HKCA Bulletin

An official publication of
The Hong Kong College of Anaesthesiologists
香港麻醉科醫學院期刊

HKCA BULLETIN 香港麻醉科醫學院期刊

VOLUME 16 • NUMBER 2 • JULY 2007

Volume 16 Number 2 July 2007

Contents

The Editorial Board (2005-2007)

Email: mtvchan@cuhk.edu.hk
Address: Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong
Phone: 2632 2736
Fax: 2637 2422

Disclaimer

Unless specifically stated otherwise, the opinions expressed in this publication are those of the author's personal observations and do not necessarily reflect the official policies of the Hong Kong College of Anaesthesiologists.

Typeset and printed in Hong Kong by the ***Best e-Publishing Group Limited***

博思電子出版集團有限公司
BEST e-PUBLISHING GROUP LIMITED

Guide for Authors
The Bulletin of the Hong Kong College of Anaesthesiologists

Manuscripts should be sent to:
Dr Matthew Chan, Editor-in-Chief, *Bull HK Coll Anaesthesiol*
c/- Department of Anaesthesia and Intensive Care,
The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, NT. E-mail address: mtvchan@cuhk.edu.hk
Phone: (852) 2632 2894; Fax: (852) 2637 2422

About the Bulletin of the Hong Kong College of Anaesthesiologists
The Bulletin is an official publication of the Hong Kong College of Anaesthesiologists (HKCA). Acceptance of manuscripts submitted to *Bull HK Coll Anaesthesiol* is based on significance, originality, and validity of the material presented. Types of submissions accepted include reviews, clinical and laboratory investigations, case reports, technical communications, letter to the editor and other special articles describing the historic, social and current trends in anesthesia, intensive care and pain medicine.

Manuscript Preparation and Submission
Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals, www.icmje.org. The manuscript cover letter must stipulate that all persons listed as authors have contributed to preparing the manuscript. Authors will be asked to transfer copyright of articles accepted for publication to the Hong Kong College of Anaesthesiologists. A Copyright Transfer form, signed by the authors, may be faxed or mailed to the Editorial Office at the time of submission. The form can be downloaded from the College's website.

Manuscript Preparation
Document files should be prepared in "A-4" paper. Manuscripts should be double spaced (to allow room for editing) throughout, including references and table and figure legends. By inserting a manual page break, begin each of the following sections on separate pages: title page, summary and key words, text, acknowledgments, references, tables, and legends. (Each table, complete with title and footnotes, should be on a separate page.) Number pages consecutively, beginning with the title page.
Authors should keep copies of everything submitted and all correspondence from the editorial office and its board members. No submitted materials (manuscripts, figures or tables) will be returned to the authors.

Ethics approval
No manuscripts describing investigations performed in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, from parents. This statement should appear at the beginning of the Methods section. Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers. Similarly, manuscripts describing investigations in animals will not be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Title Page
The title page should contain the title of the article, which should be concise but informative. First and last name of each author, with all relevant academic degree(s) including fellowship and affiliations.

Name of department(s) and institution(s) to which the work should be attributed. Disclaimers, if applicable; Name, address, telephone and Fax number, and email address of author responsible for correspondence about the manuscript.

The source(s) of financial support from foundations, institutions, pharmaceutical, and other private companies in the form of grants and awards.

Summary and Key Words
The second page should have an abstract. All articles (except editorials) must include unstructured abstracts consisting of one complete paragraph. Summary should be no more than 300 words for all articles including case reports and reviews.

The summary should state the purposes of the investigation, basic procedures, main findings and the principal conclusions. Emphasize new and important aspects of the study or observations. Below the abstract, provide (and identify as such) 3 to 10 keywords that will assist indexers in cross indexing the article.

The Text
The text of observational, experimental, and general articles is usually but not necessarily divided into sections with the following headings: Introduction, Methods, Results, and Discussion.

Introduction: State the purpose of the article. Summarize the rationale for the study or observation.
Methods: Describe the selection of observational or experimental subjects (patients or experimental animals, including controls). Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.
Results: Present the results in logical sequence in the text, tables, and illustrations.
Discussion: Emphasize the new and important aspects of the study and conclusions that follow from them. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.

Abbreviations and Units of Measurement
Units of measurement: Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in SI units with, if desired, present conventional metric units in parentheses. Continue using abbreviations consistently; do not revert to the spelled-out term.

References
All references must be available to all readers. Cite only references to books and articles or abstracts published in peer-reviewed journals. Number references consecutively in the order in which they are first mentioned in the text. Double-space between all lines of each reference and between references when typing the reference page. Identify references in text, tables, and legends by arabic numerals. References must be verified by the author(s) against the original documents, and the entire list must be checked for nonduplication. Use the style of the examples below:

Examples:
Standard journal articles (List all the authors when four or less; when five or more, list only the first three and add *et al*.): Lam DW, Chui PT. A prospective evaluation of a microcoagulation analyzer. Bull HK Coll Anaesthesiol 2005;14:9-12.
Personal author(s) of books and monographs: Myles PS, Gin T. Statistical Methods for Anaesthesia and Intensive Care. Oxford: Butterworth Heineman, 2000.
Chapter in a book: Chui PT, Low JM. Acute hypotension and vasodilators. In: Oh TE, ed. Intensive care manual. Oxford: Butterworth Heineman, 1997:153-62.

Tables
Type each table double-spaced on a separate sheet. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. In footnotes, define all abbreviations that are used in each table. Repeat definition if the abbreviation is used in a subsequent table. For footnotes, use lower-case italicized letters in alphabetical order. Cite each table in the text in consecutive order.

Illustrations
Computer generated figures are satisfactory for publication but authors should be aware that most figures will be reduced in size and should design their illustrations accordingly. Each figure should be identified by number. Color figures may be published at the discretion of the Editor-in-Chief. Figures should be cited in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from both the author and the publisher to reproduce the material. Define all abbreviations used in each illustration. Repeat definition if the abbreviation is used in a subsequent legend.

History of Academic Dress:
With Special Reference to the Hong Kong College of Anaesthesiologists

[1]Brigadier Ivan T Houghton

The Hong Kong College of Anaesthesiologists

SUMMARY

Dress, of which academic robes are an example, can be a potent symbol of identity and authority. Although the Chinese were the first to use official forms of dress, the Western academic dress is newer with it origins being traceable to the Mediæval era. The ancient universities were essentially ecclesiastical communities of scholars and teachers, all of whom would have been in at least minor ecclesiastical orders even if not ordained as priests. Their dress was, at first, similar to that of the laity, but over time, a form of academic dress was developed, although it still continued to be considerably influenced by the everyday dress of the general population. The academic dress of the Universities of Oxford and Cambridge have generally been the model for the academic dress of most of the universities of Great Britain, the Commonwealth and Colonies with Cambridge still retaining the most complete system for academic dress. Academic dress now consists of a gown, a hood and a headdress. The history and the rationale for the various elements of the dress are traced over time with particular reference to those features that have influenced the design of the academic dress of the Hong Kong College of Anaesthesiologists.

Bull HK Coll Anaesthesiol 2007; 16:64-70

Dress can be a potent symbol of identity and authority whilst being a powerful tool for team building and encouraging the virtues of discipline and ceremonial dignity. It is thought that the Chinese were the first to use official forms of dress that developed into the official robes that signified the 'degrees' earned through the imperial civil service examinations.[1,2] The dress consisted of a red long round-collar robe with long sleeves (*Yuanlingshan,* 圓領衫) worn with a cap (*Putou,* 幞頭), although the patterns of modern Chinese academic dress now worn are based more on styles of Western academic dress than those of the Imperial civil service.[1]

The use of academic dress in Europe is more recent, dating from Mediæval times when it was derived from the ordinary secular and clerical dress worn in the universities of Europe.[3,4] More specifically, the academic dress worn in the universities of the Commonwealth and former colonies of Great Britain is usually based on that of the Universities of Oxford and Cambridge.[5]

[1]MA(Cantab), MD(CUHK), LLM(Wales), FHKCA FHKAM(Anaesthesiology); Visiting Research Fellow, *Sir John Cass Department of Art, Media and Design, London Metropolitan University, Researcher, Frames Conservation Section, Tate, Millbank, London; Formerly Honorary Secretary, the Hong Kong College of Anaesthesiologists*

Address correspondence to: Brigadier Ivan Houghton, 113 Berkeley Tower, 48 Westferry Circus, London, E14 8RP, United Kingdom.
E-mail: ivan.houghton@btinternet.com

Figure 2. Diagram showing parts of a 'full shape' hood (not to scale). The cowl is usually folded back on itself to show the lining (as illustrated in blue).

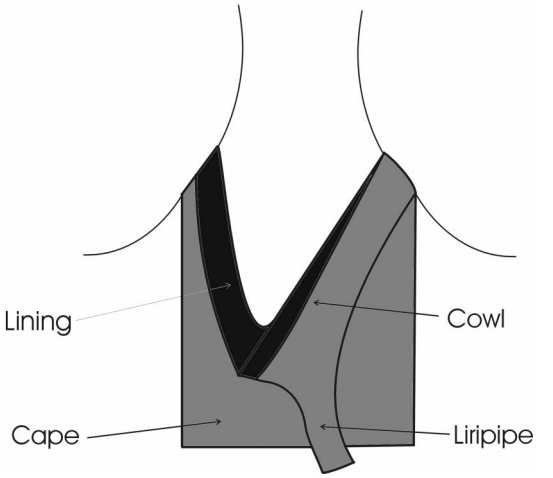
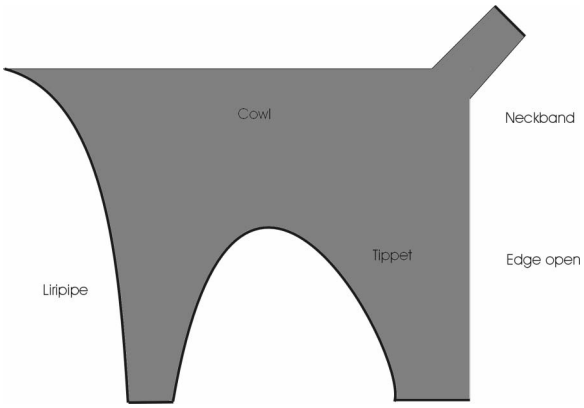


Figure 2. Diagram of 'full style' hood. The black edging shows that the edges are sewn, no thick line shows that edge is open. Adapted from Haycraft, 1923, v.



These ancient universities were essentially ecclesiastical communities of scholars and teachers. All were clerics and all would have been, at least, in minor ecclesiastical orders even if not actually ordained as priests.[3,6] The secular clerics wore very similar dress to that of all classes of the laity which served as the fashion model[7]. A hood was used to protect the head in inclement weather.[8] Anybody might wear a loose cape with a hood and a hole for the head and a slit in front for the arms and hands. This differed little from a priest's pluvial (originally a rain-cloak but now in ecclesiastical use for a long cloak or cope worn as a ceremonial vestment).[3,9] In 1222, at the Council of Oxford, Archbishop Langton of Canterbury ordered clerks to wear the *cappa clausa*,[6] which was the clerical outdoor dress already used on the continent. This garment was a development of the pluvial and it became regarded as the academic dress on formal occasions for Doctors of Theology and Masters of Arts.[3] The clergy, in general, over the years disregarded the rules concerning the c*appa*[*] *clausa* and the garment became to be considered as being exclusively academic[3]. Under the *cappa*, a black *roba*[†] (or *toga talaris*) was worn[6]. In the later fifteenth century, fashions changed towards shorter and more open costumes and the heavy outer dress was often left off so that an open-fronted *roba* or *toga* (or tunic)[‡] became the outer garment and is the forerunner of the modern academic gown.[6] The fur linings were developed into the facings of later gowns. Various forms of sleeves such as the bag sleeve were taken up from lay fashion and their length increased in the sixteenth century.[3]

At first, university statutes concerning dress were somewhat vague but the authorities usually modified lay fashions to produce academic dress.[7,8] The cut and shape were specified but colour was not of significance until later.[3]

The Reformation in Europe resulted in a breakdown of discipline of collegiate life with a diminishing observance of the rules concerning dress.[3,§] However, an insular conservatism led to

[*]A cloak forming part of a religious habit; a cloak[10].

[†]Ancestor of the gown and cassock[6].

[‡]The *roba* was initially closed in front but by the sixteenth century it was being worn with an open front. It is the closed front form that is more usual in American Universities[5].

[§]For life in a Mediæval university see Rait[7] and Sybolt.[11]

Figure 3. Photograph of Tudor bonnet.

the retention of academic dress at Oxford and Cambridge whilst a powerful church discipline preserved the tradition in Spain and Portugal.[3]

The hood had become a recognized feature of academic dress by the mid-fifteenth century, long after it had been abandoned in ordinary dress.[5] It was joined to a shoulder piece which covered the shoulders and upper part of the arm. In England the shoulder piece was abandoned and by 1592 the hood had been greatly elongated. A liripipe was a feature of the English hood that had appeared during Henry III reign, which originally was used to pull the hood on and off and to help hold the hood in position by binding it around and fastening it under the chin.[3]

The Tudor bonnet with its stiff brim and soft velvet top was the height of ordinary fashion in Henry VIII's time. It is now commonly used by those who have graduated PhD or to the higher doctorates (e.g. DD, LLD, MD, DMus, ScD, and, DLitt).[12] The bonnet is bound with a string and the tassels lie on the left side.

The current mortarboard (or trencher or square) is a development from the *pileus* [**] *quadratus* introduced in *circa* 1520 at the University of Paris.[3] When the square cap increased in size, a board was inserted to prevent the corners from flopping over and obstructing the eyes.[13] A skull cap had traditionally been worn under the *pileus* and the mortar board combined the two. Oxford approved a tassel for the mortar board in 1770.[3]

An undergraduate gown at Cambridge[††,3, 12, 14, 15] is of knee length and is typically of black stuff.[16] It is gathered at the back into a yoke. After graduation, the Bachelor of Arts wears a similar gown of black stuff[‡‡] which falls just below the knees and has long bell-shaped sleeves which are slit vertically from shoulder to the wrist through which the arms are placed.[§§] The hood of black stuff is trimmed with rabbit fur,[***] which harks back to the days when a lining of cheap fur was needed for warmth.[16] The Master of Arts wears a longer black gown with boot sleeves which are long, rectangular and closed at the ends. A crescent is cut out of the each sleeve end and there is a horizontal arm-slit at elbow level[20]. It can be made of silk. The hood is made of black corded ottoman silk and is fully lined with white silk.[†††] It includes the vestigial elements of a cowl (*cucullus*),[19] liripipe[‡‡‡] and a cape[19] and as such is described as 'full shape'.[20] The hood (*caputium*)[19] is usually worn with the cowl turned inside out for part of its width to show the lining material (Figures 1 and 2).

[**]A felt cap without a brim.[9]

[††]Oxford undergraduate's gowns are shorter.

[‡‡]Russell cord, being a wool and cotton mixture,[15] is used for better-quality gowns but synthetic materials such as polyester are cheaper and gaining popularity.[5]

[§§]Examination of earlier descriptions such as by Wood[17] and compared with more recent such as Shaw[12] and Gibson[16] shows that designs and colors of linings etc. have changed over the years even at Cambridge.

[***] Cony (budge) or lambskin was specified in 1414,[16] although synthetic fur is now usually used[5].

[†††]Formerly it would have been lined with the more exotic plain white fur, miniver, as used for the lining and trimming of ceremonial dress. Now such fur is from a stoat or ermine in its white winter-coat.[10] However the silk lining came to be worn in summer, being first permitted in Cambridge in 1560.[18]

[‡‡‡]Purse or pocket.

Figure 5. Diagram of Mortar Board showing union of skull cap with *pileus* (from front).

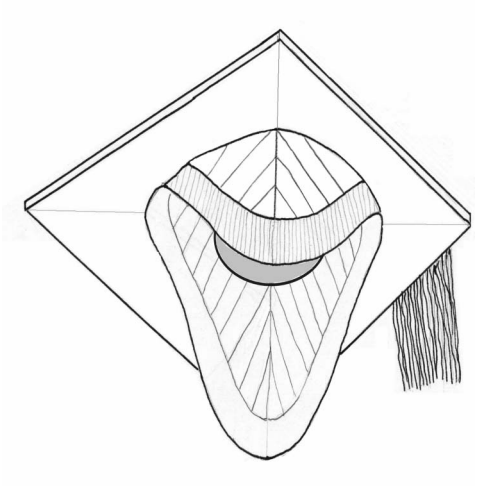


Figure 5. Photograph of mortarboard.

Doctors in Cambridge have two forms of academic dress.[12,20] The undress gown is black and is similar to the MA gown for the PhD, DLitt and ScD but the LLD, MD and MusD gown resembles a lay-type gown as worn by Queen's Counsel. The different doctorates are distinguished by the arrangement of the lace on the sleeves, facings or flap collar. The gown may be made of silk. The hoods of the higher doctorates are made of red cloth lined with silk in the faculty colour (mid-cherry for medicine).[12,18]

Full dress (or scarlet) is only worn on formal college and university occasions such as degree-conferment ceremonies and major church-festivals. For higher doctorates, the scarlet gown is voluminous with open sleeves that hang long at the back and at the front, the lining is turned outwards being fixed with a twisted cord(s) and button(s).[20]

The 1958 Cambridge ordinances[22] specified that a jacket and tie (ordinary or bow) were worn when wearing the basic academic dress (i.e. gown only) for such daily matters as attending lectures, seeing a college tutor or official, evening dinner in hall and after dark in the town (for those *in statu pupillari*). These regulations have since been relaxed by the 1970 ordinances.[23] For chapel on Sunday or special

Figure 6. Diagram of bands.

occasions, garden parties, or as a lecturer at a major public-lecture, a hood is also worn by those so entitled. However for formal occasions such as receiving or presenting a candidate for a degree, full academic-dress is worn. The clothing that is worn formally under the gown on these occasions (*sub fusc*) was a dark suit (black, such as a dinner jacket or morning dress with black trousers) with a plain white shirt, wing collar, white bow-tie, bands, and, black socks and shoes.[24] Bands were worn. Bands are now a feature only found in academic, clerical and legal dress but are derived from a separate long pointed collar fashionable in Mediæval times.[25] They used to be made of Holland (linen)[3] and can be worn with either a stand up collar such as the wing collar or a more modern turn-down collar.[3,24] Nowadays, a black lounge-suit is acceptable and bands are not required. National dress or military uniform are accepted alternatives.[25]

At Oxford and Cambridge, it is a modern tradition for men (unless university officials) that they do not wear academic caps indoors.[5] The mortarboard, if worn, should be parallel to the ground[5]. When service uniform is worn, a service cap is worn rather than an academic cap.[25]

The Academic Dress of the Hong Kong College of Anaesthesiologists

The academic dress of Cambridge University has been described in quite a lot of detail as the Hong Kong College of Anaesthesiologists' academic dress was based on the Cambridge tradition.

