer the questions posed by their patients. A copy should be in every medical library and any doctor interested in pollution will want their own copy.