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 in the USA and Magill 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treatment of infective lung disease and, coupled with the increase in cigarette consumption, infective pathology was superseded by malignancy as the main indication for pulmonary resection.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 and intensive postoperative care (particularly physical therapy) are vital in minimising the most frequent postoperative respiratory complications of atelectasis and pneumonia 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 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.10

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 but have received conflicting support in more recent reviews.8,14

In its extreme form PPE follows a clinical and histological course indistinguishable from the acute respiratory distress syndrome (ARDS),15 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, 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),23–25 a unique physiological control mechanism distinguishing the pulmonary from the systemic circulation (which dilates in response to hypoxia).26–28 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.29 Significantly, HPV is lost in patients with ALI/ARDS, contributing to an increase in shunt fraction and resulting in refractory hypoxaemia.30 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.31 32 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.33 34

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 cell injury, interstitial oedema and, ultimately, cell death. The mechanisms for ischaemia-reperfusion injury are multiple and complex. A variety of mediators can be implicated in the pathogenesis of lung injury following PPE. Reperfusion injury mediated by reactive oxygen species and their effects on the endothelium in alteration 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.35

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 vasoactive 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;36 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.41

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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P GOLDSTRAW

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*Thorax* 1996 51: 114-116
doi: 10.1136/thx.51.2.114

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LETTER TO
THE EDITOR

Lung disease induced by
drug addiction

In their editorial on the pulmonary con-
sequences of illicit drug use (November 1995;
50:1125-7) Benson and Bentley draw at-
tention to the complications of cocaine
inhalation. Pneumothorax, pneumo-
mediastinum, and pneumopericardium have
also been described, however, in association
with the use of marijuana, a drug that is
more widely used in England and Australia
than cocaine. The mechanism of injury is
thought to be by coughing while breath-
holding in inspiration, or by performance of a
Valsalva manoeuvre. The latter has been
recognised as a cause of spontaneous pneu-
mediastinum since the 17th century. 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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1 Miller WE, Spiekerman RE, Hepper NG. Pneu-
mediastinum resulting from performing
Valsalva manoeuvres during marijuana smok-
2 Feldman AL, Sullivan JT, Passero MA, Lewis
DC. Pneumothorax in polystyrene-abusing
marijuana and tobacco smokers: three cases.
3 Munsell WP. Pneumomediastinum. JAMA

BOOK NOTICES

Lung Cancer. Desmond N Carney. (Pp 280;
£60.00). London: Arnold, 1995. 0-340-
56759-7.

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 is a multiauthored work. In its
280 pages it covers numerous recent advances
in our knowledge of lung cancer, is well ed-
ited, and has a pleasant uniformity of style.
It is divided into two parts. The first contains
chapters on chemoprevention, pathology, and
staging of lung cancer. Four chapters - the
best in my opinion - are focused on the
management of the disease. The preparative
therapy and surgery, as well as the chemo-
therapy and radiation for lung cancer, are
described in a thorough and generally well
referenced fashion. There are also two well
written chapters on cytokines and biological
response modifiers in the treatment of lung
cancer. The second part addresses the biology
of the disease. In its seven chapters the latest
aspects about the neuropeptide growth fac-
tors, monoclonal antibodies and molecular
and genetics of lung cancer are thoroughly ana-
lysed.

In general all of the chapters are well written
with tables and figures and an extensive up
to date bibliography. Controversial topics are
well presented and the areas in which our
knowledge is incomplete are indicated. The
authors emphasise the need for ongoing
multicentre clinical trials to resolve con-
traversial issues. The book also provides
valuable summaries of a vast amount of knowl-
dge pertaining to virtually every aspect of
lung cancer.

Because each chapter is written by a differ-
ent author, there is - as in most multiauthored
books - a heterogeneity in the depth at which
the topics are covered; for example, very little
is provided on the radiology of non-small
lung cancer. Nevertheless, this book is well
written, clearly organised, and comprehensive
in scope. It is useful for anyone who is in-
volved in the treatment and care of patients
with lung cancer. - AR.

Atlas of Human Cross-Sectional An-
tomy. 3rd Edition. Donald R Cahill, Mat-
thew J Orland, Gary M Miller. (Pp 312;
£122.50). USA: Wiley-Liss Inc, 1995. 0 471
91653 3.

Atlases of human anatomy have undergone
a renaissance thanks to cross-sectional imaging
techniques, notably computed tomography
(CT) and magnetic resonance imaging
(MRI), which provide an alternative view
to beautiful but sometimes arcane dissections.

In the third edition of this handsome atlas
attention is again focused on the fine detail
of line drawings of transverse sections of
cadavers. At a rough estimate, there is four
times as much labelling on the meticulous
line drawings than on the cross-sectional pho-
tographs or MRI images. Despite the fact
that the CT images can no longer be regarded
as state-of-the-art (as the authors ac-
knowledge), there is more anatomical detail
in these images than the labelling suggests.

Perhaps this is a deliberate ploy to get readers
to find out what the unlabelled bits and pieces
are by looking at the line drawings. The most
surprising discovery is the cursory coverage
of the bronchial tree (for example, the right
middle lobe bronchus does not appear in the
index or in any illustrated section). There is
no attempt to tackle the three-dimensional
puzzle of the bronchopulmonary seg-
mental anatomy. Indeed, the CT sections of
the thorax are merely cut-outs of the
mediastinal detail. For readers of Thoras this
must be regarded as a major disadvantage; it
is difficult to be impressed with rudimentary
labeling that is confined to the lobes of the
lungs. Overall, the treatment of the thorax is
slight - 10 pages devoted to the knee versus
nine pages covering the chest seems un-
balanced. Nevertheless this is a fine example
of an atlas that takes full advantage of cross-
sectional imaging and can be considered a
more than adequate refresher of anatomy,
particularly that outside the thorax. - DMH

Thoras 1996;$1556

Air pollution has been a hot topic in the
media in the last few years and has been
blamed for many respiratory problems. Doc-
tors are often drawn into the debate by
patients wishing to know who 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 mech-
nisms, (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 con-
sisted 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
disable 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. - MGP

NOTICE

British Association for
Lung Research

The Summer Meeting of the British Associa-
tion for Lung Research will be held at the
Biological Sciences Building (Bentleywood),
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 one lung an-
esthesia 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.