Originally a black gown, perhaps akin to that used by the then Faculties of Anaesthetists of the Royal College of Surgeons of England and the Royal Australasian College of Surgeons was mooted in the discussion of academic dress by the Board of Studies. However, Dr Jean Allison suggested that the College should wear scarlet. This was readily agreed and it was decided to have the colour of the gown as oxygenated haemoglobin. It is a particular problem with patterns for uniform that the pattern and colour should be readily reproducible. By using oxygenated haemoglobin, a known colour could be reproduced. The facings were black, edged with white, which represented the then British Standard colouring for medical oxygen cylinders.§§§

In the Cambridge tradition, it is usual to have a different gown for each degree with separate distinguishing details.[12,20] However, the University of Liverpool had already set a precedent for using the same gown throughout.[12] The Board decided to use the same gown throughout but differentiate the grades of council, honorary fellow, fellow and member by using a different hood so as to reduce the expense on promotion through the grades. A bell-shaped arm, trimmed with black, was chosen.**** The hoods in the Cambridge full-shape complete with cowl, liripipe and cape were made of black taffeta with the colours for the lining of the hoods chosen from the British Standard colour chart for medical gas cylinders, cyclopropane orange, nitrous oxide blue and carbon dioxide grey.[9] These colours were accurately defined.†††† Although it was not considered at the time, it is appropriate that the hood was black rather than oxygenated haemoglobin red as it is only the higher doctorates such as the MD that have scarlet hoods matching the gowns whereas lower doctorates such as PhDs have black hoods.[12] A diploma of fellow equates more with a PhD than that of a higher doctorate.

Silk was chosen as the material of the gown as it was felt that this was more appropriate for a Chinese gown and the sub-tropical Hong Kong climate.

---

§§§BS 1319C: 1976 now superseded.

****As worn by some Cambridge pensioners and by scholars in Oxford after 1666.[16]

††††There can be considerable difficulty in defining colours as noted by Haycraft.[21]

The oxygenated-haemoglobin coloured gown can be seen to equate with a doctor's scarlet dress and the wearing of scarlet for the diploma conferment congregations of the College is entirely appropriate. However it was thought that there should be provision for a College undress gown, albeit unlikely to be used frequently. The byelaws specify a black gown with white facings as the undress gown and the College's robe maker made one such gown for the College.

The President's robe was based on the same gown as that of the other members of the college but with a modern hand-embroidered gold stole. Bands were also specified which can be worn, probably best with a bow tie, but an ordinary neck tie is quite acceptable.

Conclusion

The appropriate use of academic robes enhances the dignity of academic proceedings. The robes of the Hong Kong College of Anaesthesiologists were based on the traditions of the University of Cambridge and the designs can be traced back through the centuries to those of the Mediæval scholars, bachelors (*baccalaureus)*, masters (*magister*) and doctors.

The research for this paper has shown that some of the descriptions used in the Byelaws of the Hong Kong College of Anaesthesiologists were inaccurate when compared with the actual patterns used and it is suggested that the Byelaws be revised to correct these mistakes.

References

1. http://en.wikipedia.org/wiki/Chinese_academic_dress; accessed 26/05/2007.
2. http://en.wikipedia.org.wiki/Imperial_civil_service_examination; accessed 15/07/2007.
3. Mawdsley WNH. The History of Academical Dress in Europe until the End of the Eighteenth Century. Oxford: Oxford University Press, 1963.
4. www.academicapparel.com/caps/GraduationGownHistory.html; accessed 26/05/2007.
5. http://en.wikipedia.org/wiki/Academic_dress; accessed 26/05/2007.
6. Goff P. University of London Academic Dress. London: University of London, 1999.
7. Rait R. Life in the Mediæval University. Cambridge: Cambridge University Press, 1918.
8. Gieysztor A. Management and Resources. In: de Ridder-Symoens H, ed. A History of the University in Europe. Rüegg W, general editor. Cambridge: Cambridge University Press, 1992: Volume 1 of III, 108-43.
9. Macalister RAS. Ecclesiastical vestments: their development and history. London: Elliot Stock, 1896.
10. Brown L, ed. The New Shorter Oxford English Dictionary on Historical Principles. Oxford: Clarendon Press, 1993.
11. Seybolt RF, translator. The Manuale Scholarium. Cambridge, Mass: Harvard University Press 1921.
12. Shaw G. Academical Dress of British and Irish Universities. Chichester: Philmore and Co. Ltd, 1995.
13. Rashdall Sir H. The Universities of Europe in the Middle Ages. Powicke FM. Emden AB, eds. Oxford: Oxford University Press, 1936. Volume III of III.
14. Almond AG. Gowns and Gossip. (On Cambridge academic robes). Cambridge: Bowes and Bowes, 1925.
15. http://www.geocities.com/noelcox/Modern_Academical_Dress.htm?200726 accessed 26/05/2007.
16. Gibson W. The Regulation of Undergraduate Dress at Oxford and Cambridge, 1662-1832. The Burgon Society Annual Report 2004; 26-41.
17. Wood TW. The Degrees, Gowns, and Hoods of the British, Colonial, Indian and American Universities and Colleges. London: Thomas Pratt and Sons, 1883.
18. Groves N. Historical English Academic Robes: a Basis for a National System. The Burgon Society Annual Report 2004: 59-62.

19. Johnson RB. The Undergraduate. From Dr C. Wordsworths "Social Life at the English Universities in the Eighteenth Centuries". revised, abridged, and re-arranged with an introduction, by R. Brimley Johnson [and with revisions and additions by the author]. London: Stanley Paul and Co, 1928.
20. Smith H, Sheard K. Academic Dress and Insignia of the World. Cape Town: AA Balkema, 1970. Vols I - III.
21. Haycraft F. The Degrees and Hoods of the World's Universities and Colleges. Ware, Hertfordshire: Jennings and Bewley, 1923.

The Interaction Between Blood Polymorphonuclear Cells and Vascular Endothelium in Patients with Systemic Inflammatory Response Syndrome

[1]Emily Gar Yee KOO

Department of Immunology, The Rayne Institute, St.Thomas' Hospital, Guy's, King's and St. Thomas' Medical and Dental School(GKT) London

SUMMARY

Blood polymorphonuclear leucocytes (PMNs) are believed to play a prominent role in the pathogenesis of the systemic inflammatory response syndrome (SIRS). This study evaluated the attachment of PMNs from 32 patients with SIRS, 7 patients without SIRS but were in the intensive care unit (ICU controls) and 22 healthy normal subjects to human umbilical cord vein endothelial cell monolayers that were either unstimulated or stimulated with tumor necrosis factor-α (TNFα). Overall, PMNs from SIRS patients were more adherent to untreated endothelium (mean increment 44%, $P < 0.01$) and to TNFα treated endothelium (mean increment 73%, $P < 0.001$) than PMNs from healthy controls. Adherence of PMNs from ICU controls was comparable to those of SIRS patients. The anti-sialylated Lewis x antibody-blocking studies showed that inhibition of PMN adhesion to TNFα treated endothelium occurred when PMNs were incubated at 37°C with antibody. Incubation of patient PMNs with the anti-CD11a and anti-CD11b antibodies at 4°C reduced the adhesion of patient PMNs to untreated and treated endothelium although no overall pattern of inhibition was noted. Abnormally adherent PMNs in SIRS patients may contribute to microvascular occlusions or transendothelial migration resulting in multiple organ damage.

Bull HK Coll Anaesthesiol 2007; 16:71-87

Inflammation is typically a tightly controlled response. When this control is lost, there is an exaggerated systemic activation of pro-inflammatory mediators leading to what is known as the systemic inflammatory response syndrome (SIRS). It may occur in a variety of disease states such as infection, trauma, burns, and pancreatitis. SIRS is defined as a characteristic clinical response manifested by two or more of the following:[1]

(1) temperature > 38°C or < 36°C;
(2) heart rate > 90 beats/minute;
(3) respiratory rate > 20 breaths/minute or $PaCO_2$ < 4.3 kPa;
(4) white blood cell count > 12 x 10^9 or < 4 x 10^9 or > 10% immature neutrophils.

Most of the information concerning SIRS has been derived from studies of sepsis, which is

[1]MB BS, BSc; Research Student, *Department of Immunology, The Rayne Institute, St.Thomas' Hospital, Guy's, King's and St. Thomas' Medical and Dental School(GKT) London.* Current affiliation: Resident, *Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong.*

Address correspondence to: Emily Koo, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong. E-mail: egykoo@gmail.com

defined as SIRS accompanied by infection.[1] Both SIRS and sepsis are part of a continuum where there is progression to shock, multiple organ dysfunction syndrome (MODS) and ultimately death.[2] It has previously been quoted that 40-70% ICU patients develop SIRS and that despite potent antibiotic therapy and intensive care support, mortality from sepsis remains high at > 35%.[3,4,5]

Neutrophils and SIRS

The neutrophil is thought to play a central pathological role in the pathogenesis of SIRS as indicated by autopsies of SIRS, septic and MODS patients who demonstrate endothelial swelling, edema, hemorrhage and neutrophil accumulation within the organs. Neutrophil aggregation and margination within the microvasculature leading to microthrombi, are also present.[6,7]

Neutrophils induce tissue damage by a number of mechanisms:[8,9]

(a) The *membrane-associated system* damages DNA and lipid membranes by producing reactive oxygen species.
(b) The *cytosolic system* consists of primary, secondary and tertiary granules. The primary granules contain numerous enzymes including anti-bacterial agents such as lysozyme and myeloperoxidase, and proteases such as elastase and collagenase. Secondary granules store similar enzymes in addition to lactoferrin whilst tertiary granules store CD11b, the α-subunit of one of the β_2-integrins involved in cell adhesion.

Neutrophils also induce damage by cell-cell aggregation leading to the formation of micro-thrombi. Occlusion of microvasculature further interrupts oxygen delivery and so compromises organ function.

Adhesion Molecules

The sequestration of neutrophils within organs involves complex interactions between neutrophils and endothelial cells (ECs) through various adhesion molecules. The adhesion molecules involved fall into one of three families: the selectins, the β_2-integrins and the *immuno-globulin gene superfamily*.[10,11,12]

Selectins are a family of three glycoproteins:

(a) E-selectin expressed on endothelial cells
(b) P-selectin expressed on endothelial cells and platelets
(c) L-selectin expressed on leucocytes.

There are numerous ligands for the selectins. They are usually sialylated and fucosylated carbohydrates, such as the sialylated Lewis *x* antigen.

Integrins are cell surface proteins that bind the cell cytoskeleton to the extracellular matrix or to other cells. The β_2-integrins share a common β-chain (CD18) which is non-covalently bound to one of three α-chains: CD11a, CD11b or CD11c. In the neutrophil, CD11a/CD18 is constitutively expressed whilst intracellular stores exist for CD11b/CD18 and CD11c/CD18.

The *immunoglobulin* (Ig) *gene superfamily* members include ICAM-1 and ICAM-2 found on endothelium. CD11a/CD18 binds ICAM-1 and ICAM-2 whereas CD11b/CD18 binds ICAM-1 only.

The process of adhesion and emigration of the neutrophil into tissue is divided into different phases: rolling, firm adhesion and activation, then transmigration through endothelial cell junctions. Specific adhesion molecules mediate each stage.

Rolling is a prerequisite for firm adherence of neutrophils to ECs due to high shear forces in the blood. The loose interaction between selectins and their ligands mediates this process.[13] L-selectin is constitutively expressed and shed from the neutrophil surface after activation. It binds endothelial GlyCAMs or PGSL-1 and is involved in "capture" of neutrophils from the circulation. E-selectin expression on ECs is stimulated by inflammatory cytokines. It binds sialylated lewis x antigens on neutrophils. This interaction is stronger and is not broken by shear stress.[14,15]

Activation of the endothelium induces expression of platelet activating factor (PAF) and IL-8. These surface-bound chemo-attractants and those found within the blood during SIRS such as leukotriene-B4 and complement C5a are capable of activating the neutrophil to increase surface expression of CD11b/CD18 and to shed L-selectin by proteolytic cleavage. Hence, increased CD11b/CD18 and decreased L-selectin expression are markers of activation. Lipopolysaccharide, IL-1 and TNF-α will also induce these changes.[16] Shedding of L-selectin may be a mechanism for preventing activated neutrophils, freed by shear forces, from entering other non inflamed sites. L-selectin has another important function where cross-linking or binding to its endothelial counterpart induces conversion of cell rolling to cell arrest via CD11a and CD11b dependent mechanisms.[17] Experiments have suggested that E-selectin mediated interactions activates CD11b expression and that E-selectin is also a chemoattractant.[18]

Stimulation of ECs with LPS, IL-1 or TNFα increases the expression of ICAM-1 without an effect on ICAM-2.[19] Bonding between ICAMs and β_2-integrins induces *cellular arrest* and *firm adhesion*. Antibodies against ICAM-1 or CD18 display the same degree of inhibition of adhesion with no additive effect.[20] Indeed, the firm adhesion mediated by the integrins does not solely depend on increased surface expression. Although the expression of CD11b increases by 2- to 10-fold, it has been shown that stimulation of granule depleted neutrophils may also induce adhesion to HUVECs.[21] Change in avidity and conformation of CD11b has been detected by monoclonal antibodies against epitopes unique to CD11b on activated neutrophils.[22] Engagement of the integrins promotes spreading of the cell, re-organization of actin filaments and prepares the neutrophil for its respiratory burst.[23]

E-selectin appears to play a role in CD18-independent mechanisms of neutrophil adherence to stimulated ECs *in vitro* whilst the evidence supporting the relative importance of CD11a, CD11b and CD11c is inconclusive.[24,25] However, it is generally accepted that CD11a mediates unstimulated neutrophil adhesion to activated HUVECs whereas chemotactically stimulated neutrophils utilize CD11a and CD11b.[26]

Transmigration follows adherence where neutrophil adhesion to stimulated ECs induces disorganisation of endothelial adherens junctions[27,28] allowing space for passage of the neutrophil into the interstitium and increasing vascular permeability. Antibodies against β_2-integrins will inhibit this response.

Adhesion Molecules, SIRS and Sepsis

Patients with SIRS have increased neutrophil CD11b expression and increased adhesion after surgery with levels being highest in those with sepsis[30] and those requiring intensive care.[31] These neutrophils were also found to be maximally stimulated. Another marker of neutrophil activation, decrease in surface expression of L-selectin, has also been documented in SIRS patients.[32]

Experiments show that septic patients have increased concentrations of soluble adhesion molecules in the plasma compared with controls including E- and L-selectins, ICAM-1 and VCAM-1.[33] As E-selectin is specific to ECs, it is therefore a marker of EC activation. Elevated soluble E-selectin concentrations in SIRS correlate with increased multiple organ dysfunction and mortality.[34] The precise function of these circulating adhesion molecules is unresolved.

Chen *et al*[35] have demonstrated that PMNs from SIRS patients exhibit increased adherence compared with pre-operative patients and controls. Successful inhibition of neutrophil mediated injury by blockade of adhesion molecules has been achieved by e.g. the administration of anti-CD18 monoclonal antibodies in myocardial infarction[36] which reduced neutrophil adhesion or transmigration. Another example involves the use of anti-P-

selectin antibodies in conjunction with anti-E-selectin antibodies to decrease neutrophil sequestration within the lungs and gut of burned rats.[37] Although these experiments have been successful, no attempt to characterize the relative importance of each individual adhesion molecule in SIRS has been made. Animal models of e.g. lung injury, which also occurs in SIRS, are not entirely representative of what takes place in humans. The observation that anti-E-selectin antibodies will reduce neutrophil mediated lung injury induced by immune complexes whilst P-selectin is important in cobra venom factor induced lung injury[38] indicates that adhesion molecules have different roles depending on the stimulus even though the outcome is similar. Therefore, the contribution of each adhesion molecule in SIRS must be assessed.

The aim of this study was to determine whether polymorphonuclear cells (PMNs) from SIRS patients exhibited an abnormal adherence to untreated and TNF-α treated cultured endothelial cells. Also, antibody blocking studies, were used to determine the contribution of the adhesion molecules CD11a, CD11b and the sialylated Lewis x antigens to the interaction of PMNs from SIRS patients with endothelial cells.

Materials and Methods

Experimental design

Polymorphonuclear cells from 32 patients with SIRS (12 females and 20 males, mean age of 58 years) from the intensive care unit (ICU) at St. Thomas' Hospital, London, 7 patients without SIRS in the ICU (2 females and 5 males, mean age of 60 years) and 23 healthy controls (15 females and 8 males, mean age of 24 years) were examined for their ability to bind to untreated and TNF-α treated endothelium. In each experiment, the adhesion of PMNs from a SIRS patient was compared with PMNs from either a non-SIRS ICU patient or a healthy control on HUVECs prepared from the same umbilical cord. The contribution of the adhesion molecules CD11a, CD11b and sialylated Lewis *x* to the adhesion of PMNs from SIRS patients and healthy controls to untreated and TNFα treated endothelium was assessed by using blocking antibodies.

Culture of HUVECs: Primary culture

Endothelial cells were cultured from human umbilical cords by a technique adapted from Jaffe *et al*. Umbilical cords were obtained from the Maternity Unit at St Thomas' Hospital and cleaned using 70% alcohol. The ends of the cord were cut off and clamped or damaged sections were removed. The umbilical vein was cannulated at each end with blunt 16-gauged needles attached to syringes and secured with string. Heparin (Leo Labs, Bucks, UK) in Dulbecco's Modified Eagle's Medium (Sigma, Irvine, UK) supplemented with 1 mM sodium pyruvate (Sigma), 4 mM L-glutamine (Sigma), 50 mg/l gentamycin (Roussel, Uxbridge, England) and 100 μg/ml streptomycin sulphate (Sigma) was flushed through the vein to remove remaining blood and blood clots. This supplemented DMEM will now be referred to as *DMEM+*. The vein was then filled with 0.2μm filtered type II collagenase (200 U/ml, Sigma) in DMEM+, to harvest the endothelial cells and the cord was gently kneaded for 10-15 min to help dislodge them. The solution was aspirated and the vein was flushed through with DMEM+ containing 10% fetal calf serum (FCS) (Gibco, Paisley, Scotland). The aspirates were pooled together and washed by centrifugation at 800 *g* for 10 min. The cell pellet was re-suspended in 5 ml *culture medium* (DMEM+ containing 20% FCS), pipetted into a 25 cm^2 culture flask pre-treated for 2 h with 1% gelatin (Sigma), and incubated at 37°C, 7% CO_2 in a humid atmosphere until a confluent monolayer was obtained. The culture medium was changed every 2 days using DMEM+/10% FCS. Confluency was determined by a cobblestone appearance on examination by light microscopy.

