ANESTHESIOLOGIE EN HAAR INTERACTIE MET DE COMPONENTEN VAN DRINGENDE MEDISCHE HULPVERLENING

ANAESTHESIA AND ITS INTERACTIONS WITH THE COMPONENTS OF CRITICAL CARE MEDICINE

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. M.W. VAN HOFF
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
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DOOR

MARINUS PIETER BOIDIN

GEBOREN TE OOSTBURG

PROMOTOR : PROFESSOR DR. W. ERDMANN

"Shibumi (japanese) means understanding, rather than knowledge, elegant tranquility that is not passive, it means authority without domination".

Shibumi by Trevanian.
Ballentine Books,
New York 1979, page 74.

voor poppie en de boys

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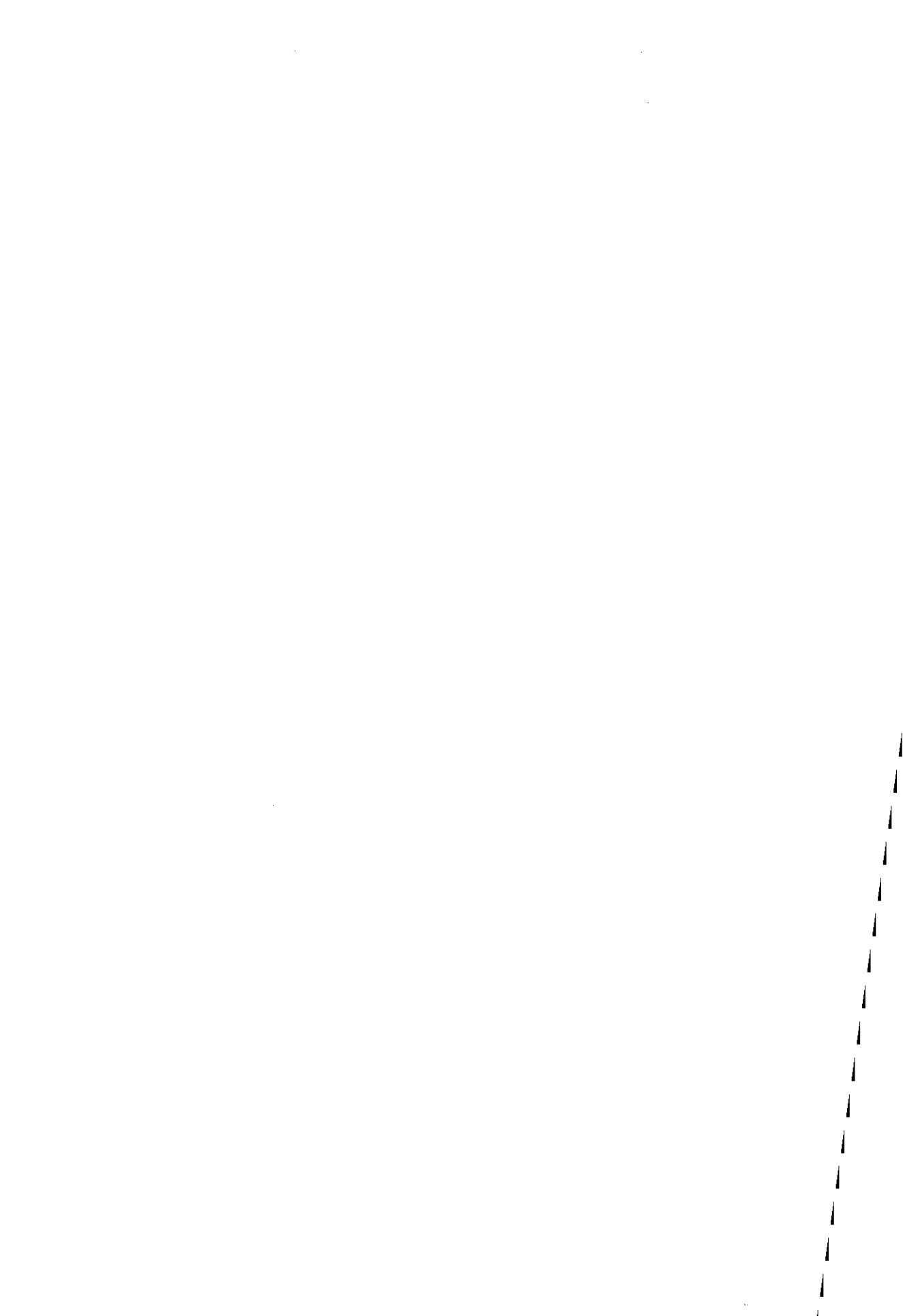

FOREWORD - Prof. Dr. W. Erdmann

When Dr. Boidin approached me with the question of supervising his thesis, I was delighted to do so. Dr. Boidin has considerable experience in the field of CCM. From the beginning, when he became a registered anaesthetist, he began investigations into subjects which were important and relative to the daily practice of CCM. Because he was working in anaesthesia and CCM at the same time this gave him the opportunity to perceive and solve problems in a unique way. His critical mind detected the problems in CCM which he transferred to the operating theatre. In the theatre the problems were investigated during elective surgery, generally without disrupting the daily routine.

The author asked my opinion concerning the possible theme of this thesis. Should it be primarily about ventilation or should the subject be etomidate toxicity? I asked Dr. Boidin to include both themes in one thesis. So he suggested taking the whole field of CCM as the subject for his book. This idea appealed to me greatly because, in the Netherlands, it is frequently not clear as to the exact role and possible contributions the anaesthetist can offer to the field of CCM. This thesis actually illustrates how the anaesthetist can actively contribute to the quality of care in CCM. In addition, it shows how anaesthesia can serve as a very valuable partner in the cooperative treatment of CCM patients, together with the various other specialities involved.

Rotterdam, January 1985.

PREFACE

During my medical training at the Erasmus University in Rotterdam (1967-1974) I was partly coached by Dr. P. Lust, head of the Emergency Medical Department in the St. Jan's Hospital in Brugge, Belgium. In this medieval hospital, situated in the 'natural' capital of my native province, I was first confronted with Critical Care Medicine (CCM). Dr. Lust was thus the first person who actively aroused my interest in CCM and from that time determined, to a great extent, the direction of my career.

Professor P. Safar published his book "Public health aspects of critical care medicine and anaesthesiology" in 1974, coinciding with the finish of my medical training. This eminent book served to give me a broader understanding of Critical Care Medicine in its wider aspects. This book showed the possibilities of creating a CCM system that not only has an impact on society in general, but also extends to influence humanity and even the evolution of mankind. Dr. Safar specified why anaesthesia and CCM were interrelated functions that should not become separated. My belief in this proposition has provided the motivation for and, eventually, the title of this thesis.

The aim of this thesis is to show how anaesthesia and CCM are essentially interactive and how the quality and standard of care in these two specialities are interdependent. As a direct result of this thesis some of the old and well-established principles in anaesthesia and CCM were revised and new options in therapy were created. The investigations, and eventual results, could only be realised because the author has had the opportunity to work in both specialities at the same time.

M.P. Boidin Breda, 11th November 1984

ACKNOWLEDGEMENT

I would like to thank everybody who has encouraged me to continue writing this thesis. Especially my good friends who have given me great mental and moral support.
Above all, I would like to express my gratitude to my lovely wife.

CHAPTER I : PHILOSOPHICAL BACKGROUND TO THE INVESTIGATIONS AND GENERAL INTRODUCTION

The understanding of the concept Critical Care Medicine (CCM) is not 'common sense' in the Netherlands. Therefore, it seems appropriate to introduce some clarification at the beginning of this thesis. The most logical way of achieving this is to give the reader an excerpt from the first chapter of P. Safar's book (1). This chapter was entitled "Health care delivery, problems and goals; a personal philosophic appraisal". Here, Safar presents the ideas which he assembled during the period 1966-1974 and discusses his terminology and classification of the specialities. The same classification and terminology are also used in this thesis.

Critical Care Medicine

Critical Care Medicine (CCM) is composed of those aspects of medical service which are concerned with patients having impaired vital functions.

Total CCM (2,3,4) includes the areas of :

a) Resuscitation
b) Emergency Medical Care (EMC) and
c) Intensive Care (IC)

This triad supports the critically ill or injured patient from the site where the injury occurs or where the illness is discovered, during transportation to the hospital and, finally, within the various critical care facilities of the hospital. CCM continues until the patient either dies or is transferred to standard medical care (1).

CCM is a multidisciplinary endeavour that of necessity crosses traditional barriers since no physician can master all the skills and possess all the knowledge that CCM patients may require (1,2,3,4,5). Modern management and treatment of critically ill patients requires physicians with special training and experience. These physicians should be trained in all aspects of CCM which can be divided into ten major components (1) :

1) recognition of the emergency and immediate aid from bystanders
2) initiation of the EMC system

3) on the spot treatment by the EMC team
4) transportation to hospital with support of vital functions
5) treatment in hospital EMC department
6) treatment in hospital operating room if necessary
7) treatment in hospital intensive care unit (ICU)
8) organisation and communication to consolidate stages 1 - 7
9) planning, education and evaluation of the total system
10) research, innovation and experimental patient care

The CCM system is only as strong as the weakest link. No matter how sophisticated one of the components may be, the patient is doomed if any other component is ineffective or not sufficiently developed. The sooner support of the vital functions is applied, the greater is the chance of survival without permanent incapacitation of the patient. The more that is invested in improving CCM systems, the more money may later be saved on nursing homes and disability pensions (1).

Anaesthesia

Anaesthesia is the medical speciality dealing with :
1) the management of procedures that render the patient insensible to pain during surgical intervention
2) the support of vital functions under the stress of surgical procedures
3) clinical management of the vital functions in the unconscious patient
4) pain relief
5) resuscitation
6) specific methods of inhalation therapy
7) the management of fluid, electrolyte and nutritional disbalances, especially during inhalation therapy

During the initial growth of clinical anaesthesia, activity was focused primarily on the operating room and anaesthesia research. Few anaesthetists were among the pioneers in CCM and clinical anaesthetists did not initially support or stimulate extra operating room activities. It is possible that this attitude was caused by : fear that this would dilute the already inadequate physician manpower in anaesthesia (6), fear of confrontation or competition with other disciplines, or the fear of loss of income.

Innovation and development in CCM is an essential and challenging process. Unfortunately, due to interdisciplinary rivalry and the inability of some physicians to appreciate the need for titrated management by skilled specialists, its course may be difficult and frustrating. Because anaesthetists were not initially very active in CCM it was not until recently that patients could fully benefit from their specialised knowledge. If medical training programmes stress that anaesthesia is concerned with more than just intubation, and if details of the full range of expertise (points 1 - 7 above) are communicated to other disciplines, it is possible that the speciality of anaesthesia may be subject to a considerable growth in the near future.

A survey of anaesthesia, carried out in 1965, revealed that the area of acute care represents a strong attraction for medical students choosing to enter anaesthesia training (7). Indeed, experience has shown that intensive care training makes better clinicians of anaesthetists (7). Another random survey has revealed a considerable need for trained anaesthetists in CCM (8). Committing as many anaesthetists as possible to the operating room is neither desirable nor reasonable. There is already an enormous underkill in the operating theatre, but in CCM there is still a relatively high mortality rate and in the intensive care area it may even be as high as 20%. But, when the unique life-supporting skills of anaesthetists are applied to medicine in general, this could considerably decrease the mortality rate of acute cases. CCM anaesthetists should not entirely relinquish clinical anaesthetic work because this is an important part of the expertise that they bring to the area of CCM.

Anaesthesia, as a hospital service will certainly continue to exist even though modern technology and safer drugs may simplify certain aspects of the speciality. The future role of the new generation of anaesthetists in this society will depend on (4) :

1) quality, rather than quantity, oriented trainees
2) improvement of anaesthesia training
3) participation in resuscitation therapy employing latest mechanical devices
4) involvement with the pain diagnostic and pain treatment groups within the hospital
5) individual involvement as leader or team member in all critical

care areas provided by the hospital

6) innovation and research

7) study and knowledge of the literature concerned with anaesthesia, CCM and related fields.

Technology

Innovative instrumentation may help to close the manpower gap by maximising the development of skills and judgement, by more effectively visualising special effects during training and thus minimising teaching time. Other items which could close the gap include : computerised acquisition and update of patient data, computerised evaluation of therapy, and patient care devices for more efficient titrated therapy. Servo controlled therapy with oxygen and drugs is possible and feasible in general practice. These technological innovations could stimulate more effective use of the human expertise in anaesthesia and CCM.

In order to withstand the vigours of theatre exposure and in order to be most useful to the greatest possible number of patients, instruments should be simple, reliable, rugged, inexpensive and should meet the anaesthetist's requirements. The demands for use in the area of anaesthesia and CCM are essentially the same, provided that they are compatible with the limitations of the location. For example, if there is a limited stock of oxygen, the list of requirements should be the same for EMC as for clinical anaesthesia, but must also stipulate that the apparatus must have a low oxygen consumption. The requirements for quality and stability should be the same in both fields. New gadgets must be capable of adapting to existing equipment so that they can be put to use, immediately and safely, without major additional expenditure.

Equipment should not distract personnel from the patient, nor should it be the cause of hazards or iatrogenic damage. Anaesthesia and CCM are concerned with the treatment and monitoring of vital functions. The future of instrumentation in CCM and anaesthesia lies in closing the gap between patient and apparatus, with alarm systems that will summon human assistance when necessary. Technology should be a support for the anaesthetist, it should not supplant the intensive care team or the team in the operating theatre.