Secondary culture

The endothelial cell monolayer was rinsed with saline and incubated for 5 min with 3 ml trypsin-ethylene diamine tetracetic acid solution

(5 U/ml, Sigma) to detach the cells from the flask. DMEM+/10% FCS was added to the cell solution to inactivate the enzyme and to wash the flask. This was aspirated and washed by centrifugation at 800 *g* for 10 min. The cell pellet was re-suspended in 20 ml culture medium and 200 µl aliquots were dispensed into each well of a 96 well plate pre-treated with 1% gelatin. The plate was incubated at 37°C, 7% CO_2 in a humid atmosphere until confluence was reached.

Isolation of PMNs

10 ml fresh venous blood was collected in a heparinised syringe (10 U/ml) from each patient fulfilling the criteria for SIRS whilst 20 ml was collected from non-SIRS patients in the ICU and healthy controls. Samples were diluted with an equal volume of saline. The diluted blood was layered onto warmed Histopaque 1077 (Sigma), a separation gradient, in a ratio of 2:1 and centrifuged for 20 min at 800 *g*. The supernatant was aspirated and the remaining red cell pellet with polymorphonuclear cells (PMNs) was lyzed with 0.83% NH_4Cl-Tris buffer at pH 7.2 (8.3 g NH_4Cl (AnalaR, Poole, England), 100 ml of 0.1M Trizma base (Sigma) and 900ml distilled water) for 10 min. The solution was centrifuged at 800 *g* for 10 min, the supernatant removed and lysis repeated until no erythrocytes remained. The PMN pellet was re-suspended in Ca^{2+} and Mg^{2+} ion free Hank's Balanced Salt Solution (HBSS) (Sigma) and counted. Viability of the PMNs was >95%, calculated by staining with trypan blue (Sigma) and purity was > 98 %, assessed using methyl green thionin. The PMNs were washed by centrifugation at 800 *g* for 10 min and the final cell pellet re-suspended in HBSS at between 10 and 20 x 10^6 cells/ml.

Preparation of the endothelial cells for the adhesion assay

The culture medium was aspirated from each well and replaced by 100 µl of the required TNFα concentration, ranging from 0.01 to 100 U/ml. TNF*α* (NIBSC, South Mimms, Herts, England) solutions were prepared in DMEM+/10% FCS. The plate was incubated at 37°C, 7% CO_2 in a humid atmosphere for 5 h.

Radiolabeling of PMNs

The PMNs were labeled with 5µCi (185kBq) of ^{51}Chromium (Amersham Pharmacia Biotech, UK) per 10^6 cells, taking into account the decay factor of the radioisotope, by incubation for 1 h with the chromium at 37°C and re-suspending at 10 min intervals. Excess chromium was washed off by centrifugation at 800 *g* for 10 min with HBSS/5% FCS twice, counted and viability assessed again before washing for the third time. If antibody-blocking studies were not being performed, the final pellet was re-suspended at 10^6 cells/ml in cold DMEM+/10%FCS.

Antibody blockade of adhesion molecules on PMNs

After labeling, the final cell pellet was re-suspended to a concentration of 10^6 cells/100 µl in HBSS. The required amount of antibody was then incubated with the PMNs for 45 min at 4°C or 37°C, re-suspending at 10 min intervals. Cold DMEM+/10%FCS was then used to suspend the cells up to a concentration of 10^6/ml. The blocking antibodies used were a monoclonal mouse IgG_{2a} anti-human CD11a antibody (clone 28, R and D Systems), a monoclonal mouse IgG_1 anti-human CD11b antibody (clone 44, R and D Systems) and a monoclonal mouse IgM anti-human CD15s antibody (clone KM93, Serotec Ltd, Oxford, UK).

Adhesion assay

The medium containing TNF*α* was removed from the HUVECs and each well was washed with 100 µl medium prior to addition of the PMNs. 2 x 10^5 PMNs were added to each well and allowed to adhere for 1 h at 37°C. Aliquots of 2 x 10^5 PMNs were also dispensed into several LP3 tubes. Non-adherent cells were removed by washing each well on 5 occasions with 100 µl HBSS. The number of washes required to remove non-adherent or loosely adhered cells, the number of cells added to each well and the time of incubation allowing optimal adhesion were all determined by previous experiments in the laboratory. The cells were then examined under a light microscope and the contents of each well were lyzed with 200 µl 0.1M NaOH solution for 30 min. The cell lyzate from each

well was transferred to individual LP3 tubes. The content of each tube was counted by a gamma scintillation counter for 1 min and the percentage of neutrophil adhesion was calculated by the following equation:

$$\% \text{ adhesion} = \frac{\text{cpm of cell lyzate - background cpm}}{\left(\begin{array}{c}\text{cpm of original}\\ \text{neutrophil suspension}\end{array}\right) - \text{background cpm}} \times 100\%$$

where cpm is the number of counts per minute.

Statistical analysis

All results are the mean value of quadruplicate measurements. Statistical significance was assessed by the Wilcoxon paired signed rank test if data were non parametric and paired, or by the Student's *t*-test if normally distributed.

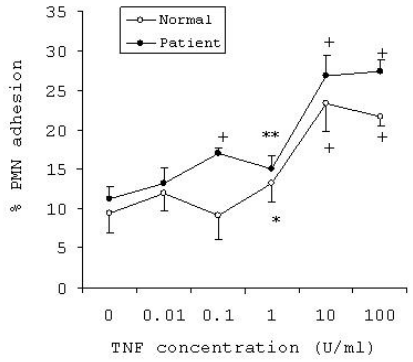
Results

Attachment of PMNs to endothelial monolayers stimulated with TNFα

An experiment was performed to determine the concentration of TNFα that would produce maximal adhesion of PMNs from a patient with SIRS and from a healthy control subject to endothelial cells. Varying concentrations of TNFα at 0.01, 0.1, 1.0, 10 and 100 U/ml were used. Figure 1 shows that the percentage of PMNs adhering to endothelium increases following treatment with TNFα. The maximum level of adhesion occurred at 10 and 100 U/ml TNFα ($P < 0.05$). There was a 130 ± 19% increase in control PMN adhesion and a 192 ± 11% increase in patient PMN adhesion when endothelial cells were stimulated with 100 U/ml TNFα as compared with untreated endothelium. As a result of these findings, 100 U/ml TNFα was used to treat endothelium requiring activation in all further experiments.

Adherence of PMNs from SIRS patients and from healthy control subjects to unstimulated and TNFα stimulated endothelium

Figure 1. Adhesion of PMNs from a patient with SIRS and from healthy control subject to cultured endothelial cells stimulated with TNFα.

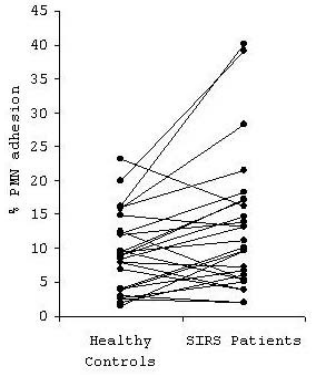


PMNs from a patient with SIRS and a healthy control were allowed to adhere to untreated cultured endothelial cells and to endothelial cells pre-treated with 0.01, 0.1, 1.0 or 100 U/ml TNFα. Results are expressed as percentage adhesion and each data point is the mean of quadruplicate measurements. $^{*}P < 0.05$, $^{**}P < 0.002$, $^{+}P < 0.001$ compared with untreated endothelial cells.

A series of experiments were undertaken to compare the adherence properties of PMNs from 26 SIRS patients with 23 healthy controls to untreated endothelial cells. Figure 2 shows that the PMNs from the SIRS patients were 44% more adherent ($P < 0.01$) than PMNs from healthy subjects. Because the data was not normally distributed, median values of percentage adhesion were calculated. The median percentage of adhesion of PMNs from control subjects was 9 % (range 2-23%) and for PMNs from SIRS patients was 11% (range 2-40%).

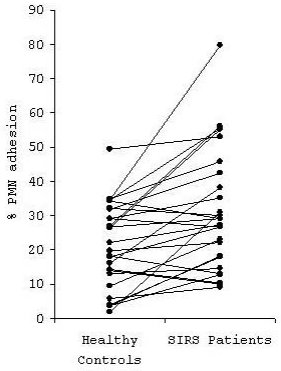
The same PMNs from patients and controls were also applied to endothelial cells pre-treated with 100 U/ml TNFα. In general, PMNs from patients and controls showed an enhanced attachment to TNFα treated endothelium when compared with untreated cells. Figure 3 shows

Figure 2. Comparative adhesion of PMNs from patients with SIRS and healthy controls to unstimulated endothelium.



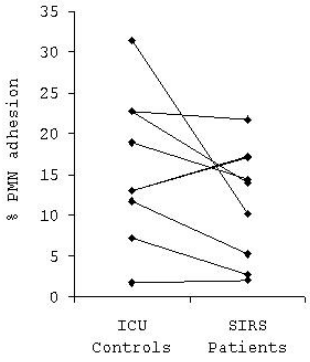
Each line represents an experiment in which PMNs from a patient with SIRS and from a healthy control were added to untreated endothelial cells cultured from the same umbilical cord vein. A total of 26 patients and 23 control subjects were studied. Overall, the patient PMNs were more adherent than normal blood PMNs ($P < 0.01$).

Figure 3. Comparative adhesion of PMNs from patients with SIRS and healthy controls to TNFα stimulated endothelium.



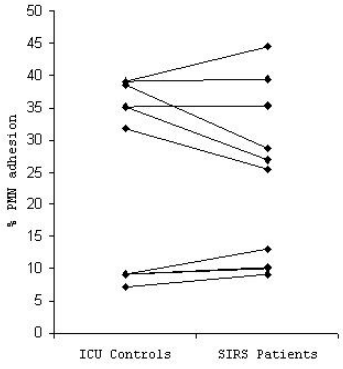
Each line represents an experiment in which PMNs from a patient with SIRS and from a healthy control subject were added to endothelial cells pre-treated with 100 U/ml TNFα for 5 h, and cultured from the same umbilical cord vein. A total of 26 patients and 23 control subjects were studied. Overall, the patient PMNs were more adherent that normal blood PMNs ($P < 0.001$).

Figure 4. Comparative adhesion of PMNs from patients with SIRS and non-SIRS patients (ICU controls) to unstimulated endothelium.



Ten patients and 7 control subjects were studied. Each line compares the adhesion of PMNs from a patient with SIRS and an ICU control to endothelial cells cultured from the same umbilical cord vein. Overall, the ICU control PMNs were more adherent than PMNs from SIRS patients $P < 0.05$) to untreated endothelium.

Figure 5. Comparative adhesion of PMNs from patients with SIRS and non-SIRS patients (ICU controls) to TNFα stimulated endothelium.



Ten patients and 7 control subjects were studied. Each line compares the adhesion of PMNs from a patient with SIRS and an ICU control to endothelial cells cultured from the same umbilical cord vein. PMNs were allowed to adhere to the endothelium after stimulation with 100 U/ml TNFα. The adherence of PMNs from SIRS patients was similar to that of PMNs from ICU control subjects.

the adhesion of PMNs from 26 SIRS patients to TNFα treated endothelium was significantly greater than that of PMNs from healthy controls ($P < 0.001$). The median percentage of adhesion of PMNs from control subjects and SIRS patients was 22 % (range 2-49 %) and 28 % (range 9-80 %) respectively. Overall, the patient PMNs were 73 % more adherent than PMNs from healthy controls.

Adherence of PMNs from SIRS and from non-SIRS patients to unstimulated and TNFα stimulated endothelium

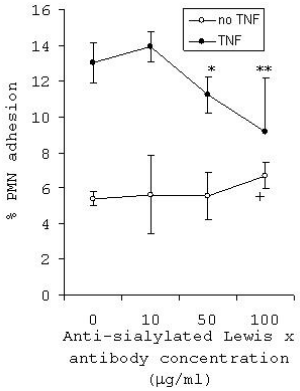
To determine whether the enhanced adhesion of PMNs from SIRS patients was due to the intensive care setting or due to the syndrome itself, the adhesion of PMNs from non-SIRS patients in the ICU was compared with that of PMNs from SIRS patients. Figure 4 shows that the adhesion of PMNs from 7 ICU controls to untreated endothelial cells was significantly greater than PMNs from 10 SIRS patients ($P < 0.05$) to untreated endothelium. The median percentage of adhesion of PMNs from ICU controls was 13% (range 2-32 %) and from SIRS patients 12% (range 2-22 %). Overall, the ICU control PMNs were 52% more adherent to untreated endothelium.

Figure 5 shows that there was no difference between the adhesion of PMNs from 10 SIRS patients and 7 ICU controls to TNFα treated endothelium $P = 0.45$). The median percentage of adhesion of PMNs from SIRS patients was 26% (range 9-44%) and from ICU controls, 32% (range 7-39%).

Effect of anti-sialylated Lewis x antibodies on the adhesion of PMNs to endothelial monolayers

Figure 6 shows the results of an experiment to determine the concentration of anti-sialylated Lewis x antibody necessary to produce inhibition of PMN adhesion. PMNs from a SIRS patient were incubated with 10, 50 and 100 μg/ml of the antibody. The attachment of treated and untreated PMNs to TNFα stimulated endothelium was greater than to unstimulated endothelium. Adhesion of PMNs

Figure 6. Anti-sialylated Lewis *x* antibodies and the adhesion of PMNs from a SIRS patient to unstimulated and TNFα stimulated endothelial cells.



PMNs from a patient with SIRS were incubated with 10, 50 and 100 μg/ml anti-sialylated Lewis *x* antibody for 45 min at 37°C. The PMNs were then allowed to adhere to untreated and 100 U/ml TNF-α treated cultured endothelium from the same umbilical cord. Each data point is the mean of quadruplicate measurements. *$P < 0.05$, decreased adhesion compared with untreated PMNs; **$P < 0.01$ decreased adhesion compared with untreated PMNs; $^{+}P < 0.005$ increased adhesion compared with untreated PMNs.

to 100 U/ml TNFα treated endothelium was significantly inhibited by 50 μg/ml (14% inhibition, $P < 0.05$) and 100 μg/ml antibody (30% inhibition, $P < 0.01$).

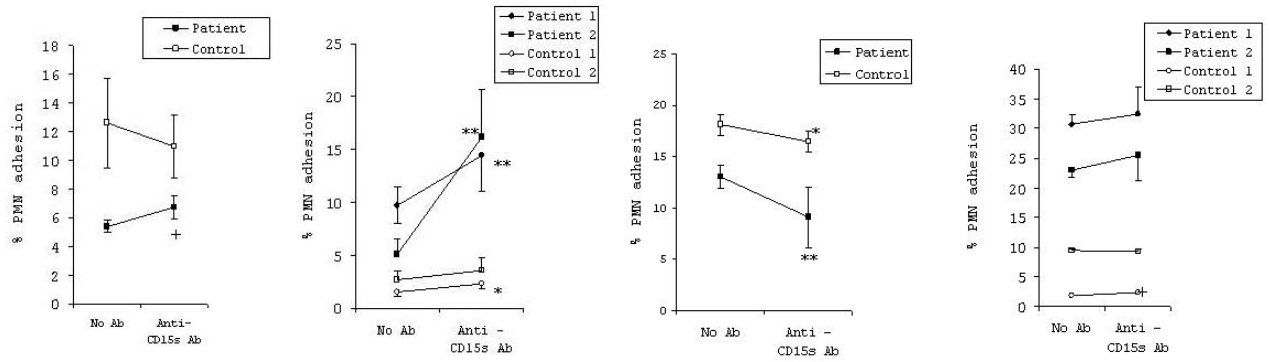
The manufacturer's suggested working concentration was between 10 to 100 μg/ml and as a result of these findings, 100 μg/ml anti-sialylated Lewis *x* antibody was used in all subsequent experiments.

Although anti-sialylated Lewis *x* antibody inhibited the attachment of PMNs to stimulated endothelium, this effect was not seen with unstimulated endothelium. In fact, 100 μg/ml antibody *increased* the adhesion of patient PMNs by 24 % ($P < 0.005$).

In order to assess the contribution of sialylated Lewis *x* antigens to the adhesion of

Figure 7. Effect of anti-sialylated Lewis *x* antibodies on the adhesion of PMNs from SIRS patients and healthy controls to untreated and TNFα treated endothelium.

(a) (b) (c) (d)



PMNs from patients with SIRS and from healthy control subjects were incubated with 100 μg/ml anti-sialylated Lewis *x* antibody for 45 min at (a) 37°C and (b) 4°C. The PMNs were then allowed to adhere to untreated cultured endothelium. **P*<0.05 increased adhesion compared with untreated cells; ***P*<0.01 increased adhesion compared with untreated cells; $^{+}$*P*<0.005 increased adhesion compared with untreated cells

PMNs from patients with SIRS and from healthy control subjects were incubated with 100 μg/ml anti-sialylated Lewis *x* antibody for 45 min at (c) 37°C and (d) 4°C. The PMNs were then allowed to adhere to 100 U/ml TNF-α treated cultured endothelium. + *P*<0.05 increased adhesion compared with untreated cells; **P*<0.05 decreased adhesion compared with untreated cells; ***P*<0.01 decreased adhesion compared with untreated cells

PMNs from SIRS patients, PMNs from a patient were incubated at 37°C with 100 μg/ml anti-sialylated Lewis *x* antibody. Figure 7a shows the attachment of PMNs to unstimulated endothelium. Adhesion of PMNs from the SIRS patient unexpectedly *increased* by 24% ($P < 0.005$) when antibody was added whilst the adhesion of PMNs from the healthy control was not significantly changed. Figure 7c shows the effect of incubating PMNs and anti-sialylated Lewis *x* antibody at 37°C on the adhesion of PMNs to TNFα stimulated endothelium. Here, the antibody significantly inhibited the adhesion of both SIRS patient and healthy control PMNs to endothelium by 30% ($P < 0.01$) and 9% ($P < 0.05$).

Because there was an unexpected increase in patient PMN adherence to unstimulated endothelium at 37°C, experiments were also performed at 4°C (figures 7b and 7d). This lower temperature was used in order to attempt a reduction in Fc receptor (FcR) interactions, which was thought to enhance the patient PMN attachment to endothelium.

Figure 7b shows that incubation of the antibody with PMNs at 4°C still enhanced adhesion of PMN samples to untreated endothelium. PMN adhesion was enhanced by up to 218% ($P = 0.01$) in SIRS patient 2.

Figure 7d shows that incubation of the antibody with PMNs at 4°C also generally produced no significant change when allowed to adhered to TNF stimulated endothelium.

In summary, incubation of anti-sialylated Lewis x antibody and PMNs at 37°C, inhibited the attachment of patient and control PMNs to TNFα stimulated but not to untreated endothelium. At 4°C it either had no effect or enhanced the adhesion of both patient and healthy control PMNs to endothelium.

Effect of anti-CD11a and anti-CD11b antibodies on the adhesion of PMNs to endothelial monolayers

Polymorphonuclear cells from a SIRS patient were incubated at 37°C with either anti-CD11a or anti-CD11b antibody at concentrations

of 5, 10 and 50 μg/ml, or with a combination of anti-CD11a and anti-CD11b antibodies at 50 μg/ml each. The PMNs were then allowed to adhere to untreated or TNFα treated endothelium. Figure 8 shows that as the concentrations of anti-CD11a and anti-CD11b antibodies increased, the percentage PMN adhesion to TNFα treated endothelium decreased. Maximal inhibition was observed at 50 μg/ml anti-CD11a (20 %) and at 50 μg/ml anti-CD11b antibody (30 %) ($P < 0.001$). The largest inhibition occurred when using a combination of anti-CD11a and anti-CD11b antibodies (45% reduction in adhesion, $P < 0.001$). The inhibition produced by anti-CD11a/anti-CD11b was significantly greater than that produced by 50 μg/ml anti-CD11a alone. However, when the effect of this combination of anti-CD11a/CD11b was compared with that of anti-CD11b alone at 50 μg/ml, the decrease was insignificant ($P = 0.06$) although a further 15 % inhibition was produced. Using untreated endothelium, only 10 μg/ml anti-CD11b antibody reduced the attachment of PMNs (mean 20%, $P < 0.05$) whilst anti-CD11a antibody at 5 and 10 μg/ml *increased* the adhesion of PMNs from the SIRS patient by 20 % and 53 % ($P < 0.05$).

As a result of these findings, all further anti-blocking experiments used anti-CD11a and anti-CD11b antibodies at concentrations of 50 μg/ml each.

To determine the effect of anti-CD11a and anti-CD11b antibodies on the adhesion of SIRS patient PMNs to untreated and TNFα treated endothelium, three additional experiments (numbers 2, 3 and 4) were performed. Figure 9 shows the results of the adhesion of PMNs incubated at 37°C with the various antibodies. Overall, no general trend was observed in these studies. Anti-CD11a and anti-CD11b antibodies enhanced the adhesion of patient PMNs in experiment 2 to both treated and untreated endothelium. All increases were highly significant with values ranging from 61% (anti-CD11b, TNF treated endothelium) to 305% (anti-CD11a, untreated endothelium).

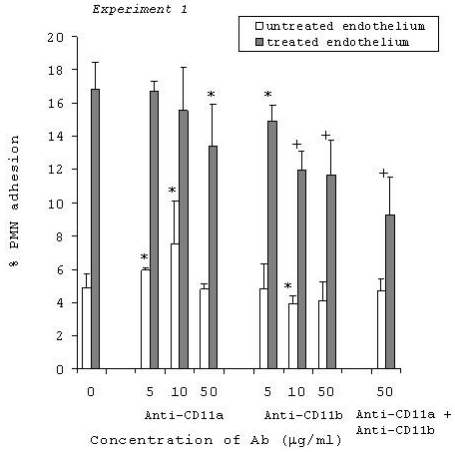
In experiment 3, the antibodies had no effect on the adhesion of patient PMNs to TNFα treated endothelium but enhanced adhesion to untreated endothelium by 42% (anti-CD11a, $P < 0.05$), 73% (anti-CD11b, $P < 0.01$) and 66 % (anti-CD11a/anti-CD11b, $P < 0.01$) respectively. In contrast, anti-CD11b and the combination of anti-CD11a/anti-CD11b antibodies significantly inhibited the attachment of PMNs to untreated endothelium in experiment 4. Anti-CD11b reduced adhesion by 18 % ($P < 0.01$) and anti-CD11a/anti-CD11b by 23 % ($P < 0.01$).

Figure 10 (experiment 5) shows the adhesion of PMNs from a healthy control subject to endothelium after incubation with anti-CD11a, anti-CD11b or both antibodies at 37°C. Inhibition of adhesion to untreated endothelium was produced by anti-CD11a ($P < 0.001$), by anti-CD11b ($P < 0.01$) and by anti-CD11a/anti-CD11b ($P < 0.01$) at 37%, 25% and 34% respectively. The antibodies also reduced attachment of PMNs to TNFα stimulated endothelium: anti-CD11a inhibited adhesion by 34% ($P < 0.001$), anti-CD11b by 23% ($P < 0.05$) and anti-CD11a/anti-CD11b by 23% ($P < 0.05$).

It is possible that at 37°C non-specific binding of the anti-CD11a and anti-CD11b antibodies to Fc receptors on the PMNs was responsible for the enhanced adhesion of patient PMNs to endothelium observed in two of the three experiments shown in Figure 9. Therefore, antibody-blocking assays were performed where antibodies were incubated with PMNs at 4°C to eliminate this interference.

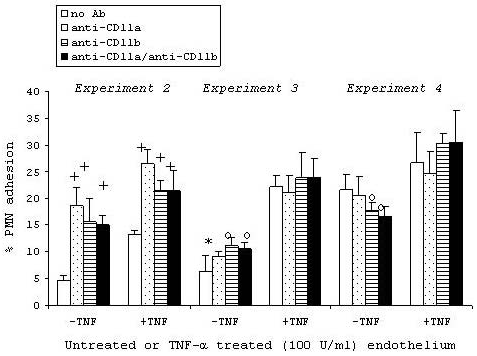
Anti-CD11a, anti-CD11b and anti-CD11a/anti-CD11b antibodies were incubated at 4°C with PMNs isolated from 3 SIRS patients (experiments 6, 7 and 8) and applied to untreated and TNFα treated endothelial monolayers. The results are shown in Figure 11. Experiment 6 shows that the combined anti-

Figure 8. Anti-CD11a and anti-CD11b antibodies impede the binding of PMNs from a SIRS patient to TNFα treated endothelium.



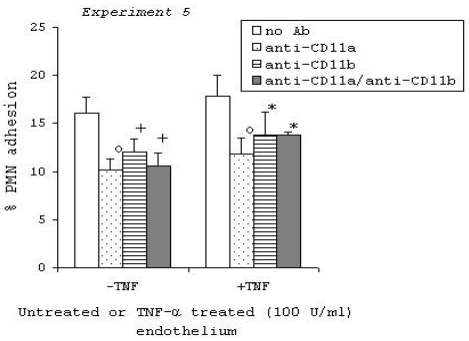
PMNs from a SIRS patient were incubated at 37°C for 45 min with either anti-CD11a or anti-CD11b antibody at concentrations of 5, 10, 50 μg/ml, or with both anti-CD11a and anti-CD11b antibodies at a final concentration of 50 μg/ml each. The PMNs were then allowed to adhere to untreated and 100 U/ml TNFα treated endothelium. **P* < 0.05 compared with untreated PMNs, + *P* < 0.001 compared with untreated PMNs.

Figure 9. Effect of anti-CD11a and anti-CD11b antibodies on the adhesion of PMNs from SIRS patients to unstimulated and TNFα stimulated endothelium at 37°C.



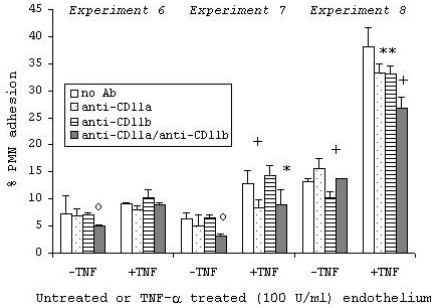
In each of the 3 experiments, PMNs from a different SIRS patient were incubated at 37°C with either 50 μg/ml anti-CD11a or 50 μg/ml anti-CD11b antibody or with a combination of anti-CD11a and anti-CD11b antibodies (50 μg/ml each). The PMNs were then allowed to adhere to either untreated endothelium or 100 U/ml TNF-α treated endothelium. **P* < 0.05 compared with untreated PMNs, °*P* < 0.01 compared with untreated PMNs, +*P* < 0.001 compared with untreated PMNs

Figure 10. Effect of anti-CD11a and anti-CD11b antibodies on the adhesion of PMNs from a healthy control subject to unstimulated and TNFα stimulated endothelium at 37°C.



The PMNs from a healthy subject were pre-treated with 50 μg/ml anti-CD11a antibody, 50 μg/ml anti-CD11b antibody or 50 μg/ml of both antibodies for 45 min at 37°C before being added to untreated or 100 U/ml TNF-α treated endothelium. **P* < 0.05 compared with untreated PMNs, + *P* < 0.01 compared with untreated PMNs, ° *P* < 0.001 compared with untreated PMNs.

Figure 11. Effect of anti-CD11a and anti-CD11b antibodies on the adhesion of PMNs from SIRS patients to unstimulated and TNFα stimulated endothelium at 4°C.



In each of the 3 experiments, PMNs from different SIRS patients were incubated at 4°C with 50 μg/ml anti-CD11a, 50 μg/ml anti-CD11b or both antibodies (50 μg/ml each) for 45 min. They were then allowed to adhere to untreated and 100 U/ml TNF-α treated endothelium. **P* < 0.05 compared with untreated PMNs, +*P* < 0.01 compared with untreated PMNs, °*P* < 0.005 compared with untreated PMNs.

CD11a/anti-CD11b antibodies inhibited PMN adhesion to untreated endothelium by 29% ($P < 0.005$) but neither of the antibodies alone or in combination modified PMN adhesion to TNFα treated endothelium. Adhesion of PMNs in experiment 7 to untreated endothelium, was again inhibited by anti-CD11a/anti-CD11b antibodies (51%, $P < 0.001$) whereas anti-CD11a alone and a combination of anti-CD11a/anti-CD11b antibodies reduced adhesion of patient PMNs to stimulated endothelium by similar percentages (34%, $P < 0.01$ and 31%, $P < 0.05$).

Experiment 8 shows that the attachment of PMNs incubated with anti-CD11b antibody to untreated endothelium was decreased by 22 % ($P < 0.01$). All combinations of antibodies produced inhibition for TNFα treated endothelium where anti-CD11a and anti-CD11b antibodies reduced PMN adhesion by 13 % (both $P < 0.05$) and anti-CD11a/anti-CD11b antibodies by 30 % ($P < 0.01$).

Discussion

This study shows that PMNs from patients with SIRS are more adherent to unstimulated and TNF-α stimulated cultured endothelial monolayers, than PMNs from healthy control subjects. In addition, it was noted that PMNs from non-SIRS patients in the ICU had comparable adhesive properties to those of PMNs from SIRS patients. The relative contribution of the sialylated Lewis *x* antigens and the CD11a and CD11b β_2-integrins to the adhesion of PMNs from SIRS patients requires further investigations although it seems that CD11a and CD11b are both involved in the attachment of patient PMNs to unstimulated and stimulated endothelium at 4°C.

The proinflammatory cytokine TNFα, was chosen to stimulate endothelial monolayers to provide a model of the inflammatory endothelium present in SIRS. There are reports of elevated plasma levels of TNFα in SIRS and septic patients[39,40] and as TNFα is a pleiotropic cytokine, one of its effects is to stimulate the expression of adhesion molecules on endothelium. HUVECs constitutively express low levels of ICAM-1, high levels of ICAM-2 and sialylated Lewis *X* antigens. Following stimulation with TNFα, there is upregulation in ICAM-1 and induced expression of E-selectin. Evidence for endothelial activation in SIRS and sepsis arises from the detection of soluble E-selectin in the plasma[41] because E-selectin is specifically expressed by activated endothelial cells. The importance of TNFα in SIRS is emphasised by experiments showing that anti-TNFα antibody infusions successfully prevent septic shock during lethal bacteraemia in baboons.[42]

The experiments described in this project show that there is supranormal adhesion of PMNs from SIRS patients to unstimulated and TNFα stimulated endothelium, in comparison with healthy control PMNs. The large variations in the adherence values of PMNs to endothelium are probably due to inherent adhesive properties of the endothelial cells isolated from different umbilical cords or to patients being at different stages of the disease. *In vivo*, it is likely that the adhesion of SIRS patient PMNs are higher than those found in this study because blood drawn from patients would contain PMNs from the circulating pool only i.e. the less adherent PMNs. Histological studies have implicated the neutrophil in the pathogenesis of SIRS, sepsis and MODS where there is aggregation and margination within the microvasculature. This study investigated the attachment of PMNs, rather than neutrophils alone, to endothelium. Polymorphonuclear cells include neutrophils, basophils and eosinophils however, neutrophils contribute to 60-70% of the white blood cell count compared with 2-4% by eosinophils and 0.5-2% by basophils. Therefore it was considered that most of the PMNs would indeed be comprised of neutrophils. This combined with the neutrophilia present in most SIRS patients ensured that only a negligible number of eosinophils and basophils were present in the adhesion assays. Additional studies are required to determine whether this abnormal PMN adhesion leads to transendothelial migration because some reports have emphasised the lack of neutrophils present in the interstitium and instead, have stressed the importance of neutrophil sequestration within the micro-vasculature of the organs.[43] Neutrophils are capable

of inducing damage from the vascular side of the endothelium as engagement of CD11b/CD18 by ICAM-1 enhances hydrogen peroxide secretion by neutrophils thus promoting neutrophil-mediated cytotoxicity.[44]

In addition to the enhanced adhesion leading to microvascular occlusions or transendothelial migration, there is also evidence of abnormal PMN function in SIRS. For example, PMNs from SIRS patients have abnormal phagocytosis and intracellular production of hydrogen[45] and septic and MODS patients also have raised plasma levels of free radicals.[46] Dysregulated PMN function is illustrated by the presence of activated apopotosis-resistant neutrophils in patients who have undergone major surgery.[47]

The finding that PMNs from non-SIRS patients in the ICU had similar or elevated adhesive properties compared with PMNs from SIRS patients, in the same ICU, suggests that the abnormal adhesion observed in SIRS may be due to the intensive care setting as opposed to the syndrome itself. Many patients (40-70%) in the ICU develop SIRS and all patients in the ICU are bacteraemic to a certain level due to catheter and injury sites, for example. Local infection at these sites would be sufficient to activate neutrophils and since samples of blood were drawn from intravenous lines, it is possible that PMNs from ICU controls expressed high levels of adhesion molecules. In future studies, the effect of infection on adhesion of PMNs could be evaluated by distinguishing between SIRS and septic patients as patient selection in this study did not separate the two populations.

Having established that PMNs from SIRS patients were more adherent than normal PMNs, attempts were made to characterize the contribution of known adhesion molecules. The first adhesion molecule studied was sialylated Lewis *x*. The ligand for this is E-selectin which is maximally expressed on endothelium stimulated with TNFα for 5 h.[48] The chromium–release assay adopted in this project measures strong leucocyte-endothelial interactions. Although E-selectin is implicated in rolling interactions between the neutrophils, it is the most resistant of the vascular selectins to shear stress.[15] It appears that sialylated Lewis *X* antigens were indeed contributing to firm adherence to TNFα treated endothelium (at 37°C) as indicated by our initial antibody-blocking studies. When antibody was incubated with PMNs at 37°C, sialylated Lewis *x* was found to contribute *more* to the adherence of patient PMNs to stimulated endothelium, than to that of healthy control PMNs.

The unexpected increased binding of patient PMNs compared with controls (incubated with antibody at 37°C) to unstimulated endothelium, may have been due to non-specific binding of the Fc portion of the antibody with surface Fc receptors. This may have activated the cells and made them generally more adherent. PMNs from SIRS patients have been reported to express more FcγRI (CD64), a high affinity receptor for monomeric IgG. The acquisition of CD64 by PMNs is regarded as an indicator of cell activation and in SIRS there are far more cells bearing CD64 than normal PMNs together with an increased distribution of CD64 molecules on the cell surface.[49]

There are 3 classes of Fcγ receptors, FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16). CD64 is the high affinity receptor for human IgG_1 or IgG_3 whilst CD32 and CD16 bind with low affinity to complexed IgG. CD64 and CD32 are found constitutively on monocytes, and CD32 and CD16 are naturally expressed by neutrophils. Healthy neutrophils express few CD64 receptors, <3000/cell, but exposure to low concentrations of IFN-γ will increase this number.[50] CD64+ cells could have originated from local areas of infection (commonly found in ICU patients) where IFN-γ concentrations would be high due its release from bacteria stimulated T lymphocytes or natural killer cells. It is generally thought that neutrophils do not recirculate, so how would the CD64+ PMN return to the circulation? A recent report by Lemaire *et al*[51] found that lymph from thoracic ducts of SIRS patients contains a disproportionately high number of PMNs.

Lowering the antibody/PMN incubation tmperature to 4°C will reduce non-specific binding of *IgG* to CD64. However, the isotype of the antibody used in these anti-sialylated Lewix *x* antibody-blocking studies was actually IgM, which does not bind CD64. Nevertheless, experiments were repeated with incubation at 4°C. At this temperature, all significant changes with unstimulated and TNF-α stimulated endothelium were again, unexpectedly, *increases* in adhesion. A report by Stocks *et al*[52] showed that a mouse IgM anti-Lewis *x* antibody at low concentrations enhanced adhesion but this effect was eliminated at high concentrations where inhibition occurred instead. The concentration of antibody used in the present experiments was 100 μg/ml, which exceeded those enhancing adhesion in the study by Stocks *et al*. The remainder of the results at 4°C showed no significant change. Hence, no overall conclusion may be drawn concerning the contribution of anti-sialylated Lewis *x* to the attachment of patient PMNs to endothelium. The main problem here was that only a small number of experiments were performed. Further experiments will need to be done to clarify these issues.