Future development in CCM

Various changes are necessary to improve CCM and anaesthesia, these include (1) :

1) giving priority to the wide variety of outpatient care
2) team approach for patient care in CCM without losing the continuity of individual patient care
3) multidisciplinary approach of management in intensive care and emergency medical care
4) 24 hour availability of physicians (shift system) in CCM
5) physicians specially trained in CCM techniques
6) a transition from departmentalised attitudes and narrow-minded interests to a multidisciplinary approach
7) involvement of non-medical personnel in all fields of CCM
8) development of educational programs focusing on the prime objective of improved patient care
9) intensified CCM education for medical students, medical and paramedical personnel
10) a nation-wide resuscitation training programme in educational establishments and during military service
11) better salaries for specialised nursing personnel
12) flexible and multiple career opportunities for CCM personnel
13) deep compassion for patients and their families

Traditional medical specialities sometimes seem to have reached the peak of their potential in terms of patient care and scientific progress. To enable further progress there is a need to minimise the existing barriers between departments and specialities. Restructuring of medical schools and traditional hospital organisations, and the establishment of multidisciplinary teams could all advance progress in patient care. Physicians participating in multidisciplinary programs should be provided with sufficient funds, staff and easier access to patients.

Safar ended the philosophic appraisal of his chapter with the remarks : " Medicine should be practiced not only scientifically but also artistically. The physician who 'knows everything' but understands little, who applies his knowledge too late or who only talks about the problems without solving them, is ineffective in his performance. To be practiced artistically, medical skills, knowledge, experience and

judgement, supported by the vast array of technological aids, must be accomplished with virtuosity in a flexible manner".

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The goal of this thesis is to illustrate, rather than to prove, how anaesthesia and Critical Care Medicine (CCM) can achieve an effective interaction. How quality of care in both these specialities is essentially interdependent as both specialities are dealing with the support of vital functions of patients in a specific manner. That only the location varies - anaesthesia is generally associated with patients in the operating area and CCM deals with patients at the scene of the emergency, during transport and in the Intensive Care Unit (ICU). Thirteen articles, submitted to or published in various journals, are presented in this thesis to illustrate the interaction of CCM and anaesthesia (fig. 1).

All investigations in this thesis have in common that they were dedicated to CCM and all were performed in the operating theatre. In most cases it proved to be impossible to conduct the tests or measurements under Critical Care situations. Therefore, it was decided to perform the investigations or tests under clinical conditions during general and elective surgery. This offered the advantages of a consistently standard and safe environment for the studies, and the possibility of selecting relatively healthy volunteer patients. These patients have a relatively large reserve of strength which affords the opportunity of a safer and wider range of measurements. A specific disadvantage of measuring and testing in the operating theatre is that the condition of the patient is sometimes unstable which can be a cause of possible error.

In the ICU, or in other critical care situations, patients generally display multiple organ failure. However, even in this poor physical condition there is frequently a stable situation. Unfortunately, their reserve of strength is usually so small that it does not allow a safe margin for a full range of measurements. Moreover, it is often impossible to ask, or receive, the patient's permission to perform the tests. Another disadvantage is that, during CCM, there is generally no time or opportunity to perform adequate tests. For example, when a patient needs a certain level of Positive End Expiratory Pressure (PEEP) during ventilation, the level of PEEP cannot be increased or lowered to adequately test a PEEP valve function. Pressure measurements during transport and in the street are presently un-

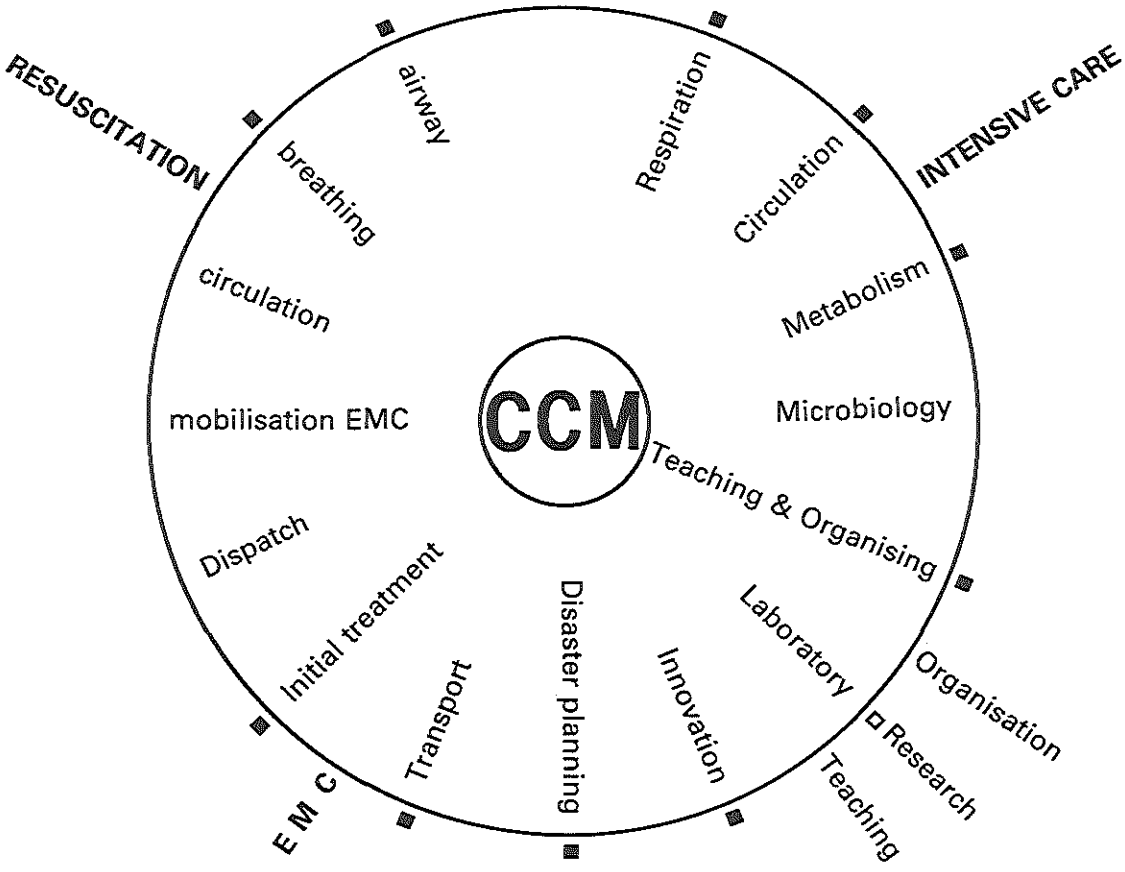

Figure 1. Diagram of the Critical Care Medicine system and its components. The items studied in this thesis are indicated ■

reliable for research purposes. This type of inherent disadvantage in the field of critical care is not present in the operating theatre, thus many innovations applicable to CCM can be originated by the anaesthetist and investigated during general surgery.

The study of airway patency in the unconscious patient (Chapter II) could only be realised in the operating theatre, as stable experimental conditions are impossible to find in critical care situations. For this study, it was not necessary to put healthy volunteers to sleep and give them muscle relaxants. Volunteer patients who were to undergo minor operative procedures offered sufficient opportunity to perform the necessary measurements and observations, without any danger or discomfort. Primarily, the results of this study are important for all situations where a free airway is life-saving. Secondly for all situations where mouth-to-mouth breathing, or bag and face mask ventilation is performed and, last but not least, for all training programmes in CCM and anaesthesia.

The second and third articles of Chapter II are concerned with technical innovations for resuscitation equipment. The self-inflating resuscitation bags were tested both in the laboratory and in the operating theatre. For a reliable measurement of arterial oxygen partial pressure in relation to the fraction of inspired oxygen, it was preferable to perform measurements in patients with a small intrapulmonal shunt. In the ICU, patients frequently do not fulfil this requirement, but during anaesthesia with air ventilation the measurements were easy to perform with no discomfort to the patient. Similarly, if an ICU patient needing an FiO2 of 0.4 were ventilated with a defective air-enrichment system on the resuscitator, this could be potentially dangerous. Patients in the operating theatre, however, do not present this restriction. Ventilation with air, in a patient without shunt, gives a PaO2 of approximately 12-15 Kpa.

The study concerning the portable PEEP valve (Chapter III) illustrates the necessity of testing the resuscitation equipment in a stable environment. The PEEP valve was tested in the laboratory and was found to be reliable for clinical use. In the theatre it was tested using an AMBU bag and no leakage of expired air occurred. After these facts became known in the hospital, the PEEP valves were used in combination with Laerdal adult resuscitators via an expiration diverter.

Unfortunately, the old expiration diverters were not totally airtight and consequently two patients suffered from short periods of anoxia. It was only because of the alertness of the attending anaesthetists that no damage occurred to these patients. The doctors were relying on the tests for one piece of equipment without having initiated tests for a new specific combination. Subsequent tests indeed confirmed the leak, the manufacturer was informed and the expiration diverter was redesigned. Later tests proved that there was no leak of the Laerdal resuscitator, in combination with the expiration diverter, with pressures up to 300 mm Hg.

The transport ventilator, discussed in the second part of Chapter III, presented problems comparable to those of the PEEP valve. Having been adequately tested in the operating room it later showed some minor deficiences during its use in CCM situations. These small problems were later solved in the operating theatre. After new tests it proved more reliable and safe for use during emergency transport. In addition, this type of ventilator now has many of the options offered only by very expensive anaesthesia ventilators. Moreover, this ventilator has also proved to be highly suitable for use in Third World countries. It is cheap, reliable, robust and safe, and is adaptable to the varying situations in these lands. Because it is low-pressure actuated, the ventilator can be used in combination with the EMO vaporiser for ether anaesthesia and this technique is currently the most frequently used method of anaesthesia in Third World countries. Indeed, the options and demands for Disaster Medicine and for medical service in the Third World are very similar. Therefore, the contribution made by studies concerning Disaster Medicine in 'sophisticated' lands can also lead to improvement in the quality of care in Third World countries.

The third part of Chapter III is concerned with a method of combining blood gas analysis with other biochemical tests. The original idea was to obtain blood samples in the pre-hospital phase of resuscitation. The results should have increased the knowledge of the physical state of resuscitated patients during the out-of-hospital phase. Sampling in the field is very clumsy and difficult. Therefore, all samples should be taken in one syringe which should be sealed off. Estimations could then be made after admission of the patients.

The results of this study became very interesting for both CCM and anaesthesia because nowadays blood samples are taken more frequently and they have become smaller in order to avoid excessive spilling of blood. This is particularly important in the case of children and for the multiple sampling that is necessary in the ICU. It proved that addition of heparin solution to a sample changed the results of some estimations. Therefore, a new heparin solution was developed and compared with other heparin solutions in relation to arterial blood gas analysis. Other biochemical tests were performed in serum and plasma using the new heparin solution. After comparing the results, it was shown that arterial blood gas analysis and other biochemical tests could indeed be performed in one blood sample. A concomitant advantage is that this method is very useful for blood gas analysis, and other tests, in small laboratory animals. Other scientific investigations have already been carried out using this new heparin solution.

Chapter IV deals with the problem of sedation in the ICU. It was noticed that patients, who received etomidate as a continuous infusion during intensive care, displayed haemodynamic instability. No diagnosis was possible until it was observed that patients coming from the operating theatre showed a similar instability. Differential diagnosis made in pursuance of the symptoms included (amongst others): Addisonian crisis. In the ICU this could not be confirmed. Fortunately, the diagnostic symptoms could be immediately confirmed during the operation. It proved to be an Addisonian crisis because serum cortisol levels decreased to pathological low serum concentrations. This was confirmed by the in vitro data given in the second part of Chapter IV.

The third part of Chapter IV explains why this side effect occurred. The blockade proved to be at the site where cholesterol is hydroxylised. The fourth part describes the patholgical symptoms during and after the administration of etomidate. After a study of the available literature it became clear that ascorbic acid could be related to cortisol synthesis. When this vitamin was administered there was indeed a rise in serum cortisol concentration. Moreover, the symptoms of patients treated with etomidate disappeared when ascorbic acid was administered. Then it became clear why it was not possible to show the etomidate toxicity in the ICU. All patients in this ward received a daily amount of ascorbic acid in the total parenteral nutrition, thus it was not possible to measure pathological serum cortisol levels.

Again, in this study it was impossible to perform a successful investigation until the problem was transferred to the operating theatre. The solution to the problem of etomidate toxicity could only be found by observing the differences in CCM and anaesthesia at the same time. An additional advantage in this study was that the same group of anaesthetists treated the patients in the theatre, as well as in CCM.

The last section offers a new hypothesis based on the data in Chapter IV. Suggestions for future investigations are made and discussed.

CHAPTER II : RESUSCITATION

Resuscitation is the subdivision of Critical Care Medicine (CCM) which includes artificial support of the vital functions of the patient. It has three components :

1) establishment of the free airway of unconscious patients
2) ventilation in place of spontaneous respiration
3) establishment of circulation by chest compression or by squeezing the heart.

The first section of Chapter II is concerned with the mechanisms of opening and closing the airway in unconscious patients. This item can be very effectively studied in the operating theatre as the patients are frequently unconscious, muscle tone can be controlled and the patients are not necessarily intubated with an endotracheal tube.

The second part of this chapter deals with the improvement of the air intake system of resuscitation bags. Until recently, it was not possible to administer a stable FiO2 to patients during manual ventilation with a resuscitation bag. In clinical situations it is undesirable to ventilate patients with an unknown gas mixture. The same criteria should apply to situations during resuscitation.

The third section deals with changes in the intake system which makes the resuscitator more suitable for use in field situations. Oxygen consumption was reduced which compensates for the limited supply of oxygen in the field. Another requirment for resuscitation is that it should be possible to administer 100% oxygen, this has been achieved.

AIRWAY PATENCY IN THE UNCONSCIOUS PATIENT

M.P. Boidin

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Keywords : AIRWAY - obstruction
ANATOMY - larynx

INTRODUCTION

Unconsciousness may lead to asphyxia from obstruction of the upper airway. To overcome such airway obstruction, forward displacement of the mandible was first recommended by Heiberg over a century ago in 1874 (1). In 1956 Finck (2) described passive closure of the glottis, which occurred in relatively deep anaesthesia and was initiated by the inspiratory gasflow when the Bernoulli effect was unopposed by abduction of the vocal cords. However, in 1962 Shelton and Bosma (3) showed that a pharyngeal airway was maintained, in conscious babies, despite changes in posture or movements of the pharyngeal structures. Even when the tongue was pushed backwards forcibly, an airway could be maintained in all babies. They concluded that the relative position of the mandible, hyoid and sternum, and their relation to the 6th cervical vertebra, were maintained because of traction on the hyoid bone by the submandibular muscles only.

The purpose of this study was to determine whether obstruction of the upper airway was primarily a result of the tongue falling back, or if another mechanism could be held responsible for airway closure in the unconscious patient.

PATIENTS, MATERIALS AND METHODS

Anatomical preparations

The relationships of the pharynx, larynx, hyoid bone and the tongue were studied in six fresh cadaver preparations, which were fixed later in formaldehyde and preserved in alcohol.

Patients

Twenty patients (11 male/9 female, all ASA I) scheduled for minor operations on the extremities were selected for study. Most were young (mean age 33 yr, range 18–62 yr), of average constitution and free from any disease of the air passages or lungs. Three patients had a dental prosthesis which was removed during the study. Each patient gave informed consent before entering the study.

Anaesthesia was induced with thiopentone 4 mg kg^{-1} i.v., followed by spontaneous breathing. A mixture of oxygen, nitrous oxide and halothane was administered via a well-fitting face mask attached to a circle system. A fresh gas flow of 1.5 times the patient's estimated minute volume was used. The depth of anaesthesia was maintained at Guedel-stage 3-2 without additional opioids. The patients were in a supine position on a flat operating table. Neuromuscular blocking drugs were not given.

A flexible bronchoscope (Olympus, type BF-B3R) with an operative length of 60 cm and a diameter of almost 6mm, was passed through a hole in the face mask via the nose into the naso-pharynx. No leak of gas was allowed and the expired volume was measured breath-by-breath (Dräger Volumeter). The angle of retroflexion was recorded as the angle between the horizontal plane of the operating table and the line connecting the lateral corner of the eye and the tragus of the ear. The angle subtended by the head in the neutral position without manipulation was recorded initially, then the head was extended slowly with the mouth closed until a free airway was established (fig. 1). A clear airway was indicated by the expired tidal volume becoming maximal.The manipulation was repeated with an oral (mouth open) and a nasal pharyngeal airway (mouth closed) in place.

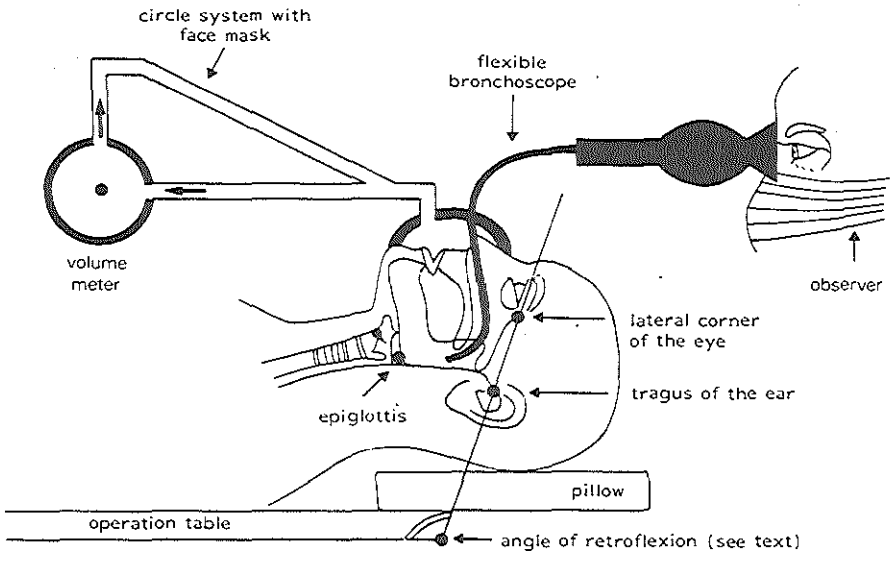

FIG. 1. The breathing circuit, flexible bronchoscope, pillows and landmarks (•) used in this study to measure the position of the patient's head and to observe the mechanism of airway closure.

The first measurements were undertaken without elevation of the occiput. All measurements were then repeated with pillows to produce a 4- and 8-cm elevation of the occiput above the operating table. During the measurements the flexible bronchoscope remained in position behind the uvula, looking proximally at the structures in the mouth, the vocal cords and the epiglottis. The bronchoscope could be advanced in the direction of the lower pharynx when necessary.

Statistical analysis of the angles of retroflexion was performed using Student's t test for paired values. Measurements with and without the artificial airways were compared, and measurements at various heights of the occiput (above the table) were compared with elevation of the occiput to 4 cm.

RESULTS

Anatomical preparations

In the cadaveric preparations it was observed that the tongue did not usually reach to the posterior pharyngeal wall, because it was attached mainly to the posterior aspect of the mandible at the chin. When the tongue of the cadaver was pushed forcibly into the mouth, obstruction occurred mainly at the level of the soft palate - by closure of the natural oral airway. When more pressure was exerted, the natural nasal airway was occluded also, the soft palate being pushed against the posterior pharyngeal wall. In the lower pharynx, two mechanisms of obstruction occurred - which were independent of manipulation of the tongue. The base of the epiglottis closed over the trachea and the rims of the epiglottis came into contact with the posterior pharyngeal wall and could close the respiratory tract. The visible part of the epiglottis, the pars glottica, could extend into the oesophagus and seems to protect the interarytenoid fold from contamination with foreign material. In one cadaveric preparation the tongue was removed from the hyoid bone and it was observed that it was possible to obtain an airtight seal in the upper airway with the epiglottis alone.

The hyoid bone is horse-shoe shaped and can be moved in all directions by the action of the extrinsic pharyngeal muscles, although there is some restriction to movement in a caudal direction. The thyroid cartilage is suspended from the hyoid bone and it is fixed dorsally to the

dorsal conjoined tendon of the pharyngeal muscles, which is in turn connected to prevertebral fascia.

The epiglottis hangs, like the lid of a bin, from the posterior aspect of the hyoid with the thyro-epiglottic ligament acting as a hinge and the hyo-epiglottic ligament acting as the lever for the lid. In the cadaveric preparations it was demonstrated that the position of the epiglottis in the hypopharynx depended principally on the relative position of the hyoid bone in relation to the thyroid cartilage.

Patients

The angle of retroflexion (Table I) necessary to open the airway was not altered substantially by the use of artificial airways in the hypopharynx. However, in eight of the 20 patients, with a nasopharyngeal airway at 8 cm elevation, and also in one patient with 4 cm elevation, there was only a small difference in the required angle of retroflexion as compared with the angle in the neutral position. In these cases the nasal airway supported the epiglottis clear of the retropharyngeal wall. The angle of retroflexion required to achieve a clear airway became smaller as the occiput was elevated and, once the airway began to open, only a little more tilt was required to open it fully (fig. 2).

TABLE I. *Angles of retroflexion of the head (mean (SD)) in 20 patients. Significance calculated with the* t *test for paired values: conditions compared with the "no-adjunct" group — †P < 0.001; elevations of 0 and 8 cm compared with the values measured at 4 cm — **P < 0.01; ***P < 0.001*

	Upper airway closed	Upper airway clear		
Elevation of occiput	Neutral position	No adjunct	Oral airway	Nasal airway
0 cm	105 (9.1) † ***	114 (7.1) **	114 (5.5) ns **	112 (6.8) ns ***
4 cm	96 (6.5) †	109 (5.5)	110 (5.5) ns	106 (7.1) ns
8 cm	91 (2.3) † **	102 (8.2) ***	101 (9.3) ns ***	97 (10.8) † ***

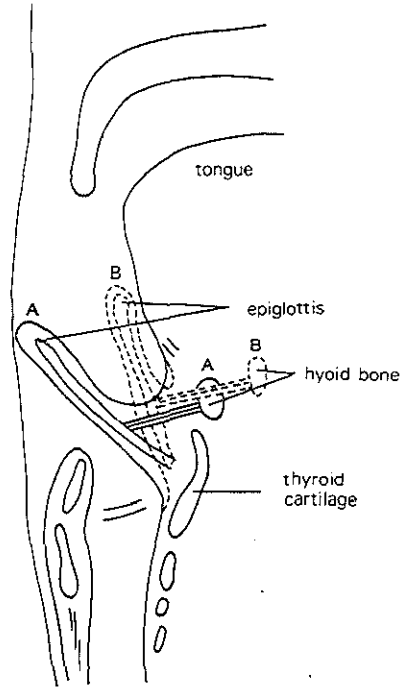

FIG. 2. Cross-section of the larynx, showing obstruction of the upper airway by the epiglottis (A). Anterior displacement of the hyoid bone by the extra pharyngeal muscles clears the airway (B).

The mechanism of airway closure was visualised using the flexible bronchoscope. With this method it could be demonstrated that the base of the epiglottis was sucked over the entrance to the trachea by the inspiratory pressure and this occurred well before the tongue even approached the posterior pharyngeal wall. The airway was closed as the rims of the epiglottis reached the pharyngeal wall. When attempts were made to ventilate a patient with the epiglottis in this position, the pars glottica could be seen being forced into the oesophagus. The gas mixture might then enter the oesophagus and then be passed into the stomach. As the head was extended the epiglottis was withdrawn from the tracheal entrance. When partial obstruction occurred and the top of the epiglottis vibrated in the lower pharynx, the characteristic snoring sound could be heard.

DISCUSSION

These observations indicate that the tongue is not the only factor concerned with upper airway obstruction. The mechanism is thus more complicated and it seemed necessary to reconsider the facts. The data presented by Safar and colleagues in 1959 (4) were accurate, but their

conclusion, that the tongue is the sole source of upper airway obstruction, is not wholly justified, as it has been shown that the airway may close even when the tongue is bypassed.

The hyoid bone can be considered as forming the boundary of the wide end of two funnels, the larynx and the pharynx, both of which are suspended from the base of the skull and extend into the thorax. Which funnel is opened/closed is determined by the position of the epiglottis which, in turn, depends on the antero-posterior position of the hyoid bone in relation to the thyroid cartilage (fig. 3). This position may be altered voluntarily by the extrapharyngeal musculature of the hyoid bone, whereas the thyroid cartilage remains rather immobile. It seems that the omohyoid muscle, and the anterior belly of the digastric muscle, are essential to manoeuvre the hyoid bone to its ventral position. It is obvious that this does not occur in unconscious patients. For the same reason, it is probable that the triple airway manoeuvre (retroflexion of the head, jaw thrust, mouth open) (5) remains the most successful method of opening the airway because this manoeuvre moves the hyoid ventrally. On the other hand, the introduction of a stomach tube and an oesophageal obturator airway should be assisted by flexion of the neck, to push the hyoid bone backwards.

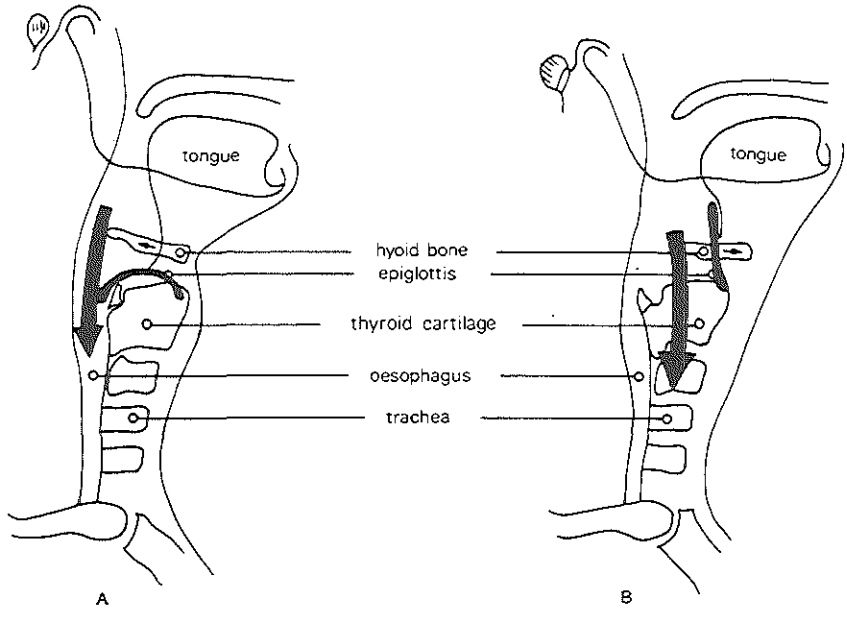

FIG. 3. The position of the hyoid bone determines which of two funnels is opened/closed. Note that the tongue is pushed away by the pressure of the epiglottis in position (B).