The next cell adhesion molecules to be studied were CD11a and CD11b β_2-integrins. β_2-integrins have been found to be expressed to a lesser degree on PMNs of survivors of sepsis compared with non-survivors.[53] Whilst CD11a is known to contribute to PMN adhesion to unstimulated endothelium, both CD11a and CD11b are involved in adhesion to stimulated endothelium when ICAM-1 is upregulated.[10] This study's initial anti-CD11a and anti-CD11b antibody-blocking experiment suggested that CD11a and CD11b both play a role in the adhesion of PMNs from SIRS patients to stimulated endothelium with the effect of anti-CD11a and anti-CD11b antibodies being additive. However, this result was not reproduced in any of the subsequent experiments where antibodies were incubated with patient PMNs at 37°C. In fact, on several occasions, enhanced adhesion to both unstimulated and stimulated HUVECs on addition of antibody was observed. This enhanced attachment together with the finding that healthy control PMNs (low CD64 expression) incubated with anti-CD11a and anti-CD11b antibodies at 37°C inhibited adhesion, suggested non-specific binding of CD64. Mouse IgG_{2a} and IgG_3 binds with high affinity to CD64 and the anti-CD11a antibody used was of the IgG_{2a} isotype whilst the anti-CD11b antibody was IgG_1. Although intact antibodies recognising epitopes of CD11b/CD18 have been demonstrated to reduce normal PMN adhesion to TNF-α treated endothelium,[54] antibody-blocking studies were repeated at 4°C to minimise any possible CD64-mediated enhanced adhesion. At this temperature, significant reductions in patient PMN adherence was observed. As a result, more patients need to be analysed but there does appear to be a role for CD11a and CD11b in the adhesion of patient PMNs to endothelium.

Two main confounding factors need to be addressed in this study. Firstly, this was a pilot study and the number of experiments performed were few making it difficult to draw conclusions. Increasing the number of cases studied will hopefully clarify unresolved issues. Secondly, it is unclear if PMN Fc receptor upregulation and its binding with our blocking antibodies had a role in producing our mixed results. To clarify this, further experiments with anti-Fc receptor antibodies could be performed. Qureshi et al[55] have already demonstrated that PMNs from SIRS patients not only were likely to express CD64 but also at a higher intensity. The supranormal binding of these cells to endothelium was also impeded by anti-CD64 antibodies.

In summary, this study has shown that increased adhesion of PMNs from SIRS patients may have a role in the pathogenesis of the syndrome. The anti-sialylated Lewis *x* antibody-blocking studies showed that inhibition of PMN adhesion to TNFα treated endothelium occurred when PMNs were incubated at 37°C with antibody. Incubation of patient PMNs with the anti-CD11a and anti-CD11b antibodies at 4°C reduced the adhesion of patient PMNs to untreated and treated endothelium although no overall pattern of inhibition was noted.

Further studies in this area are warranted as specifically designed leucocyte depletion filters may improve the outcome of SIRS. The use of such filters has been validated in cardiopulmonary bypass[56] and more recently in SIRS.[57]

Acknowledgement
The author would like to thank Dr KA Brown of the Rayne Institute, London for supervising the work.

References

1. Bone RC, Balk RA, Cerra FB et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101:1644-55.
2. Rangel-Frausto MS, Pittet D, Costigan M et al. The natural history of the systemic inflammatory response syndrome (SRIS). A prospective study. JAMA 1995; 273:117-23.
3. Parker MM and Pariillo JE. Septic shock: haemodynamics and pathogenesis. JAMA 1983; 250:3324-27.
4. Bone RC, Fisher CJ Jr., Clemmer TP et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Eng J Med 1987; 317:653-58.
5. Schoenberg MH, Weiss M, Radermacher P. Outcome of patients with sepsis and septic shock after ICU treatment. Langenbecks Arch Surg 1998; 383:44-8.
6. Astiz ME, Rackow EC. Septic shock. Lancet 1998; 351:1501-05.
7. Goris RJA. MODS/SIRS: Result of an overwhelming inflammatory response? World J Surg 1996; 20:418-21.
8. Weiss SJ. Tissue destruction by neutrophils. N Eng J Med 1989; 320:365-76.
9. Windsor ACJ, Mullen PG, Fowler AA et al. Role of the neutrophil in adult respiratory distress syndrome. Br J Surg 1993; 80:10-7.
10. Carlos TM, Harlan JM. Leukocyte-endothelial adhesion molecules. Blood 1994; 84: 2068-101.
11. McEver RP. Selectins. Curr Opin Immunol 1994; 6:75-84.
12. Bevilacqua MP. Endothelial-leukocyte adhesion molecules. Ann Rev Immunol 1995; 11:767-804.
13. Ley K, Azkrzewicz A, Hanski C et al. Sialylated O-glycans and L-selectin sequentially mediate myeloid cell rolling in vivo. Blood 1995; 5:3727-35.
14. Vestweber D, Blanks JE. Mechanisms that regulate the function of the selectins and their ligands. Physiol Rev 1999; 79:181-213.
15. Lawrence MB, Springer TA. Neutrophils roll on E-selectin. J Immunol 1993; 151:6338-46.
16. Kishimoto TK, Jutila MA, Berg EL et al. Neutrophil Mac-1 and MEL-14 adhesion proteins inversely regulated by chemotactic factors. Science 1989; 245:1238-41.
17. Gopolan PK, Smith CW, Lu H et al. Neutrophil CD18-dependent arrest on intercellular adhesion molecule 1 (ICAM-1) in shear flow can be activated through L-selectin. J Immunol 1997; 158:376-75.
18. Lo SK, Lee Suining, Ramos RA et al. Endothelial-leukocyte adhesion molecule 1 stimulates the adhesive activity of leukocyte integrin CR3 (CD11b/CD18, Mac-1, $\alpha_m\beta_2$) on human neutrophils. J Exp Med 1991; 173:1493-500.
19. Carlos TM, Harlan JM. Leukocyte-endothelial adhesion molecules. Blood 1994; 84:2068-101.
20. Smith CW, Rothlein R, Hughes BJ et al. Recognition of an endothelial determinant for CD18-dependent human neutrophil adherence and transendothelial migration. J Clin Invest 1998; 82:1746-56.
21. Veddar NB, Harlan JM et al. Increased surface expression of CD11b/CD18 (Mac-1) is not required for stimulated neutrophil adherence to culture endothelium. J Clin Invest 1988; 81:676-82.
22. Altieri DC, Bader R, Mannucci PM et al. A monoclonal antibody reacting with distinct adhesion molecules defines a transition in the functional state of the receptor CD11b/CD18 (mac-1). J Immunol 1988; 141:2656.
23. Seaver B, Seaver S. Tumor necrosis factor and CD11/CD18 (β2) integrins act synergistically to

lower cAMP in human neutrophils. J Cell Biol 1990; 111:2171-81.
24. Luscinskas FW, Brock AF, Arnaout MA et al. Endothelial-leukocyte adhesion molecule-1-dependent and leukocyte (CD11b/CD18)-dependent mechanisms contribute to polymorphonuclear leukocyte adhesion to cytokine-activated human vascular endothelium. J Immunol 1989; 142:2557-63.
25. Arnaout MA, Lanier LL, Faller DV. Relative contribution of the leukocyte molecules Mo1, LFA-1, and p150,95 (LeuM5) in adhesion of granulocytes and monocytes to vascular endothelium is tissue- and stimulus-specific. J Cellular Physiol 1988; 137:305-9.
26. Smith CW, Marlin SD, Rothelin R et al. Cooperative interactions of LFA-1 and Mac-1 with intercellular adhesion molecule-1 in facilitating adherence ad transendothelial migration of human neutrophils in vitro. J Clin Invest 1989; 83:2008-17.
27. Mashio AD, Zanetti A, Corada M et al. Polymorphonuclear leukocyte adhesion triggers the disorganisation of endothelial cell-to-cell adherens junctions. J Cell Biol 1996; 135:497-510.
28. Allport JR, Ding H, Collins T et al. Endothelial-dependent mechanisms regulate leukocyte transmigration: a process involving the proteasome and disruption of the vascular endothelial-cadherin complex at endothelial cell-to-cell junctions. J Exp Med 1997; 186:517-27.
29. Christofidou-Solomidou M, Nakada MT, Williams J et al. Neutrophil platelet endothelial cell adhesion molecule-1 participates in neutrophil recruitment at inflammatory sites and is down-regulated after leukocyte extravasation. J Immunol 1997; 158:4872-8.
30. Klava A, Windosr AC, Ramsden CW et al. Enhanced polymorphonuclear leucocyte adhesion after surgical injury. Eur J Surg 1997; 163:747-52.
31. Tellado JM, Christou NV. Activation state of polymorphonuclear leukocytes in surgical patients: Characterization of surface receptor expression. Surgery 1993; 113:624-30.
32. McGill SN, Ahmed NA, Hu F et al. Shedding of L-selectin as a mechanism for reduced polymorphonuclear neutrophil exudation in patients with the systemic inflammatory response syndrome. Arch Surg 1996; 131:1141-47.
33. Gearing AJH, Newman W. Circulating adhesion molecules in disease. Immunol Today 1993; 14:506-12.
34. Cowley HC, Heney D, Gearing AJ et al. Increased circulating adhesion molecule concentrations in patients with the systemic inflammatory response syndrome: a prospective cohort study. Crit Care Med 1994; 22:651-7.
35. Chen X, Christou NV. Relative contribution of endothelial cell sand polymorphonuclear neutrophil activation in their interactions in systemic inflammatory response syndrome. Arch Surg 1996; 131:1148-54.
36. McDonagh PH, Wilson DS, Iwamura H et al. CD18 antibody treatment limits early myocardial reperfusion injury after initial leukocyte deposition. J Sur Res 1996; 64:139-49.
37. Hansbrough JF, Wikstrom T, Braide M et al. Effects of E-selectin and P-selectin blockade on neutrophil sequestration in tissues and neutrophil oxidative burst in burned rats. Crit Care Med 1993; 24:1366-72.
38. Mulligan MS, Watson SR, Fennie C et al. Protective effects of selectin chimeras in neutrophil-mediated lung injury. J Immunol 1993; 151:6410-7.
39. Pinksy MR, Vincent JL, Deviere J et al. Serum cytokine levels in human septic shock. Chest 1993; 103:565-75.
40. Simons RK, Hoyt DB, Winchell RJ et al. Elevated selectin levels after severe trauma: a marker for sepsis and organ failure and a potential target for immunomodulatory therapy. J Trauma 1996; 41:653-62.
41. Cowley HC, Heney D Gearing AJ et al. Increased circulating adhesion molecule concentrations in patients with the systemic inflammatory response syndrome: a prospective cohort study. Crit Care Med 1994; 22:651-7.

42. Tracey KJ, Fong Y, Hesse DG et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature 1987; 330:662-4.
43. Goldman G, Welbourn R, Klausner JM et al. Ischaemia activates neutrophils but inhibits their local and remote diapedesis. Ann Surg 1990; 211:196-201.
44. Luscinkas FW, Cybulsky MI, Kiely JM et al. Cytokine-activated human endothelial monolayers support enhanced neutrophil transmigration via a mechanism involving both endothelial-leukocyte adhesion molecule-1 and intercellular adhesion molecule-1. J Immunol 1991; 146:1617-25.
45. Simms HH and D'Amico R. Polymorphonuclear leukocyte dysregulation during the systemic inflammatory response syndrome. Blood 1994; 83:1398-407.
46. Galley HF, Davies M, Webster NR. Zanthine oxidase activity and free radical generation in patients with sepsis syndrome. Crit Care Med 1996; 24:1649-53.
47. Jimenez MF, Watson RW, Parodo J et al. Dysregulated expression of neutrophil apoptosis in the systemic inflammatory response syndrome. Arch Surg 1997; 132:1263-9.
48. Leeuwenberg JF, Jeunhomme GM, Buurman WA. Adhesion of polymorphonuclear cells to human endothelial cells. Adhesion-molecule-dependent, and Fc receptor - mediated adhesion molecule independent mechanisms. Clin Exp Immunol 1990; 81:496-500.
49. Akerley WL, Guyre PM, Davis BH. Neutrophil activation through high-affinity Fcγ receptor using a monomeric antibody with unique properties. Blood 1991; 77:607.
50. Buckle AM, Jayaram Y, Hogg N. Colony-stimulating factors and interferon-gamma differentially affect cell surface molecules shared by monocytes and neutrophils. Clin Exp Immunol 1990; 81:339-45.
51. Lemaire LCJM, Van Deventer SJH, Van Lanshcot JJB et al. Phenotypical characterization of cells in the thoracic duct of patients with and without systemic inflammatory response syndrome and multiple organ failure. Scand J Immunol 1998; 47:69-75.
52. Stocks SC, Kerr MA. Stimulation of neutrophil adhesion by antibodies recognizing CD25 (Le^x) and CD15-expressing carcinoembryonic antigen-related glycoprotein NCA-160. Biochem J 1992; 288:23-7.
53. Thiel M, Zourelidis C, Chambers JD et al. Expression of beta-2 integrins and L-selectin on polymorphonuclear leukocytes in septic patients. Eur Surg Res 1997; 29:160-75.
54. Gamble JR, Harlan JAM, Klebanoff SJ et al. Stimulation of the adherence of neutrophils to umbilical endothelium by human recombinant tumor necrosis factor. Proc Natl Acad Sci 1985; 82:8667-71.
55. Qureshi SS, Lewis SM, Gant VA et al. Increased distribution and expression of CD64 on blood polymorphonuclear cells from patients with the systemic inflammatory response syndrome (SIRS). Clin Exp Immunol 2001; 125:258-65.
56. Morris SH. Leukocyte reduction in cardiovascular surgery. Perfusion 2001; 16:371-80.
57. Brown KA, Lewis SM, Hill TA et al. Leucodepletion and the interaction of polymorphonuclear cells with endothelim in systemic inflammatory response syndrome. Perfusion 2001; 16 (suppl):75-83.

Intrathecal Morphine for Post-Cesarean Analgesia: A Prospective Audit of 1,750 Cases

[1]Anne KWAN, [2]Arthur YW LUI, and [3]Angela WAI

Department of Anaesthesiology and Pain Medicine, United Christian Hospital.

SUMMARY

Single dose of intrathecal morphine is frequently used to provide postopeartive analgesia after cesarean section. The main concern for the use of intrathecal morphine rests on its safety. The minor complications are nausea, vomiting, pruritis, hypotension, drowsiness, urinary retention and the serious complications are neurological damage and respiratory depression. The aim of this audit is to examine the safety of intrathecal morphine 0.2 mg for analgesia after cesarean delivery in a large general hospital. All patients who received intrathecal morphine for postoperative analgesia after cesarean section between January 1998 and December 2002 are included in the study. Data recorded include patients' demographic data and associated medical diseases, routine postoperative observations (heart rate, blood pressure, respiratory rate), postoperative pain, sedation, nausea and vomiting scores. Other complications are also recorded. Of 1,750 eligible patients, 1,422 (81.3%) had pain scores ≤ 2 and 1,697 (97%) had pain scores ≤ 4 at rest. Upon coughing or movement, 631 (36%) had pain scores ≤ 2 and 1,331 (76%) patients had pain scores ≤ 4. 1,530 (87.5%) patients gave a satisfaction scores of good or excellent for the acute pain service. The incidence of nausea or vomiting was 25.8%, pruritus is 59%, and urinary retention requiring catheterization was 21.6%. 25 (1.43%) patients are drowsy at some stage of postoperative period. There was no respiratory depression defined by respiratory rate of less than 12 breaths per minute. In conclusion, addition of morphine 0.2 mg to bupivacaine administered intrathecally is a safe method for providing analgesia after cesarean section.

Keywords:

Intrathecal, Spinal; Morphine, Opioid; Pain, Analgesia; Safety

Bull HK Coll Anaesthesiol 2007; 16:88-94

[1]MB BS, FFPMANZCA, FANZCA, FHKCA, FHKAM (Anaesthesiology), Dip Pain Mgt (HKCA), Dip Epi & Biostat, M Pal Care, Chief of Service and Consultant; [2]MBBS, FHKAM (Anaesthesiology), FHKCA, Medical Officer; [3]MBBS, FRCA, FHKCA, FHKAM (Anaesthesiology), Associate Consultant. *Department of Anaesthesiology and Pain Medicine, United Christian Hospital*

Address correspondence to: Dr Anne Kwan, Department of Anaesthesiology and Pain Medicine, United Christian Hospital, 130 Hip Wo Street Kwun Tong Kowloon Hong Kong SAR. Email: kwansk@ha.org.hk

Intrathecal morphine has been used for postoperative analgesia for over 20 years. Administration of opioid to animal spinal cords was found to produce profound analgesia in 1976.[1] In 1980, a study in human reported prolonged analgesia after a dose of 0.5 mg morphine administered with intrathecal amethocainc after herniorrhaphy.[2] The main concern for the use of intrathecal morphine however, rests on its safety. The minor complications include nausea, vomiting, pruritus, hypotension, drowsiness and urinary retention. The more serious complications which cause

significant apprehension to the anesthetist are neurological damage and respiratory depression.[3] Following intrathecal opioids, respiratory depression might appear 6-11 hours after administration and may persist up to 23 hours.[4]

The aim of this prospective audit was to examine the efficacy and safety of 0.2 mg of intrathecal morphine for postoperative analgesia after cesarean section in a large general hospital.