This investigation showed that the airway is almost invariably closed (under anaesthesia) when the head is in its neutral position, and that the use of artificial airways can not always guarantee a clear airway. The airway was clear when the nose or mouth, or both, were open and the epiglottis did not reach to the posterior pharyngeal wall. The tongue may obstruct the upper airway in two ways. It may push the soft palate against the posterior pharyngeal wall, obstructing both the nasal and oral cavities. The tongue may close the oral cavity when the nose is obstructed, in this case acting as a one-way valve obstructing expiration. In both cases of obstruction by the tongue there is an indication for Mayo or Guedel type airways. Obstructions of this type were not seen during this study, but are occasionally noticed in patients with long-standing dental prosthesis. The effect of opening the mouth with a Mayo airway does not decrease significantly the angle of retroflexion, nor does the introduction of artificial airways. Only the elevation of the head decreases the head tilt necessary to clear the airway. When the head is elevated, a nasal pharyngeal airway of sufficient length to support the epiglottis will often provide a clear airway and decrease the angle of retroflexion significantly. However, also in these patients it was possible to obstruct the upper airway by flexion of the neck.

This concept of airway closure may contribute to the training of medical and paramadical personnel and explain the management of the airway and the use of artificial airways, stomach tubes and tracheal tubes. However, at present it does not seem prudent to give such complicated detailed information during the training of the lay public, although it may be possible to use a simplified version of this concept.

CONCLUSIONS

Many unconscious patients will develop upper airway obstruction in the neutral supine position. However, the tongue is not the main cause of upper airway obstruction. The rims of the epiglottis make contact with the retropharyngeal wall before the tongue obstructs the airway. The pars glottica of the epiglottis can be forced into the oesophagus by excessive pressure during ventilation against a closed glottis. By the head tilt/jaw thrust method, the epiglottis can be effectively removed from the trachea. Traction from the submandibular muscles to

the hyoid bone caused ventral displacement of the hyoid and of the epiglottis. Opening of the mouth did not change the angle of retroflexion, but elevation of the head caused a significant reduction of this angle. Adjuncts for a free airway are only indicated when the tongue obstructs the passage of air in the oral and/or nasal cavity. Adjuncts for a free airway, except occasionally for long nasopharyngeal airways, do not significantly reduce the angle of retroflexion of the neck necessary to open the airway.

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CONTROLLED ADMINISTRATION OF OXYGEN WITH SELF INFLATING RESUSCITATION BAGS

M.P. Boidin, B. Mooi, W. Erdmann

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Keywords : EQUIPMENT - resuscitation bags,
OXYGEN THERAPY - venturi, FiO2,

Self inflating resuscitation bags were originally developed for air ventilation only. In order to increase the oxygen fraction of the inspiratory gas mixture (FiO2), different methods of air enrichment were used (1,2,3,4,5,6,).

1. oxygen was directed straight into the bag. Main disadvantages were that safety systems had to be built in and only low oxygen concentrations could be achieved, which were dependent on the minute volume (fig 1 - I and fig 2 - A).

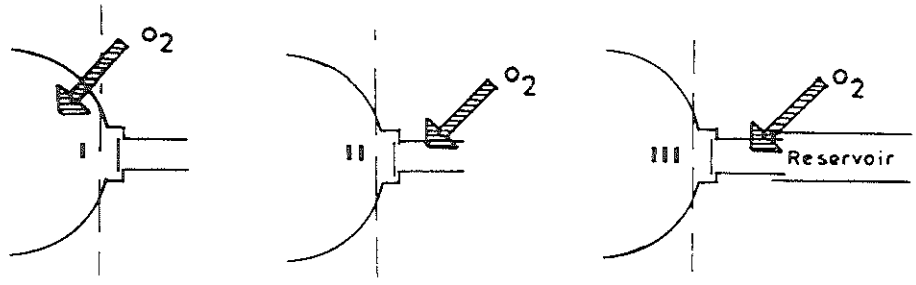

Figure 1. Selfinflating bags with different methods of air enrichment.

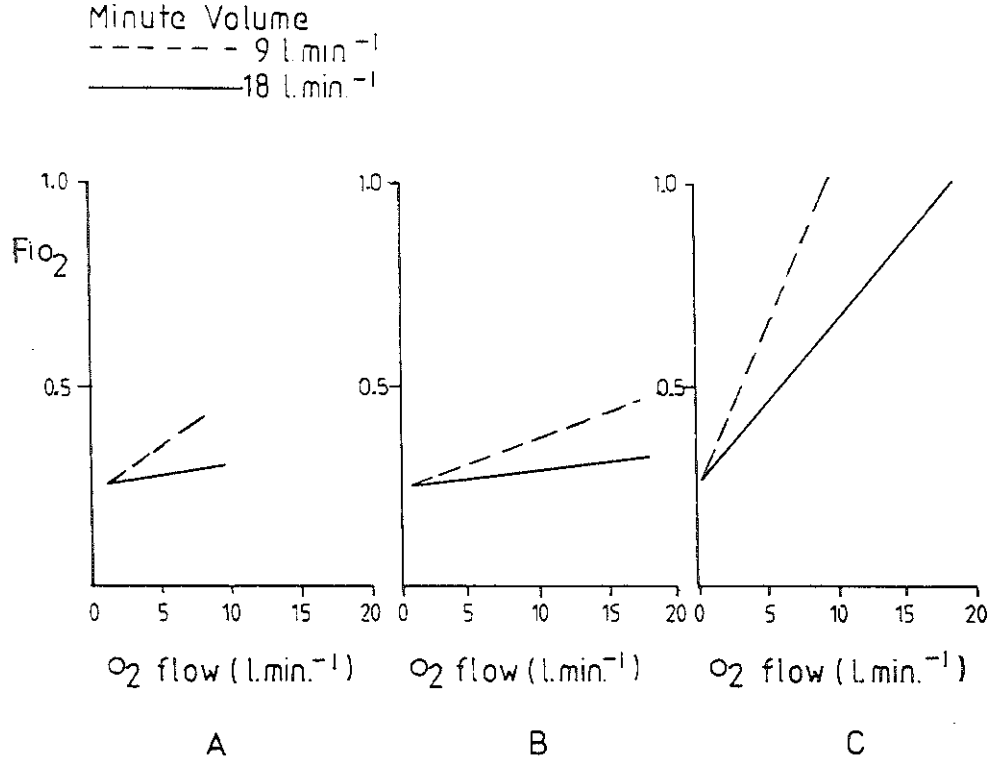

Figure 2. Relationship between FiO2 and oxygen flow at two different minute volumes. A, B, C correspond with I, II, III in figure 1.

2. oxygen could be delivered to the air intake valve of the resuscitator. The maximal oxygen concentration was 30% at an oxygen flow of 15 liters and a ventilatory minute volume not exceeding 6 liters (fig 1 - II and fig. 2 - B)

3. in a later development the oxygen was delivered into a reservoir bag attached to the air intake valve of the resuscitator. The self inflating bag obtained its fresh gas mixture from this reservoir (fig. 1 - III and fig. 2 - C). One disadvantge of this method was that the reservoir was large and clumsy. In addition the FiO2 was, to a large extent, dependent on the ventilatory minute volume, but this was the only possible method to supply the patient with 100% oxygen.

All systems showed that it was not possible to predict the exact oxygen concentration of the inspiratory gas mixture. Therefore, an attempt was made to develop a new method based on the venturi system.

Basic principles of the new system

According to the Bernoullis principle, a static proportion of room air is entrained into a wide tube system when gas is blown with a high velocity through a narrow hole into that wide tube. The high velocity of the oxygen flow creates a negative pressure at the opening of a jet system. The negative pressure entrains room air from the surroundings into the gas flow (7,8). The amount of entrained room air is increased with increasing oxygen flow, whereby the concentration of oxygen in proportion to room air remains constant. In some venturi systems the size of the inlet ports for room air can be changed. This method was actually used to regulate the admixing of room air with oxygen flow. Thus the FiO2 could be changed by adjusting the size of the inlet port. It is known (8) that the FiO2 is not dependent on oxygen flow in venturi systems. Thus the oxygen concentration remains constant when the flow of oxygen to the jet system is changed, without changing the size of the inlet ports (fig. 3).

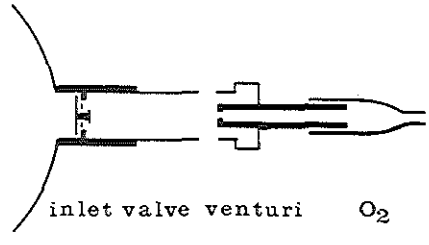

Figure 3. Venturi device

The advantages of the venturi system are :

1) the FiO2 is not dependent on the ventilated minute volume because of the proportional flow/volume increase of the venturi system.
2) the described high flow oxygen system can deliver 24-60% oxygen precisely as required.
3) the temperature and humidity can be easily controlled by additional heating and humidification.
4) medicaments for inhalation can also be added.

Before application of the venturi to the air intake valve, two special topics had to be considered. The venturi system works only in a continuous forward flow situation. Obstruction raises a counter pressure whereby the mechanism of the venturi is disturbed. The first question was if this type of counter pressure was present in this model. The air inlet of the self inflating bag is closed during inspiration and sucks air into the bag at a certain velocity during the decompression phase of the bag - this posed the second question as to whether it would be possible to adjust the total gas flow from the venturi system to the bag according to the needs of the self inflating bag.

MATERIAL AND METHODS

In the test period AMBU, AMBU-paedi and Laerdal adult resuscitators were used. A venturi system from Accurox was attached to the self inflating bags. The Accurox venturi system gave the option of changing the size of the inlet ports for the selection of different oxygen concentrations. Two different Accurox systems with changeable precalibrated settings of the inlet ports were used. One system had settings of 0.24 and 0.30 at an oxygen flow of 3 liters/min, and the other had settings of 0.40 and 0.50 at 6 liters/min oxygen flow. FiO2 was measured by means of a Beckman OMII oxygen analyser, with a response time of $\pm$ ½ a second. Volumes and flow were measured with a Gould pneumotachygraph.

RESULTS

The FiO2 from the two different venturi systems (3 liter/min for 0.24 and 0.30; 6 liter/min for 0.40 and 0.50) were measured and showed that the preselected oxygen concentration was constant from 1-6 liters oxygen flow/min for the 3 liter system, and from 1-15 liters for the 6

liter system. Oxygen concentration was delivered exactly as indicated on a predictive setting of the inlet port. The total flow (oxygen mixed with air) emerging from the venturi system was calculated from the equation:

$$\text{TOTAL FLOW} = \frac{1}{FiO2} \times \text{oxygen flow } (0.2 \times \text{entrainment factor} + 1)$$

The results shown in fig. 4 demonstrate clearly that the air entrainment at different oxygen flow rates sum up to the total gas flow emerging from the venturi.

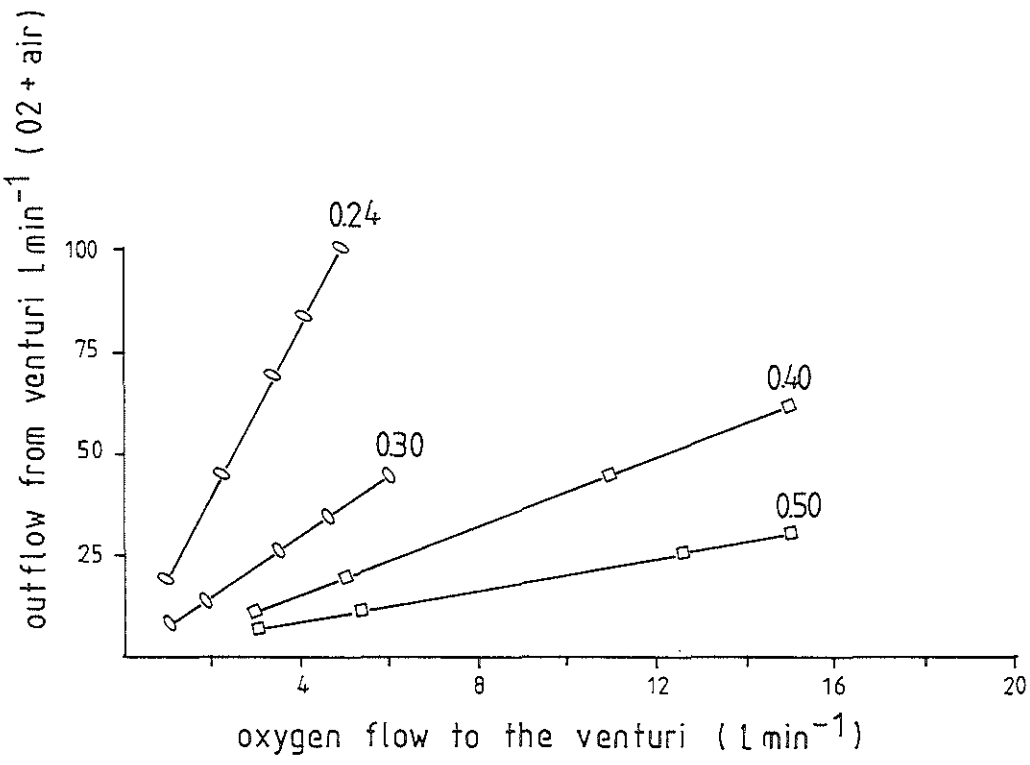

Figure 4. Relationship between oxygen flow and total outflow of two venturi systems. Two settings of each venturi system are shown.

The flow into the air inlet of the self inflating bag was measured during decompression of the bag in order to determine the total flow needed from the venturi system to meet the demands of the bag. For the AMBU and the Laerdal resuscitators it was 40 liters/min. For the AMBU-paedi 20 liters/min was measured.

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A further step was to measure the FiO2 of the gas mixture leaving the self inflating bag at the patient side. This was measured when the 0.40 and 0.50 venturi system was applied at different oxygen flow rates to the venturi system. The 0.40 and 0.50 venturi system was preset to an FiO2 0.50 and connected to the self inflating bag having an inflow of 40 liters/min during the decompression period. The oxygen flow was adjusted to 15 liters/min (maximum flow to be applied as indicated above). Then the FiO2 never reached 0.50 at the outlet of the bag. This indicated that the bag entrained additional air from the surroundings because the total gas flow from the venturi system reached its maximum and only delivered 25 liters/ min at the 0.50 setting, thus not meeting the demands of the bag (fig. 5).