Methods

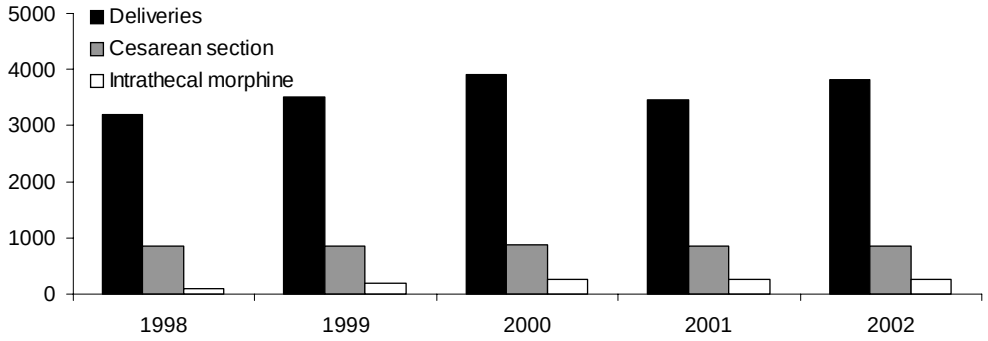
The audit was approved by the local ethics committee. All patients who received intrathecal morphine for their postoperative analgesia after cesarean section between January 1998 and December 2002 were included in the study. Patients who had failed spinal anesthesia for cesarean section were excluded. All patients consented to spinal anesthesia and intrathecal morphine for postoperative analgesia. Each patient received preservative free morphine 0.2 mg with isobaric or hyperbaric bupivacaine 2.0-2.4 ml via a 25 G pencil tip spinal needle. After surgery, all patients were monitored in the postnatal ward for complications. Observations included heart rate, blood pressure, respiratory rate, verbal pain scores, sedation scores were recorded and other complications within 24 hours of operation were noted and were treated according to departmental guidelines, if necessary. During the preoperative visit, patients were given detailed information about postoperative analgesia and were instructed to report to the attending nurses, or the acute pain team of any side effect as soon as possible. These included nausea or vomiting, dizziness, pruritus, lower limb weakness, or urinary retention. The definition of respiratory depression was bradypnea (< 12 breaths per minute). Whenever respiratory depression occurred, nursing staff was instructed to inform the duty anesthetist immediately and to start oxygen administration. Nurses will also gently shake patient to encourage her for breathing. If appropriate, naloxone 0.2 mg IVI was given every 5 minutes until resumption of normal respiration and oxygen saturation returned to >90%.

Hypotension was defined as a decrease in systolic blood pressure of more than 30% of the baseline preoperative value. After assessment and resuscitation by the on-call anesthetist, obstetrician would be informed if surgical complications were suspected to be the cause.

Table 1. Scoring systems of the observations

Verbal pain scores (0-10)	0	= no pain
	10	= worst pain
Nausea and vomiting scores	0	= no nausea
	1	= nausea
	2	= vomited
	3	= require antiemetic treatment
Sedation scores	0	= awake
	1	= drowsy
	2	= unrousable
Satisfaction scores	0	= poor
	1	= fair
	2	= good
	3	= excellent
Pruritus	0	= none
	1	= mild
	2	= moderate
	3	= needing treatment
Urinary retention	0	= none
	1	= catheterized intraoperatively
	2	= require catheterization for urinary retention

Figure 1. Deliveries, cesarean section, and intrathecal morphine rates between 1998-2002.



Moderate to severe nausea and vomiting were treated with metoclopramide 10 mg IVI every 6 hours. Pruritus was treated with chlorpheniramine 10 mg intramuscularly or intravenously every 4 hours.

We used a specially designed Pain Observation Chart for prospective patient data recording. Data recorded include patient's demographic data and associated medical diseases, routine postoperative observations (heart rate, blood pressure, respiratory rate), postoperative pain, sedation, nausea and vomiting scores. The rating of each scoring system is summarized in Table 1. Complications were also noted. The recordings were done by the post-natal ward nursing staff. All postnatal ward nursing staff was instructed to record the events and informed anesthetist when necessary. 24 hours after operation, one of the pain nurses from the acute pain team would visit all patients for management of postoperative pain and auditing. Oral dologesic (containing dextropropoxyphene 32 mg and paracetamol 500 mg) tablet was prescribed every 4 hours for rescue analgesia. Alternatively, pethidine 50 mg IMI was given for severe pain.

Results

During the period between January 1998 and December 2002, a total of 1,750 patients received intrathecal morphine for postoperative analgesia after cesarean section. In addition, 60 (3.3%) patients had failed spinal and were excluded from the analysis. Approximately half of the cesarean sections were performed during emergency setting. The mean age of the patients is 31 (range 18 - 43) years. The incidence of cesarean delivery and spinal anesthesia for the period are shown the Figure 1. No patient

Figure 2. Verbal pain scores during the first 24 hours after surgery.

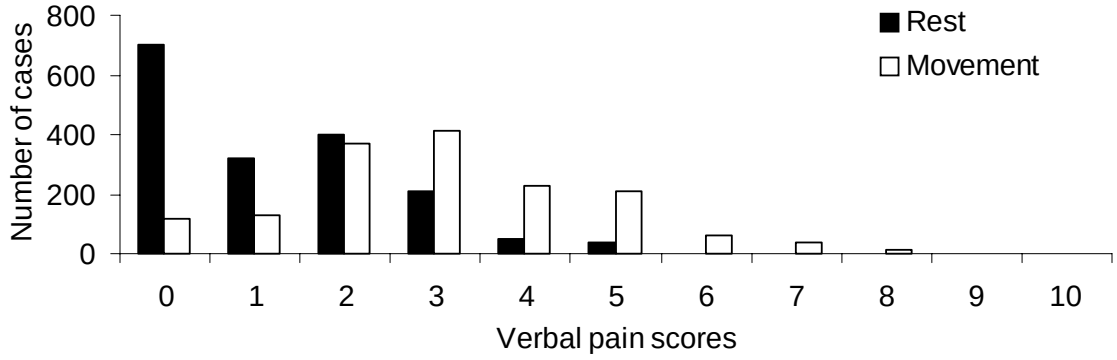
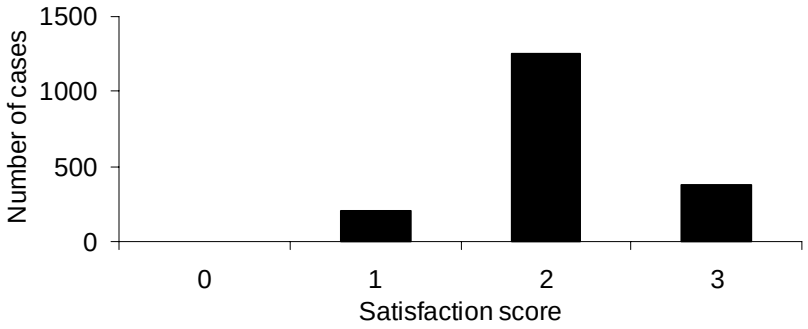


Figure 3. Satisfaction scores of the acute pain services.



requested intramuscular opioid and only 53 (3%) patients had oral dologesic for rescue analgesia within 24 hours of cesarean section (Figures 2 and 3). The incidence of complications is shown in Table 2. Only one patient has a brief episode of hypotension whom required fluid resuscitation. A total of 62 (3.5%) patients had postdural puncture headache (PDPH) but most of the headaches were mild and 7 (0.4%) patients required blood patch for the management of headache. No patient had respiratory depression. We found that 451 (25.8%) patients had nausea or vomiting but only 124 (7%) patients required treatment. Pruritus was also common and 155 (8.9%) patients required treatment.

Discussion

During the study period, there was increasing number of patients requesting spinal anesthesia for cesarean section. The technique is simple and quick to perform. There was also a low failure rate (3.3%). The initial increase was mainly among elective cesarean sections but towards the end of the study period, there was an increase in patients requiring both elective and emergency cesarean sections.

Generally, the quality of postoperative analgesia was good. The pain scores were low at 24 hours after the caesarean section. Our audit showed that pain relief was especially good during rest. In our audit, 1,697 (97%) patients have pain scores of 4 or less at rest and 1,331(76%) patients have pain scores of 4 or less when they cough or move. Patient satisfaction was high. 1,530 (73.6%) patients regarded the acute pain service team was good or excellent. Although satisfaction scores did not measure patient's level of analgesia, it does reflect patient's impression of the hospital service. No patient requested intramuscular opioid. Within 24 hours of cesarean section, only 53 (3%) patients took oral dologesic for pain relief. These reults reflect the high efficacy of a single dose of inthrathecal morphine.

Although neurological damage is the most serious complication, it is not a concern if preservative free morphine is used. In this audit, no neurological damage was reported. Several studies indicated that intrathecal morphine at a dose of 0.1 mg provided satisfactory analgesia.[6-8] However, earlier studies routinely use higher doses of intrathecal morphine without side effects.[9,10] After careful planning, we decided to use intrathecal morphine 0.2 mg with bupivacaine 2.0 to 2.4 ml. All patients were monitored for at least 24 hours to detect potential complications especially respiratory depression. Respiratory rate together with sedation scores are considered a more reliable monitor than respiratory rate alone.[11] We used both parameters to identify respiratory complication. We have 25 sedated patients but no respiratory depression was identified. When patients are found drowsy, the monitoring level

is escalated to continuous pulse oximetry and hourly respiratory rate. During the more intensive monitoring period, all of the25 patients had hemoglobin oxygen saturation > 97%. The respiratory rate was over 12 breaths per minute. The episodes of sedation were very brief and all of the 25 patients woke up within one hour. We suspect that all of the 25 patients have sleep deprivation as all of them had prolonged labor before they were advised to have the cesarean section. The results of our audit confirmed the safety of using intrathecal morphine 0.2 mg for postoperative analgesia in a postnatal ward of a general hospital setting.

We noted that 378 (21.6%) patients require catheterization for urinary retention. 86 patients had catheter inserted before cesarean section. The main reason for preoperative catheterization is prolonged labor. The catheters were left in those patients as postoperative urinary retention was expected in these patients. The rest of the patients would have "in-and-out" urinary catheters to empty their urinary bladders before the operation. Although urinary retention is a known complication of spinal anesthesia and intrathecal morphine may contribute to this complication, we found no urinary tract infection from catheterization.

Other complications included PDPH, hypotension, nausea, vomiting, pruritus, and drowsiness. PDPH is not a complication of intrathecal morphine and it may occur when the dura is punctured during spinal anesthesia. Most of the PDPH were mild and only 7 (0.4%) patients required blood patch treatment. The very low incidence of blood patching may reflect the local culture of patients and anesthetists in adopting a more conservative approach as well as the lack of pressure from a longer hospital stay.

Hypotension occurred in only one patient and it is adequately treated with additional fluid.1,650 (99%) patients returned to oral intake within 24 hours of operation and hypovolemia is an infrequent problem. Pruritus was the commonest finding in our audit. This finding was consistent with a previous study which reported a 90% incidence when intrathecal morphine 0.2 mg is used.[12] 1,034 (59%) patients complained of pruritus but only 155 (8.9%) patients required treatment. Pruritus is an annoying side effect but most of the time, it was mild and required no treatment. Apart from chlorpheniramine 10 mg, promethazine 25 mg has been shown effective in treatment of pruritus.[13] Ondansetron, apart from its antiemetic action, can also be used to treat intrathecal morphine induced pruritus.[14] Also, rectal diclofenac has be used to treat pruritis successfully.[15] Similar to previous reports, postoperative nausea and vomiting was another common complication in our audit.[16,17] Only 124 (7%) patients request treatment. We used metoclopramide 10 mg intravenously every 4 hours to treat nausea and vomiting and all patients respond to the treatment. Ondansetron has been shown to be a more efficacious antiemetic but it has not been shown to be better than metocloprmide or even saline in one study.[18] We chose metoclopramide because it is less expensive. Intravenous naloxone can reduce intrathecal morphine induced pruitus.[19] Whereas epidural naloxone can reduce both pruritus and nausea without affecting analgesia by epidural morphine.[20,21] The main use of naloxone is for the treatment of respiratory depression. It has been shown that naloxone can reverse respiratory depression but not analgesia induced by intrathecal morphine.[22]

Adding adrenaline to the intrathecal mixture has been shown to enhance postoperative analgesia after intrathecal morphine.[9] Intrathecal morphine is least expensive compared with most other forms of postoperative analgesia techniques.[23] It is particularly suitable for postoperative analgesia after cesarean section. In conclusion, addition of intrathecal morphine 0.2 mg to bupivacaine is a safe method for providing analgesia after cesarean section.

Acknowledgement

We would like to thank all the anesthetists, pain nurses, and post-natal ward staff in participating in the survey.

References

1. Yaksh T, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. Science 1976; 192:1357-8.
2. Nelson W, Katz J. Intrathecal morphine for post-operative pain relief. Anesthesiology 1980; 53:S218.
3. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61:276-310.
4. Barron DW, Strong JE. Postoperative analgesia in major orthopaedic surgery. Epidural and intrathecal opiates. Anaesthesia 1985; 40:748-53.
5. Goldblatt M. Spinal morphine in remote practice. Anaesth Intensive Care 1996; 24:615-6.
6. Yang T, Breen TW, Archer D, Fick G. Comparison of 0.25 mg and 0.1 mg intrathecal morphine for analgesia after cesarean section. Can J Anesth 1999; 46:856-60.
7. Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose-response relationship of intrathecal morphine for postcesarean analgesia. Anesthesiology 1999; 90:437-44.
8. Swart M, Sewell J, Thomas D. Intrathecal morphine for caesarean section: an assessment of pain relief, satisfaction and side-effects. Anaesthesia 1997; 52:373-7.
9. Goyagi T, Nishikawa T. The addition of epinephrine enhances postoperative analgesia by intrathecal morphine. Anesth Analg 1995; 81:508-13.
10. Tarkkila P. Torn K, Tuominen M, Lindgren L. Premedication with promethazine and transdermal scopolamine reduces the incidence of nausea and vomiting after intrathecal morphine. Acta Anaesthesiol Scand 1995; 39:983-6.
11. Wheatley RG, Madej TH, Jackson IJB, Hunter D. The first year's experience of an Acute Pain Service. Br J Anaesth 1991; 67:353-9.
12. Sarvela J, Halonen P, Soikkeli A, KorttilaK. A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery. Anesth Analg 2002; 95:436-40.
13. Slappendel R, Weber EW, Benraad B, van Limbeek J, Dirksen R. Itching after intrathecal morphine. Incidence and treatment. Eur J Anaesthesiol 2000; 17:616-2.
14. Charuluxananan S, Somboonviboon W, Kyolong 0, Nimcharoendee K. Ondansetron for treatment of intrathecal morphine-induced pruritus after cesarean delivery. Reg Anesth Pain Med 2000; 25:535-9.
15. Pitkanen MT, Numminen MK, Tuominen MK, Rosenberg PH. Comparison of metoclopramide and ondansetron for the prevention of nausea and vomiting after intrathecal morphine. Eur J Anaesthesiol 1997; 14:172-7.
16. Alhashemi JA, Crosby ET, Grodecki W, Duffy PJ, Hull KA, Gallant C. Treatment of intrathecal morphine-induced pruritus following caesarean section. Can J Anesth 1997; 44:1060-5.
17. Ready LB, Oden R, Chadwick HS, et al. Development of an anaesthesiology based postoperative pain management service. Anesthesiology 1988; 68:100-6.
18. Colbert S, O'Hanlon DM, Galvin S, Chambers F, Moriarty DC. The effect of rectal diclofenac on pruritus in patients receiving intrathecal morphine. Anaesthesia 1999; 54:948-52.
19. Dailey PA, Lee BG, Shnider SM, Abboud TK, Kotello DM, Noueihid R, et al. The effects of naloxone associated with the intrathecal use of morphine in labor. Anesth Analg 1985; 64:658-6.
20. Choi JH, Lee J, Choi JH, Bishop MJ. Epidural naloxone reduces pruritus and nausea without affecting analgesia by epidural morphine in bupivacaine. Can J Anesth 2000; 47:33-7.
21. Saiah M, Borgeat A, Wilder-Smith OH, Rifat

K, Suter PM. Epidural-morphine-induced pruritus: propofol versus naloxone. Anesth Analg 1994; 78:1110-3.

22. Jones RD, Jones JG. Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. Br Med J 1980; 281:645-6.
23. Vercauteren M, Vereecken K, La Malfa M, Coppejans H, Adriaensen H. Cost-effectiveness of analgesia after after Caesarean section. A comparison of intrathecal morphine and epidural PCA. Acta Anesthesiol Scand 2002; 46:85-9.

Jet Ventilation

[1]Katherine LAM

The Union Hospital, Tai Wai, Shatin, Hong Kong

SUMMARY

Jet ventilation is a useful ventilatory method for airway and thoracic surgery. There are many different techniques for jet ventilation, including high or low frequency jet ventilation, supraglotic, infraglottic and transtracheal techniques. They required catheters or metal injectors. Low frequency jet ventilation offers good surgical exposure while high frequency jet ventilation creates low airway pressure and little movement in the surgical field. Jet ventilation can be used in patients with bronchopleural fistula and tracheobronchial tree disruption with small air leak. There are however disadvantages. Jet ventilation required special equipments, it may induce barotrauma and gastric distension. It is also difficult to monitor the adequacy of ventilation. Jet ventilators can be manual or automatic. The practical aspects of setting up jet ventilation were reviewed in this article.

Keywords:

Jet ventilation, jet ventilators, high frequency ventilation, bronchoscopy, laryngoscopy, thoracic surgery

Bull HK Coll Anaesthesiol 2007; 16:95-8

In 1967, Sanders first devised a method to deliver jet ventilation by way of a rigid bronchoscope, permitting positive pressure ventilation in the absence of a gas tight system.[1] Since then, jet ventilation has become an useful technique in anesthesia. As part of a planned anesthetic technique, it may be used in procedures such as laryngoscopy and vocal cord surgery, as well as in thoracic surgery such as rigid bronchoscopy, airway surgery and lung resections. Transtracheal jet ventilation can also be used as an emergency backup in the "cannot-intubate; cannot ventilate" scenario.[2] In this article, we reviewed the advantages, disadvantages and the different techniques of jet ventilation. We also include some practical tips in using jet ventilation.