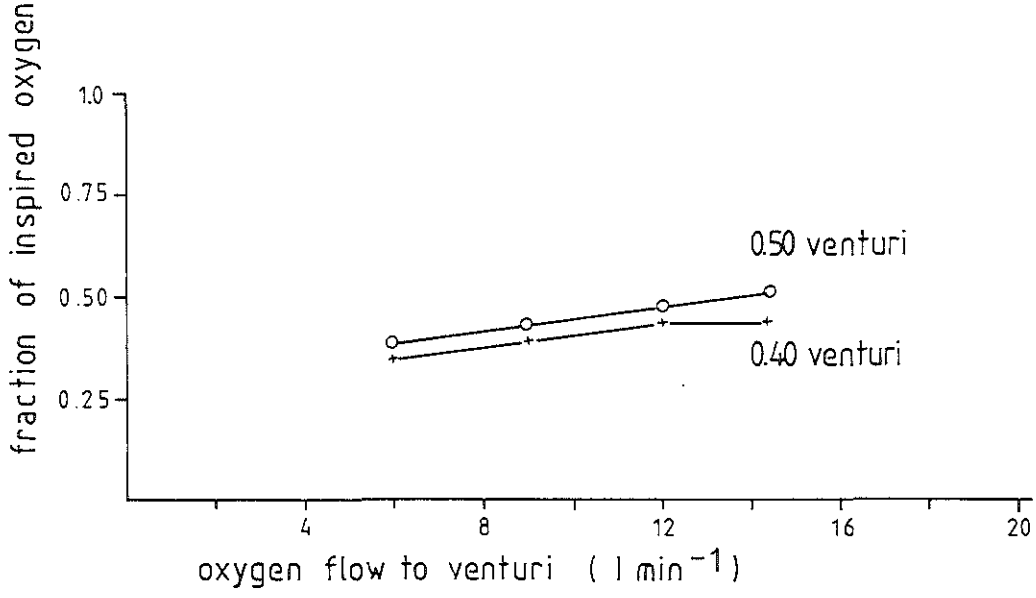

Figure 5. Relationship between oxygen flow to the venturi system and FiO2 of the ventilatory mixture. Two settings of the venturi (0.40 and 0.50) are shown.

When the 0.40 position of the air inlet was chosen, 15 liters/min oxygen flow produced a total flow of 45 liters/min (fig. 4). In this case, the FiO2 at the bag outlet was actually 0.40. The oxygen flow could even be decreased to 12 liters/min producing a total flow of 40 liters/ min. This equalled the inflow into the self inflating bag and did not change the oxygen concentration delivered to the patient. The FiO2 remained constant when the minute volumes with the self inflating bag at 0.40 setting were varied between 4 and 16 liters/min with an oxygen flow of 12 liters/min to the venturi system (fig. 6).

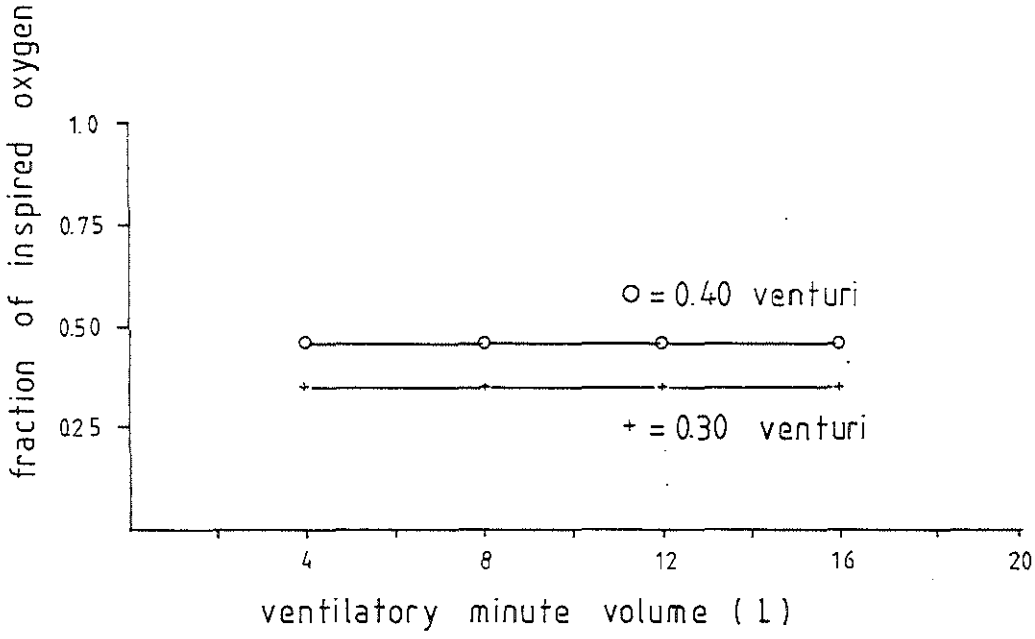

Figure 6. Relationship between the ventilatory minute volume and FiO2. Two settings of the venturi (0.3 and 0.4) are shown.

In a further study, measurements were repeated using the Laerdal bag. As this bag had the same inflow rate as the AMBU the same results were produced. For additional control the AMBU-paedi with an inflow rate of 20 liters/min was used at different oxygen flows. The oxygen flow into the venturi system could be halved compared with the flow needed in the adult resuscitation bags. The total gas flow emerging from the venturi system equalled the maximum inflow into the paediatric self inflating bag. The FiO2 also remained constant over a wide range of minute volumes using an oxygen flow of 5 liters/min for the 0.4 venturi system.

DISCUSSION

The FiO2 from a calibrated venturi system was, to a large extent, not affected by the oxygen flow to that system. The venturi could be fixed to the air intake valve of the self inflating resuscitation bag. If the total gas flow from the venturi to the self inflating bag was adjusted to (or above) the air intake flow of the bag, the FiO2 administered to the patient was predictably constant at varying minute volumes. The characteristics of the different bags were unchanged as the enriched air flow from the venturi system was applied to the outside of the bag. The venturi system did not exert pressure on the intake valve.

The venturi system in this study avoided the closed chamber phenomenon. The dead space was extremely small, preventing excess of pure oxygen being drawn into the self inflating bag. Comparison with other methods of oxygen delivery showed that all methods previously used were influenced by the ventilatory minute volume. Moreover, the direct delivery of oxygen into the bag influenced its performance and thus required a built-in safety system.

CONCLUSION

Large fluctuations in oxygen flow did not affect FiO2 in the gas mixture emerging from a venturi system, only the total outflow increased in proportion to the increasing oxygen flow into the system. Thus a venturi system proved to be an ideal way to obtain a controllable FiO2 from a semi-automatic self inflating resuscitation bag. The total outflow from the venturi can be adjusted to equal, or exceed, the maximal flow through the air inlet of the self inflating bag. The venturi system did not interfere with the characteristics of individual bags and FiO2 was not affected by changing the minute volume. This method proved to be of particular interest for intensive care and paediatric resuscitation because of the simplicity of semi-automatic resuscitation bags for manual ventilation.

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PROTOTYPE OF AN INTAKE VALVE FOR RESUSCITATION BAGS

M.P. Boidin

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Keywords : EQUIPMENT - resuscitation bags, oxygen therapy

Self inflating resuscitation bags have been developed for artificial ventilation with air, for use both inside and outside the hospital. In the past, three different methods of air enrichment with oxygen have been developed (1, 2). Delivery of oxygen directly into the bag (fig 1: I) is potentially dangerous because the non-return valve may stick in its respiratory position and the airway of the patient may be subjected to excessive pressure. It is therefore necessary to add a safety valve into the breathing circuit. All three methods (fig 2: A, B, C) have in common the fact that the percentage of inspired oxygen is dependent on the inspired minute volume.

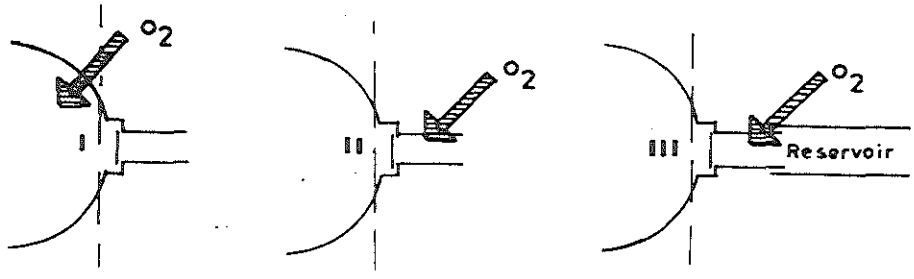

Figure 1. Selfinflating bags with different methods of air enrichment.

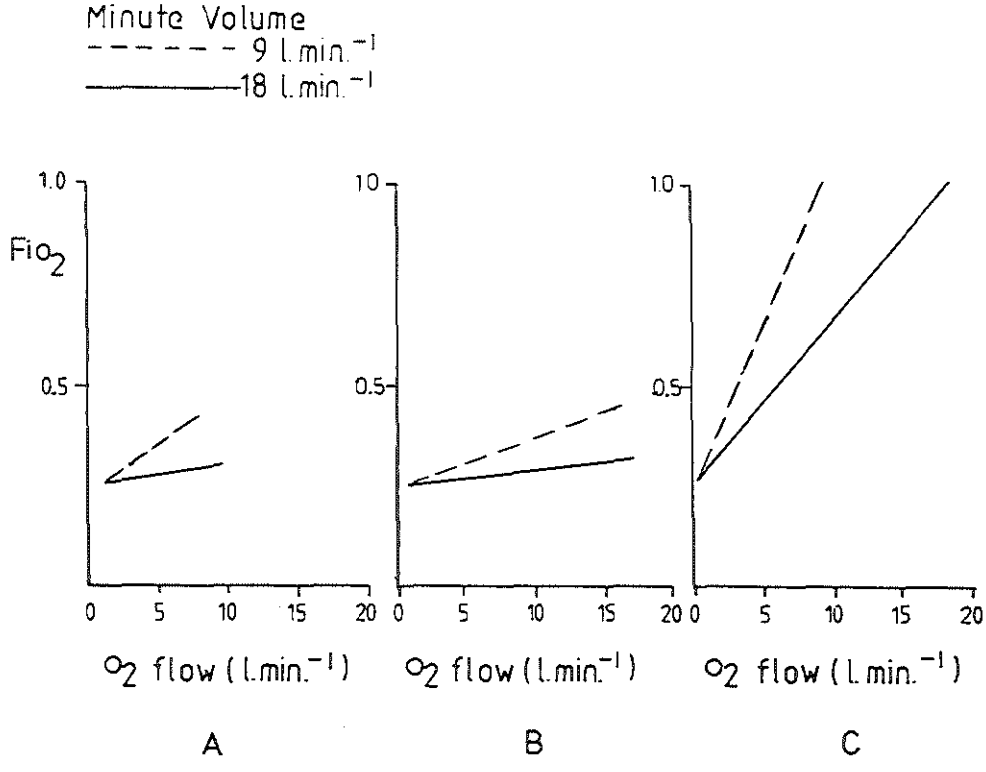

Figure 2. Relationship between FiO2 and oxygen flow at two different minute volumes. A, B, C correspond with I, II, III in figure 1.

Boidin et al (3) reported in 1980 that it was possible to control the FiO2 independently of the minute volume using a venturi system attached to the air inlet of the resuscitation bag. However, this system had the disadvantage of not being able to deliver 100% oxygen. Abundant over-consumption of medical oxygen proved to be another drawback of this method.

The aim of this study was to design an intake valve for resuscitation bags commensurate with the sophisticated standards of ventilation applied in the Intensive Care Unit, suitable for use both inside and outside the hospital. In order to achieve an inexpensive design, the device was constructed from parts of existing equipment (generally anaesthetic material). The newly designed intake valve also had to overcome the disadvantages of the design described in 1980, and the valve should not affect the safe operation of the resuscitator.

MATERIALS AND METHODS

The Laerdal adult self inflating bag was used as a basis for the construction of the new intake valve. Details of the patient side of the resuscitator with a 'blow-off' valve, a corrugated wide bore extension hose, an AMBU PEEP valve, a non-return valve, a volume meter, an airway manometer, a tube-valve interface and a scavenging system have been described elsewhere (4).

The standard air intake valve of the Laerdal resuscitator was removed and replaced by the prototype of the new intake valve. This new valve included a base-plate with two perforated areas (each 100 mm^2) sealed by a silicone membrane at the bag aspect of the base plate. The central membrane served to transmit the pressure changes from inside the bag to the atmosphere. The peripheral perforated area had a centrally fixed silicone membrane which served as the intake valve for the fresh gas mixture. The central membrane was fixed to the lever of a second stage downflow demand valve. This type of demand valve is also used in the Self-Contained-Underwater-Breathing-Apparatus (SCUBA) for diving. The second stage or demand valve opened the flow from the intermediate pressure hose from the first stage regulator at the oxygen cylinder. The first stage regulator produced a balanced flow through a highly accurate piston valve. The pressure in the intermediate pressure hose was maintained at 9.8 $kg.cm^2$ which caused oxygen to flow when the

second stage was opened by traction on the demand lever (fig. 3).

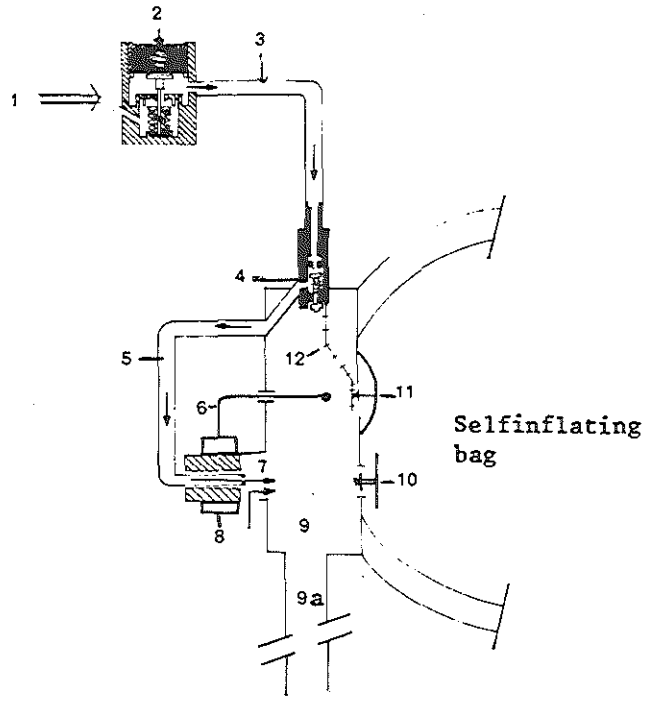

Figure 3. Prototype of an intake valve for a resuscitation bag with the venturi and demand valve for air enrichment.

1. high pressure oxygen delivery springs and bobbin
2. first stage regulator with
3. intermediate pressure oxygen
4. second stage downstream demand valve
5. low pressure oxygen hose
6. purge lever
7. venturi device
8. ring for obstruction of air entrainment, connected to 6
9. reservoir cap with reservoir hose (9a)
10. air intake valve
11. pressure transducing silicone membrane
12. demand valve lever

Oxygen was conducted to the nozzle of a venturi device at a fixed flow rate of 10 liters/min and the venturi was precalibrated for the delivery of 40% oxygen. Variations in oxygen flow did not influence oxygen concentration in the gas mixture leaving the venturi system. The air intake ports of the venturi could be occluded by means of a sliding ring around the venturi device. A purge lever connected this ring with the lever of the down-flow demand valve. When the ring was slipped over the ports, the down-flow demand valve was opened and the air mix system was closed. Thus, in this case, 10 liters of pure oxygen flowed towards

the intake valve of the resuscitator and to the reservoir hose. When the ventilatory minute volume exceeded 10 liters/min, additional air was entrained through the reservoir hose.

The wide bore reservoir hose had to serve two purposes. The cap of the intake valve had to be open to the atmosphere because the venturi system can only function in a free forward flow situation. Also, the reservoir hose had to serve as buffer capacity for pure oxygen. But it should be realised that the inflow into the bag could sometimes be greater than the 10 liters leaving the closed venturi system. The reservoir hose attached to this model had a capacity of 1.2 liters equalling the maximum tidal volume which could be administered by this resuscitator.

A Dragër test lung was used to assess the results of this device, or any part of it. Oxygen concentrations were measured with a Beckman OMII oxy-analyser, the pressure recordings with Gould-Statham transducers and displayed on Hewlett-Packard monitoring devices. The flow through the intake valve was measured on a Gould-Statham pneumotachygraph.

PRINCIPLE OF OPERATION

When the self inflating bag was compressed, the intake valve closed to the atmosphere. The content of the bag moved via the non-return valve to the lung of the patient. During this phase the down-flow demand valve closed the intermediate pressure hose and no oxygen flowed to the intake valve of the resuscitator.

When the grip on the bag was released it regained its original shape, generating a sub-atmospheric pressure within the bag. The duration and amplitude of this sub-atmospheric pressure is dependent on the diameter of the aperture of the intake valve. This negative pressure lasted until the pressure within the bag reached atmospheric level. The subatmospheric pressure sucked the silicone membrane (in centre of base plate) into the bag and the down-flow demand valve lever was displaced. The lever arrangement was constructed with a built-in momentum so that the force on the bobbin of the demand valve was multiplied by twenty. When the bobbin was moved, the pressure in the intermediate pressure hose was released and the gas flowed towards the nozzle of the venturi

device with a preset flow of 10 liters/min. Because the flow was preset and the venturi device was calibrated at 40% oxygen delivery, the flow leaving the venturi was 40 liters/min, consisting of 10 liters of oxygen and 30 liters of air. This represented a gas mixture of 16 liters of oxygen and 24 liters of nitrogen. When the negative pressure in the bag was equalised with the atmospheric pressure, the resiliance of the silicone membrane pushed the lever of the demand valve back to its original position. The bobbin of the demand valve closed the intermediate pressure hose and the flow through the venturi ceased.

The ring around the venturi device was attached to the central membrane by means of the purge lever. When this ring was moved to cover the air entrainment ports the intermediate pressure hose was opened continuously. Thus, during both inspiration and expiration, oxygen flowed into the cap of the intake valve and to the reservoir hose. The pure oxygen flowed into the bag during refilling of the resuscitator. In this case the resuscitator functioned as described in fig 1:III.

RESULTS

The negative pressure in the bag was measured. During 90% of the retraction phase there was a sub-atmospheric pressure exceeding 2 cm water pressure negative. This was sufficient to open the down-flow demand valve with the lever. The inflow through the intake valve with an aperture of 100 square mm proved to be 40 liters/min. This equalled the flow coming from the venturi device. The FiO2, with the airmix opened, was measured and proved to be exactly 0.4, also when the reservoir hose was not attached. With the airmix closed, the FiO2 was 1.0 up to a minute volume of 10 liters/min. When the minute volume exceeded the 10 liters, FiO2 decreased proportionally to 0.6 at 20 liters/min being the maximum minute volume delivery with this bag in this configuration (fig. 4). When the reservoir hose was not attached, when the air entrainment ports of the venturi were closed, the FiO2 varied between 0.35 and 0.26, depending on the minute volume being 6 liters/min (frequency: 20 cpm) and 18 liters/min (frequency: 20 cpm).

When the patient port of the breathing was closed, the pressure within the bag did not increase. The force of the flow coming from the venturi was insufficient to open the air intake valve when the air entrainment ports were opened, or when they were closed. The consumption

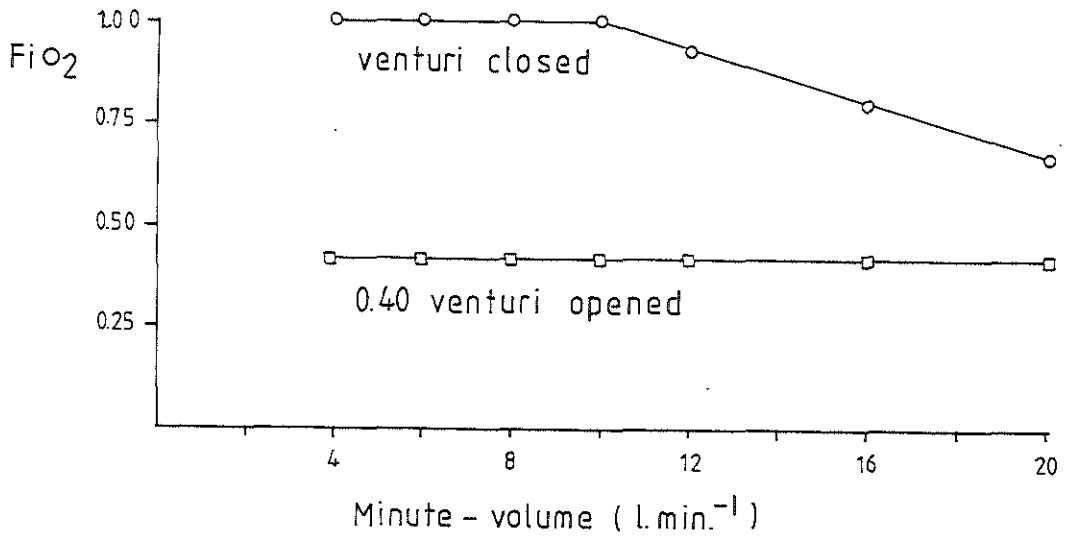

Figure 4. Relationship between FiO2 and ventilatory minute volume.

of oxygen, calculated from the pressure recordings within the bag during ventilation, was 3.0 liters/min and this result was confirmed by calculation of the reduction in cylinder pressure.

DISCUSSION

Ventilation patterns in Intensive Care Units, produced by mechanical devices, have changed over the last decades. It is appropriate, therefore, to upgrade the requirements for manual ventilation equipment. In non-hospital conditions it should be possible to supply patients with similar ventilation characteristics as in the ICU. However, special arrangements have to be made to conserve medical supplies, particularly oxygen.

Manual devices, with mechanical parts only, are generally preferred to gas or electrically powered ventilators in EMC and disaster medicine situations. Mechanical parts of the apparatus should be easily replaceable and not be subject to breakdown or damage. However, a stable performance of manual ventilation depends mainly on the skills of the operator, who has to practise in order to obtain an even delivery of tidal volumes at determined frequencies. Scheduled instruction and counting during ventilation may help to improve skills. Nevertheless, the composition of the apparatus forms the basis for providing a continuously reliable quality of performance (fig. 5).

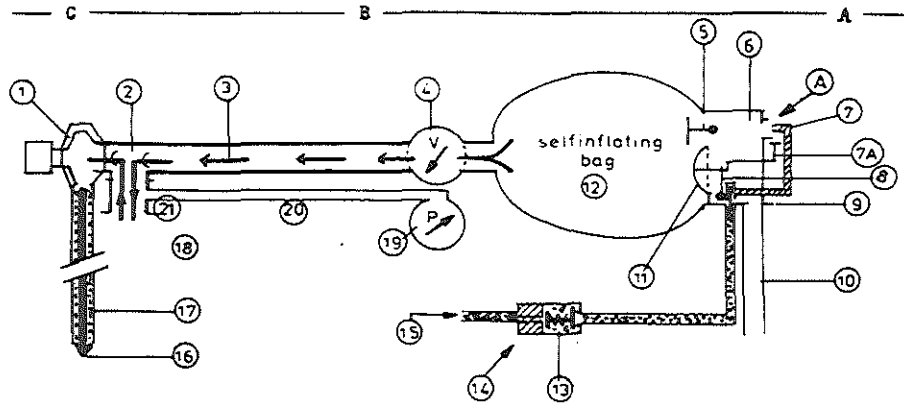

Figure 5. The complete resuscitator.

1. PEEP valve 2. non return valve 3. wide bore corrugated tube
4. volume meter 5. air intake valve 6. reservoir cap
7. venturi with the ring of the purge lever (7a) 8. lever
9. second stage regulator 10. Reservoir hose
11. pressure transducing membrane 12. selfinflating bag
13. first stage regulator 14. bronze sintered filter
15. high pressure oxygen hose 16. vacuum hose
17. scavenging system 18. patient
19. manometer 20. manometer connecting hose
21. tube-valve interface. A, FiO2 = 0.21; B - FiO2 = 0.4 or 1.0
C = the expiratory part with scavenging system.

The described prototype of the intake valve for a resuscitator offers a solution to the problem of stable FiO2. The parts of this apparatus were obtained from existing equipment and rearranged in a new design for resuscitators. Until now, the venturi fixed to the air intake valve of the resuscitator seemed to be the only system able to offer a stable FiO2 at different minute volumes. But, the consumption of oxygen could be considerably reduced in this case. The intake valve and the air enrichment system did not prejudice safety standards because the pressure near the intake valve is at atmospheric level. This was confirmed by the fact that the pressure in the bag did not increase, even when the patient port of the resuscitator was closed. The FiO2 may be set to 0.4 or to 1.0 at will.

This resuscitator is not suitable for spontaneous breathing through the bag because of its relatively high resistance, the intake valve aperture has an opening of only 100 square mm. The second disadvantage of this system is the complexity of the down-flow demand valve, being a highly sophisticated piece of technical equipment. However, both problems are solved when the venturi is used in combination with a reservoir hose. It is then necessary to determine a suitable constant flow from a flowmeter for a particular patient in a specific condition. The aperture diameter of the intake valve is unimportant in this situation.

CONCLUSIONS

The combined possibility of PEEP and air enrichment with oxygen offers the rescuer an optimal opportunity to increase the oxygen partial pressure of the blood, even in non-hospital situations.

The prototype of an air intake valve, as described in this study, offered a stable FiO2 in combination with low consumption of medical oxygen. This prototype did not affect the standards of safety, it was rugged and cheap. Thus, the apparatus meets requirements for CCM. The skills and effectiveness of the rescuer could be supported by monitoring the tidal volume and the airway pressure. With this apparatus it seemed possible to administer ventilation which could be adjusted to meet the individual needs of the patient in all conditions.

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CHAPTER III : EMERGENCY MEDICAL CARE

Emergency Medical Care (EMC) is the subdivision of Critical Care Medicine (CCM) which is concerned with outpatients having impaired vital functions, who receive medical attention from medical personnel. The components of EMC are :

1) receipt of emergency report
2) dispatch of medical personnel
3) on-the-spot medical treatment
4) transport of the critically ill patient to EMC department
5) treatment in EMC department

The first topic in this chapter deals with a portable PEEP valve to administer PEEP during ventilation of patients outside the hospital. The valve was constructed (on request of the author) by AMBU Danmark and tested both in the laboratory and during clinical surgery. The use of PEEP valves is currently restricted to trained medical personnel. The valve has become an important part of professional medical equipment.

The second part of this section is concerned with a mechanical ventilator suitable for all stages of EMC. It fulfils all the requirements of the high standard inhalational therapy of this decade and is suitable for EMC because the ventilator is low-pressure actuated with a low oxygen consumption. At this moment, the use of mechanical ventilators is restricted to physicians only.