[1]MB ChB, FHKAM (Anaesthesiology), FHKCA, FANZCA, Consultant Anesthetist. *The Union Hospital*

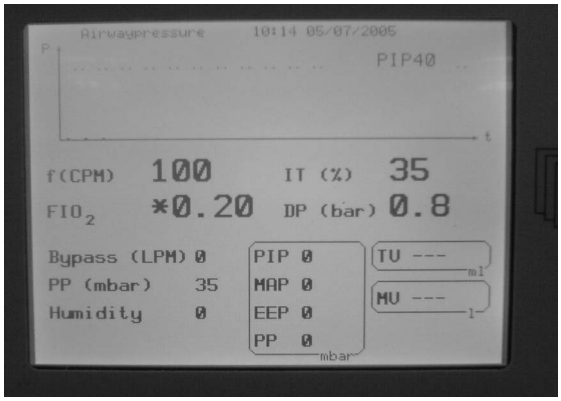
Address correspondence to: Dr Katherine Lam, The Union Hospital, 18 Fu Kin Street, Tai Wai, Shatin, N.T., Hong Kong. Email: katherinelamky@gmail.com

Different techniques of jet ventilation

Jet ventilation can be subdivided into low frequency jet ventilation (LFJV) and high frequency jet ventilation (HFJV). In LFJV the respiratory rate is less than 1Hz (60 cycles per minute), typically 10 to 20 cycles per minute is used for adults. Inspiration occurs bulk flow of oxygen is delivered, but there is also entrainment of room air via the Venturi effect. Expiration occurs with passive recoil of the lungs. Physiological tidal volumes are generated. Chest movement is clearly visible. The resultant motion of airway structures, however may necessitate intermittent periods of apnea when resection is required.[3]

Figure 1. An automatic jet ventilator

Figure 2. Screen display. DP = driving pressure, IT = inspiratory time, f = frequency, PP = peak pressure



High frequency ventilation was initially developed in the intensive care unit for ventilating patients with acute lung injury during 1970s and 1980s.[2] High frequency jet ventilation (HFJV) is one type of high frequency ventilation and has become useful in anesthesia. For HFJV, respiratory rate is very high (ranging from 1 to 10 Hz, or 60 to 600 cycles per minute) and tidal volume is typically small (2 ml/kg or around 150 ml in adults). This is close to the deadspace volume. Multiple mechanisms have been proposed to explain the resultant "deadspace ventilation". Apart from bulk flow and venture effect, other mechanisms include molecular diffusion (i.e. law of mass action), augmented diffusion (i.e. Taylor dispersion) and penduluft flow between adjacent areas of lung with varying time constants for alveolar emptying.[4]

Jet ventilation can be achieved either through a metal injector coupled to a rigid bronchoscope or a suspension laryngoscope, or through catheters placed inside the airway. Hence accordingly, jet ventilation can be supraglottic, infraglottic or transtracheal, depending on the location of the injector or catheter.

Advantages and Disadvantages

In airway and vocal cord surgery, it is always a challenge for the anesthetist to maintain good oxygenation and carbon dioxide elimination while providing optimal operating condition for the surgeons. The use of jet ventilation in these scenarios allows good surgical exposure without compromising ventilation. Jet ventilation can also be used safely in laser surgery. LFJV is frequently used in bronchoscopy and larygoscopy because of its simplicity.[5]

HFJV creates low airway pressure (typically around 5 cmH_2O), and because of the low tidal volume and high frequency it also causes less movement of the surgical field compared to both LFJV and conventional intermittent positive pressure ventilation (IPPV). Hence, its use has been described in patients undergoing thoracic surgery who cannot tolerate one lung ventilation, or that lung isolation has been technically difficult. Its use in ventilating

patients with bronchopleural fistula and tracheobronchial tree disruption has also been described as an alternative to differential lung ventilation. Because of the low airway pressure, the air leak through the fistula would be reduced compared to conventional IPPV.[4]

Complicated ventilation strategies can be specially designed for surgery to the major conducting airways using a combination of conventional IPPV and HFJV and different combinations of endotracheal or double-lumen tubes and catheters inserted into the airway.[4]

However, there are some disadvantages with the use of jet ventilation. Special equipments are required. There are also risks of barotrauma and air trapping especially when there is obstruction in the airway. Barotrauma can be presented in form of pneumothorax, pneumomediastinum and subcutaneous emphysema. The resulting lung hyperinflation and the development of auto-PEEP may impede venous return resulting in hemodynamic compromise.[3] Gastric distension may also occur. It should be clear that using this technique for airway surgery, the trachea is unprotected. It is also difficult to monitor ventilation compared with conventional IPPV, and administration of volatile agents is difficult, if not impossible. Because of the high flow of gases supplied to the patient in an open system, there is also theoretical infectious risk to other personnel in the operating theatre.

Practical tips in setting up jet ventilation

Jet ventilators can be divided into manual and automatic jet ventilators. Manual jet ventilators are usually smaller in size and simpler to use. LFJV can be achieved by connecting the ventilator to an oxygen supply, setting the driving pressure and then activating a handheld trigger to deliver the jet. The inspiratory-to-expiratory (IE) ratio is determined by the operator who controls the both the inspiratory and expiratory times.

Automatic jet ventilator (Figure 1) allows a hands-free operation for both LFJV and HFJV. Depending on the model, other facilities may include humidification, bypass flow, airway pressure monitoring, adjustable alarms and pressure limits (Figure 2).

Before the start of anesthesia, one should decide on the technique of jet ventilation (HFJV or LFJV, supraglottic, infraglottic or transtracheal technique, using injectors or catheters) and review for contraindications of jet ventilation. Obesity is a relative contraindication, and jet ventilation should be used with caution in patient with added risk of air trapping. Reassess the airway to ensure that there is a patent pathway for passive expiration for infraglottic and transtracheal technique. Lung images with CT or MR scans, lung function test using flow volume loops and previous endoscopy findings are useful to assess the airway. In case of transtracheal jet ventilation in emergency situation, one should combine triple airway maneuver and oral or nasopharyngeal airways should be inserted to ensure a patent pathway for expiration.

One should set up the jet ventilator and test its function according to manufacturer's recommendation. Correct connections with the catheter or injector should then be selected. As for anesthesia, total intravenous anesthesia with propofol infusion may be preferred. Propofol is often chosen because of the rapid emergence and return of airway reflexes.[1] Muscle relaxation is recommended. Succinylcholine is the ideal drug for short procedure in which profound muscle relaxation but rapid recovery is required. Infusion of succinylcholine has been used, but extended infusion may induce phase II blockade. The ideal short acting non-depolarizing agent has not been developed yet. Mivacurium is slow in onset and offset compared to succinylcholine and exhibits inconsistent time to maximum block.[1] Intermediate acting non-depolarizing agents can be used. One should also consider the placement of a gastric tube in order to prevent gastric distension.

Typical initial settings for LFJV and HFJV in adults are listed in Table 1.For children, use lower driving pressure (e.g. 5-10 psi or 0.35-0.7 bar for LFJV), longer IE ratio (at least 1:4), and higher respiratory rates. The settings will need to be adjusted for different sizes of catheters and injectors It should also be adjusted for different chest compliance. The anesthetists can monitor the ventilation by observing the chest excursion, pulse oximetry and arterial blood gas measurements. The use of continuous airway pressure monitoring, when available in some models of jet ventilators, helps to prevent barotraumas.[3] Always use pressure limits of less than 40 mBar (40 cmH_2O) and for children use pressure limits as low as 10 to 15 mBar.

Table 1. Typical initial setting for jet ventilation in adults. High frequency jet ventilation (HFJV); Low frequency jet ventilation (LFJV)

	LFJV	***HFJV***
Inspiratory oxygen concentration (fiO_2)	1.0	1.0
Driving pressure	2-3 bar (~30-50 psi)	1.5 bar (~22 psi)
Frequency	10	100
Inspiratory time (% of cycle)	< 25 % (hence IE Ratio at least 1:3) When large bore catheters (e.g. 14G) are used, inspiratory time should be < 1 second to reduce the chance of barotrauma	20-50%

References

1. Sanders RD. Two ventilating attachments for bronchoscopes. Del Med J 1967; 39:170.
2. Benumof J. Transtracheal jet ventilation via percutaneous catheter and high pressure source. In Benumof: Airway management, principles and practice Mosby 1996.
3. McRae K. Anaesthesia for airway surgery. Anesthesiol Clinics North Am 2001; 19:110-7.
4. Benumof J. Anaesthesia for thoracic surgery. WB Saunders 1995.
5. Magit AE, Davidson TM. Performance of rigid bronchoscopy. In Benumof: Airway management, principles and practice, Mosby 1996.

Honorary Treasurer's Report for the Financial Year 2006

Despite an increase in commitment to the Institute of Clinical Stimulation (ICS) by providing a half time nurse since end of last year, we manage to have a surplus of HK$853,966 for the 2006 financial year. Together with the retained surplus of HK$11,662,221 brought forward from 2005, out total assets at end of 2006 became HK$ 12,516,187. As the payment of some of the expenditures incurred in 2006 will be settled in year 2007, the actual surplus is less than that appeared in the year 2006 balance sheet. For the coming year we will be upgrading some office equipment and replacing some items at the ICS. We will also start working on the translation of some of the guidelines hoping to bring us closer to our mainland colleagues. With the planned expenditure, we anticipate a balanced budget in year 2007.

Income

Our major source of income still came from annual subscriptions by Members and Fellows. We had 20 new Fellows joined our college in 2006. At end of last year we had a total of 464 Members and 331 Fellows. The total income from subscriptions was over one million dollars (HK$1,006,263).

The various courses ran by the college were well received by our Fellows and Members as well as other colleagues. The income generated from courses, workshops was HK$104,933. Although the examination fees for all the examinations added up to HK$531,864, the expenses escalated to HK$803,852. The overall balance hence was a deficit of HK$276,988.

Our Annual Scientific Meeting (ASM) once again proved a very popular event. As we had more speakers in 2006 than all previous years, the total income was only a moderate amount. Our share which represented half of the profit was HK$199,712. After reimbursing our new fellows (HK$12,600), our net profit stood at HK$187,112. Although we would continue to organize the ASM with our Society, we would recover some of the seeding fund and that change would be reflected in our next financial report.

As we had a substantial sum in the fixed deposit account, we managed to have a rather steady income from this source. The total interest generated was HK$328,019.

The overall income from various activities stood at HK$1,416,736.

Expenditure

Total expenditure by our college in year 2006 was HK$ 562,770. College chamber management fee was HK$73,980. The various maintenance fees amounted to around HK$100,000. Staff salary remained as the major expense. The total salary cost added up to around HK$300,000. The increased spending mainly came from an extra staff joining from end of last year.

Annual subscription

It was resolved that the annual subscription for year 2008 would continue to be HK$2,500, and HK$625 for Fellows and Overseas Fellows respectively. The fees for Members, Overseas Members and Members over the age of 65 years will be waived for one year in view of our college's strong financial position. Similar to previous years, for Fellows over 65 years of age, a nominal subscription of HK$50 would be charged.

Appreciation

The financial status of our college remains very healthy. This is the efforts of many of our most dedicated colleagues who voluntarily invest a lot of their times to perform a range of excellent services. I would like to take this opportunity to thank them again.

Anne KWAN
HKCA Honorary Treasurer

INDEPENDENT AUDITORS' REPORT TO THE SHAREHOLDERS OF THE HONG KONG COLLEGE OF ANAESTHESIOLOGISTS (incorporated in Hong Kong with liability limited by guarantee) Report on the Financial Statements

We have audited the financial statements of The Hong Kong College of Anaesthesiologists set out on pages 101 to 108, which comprise the balance sheet as at 31st December, 2006, and the income statement, the statement of changes in equity and the cash flow statement for the year then ended, and a summary of significant accounting policies and other explanatory notes.

COUNCIL MEMBERS' RESPONSIBILITY FOR THE FINANCIAL STATEMENTS

The council members are responsible for the preparation and the true and fair presentation of these financial statements in accordance with Hong Kong Financial Reporting Standards issued by the Hong Kong Institute of Certified Public Accountants and the Hong Kong Companies Ordinance. This responsibility includes designing, implementing and maintaining internal control relevant to the preparation and the true and fair presentation of financial statements that are free from material misstatement, whether due to fraud or error; selecting and applying appropriate accounting policies; and making accounting estimates that are reasonable in the circumstances.

AUDITORS' RESPONSIBILITY

Our responsibility is to express an opinion on these financial statements based on our audit. This report is made solely to you, as a body, in accordance with section 141 of the Hong Kong Companies Ordinance, and for no other purpose. We do not assume responsibility towards or accept liability to any other person for the contents of the report.

We conducted our audit in accordance with Hong Kong Standards on Auditing issued by the Hong Kong Institute of Certified Public Accountants. Those standards require that we comply with ethical requirements and plan and perform the audit to obtain reasonable assurance as to whether the financial statements are free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditors' judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditors consider internal control relevant to the entity's preparation and true and fair presentation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates made by the council members, as well as evaluating the overall presentation of the financial statements.

We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

OPINION

In our opinion, the financial statements give a true and fair view of the state of affairs of the college as at 31st December, 2006 and of the college's profit and cash flows for the year then ended in accordance with Hong Kong Financial Reporting Standards and have been properly prepared in accordance with the Hong Kong Companies Ordinance.

R. Kadir & Company
Certified Public Accountants (Practising)
HONG KONG
25th May, 2007

THE HONG KONG COLLEGE OF ANAESTHESIOLOGISTS
INCOME STATEMENT
FOR THE YEAR ENDED 31st DECEMBER, 2006

	Note	2006	2005
		HK$	HK$
Turnover	3	1,006,263	1,021,851
Other revenue	3	410,473	742,177
		1,416,736	1,764,028
Administrative expenses		562,770	723,574
Operating surplus	4	853,966	1,040,454
Surplus brought forward		11,662,221	10,621,767
Surplus carried forward		12,516,187	11,662,221

BALANCE SHEET AS AT 31st DECEMBER, 2006

	Note	2006	2005
		HK$	HK$
NON-CURRENT ASSETS			
Property, plant and equipment	13	6,393	23,524
Held-to-maturity investments	12	4,500,000	5,100,000
		4,506,393	5,123,524
CURRENT ASSETS			
Held-to-maturity investments	12	5,100,000	1,099,833
Accounts receivable		39,053	77,864
Cash and bank balances		3,199,901	5,769,077
Prepayment		-	27,500
		8,338,954	6,974,274
LESS : CURRENT LIABILITIES			
Accounts payable and accruals		329,160	430,927
Receipt in advance		-	4,650
		329,160	435,577
NET CURRENT ASSETS		8,009,794	6,538,697
NET ASSETS		12,516,187	11,662,221
Represented by :			
RETAINED SURPLUS		12,516,187	11,662,221

THE HONG KONG COLLEGE OF ANAESTHESIOLOGISTS
STATEMENT OF CHANGES IN EQUITY
FOR THE YEAR ENDED 31st DECEMBER, 2006

	2006	2005
	HK$	HK$
Opening balance - Total equity	11,662,221	10,621,767
Net surplus for the year	853,966	1,040,454
Closing balance - Total equity	12,516,187	11,662,221

CASH FLOW STATEMENT
FOR THE YEAR ENDED 31st DECEMBER, 2006

	2006	2005
	HK$	HK$
Operating activities		
Surplus for the year	853,966	1,040,454
Depreciation	17,131	29,886
Interest income	(328,019)	(90,576)
Operating surplus before working capital changes	543,078	979,764
Decrease/(Increase) in accounts receivable	38,811	(20,994)
Decrease in trade and other payable	(101,767)	(347,257)
Decrease in prepayment	27,500	95,331
(Decrease)/Increase in receipt in advance	(4,650)	4,625
Net cash inflow from operating activities	502,972	711,469
Investing activities		
Payment for purchase of fixed assets	-	(1,280)
Payment for purchase of held-to-maturity investments	(3,400,167)	(5,100,603)
Interest received	328,019	90,576
Decrease in cash and cash equivalents	(2,569,176)	(4,299,838)
Cash and cash equivalents at 1st January	5,769,077	10,068,915
Cash and cash equivalents at 31st December	3,199,901	5,769,077

NOTES TO THE FINANCIAL STATEMENTS

1. GENERAL INFORMATION

The College was incorporated in Hong Kong on 26th September, 1989 under the Companies Ordinance and its liability is limited by guarantee. The address of its registered office and principal place of business is Room 807, Hong Kong Academy of Medicine Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong. Its principal activity is the promotion of the knowledge on anaesthesiology among the members of the College.

Under the provisions of the College's Memorandum and Articles of Association, every member shall, in the event of the college being wound up, contribute to the assets of the College to the extent of HK$100. At 31st December, 2006, the College had 455 members.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

The principal accounting policies applied in the preparation of these financial statements are set out below. These policies have been consistently applied to all the years presented, unless otherwise stated.

(a) Basis of preparation

The College's financial statements have been prepared in accordance with Hong Kong Financial Reporting Standards ("HKFRSs"). The financial statements are prepared under the historical cost convention, except that the held-to-maturity investments are stated at their amortized cost as explained in note 2 (c).

The preparation of financial statements in conformity with HKFRSs requires the use of certain critical accounting estimates. It also requires management to exercise its judgment in the process of applying the appropriate accounting policies.

The adoption of new/revised HKFRSs

In 2006, the College adopted the new/revised standards and interpretations of HKFRSs below, which are relevant to its operations.

HKAS 1	Presentation of Financial Statements
HKAS 7	Cash Flow Statements
HKAS 8	Accounting Policies, Changes in Accounting Estimates and Errors
HKAS 32	Financial Instruments: Disclosures and Presentation
HKAS 39	Financial instruments: Recognition and Measurement

The adoption of the above accounting standards has no significant effect on the financial statements of the company.

(b) Revenue recognition

Donation is recorded on the cash basis.
Entrance and subscription income is recognized when he right to receive payment is established.
Interest income is recognized on a time-proportion basis using the effective interest method.
Revenue on other events is recognized when the right to receive such revenue has been established.

(c) Held-to-maturity investments

Held-to-maturity investments are non-derivative financial assets with fixed or determinable payments and fixed maturities that the College's management has the positive intention and ability to hold to maturity. They are included in non-current assets, except for those with maturities less than 12 months from the balance sheet date, which are classified as current assets. Held-to-maturity investments are carried at amortized cost using the effective interest method.

The fair value of the held-to-maturity investments are based on the current bid prices offered by the dealers/issuers.

(d) Property, plant and equipment

Property, plant and equipment are stated at historical cost less accumulated depreciation and impairment losses. Historical cost includes expenditure that is directly attributable to the acquisition of the items.

Subsequent expenditure is charged to the asset's carrying amount only when it is probable that future economic benefits associated with the item will flow to the College and the cost of the item can be measured reliably. All other repairs and maintenance costs are expensed in the income statement during the financial period in which they are incurred.

Depreciation of property, plant and equipment is calculated to allocate cost to their residual values over their estimated useful lives, as follows:

Furniture and equipment	5 years
Computers	3⅓ years

The assets' residual values and useful lives are reviewed, and adjusted if appropriate, at each balance sheet date.

An asset's carrying amount is written down immediately to its recoverable amount if the asset's carrying amount is greater than its estimated recoverable amount.

(e) Cash and cash equivalents

Cash and cash equivalents include cash in hand, deposits held at call with banks, other short-term highly liquid investments with original maturities of three months or less, and bank overdrafts. Bank overdrafts are shown within borrowings in current liabilities on the balance sheet.