The third part of this chapter deals with a method of combining blood gas analysis and other biochemical tests which may all be estimated from one small blood sample. The original idea of this study was to test if it could be possible to take samples at the scene of the emergency and make more estimations, other than blood gas analysis, from one and the same sample. After admission of the patient in the hospital the samples could then be estimated. In this way it became possible to obtain accurate pre-hospital laboratory results. Later, this method proved to be of great assistance both to anaesthesia and to CCM in general.

A PORTABLE PEEP VALVE FOR 0-20 cm H2O

M.P. Boidin

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Key words : EQUIPMENT - valves, PEEP.

PEEP ventilation is an important part of the therapy employed in CCM. It is used for improving the oxygen saturation of the arterial blood by increasing the oxygen diffusion and by preventing the collapse of the smaller airways. This augmentation of the end-expiratory pressure may improve arterial oxygenation during ventilation of patients with an increased intra-pulmonary arterio-venous shunt. PEEP therapy can generally be applied to a variety of patients, ranging from prematures to geriatric patients, with a wide range of pathology. Clinical manifestations, for example ARDS, may become obvious outside the hospital or during disconnection from a ventilator during PEEP ventilation. When PEEP is necessary it should be applied as soon as possible, be as stable as possible and only be discontinued for very short intervals. Temporary augmentation of FiO2 is not always sufficient to replace PEEP, even for short periods. In order to deal with all situations, a portable PEEP valve should be available (1,2,3,4,5,).

When PEEP is used, it is important to be aware of the possible complications concerning its use. Thus, during the application of PEEP (6) via a face mask, the stomach can also become insufflated, pneumothorax and inpaired venous return may occur. Nowadays, the problems associated with the use of PEEP on standard ventilators has been satisfactorily solved. Recently, AMBU Danmark introduced a portable PEEP valve with a range of 0-10 cm H2O, but because of its low pressure limit there was a restriction on its clinical use. Therefore, the manufacturer has since designed a new valve, with a range of 0-20 cm H2O.

Description of the valve (fig. 1)

The portable PEEP valve is made of green transparent plastic having the dimensions : 3 cm x 6 cm. ISO fitting makes it possible to connect the valve to a number of non-return valves on resuscitation equipment.

A wide-bore channel is closed by means of a nylon plunger with a silicone membrane lining the opening. A soft green PVC cap forms the top of the valve and a spring transmits tension to the plunger. When the cap is screwed inwards, an increase of the spring tension results. This increase in spring tension in turn results in an increase of the force with which the plunger has to be displaced. Approximate calibration is indicated on the neck of the valve and ranges from 0-20 m bar.

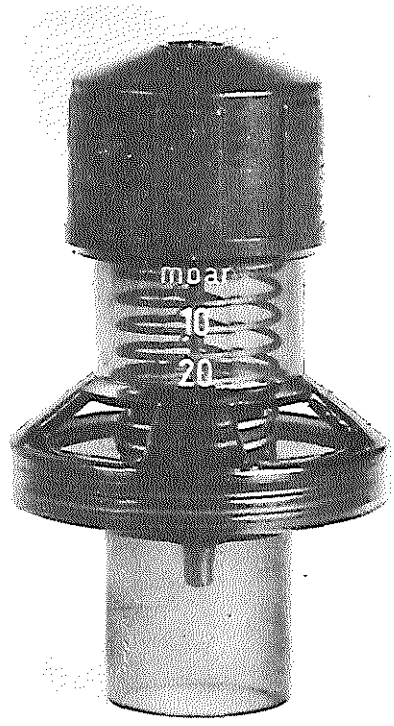

Figure 1. AMBU PEEP valve for maximally 20 mbar.

METHOD

The portable 20 m bar PEEP valve was tested for resistance characteristics at different flows (7) and for the influence of positioning, temperature and humidity (8). Pressures were measured on Gould-Statham transducers and recordings were made using a Hewlett-Packard display and recorder. Gasflow was measured (9) with a Gould pneumotachygraph. During the clinical test period this PEEP valve was used in combination with resuscitation bags and transport ventilators, standard ventilators and CPAP systems (10,11,12).

RESULTS

Figure 2 shows the pressure values at various settings with flows varying from 5 - 40 liters/min. Any variation in expiratory flow towards a PEEP valve changes the pressure in front of the valve. Because of flow restriction (limitation) by the valve, flow seldom exceeds 40

liters/min when PEEP valves are used. An increase in flow results in an increase of the pressure. All the recordings in fig. 2 were obtained with the valve in the horizontal position.

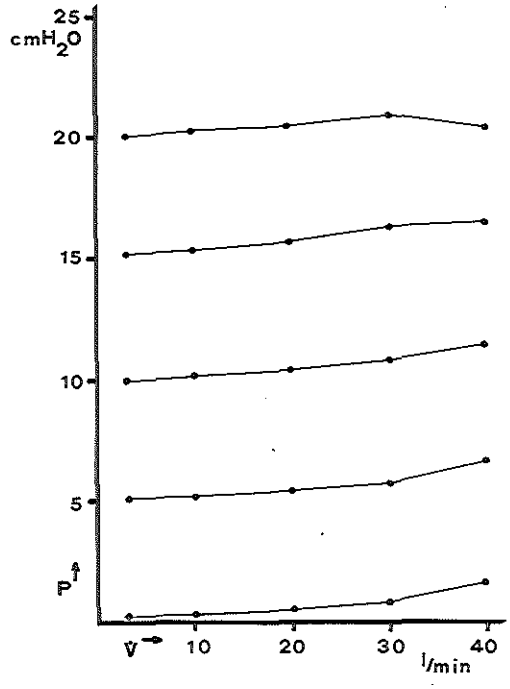

Figure 2. Resistance of the AMBU PEEP valve for different gas flow patterns.

With the valve in an upsidedown position the pressure was 1.3 cm H20 higher because of the weight of the plunger. Increase in temperatures from 6-60°C caused a decrease of tension in the spring, which resulted in a 0.75 cm H20 pressure decrease. Laboratory tests proved that the performance of the valve was not dependent upon variations in humidity.

In clinical studies, the PEEP valve was tested for a total of more than 300 hours on the AMBU resuscitation bag, the AMI Carry-Vent, the Servo 900B ventilator and it was also connected to a CPAP system for more than 300 hours. After each use the valve was sterilised in ethylene oxide at 50°C. No change in resistance characteristics were measured after the test period. Arterial oxygenation of patients remained stable when ventilation was continued by means of manual bag ventilation, using the same levels of PEEP and FiO2 that were used when the patient was mechanically ventilated.

DISCUSSION

Perel et al. (8) and Dick et al. (7) have discussed the use of portable PEEP valves in the range of 6-10 cm H2O. In clinical practice, a PEEP level of 20 cm H2O is frequently used and it is regretted that this often has to be disconnected for various medical interventions. Portable PEEP valves offers the possibility of ventilating patients during manual bag ventilation, maintaining the same expiratory pressure and FiO2, and the same minute volume and frequency (10) as when the patient was still connected to the ventilator.

Emergency medical technicians are sometimes 'over-enthusiastic', therefore it should be stressed that the use of PEEP valves is not totally without danger. Users of these valves should know the indications as well as being aware of the contra-indications and complications of use, in order to achieve maximum benefit for their patients.

CONCLUSION

The 20 m bar AMBU PEEP valve meets all the requirements for CCM and disaster medicine. Laboratory tests proved its stability. Even after intense use, no deterioration of the valve was observed. It is small, lightweight, easy to handle, multi-purpose, stable and inexpensive. Thus, this valve should be available in all fields of CCM.

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MECHANICAL VENTILATORS FOR EMERGENCY MEDICAL CARE USING A MANUAL RESUSCITATION BAG

M.P. Boidin

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KEYWORDS : CRITICAL CARE - Emergency Medical Care
- transport

VENTILATION - equipment
- minute volume divider
- resuscitation bag

Self inflating resuscitation bags were originally developed for artificial ventilation with air. Later they were introduced into daily clinical work as a complete unit, or as part of an anaesthetic circuit 1,2,3). But manual ventilation using bag and mask, or endotracheal tube, requires additional manpower. This may be short in disaster situations. During prolonged transport of critically ill patients, it is usually impossible to continue the same ventilational pattern as given in the ICU (4). Because of this fundamental disadvantage, it was decided to design a mechanical ventilator for transport conditions. A new combination of silicone resuscitation bag and a magnetic valve was explored.

MATERIAL AND METHODS

The new Laerdal adult resuscitator is made of silicone rubber and has improved physical properties. The unit is autoclavable and performance is not influenced by ambient temperature. But, unlike former models, the inside of the bag is not readily visible. The non-return valve is housed in a smoke-coloured, transparant polysulfon urethane (PSU). The valve seat has been modified and the silicone membrane valve shows less deformation when PEEP is applied. The fittings of the house have been remoulded so disconnection occurs less frequently. The new swivel-head lessens the torsion on the endotracheal tube and enables easier fitting of the face mask. As a result of recent criticism (5), the expiration diverter has been redesigned. By addition of silicone rings to the edges, the new cap forms an airtight seal with the non-return valve. The non-return valve is connected to the endotracheal tube via an interface with a side-opening. In this way, airway pressure can be measured by a manometer.

In this study an AMBU anaesthesia PEEP valve was used (6) as this allowed a Wright spirometer to be connected to one side and a scavenging system to the other. 50 cm of corrugated tubing was imposed between the bag and the valve and, as an additional safeguard, a 'blow-off' valve for 0-50 cm water pressure was placed between the bag and the corrugated tube. This was to prevent excessive airway pressures.

The Mini-Vent magnetic valve described by Cohen (7) and Mushin (8) fulfils all requirements for EMC. The magnetic valve ventilator Mini-Vent

type A5 (AMI, The Netherlands) is only used in combination with a non-return breathing circuit (4). This prevents the valve from becoming moist and avoids the possibility of the valve sticking in its inspiratory position. The magnetic valve may be used with reservoir bags of various compliance. Use of thick-walled bags is rare in clinical anaesthesia, therefore the Laerdal adult silicone resuscitator was tested. The compliance of this bag (with a content of 1.6 liters) was compared with the compliance of a thin-walled anaesthesia bag and a low compliant rubber bag, both with a content of 2 liters. For this purpose, the pressure generated inside the bag was measured when it was filled at a rate of 2 liters per minute.

The frequency, tidal volume and minute volume of the ventilator were measured with a Gould pneumotachygraph. The values were then compared with the readings from the Wright spirometer and also compared with the number of cycles per minute counted by hand. Airway pressure and pressure in the reservoir bag were measured with Gould-Statham transducers and displayed on a Hewlett-Packard monitoring device. The electronically obtained airway pressure was compared with the reading from a manometer, which was placed between the non-return valve and the endotracheal tube. All electronically obtained results were recorded on a Hewlett-Packard 8-channel recorder. Arterial blood gas analysis was estimated at regular intervals during mechanical ventilation with this new device.

MODE OF ACTION AND RESULTS

Fig. 1 illustrates the apparatus used in this study.

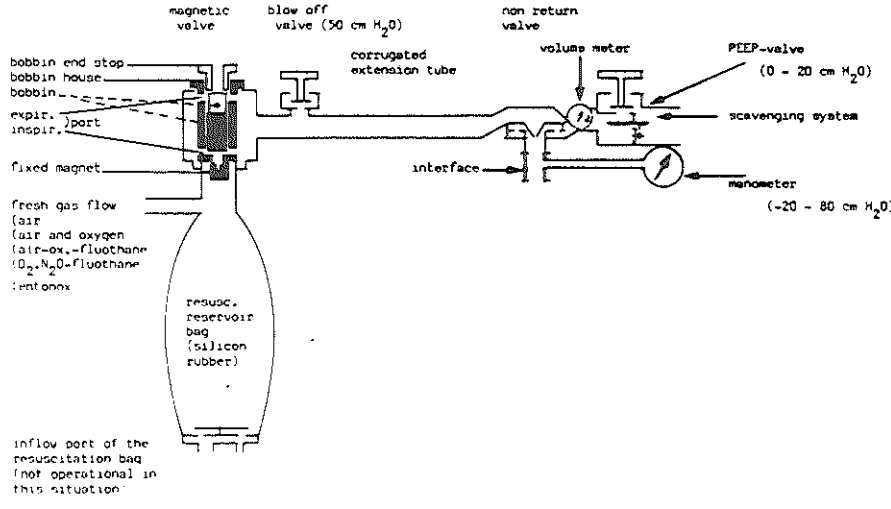

Figure 1: The complete ventilator

As the fresh gas flows into the reservoir bag it exerts an increasing force on the magnetic valve. When the pressure within the bag exceeds the magnetic force, the bobbin is moved upwards. The gas flows to the corrugated extension tube and opens the non-return valve to the patient. As a result of the gas movement, the pressure in the bag decreases and the bobbin returns to the original position. The pressure at the inspiratory port of the non- return valve decreases to atmospheric level and thus expiration begins via the expiration port, the spirometer and the PEEP valve.