(f) Employee benefits

The company has established a mandatory provident fund scheme ("MPF Scheme") in Hong Kong. The assets of the MPF Scheme are held in separate trustee-administered funds. Both the company and the employees are required to contribute 5% of the employees' relevant income, subject to a maximum of HK$1,000 per employee per month. The company's contributions to the MPF Scheme are expensed as incurred.

(g) Trade and other receivables

A provision for impairment of trade and other receivables is established when there is objective evidence that the company will not be able to collect all amounts due according to the original terms of receivables. The amount of the provision is the difference between the assets' carrying amount and the present value of estimated future cash flows, discounted at the effective interest rate. The amount of the provision is recognized in the income statement.

(h) Trade and other payables

Trade and other payables are initially measured at fair value and after initial recognition, at amortized cost, except for short-term payables with no stated interest rate and the effect of discounting being immaterial, that are measured at their original invoice amount.

3. TURNOVER AND REVENUE

The college is principally engaged in the promotion of knowledge on anaesthesiology among the members of the college.

		2006	**2005**
		HK$	**HK$**
Turnover			
Members' entrance fees and subscriptions		1,006,263	1,021,851
OTHER REVENUE			
Donation		-	15,350
Interest income		328,019	90,576
Miscellaneous		51,470	193,581
Surplus/(Deficit) from events :-			
Annual scientific meeting	7	199,712	229,955
Institute of Clinical Simulation	8	3,327	3,230
Courses	9	104,933	130,458
Examination	10	(276,988)	79,027
		410,473	742,177
TOTAL REVENUE		1,416,736	1,764,028

4. OPERATING SURPLUS

Operating surplus is stated after charging the following :-

	2006 HK$	2005 HK$
Staff costs	278,046	270,720
Mandatory provident fund	14,020	11,317

5. FINANCIAL RISK MANAGEMENT

(a) Financial risk factors

The College's activities expose it to credit risk and liquidity risk as described below. The College's overall risk management policies focus on minimizing the potential adverse effects on the College by closely monitoring the individual exposure as follows:

(i) Credit risk

The College has no significant concentrations of credit risk. It has policies in place to ensure that income from membership subscription and other events are primarily collected in cash.

(ii) Liquidity risk

The College's policy is to regularly monitor current and expected liquidity requirements to ensure that it maintains sufficient reserves of cash and cash equivalents to meet its liquidity requirements in the short and longer term.

(b) Fair value estimation

The nominal value less estimated credit adjustments of account receivables and payables are assumed to approximate their fair values.

6. CRITICAL ACCOUNTING ESTIMATES AND JUDGEMENT

The College 's management makes assumptions, estimates and judgments in the process of applying the company's accounting policies that affect the assets, liabilities, income and expenses in the financial statements prepared in accordance with HKFRSs. The assumptions, estimates and judgments are based on historical experience and other factors that are believed to be reasonable under the circumstances. While the management reviews their judgments, estimates and assumptions continuously, the actual results will seldom equal to the estimates.

Critical judgments in applying the company's accounting policies

Certain critical judgments in applying the company's accounting policies are set out as follows:

Held-to-maturity investments

The College follows the guidance of HKAS 39 on classifying non-derivative financial assets with fixed or determinable payments and fixed maturity as held-to-maturity. This classification requires significant judgment. In making this judgment, the College evaluates its intention and ability to hold such investments to maturity.

If the College fails to keep these investments to maturity other than for specific circumstances explained in HKAS 39, it will be required to reclassify the whole class as available-for-sale. The investments would therefore be measured at fair value and not amortized cost.

If the class of held-to-maturity investments is tainted, the fair value would decrease by HK$66,317, with a corresponding entry in the fair value reserve.

7. ANNUAL SCIENTIFIC MEETING

	2006 HK$	2005 HK$
Income	1,263,543	1,311,300
Less : Cost and expenses	864,118	851,390
	399,425	459,910
Less : 50% profit shared with SAHK	199,713	229,955
	199,712	229,955

From the year ended 31st December, 2006, the combined scientific meeting was organized jointly with The Society of Anaesthesia of Hong Kong ("SAHK"). The College and the SAHK agreed to share the income and expenses of the meeting equally.

8. INSTITUTE OF CLINICAL SIMULATION

	2006	2005
	HK$	HK$
Income	116,400	88,000
Less : Cost and expenses	(109,746)	81,540
	6,654	6,460
Less : 50% profit shared with the North District Hospital	3,327	3,230
	3,327	3,230

9. COURSES

	2006	2005
	HK$	HK$
Income	111,600	235,200
Less : Cost and expenses	(6,667)	104,742
Surplus	104,933	130,458

10. EXAMINATION

	2006	2005
	HK$	HK$
Income	531,864	582,220
Less : Cost and expenses	(808,852)	503,193
(Deficit)/Surplus	(276,988)	79,027

11. EXECUTIVE COMMITTEE'S REMUNERATION

None of the executive committee members received or will receive any fees or emoluments in respect of their services to the association during the year (2005: Nil).

12. HELD-TO-MATURITY INVESTMENTS

	2006	2005
	HK$	HK$
Held-to-maturity investments, at amortised cost:		
- Unlisted debt securities in Hong Kong traded on inactive market (current portion)	-	1,099,833
- Certificate of deposit (current portion)	5,100,000	-
	5,100,000	1,099,833
- Certificate of deposit (non-current portion)	4,500,000	5,100,000
	9,600,000	6,199,833
Fair value of held-to-maturity investments	9,533,683	6,143,944

The held-to-maturity debt securities represent HK$9,600,000 HSBC Certificate of deposits ("CD") which were acquired during the years 2005 and 2006. Interest is calculated based on the effective interest rate from 3.4% to 3.8% per annum on the principal amount. The CD will be matured during the period from 30th April, 2007 to 1st August, 2009.

13. PROPERTY, PLANT AND EQUIPMENT

	Furniture and equipment HK$	Computers HK$	Total HK$
At 1st January, 2005			
Cost	225,464	82,117	307,581
Accumulated depreciation	212,708	42,743	255,451
Net book amount	12,756	39,374	52,130
At 31st December, 2005			
Opening net book amount	12,756	39,374	52,130
Additions	1,280	-	1,280
Depreciation	13,012	16,874	29,886
Closing net book amount	1,024	22,500	23,524
At 31st December, 2005			
Cost	226,744	82,117	308,861
Accumulated depreciation	225,720	59,617	285,337
Net book amount	1,024	22,500	23,524
At 31st December, 2006			
Opening net book amount	1,024	22,500	23,524
Depreciation	256	16,875	17,131
Closing net book amount	768	5,625	6,393
At 31st December, 2006			
Cost	226,744	82,117	308,861
Accumulated depreciation	225,976	76,492	302,468
Net book amount	768	5,625	6,393

14. TAXATION

The College is exempt from Hong Kong profits tax by reason of being a charitable institution.

15. APPROVAL OF FINANCIAL STATEMENTS

The financial statements set out on pages 3 to 14 were approved for issue by the council members on 25th May, 2007.

THE HONG KONG COLLEGE OF ANAESTHESIOLOGISTS
INCOME STATEMENT
FOR THE YEAR ENDED 31ST DECEMBER, 2006

	Note	2006 HK$	APPENDIX 2005 HK$
TURNOVER			
Members' entrance fees and subscriptions		1,006,263	1,021,851
OTHER REVENUE			
Donation		-	15,350
Interest income		328,019	90,576
Miscellaneous		51,470	193,581
Surplus/(Deficit) from events :-			
Annual scientific meeting	7	199,712	229,955
Institute of Clinical Simulation	8	3,327	3,230
Courses	9	104,933	130,458
Examination	10	(276,988)	79,027
		410,473	742,177
TOTAL REVENUE		1,416,736	1,764,028
EXPENDITURE			
Audit fee		11,000	10,000
Bank charges		4,255	1,496
Crown rent and rates		7,722	7,242
Depreciation		17,131	29,886
Insurance		34,500	36,035
Management fee		73,980	73,980
Members' subscriptions written off		6,250	18,900
Miscellaneous		34,625	78,468
Mandatory provident fund		14,020	11,317
Office supplies		26,325	32,722
Postages, stationery and printing of educational materials		54,916	149,361
Salary		278,046	270,720
Subscriptions		-	3,447
		562,770	723,574
SURPLUS FOR THE YEAR		853,966	1,040,454
RETAINED SURPLUS BROUGHT FORWARD		11,662,221	10,621,767
RETAINED SURPLUS CARRIED FORWARD		12,516,187	11,662,221

Intensive Care In Hong Kong: Past, Present and Future

Dr. S Anandaciva

31 March 2007

Future of ICU in Hong Kong

- **There should be a combined training and examination for ICM and CCM.**
- **Doctors training for this exam should process the fellowship in medicine or anesthesia.**
- **Nurses working in ICU should have certification in ICU nursing. They should have worked for a minimum of two years in a medical or surgical ward before training in ICU.**
- **All those working in ICU should have certification in ACLS and ATLS.**
- ***A specialist must be on the floor always!***

Annual Scientific Meeting in Anaesthesiology

17 – 18 November 2007

Programme Outline*

16 November (Pre-meeting Workshop)

- Off-site Workshop on Transthoracic Echocardiography

17 November

- Off-site Simulator Workshop
- Advanced Airway Workshop
- Refresher Courses
- Plenary Lectures
- Symposia in Anaesthesia
- Nursing Seminar - Updates in Recovery Room Care
- HKCA Trainee Project Presentations
- HKCA Congregation and Dinner

18 November

- Plenary Lectures
- Symposia in Anaesthesia
- Symposia in Pain Management
- Symposia in Intensive Care
- Debate Session
- Medico-legal Session
- Free Paper Presentations

* Programme and invited faculty are indicative only and are subject to change

International Faculty*

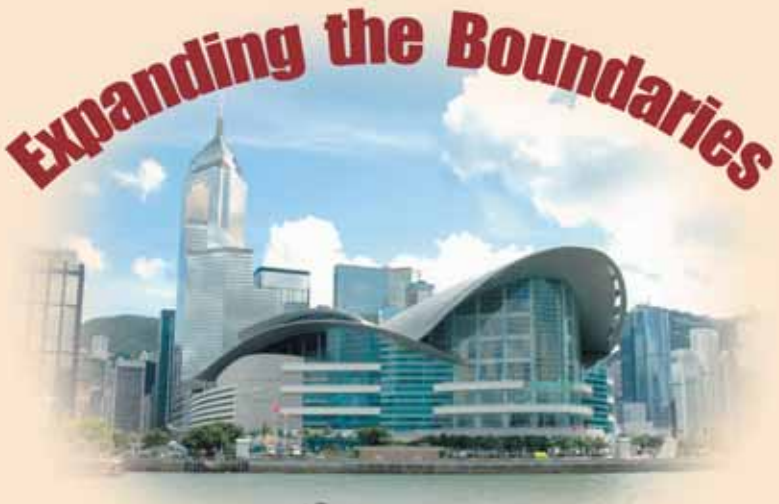
- **Professor Simon Finfer**
  Senior Staff Specialist in Intensive Care at Royal North Shore Hospital, Clinical Associate Professor in Intensive Care at University of Sydney and Director of the Critical Care & Trauma Division at The George Institute for International Health, Australia
- **Professor Pamela Flood**
  Associate Professor of Anesthesiology, Department of Anesthesiology, Columbia University, USA
- **Professor Peter Kam**
  Nuffield Professor of Anaesthetics, Royal Prince Alfred Hospital, Australia
- **Professor Kate Leslie**
  Associate Professor, Department of Anaesthesia & Pain Management, Royal Melbourne Hospital, Australia
- **Professor Alan Merry**
  Head of Department, Department of Anaesthesiology, University of Auckland, New Zealand
- **Professor Stephan Schug**
  Chair of Anaesthesiology & Director of Pain Medicine, University of Western Australia, Royal Perth Hospital, Australia
- **Dr. Tim Semple**
  Senior Consultant Anaesthetist, Department of Anaesthesia and Intensive Care, The University of Adelaide, Royal Adelaide Hospital, Australia
- **Professor Steven Shafer**
  Professor of Anaesthesiology, Department of Anaesthesia, Stanford School of Medicine, USA
- **Professor Martin Tobin**
  Professor of Medicine, Pulmonary and Critical Care Medicine, Department of Medicine, Loyola University Hospital, USA

Venue

Room 301, New Wing, Hong Kong Convention and Exhibition Centre
Wanchai, Hong Kong

Enquiries

CMPMedica Pacific Limited
Tel: (852) 2559 5888 Fax: (852) 2559 6910
E-mail: meeting.hk@asia.cmpmedica.com
Web-sites: www.hkca.edu.hk/asm2007.htm
www.sahk.hk/upcomingevents.html



Organizers

The Hong Kong College of Anaesthesiologists

The Society of Anaesthetists of Hong Kong

CHIROCAINE®
LEVOBUPIVACAINE HCl

Extending Secure Solutions in Regional Anaesthesia

Losing thorns without losing beauty

Losing toxicity without losing potency

- **Clinical Flexibility**
  Offering a broad range of applications from surgical anaesthesia to postoperative analgesia

- **Confident Capability**
  Delivering effective performance with an improved CV and CNS safety profile compared to bupivacaine*[1-8]

***Safety profile based on CV and CNS toxicity studies in animals and humans.**

References: 1. Gristwood RW, Greaves JL. Levobupivacaine:a new safer long acting local anaesthetic agent. *Exp Opin Invest Drugs.* 1999;8(6):861-876. **2.** Foster RH, Markham A. Levobupivacaine. Areview of its pharmacology and use as a local anaesthetic. *Drugs.* 2000;59(3):551-579. **3.** Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scott NB, Morrison LMM. Extradural S(-)-bupivacaine: comparison with racemic RS-bupivacaine. *Br J Anaesth.* 1998;80:289-293. **4.** Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. *Anesth Analg.* 2000;90:642-648. **5.** McLeod GA, Gennery BA, Brennan NE. Levobupivacaine: improved safety for obstetric anesthesia. *Advances in Anesthesia.* 2001;18:55-89. **6.** Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol.* 1998;46:245-249. **7.** Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. *AnesthAnalg.* 1998;86:797-804. **8.** Gristwood R, Bardsley H, Baker H, Dickens J. Reduced cardiotoxicity of levobupivacaine compared with racemic bupivacaine (Marcaine): new clinical evidence. *ExpOpin Invest Drugs.* 1994;3(11):1209-1212.

Abbott Laboratories Limited
20/F., AIA Tower, 183 Electric Road, North Point, Hong Kong.
Tel: 2566 8711 Fax: 2219 8066 Date of preparation: Aug 2007
Further information available upon request P-P223-L-1539

Abbott
A Promise for Life

Relax, you're in control with Esmeron®

Proven track record, used by over 100 million patients[1]

Organon

For further information, please contact: Organon (HK) Ltd.
Tel: 2833 6380 Fax: 2574 9151
www.organon.com.hk www.Esmeron.md www.AnesthesiaNow.com
® indicates trademark(s) registered in one or more countries

1. IMS Health Sales Data since introduction.

HK.06.ESM.02

The Hong Kong College of Anaesthesiologists

Room 807, Hong Kong Academy of Medicine Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong
Phone: (852) 2871 8833. Fax: (852) 2814 1029, Email: office@hkca.edu.hk, website: www.hkca.edu.hk

Office Bearers and Council (2005-2007)

President	Tony GIN
Vice Presidents	Po Tong CHUI
	Theresa HUI
Honorary Secretary	Simon CHAN
Honorary Treasurer	Anne KWAN
Assistant Secretary	Matthew CHAN
Assistant Treasurer	Chi Hung KOO
Council Members	Phoon Ping CHEN
	Po Wah CHEUNG
	Yu Fat CHOW
	Gavin JOYNT
	Tsun Woon LEE
	John LIU

Staff

Administrative Executive	Daniel TSO
Assistant	Cherry WONG

Board of Censor

Mike Irwin (*Censor-in-Chief*)
YF Chow (*Deputy Censor-in-Chief*)

Tony Gin	Simon Chan
PT Chui	CT Hung
Gavin Joynt	Lilian Lau
TW Lee	KC Li
John Liu	DA Sudhaman

Board of Education

YF Chow (*Chairman*)	CH Koo (*Training Officer*)
Tony Gin	Simon Chan (*Ex-officio*)
Andrew Chan	PW Cheung
PT Chui	CT Hung
Mike Irwin	Gavin Joynt
Anne Kwan	CK Koo
TW Lee	Joseph Lui
Andrea O'Regan	

Formal Project Officer: KF Ng
Matthew Chan (*Deputy Officer*)

Board of Examination

PT Chui (*Chairman*)	KK Lam (*Deputy Chair*)
Simon Chan (*Ex-officio*)	SL Tsui (*representing BoPM*)
Tony Gin (*Ex-officio*)	Peggy Tan (*representing BoICM*)
Andrea O'Regan	Mike Irwin
Cindy Aun	Theresa Hui
TW Lee	CT Hung

Board of Accreditation

John Liu (*Chairman*)	Tony Gin (*Ex-officio*)
Simon Chan (*Ex-officio*)	Tom Buckley
PP Chen	Wallace Chiu
Amy Cho	YF Chow
CT Hung	Mike Irwin
Anne Kwan	Lilian Lau
Joseph Lui	Andrea O'Regan
HY So	TS Sze

Board of Pain Medicine

PP Chen (*Chairman*)	Steven Wong (*Secretary*)
TW Lee (*Examination*)	Anne Kwan (*Accreditation*)
MC Chu (*Training Officer*)	
Tony Gin (*Ex-officio*)	Simon Chan (*Ex-officio*)
CT Hung	SL Tsui
TS Sze	

Board of Intensive Care Medicine

Gavin Joynt (*Chairman*)	Peggy Tan (*Examination*)
HY So (*Secretary*)	Tony Gin
Simon Chan	KW Au Yeung
PW Cheung	Edward Ho
Anne Leung	Karl Young

Manpower Committee

John Low (*Chairman*)	CT Hung

Resuscitation Committee

HY So (*Chairman*)	KM Ho
TY Chan	

Guidelines Committee

Anne Kwan (*Chair*)	PP Chen
Joseph Lui	Theresa Hui
Agnes Cheng	

Organizer, Basic Science Course: CH Koo, Aaron Lai
Organizers, Clinical Anaesthesiology Courses (Informative course and Crash course): Douglas Fok and Eric So
Chairman, The Institute of Clinical Simulation: PP Chen