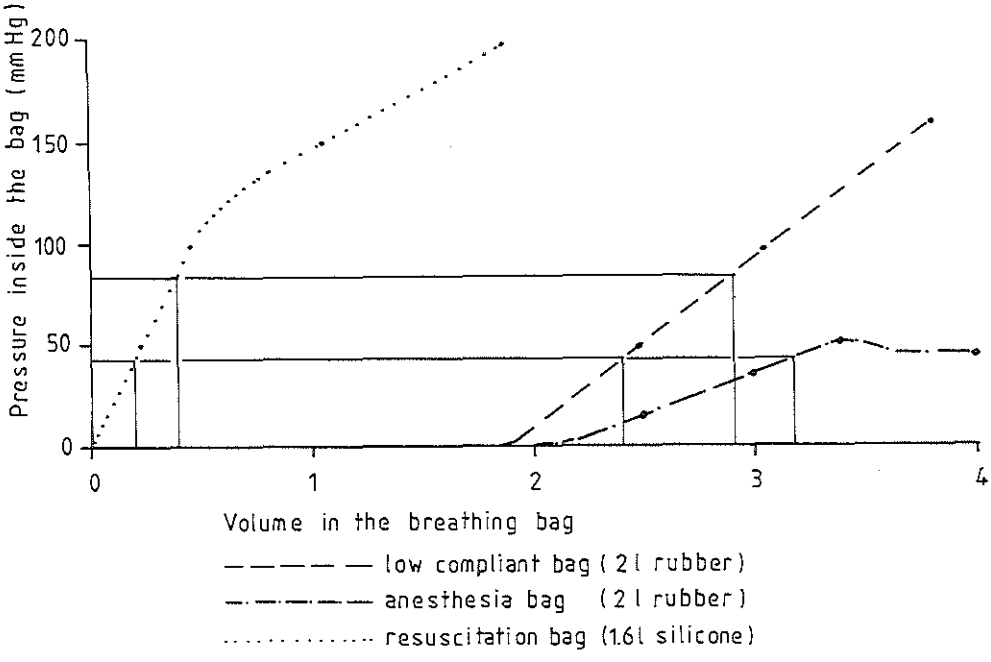

Figure 2: Relationship between pressure and volume in three different ventilation bags.

The reservoir bag acts as a pressure generator. Bags with a low compliance generate small volumes and bags with a high compliance generate large volumes (fig. 2). The silicone bag, however, has biphasic compliance characteristics, the delivered volumes being low at low pressures and increasing with higher pressures. The magnetic valve functions as a minute volume divider which loses approximately 50 ml per cycle. The ventilator may be used to deliver minute volumes (fig. 3) of 3 - 12 liters per minute, with a frequency of between 7 and 60 cycles per minute. The airway pressure cannot exceed 50 cm water pressure. Blood gas analysis can be maintained at physiological level in all patients when

the demanded minute volume is between 3 and 12 liters per minute. With the exception of the PEEP valve and the corrugated tube, all parts may be autoclaved at 136°C. Sterilisation took place in ethylene oxide after domestic cleaning. No deterioration of performance was measurable after the apparatus had been cleaned and sterilised on more than 200 occasions.

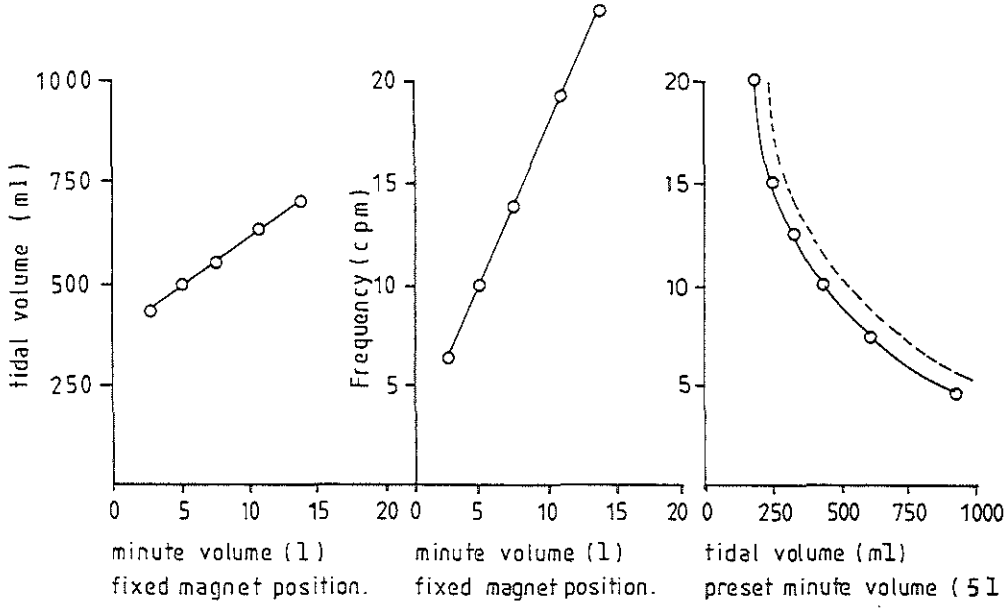

Figure 3: Relationship between frequency, tidal volume and minute volume in the Mini-Vent ventilator. ——— is the estimated frequency-tidal volume relation when no fresh gas is spilled.

During this study, the connections between the non-return valve and the accessories resisted pressures up to 300 mm Hg. The readings on the spirometer were highly unreliable when used in combination with the PEEP valve. The Wright spirometer was therefore interposed between the ventilator and the non-return valve. The readings proved to be much more reliable when this composition was used. The airway pressure measurements were very accurate and the scavenging system did not influence the performance of the ventilator.

DISCUSSION

The ventilator is capable of satisfactory patient ventilation even in the presence of high airway pressures. With correct adjustment of the magnetic valve and the PEEP valve, patient ventilation can be set to

obtain physiological blood gas analysis. During use of this transport ventilator, all patients who had been ventilated in the ICU could be transported maintaining the same ventilatory pattern and without deterioration of their blood gas analysis.

Combination of a magnetic valve and a self-inflating silicone reservoir bag is simple, safe and inexpensive. Should malfunction of the ventilator occur, or should the driving gas fail, it is easy to transfer from mechanical to manual ventilation by removing the T-piece and the magnetic valve from the circuit.

The biphasic compliance characteristic of the silicone bag makes it is as suitable for baby as for adult ventilation. However, it should be mentioned that the ventilator loses 50 milliliter gas per cycle. To calculate delivered tidal volume the following formula was used:

$$\text{Tidal Volume} = \frac{\text{total fresh gas flow} - \text{frequency} \times 50 \text{ ml}}{\text{frequency}}$$

The setting of the 'blow-off' valve must always be lower than the pressure in the reservoir bag, but higher than the peak airway pressure of the patient. This setting is obtained by closing the patient port of the non-return valve in the cycling ventilator. The ventilator should continue to cycle and the manometer should give a pressure well above the peak inspiratory pressure of the patient.

When PEEP is required, it should be applied as soon as possible and it should be disconnected only for short periods. Temporary augmentation of FiO2 is not always sufficient to replace PEEP. The quality of the AMBU anaesthesia PEEP valve is discussed elsewhere (6). However, if PEEP is applied to the expiratory port of the non-return valve, the readings on the Wright spirometer may be subject to considerable error due to the flow limitation of the PEEP valve. Thus, it is recommended that the volume meter be inserted between the Mini-Vent magnetic valve and the 'blow-off' valve, as there is no flow limitation in this part of the ventilation circuit.

The ventilator was tested on a test lung in : specific conditions, in a hyperbaric chamber up to 6 atmosphere absolute, in a deep freezer to -30°C, in tropical conditions to 40°C. No disfunction was observed, but

small adjustments to the magnetic valve and the minute volume of the fresh gas mixture were necessary to compensate for altered atmospheric conditions. The pressure and volume monitoring proved to be very helpful in these conditions. In the hyperbaric condition it was convenient to connect the scavanging system to the expiration port, thus preventing pollution of the atmosphere tank and decreasing the risk of oxygen toxicity.

CONCLUSIONS

This study proved that the combination of the Laerdal adult silicone resuscitator and the Mini-Vent A5 magnetic valve could be used as a mechanical ventilator in emergency medical and disaster medicine. The self-inflating bag was suitable as a reservoir bag and the magnetic valve was a reliable minute volume divider showing stable performance. Excessive airway pressure was prevented by the 'blow-off' valve in the patient circuit. During the test period the breathing circuit showed no disfunction. Use of the magnetic valve requires knowledge and experience with patient ventilation. Physiological blood gas analyses could be obtained in all cases when the demanded minute volume was between 3 and 12 liters.

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INFLUENCE OF DIFFERENT HEPARIN SOLUTIONS UPON BLOOD GAS ANALYSIS AND BIOCHEMICAL VALUES MEASURED IN PLASMA

M.P. Boidin, P. Jorna.

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KEYWORDS : BLOOD - plasma-serum
biochemical tests
heparin solutions

In the ICU there is a tendency to sample blood frequently and small samples are obviously preferable. To reduce blood loss and to obtain more information from one sample we attempted to combine blood gas analysis with sodium, potassium and calcium estimations. As the samples become smaller the dilution tends to increase, no matter how little heparin is used. The dead space of a 2.5 ml Braun syringe is 0.09 ml which represents a dilution of 5% when 2 ml samples are taken. Heparin acidity may also influence the blood gas analysis results. Moreover, the composition of heparin solutions is not constant, due to changes in anion concentration of the dry heparin powder. All these factors could introduce errors which may lead to clinical misinterpretation and therapy based on inaccurate laboratory results.

Tocantis and Kzal (1) found that at least 10 units/ml heparin concentration must be added to prevent coagulation of the sample. Bech-Jansen and Beck (2) found that 1000 units/ml heparin solution was superior to other preparations for the measurement of pH in small samples. It also proved impossible to make a 5000 units/ml heparin solution having the same anion concentration as serum. The dry heparin powder was therefore diluted to a 1000 units/ml solution to which sodium, potassium and calcium ions were added to achieve the same ion concentration as the normal serum values in our laboratory.

Lum and Gambino (3) showed that significant differences may be expected in the results of sodium, potassium chloride, inorganic phosphate, lactate dehydrogenase (LDH), albumin, protein and cholesterol, when serum and heparinised samples are compared. These studies could not confirm all these differences, but it should be noted that different correlations may be found when different methods are used for biochemical estimations (4).

MATERIAL AND METHODS

Twelve patients with a haemoglobin concentration over 8.00 mmol/l were sampled after obtaining their informed consent. Samples were taken from indwelling arterial and venous cannulae. Dead space fluid was removed from the cannula under sterile conditions and a 40 ml sample was taken under strict anaerobic conditions. The sample was collected in a

plastic Braun 50 ml syringe containing 0.4 ml sodium heparin solution 1000 units/ml and was well mixed. This sample contained 10 units of heparin per ml and served as a control for all measurements. The sample was stored in ice for 1 hour to rule out oxygen consumption during subsequent manipulation.

A heparin solution of a constant and known composition (Table I) was added (with a calibrated 1 ml Braun syringe) to twelve 2.5 ml plastic sterile Braun calibrated syringes. Sodium heparin (5000 units/ml) in volumes of 0.1, 0.2, 0.4, 0.8 respectively, was put into four of the syringes. The procedure was repeated for calcium heparin (25000 units/ml) and sodium heparin (1000 units/ml). The 40 ml sample was taken from the ice and continuously mixed. One 2.5 ml syringe containing no additional heparin was filled to the 2 ml mark and served as the first control sample. The 12 prepared syringes were also filled to the 2 ml mark. Another syringe containing no additional heparin served as the second control sample. The 14 samples were conserved in ice awaiting analysis. Blood gas analysis was measured by an ABL 2 (Radiometer, Copenhagen) and saturation was separately measured on an OSM 2 (Radiometer). Haemoglobin was measured colorimetrically with a Vitatron colorimeter and the total protein of the plasma was estimated optically with a refractometer (TS Meter, American Optical Instr. Co.).

Table 1. Various heparin solutions differ in their electrolyte compositions

	Sodium mmol/l	Potassium mmol/l	Calcium mmol/l	pH	pCO_2 kPa	pO_2 kPa
LEO® sodium heparin 5000 U/ml	159	6.9	0.05	5.55	1.2	25.9
Calcium heparin 25000 U/ml	135	9.2	400	5.57	1.6	26.0
Sodium heparin 1000 U/ml + electrolytes	139	4.2	2.50	5.15	1.3	25.7

For all estimations (except base excess, saturation and pH) the mean of the two control samples was nominated as 100%. The difference from the control value was calculated and the mean of all deviations was expressed graphically in percentages (fig. 1). The base excess was calculated only for the mean of 12 values and expressed graphically (fig. 1).

The saturation is already expressed as a percentage and the presented value is the mean of the deviations from the control value (fig 1). The concentration of free H^+ ion was calculated from the pH. The mean of the 12 values was calculated and from these values the mean pH was calculated. The mean percentage deviation from the control H^+ concentration was

calculated and also expressed graphically. Sodium and potassium measurements, from the same sample, were made with a Klina Flame flamephotometer (Beckmann).

10 ml fresh whole blood were collected from the same patient and compared with 10 ml plasma from the above mentioned sample containing 10 units heparin per ml sample. For the serum sample, the blood was first clotted then both samples were centrifuged. The use of heparinised samples raises a special problem for laboratories using the Sequential Mulitiple Analyser, as whole blood may clot in the small tubes of this instrument. Therefore, plasma and serum were analysed on the ACA (Automatic Clinical Analyzer: Dupont, USA).

Data were collected and the 12 results were calculated for mean and standard deviation and the significance was estimated using the Student's t test for paired values.

RESULTS

A decrease in pH was observed in the series having more concentrated heparin solutions. When 1000 units/ml heparin solution was used no decrease in pH could be measured, even at 40 volume % dilution. A linear decrease in pCO2 was observed with the 1000 units/ml solution. However, with the more concentrated heparin solutions different curves were plotted and less deviation was observed than could be predicted from the dilution alone.

Bicarbonate values were calculated from pH and pCO2 values and the graphs reflect the characteristics of both these values. Base excess was calculated from pH and bicarbonate values and the curves were therefore influenced mainly by pH and, to a lesser extent, by the pCO2. pO2 and oxygen saturation showed only small deviations from the control sample and the difference was not significant.

Protein and haemoglobin content decreased linearly in relation to the added volume for all three heparin solutions. The linearity indicates that there is a straight dilution effect for these two parameters, which can be used to recalculate the dilution.

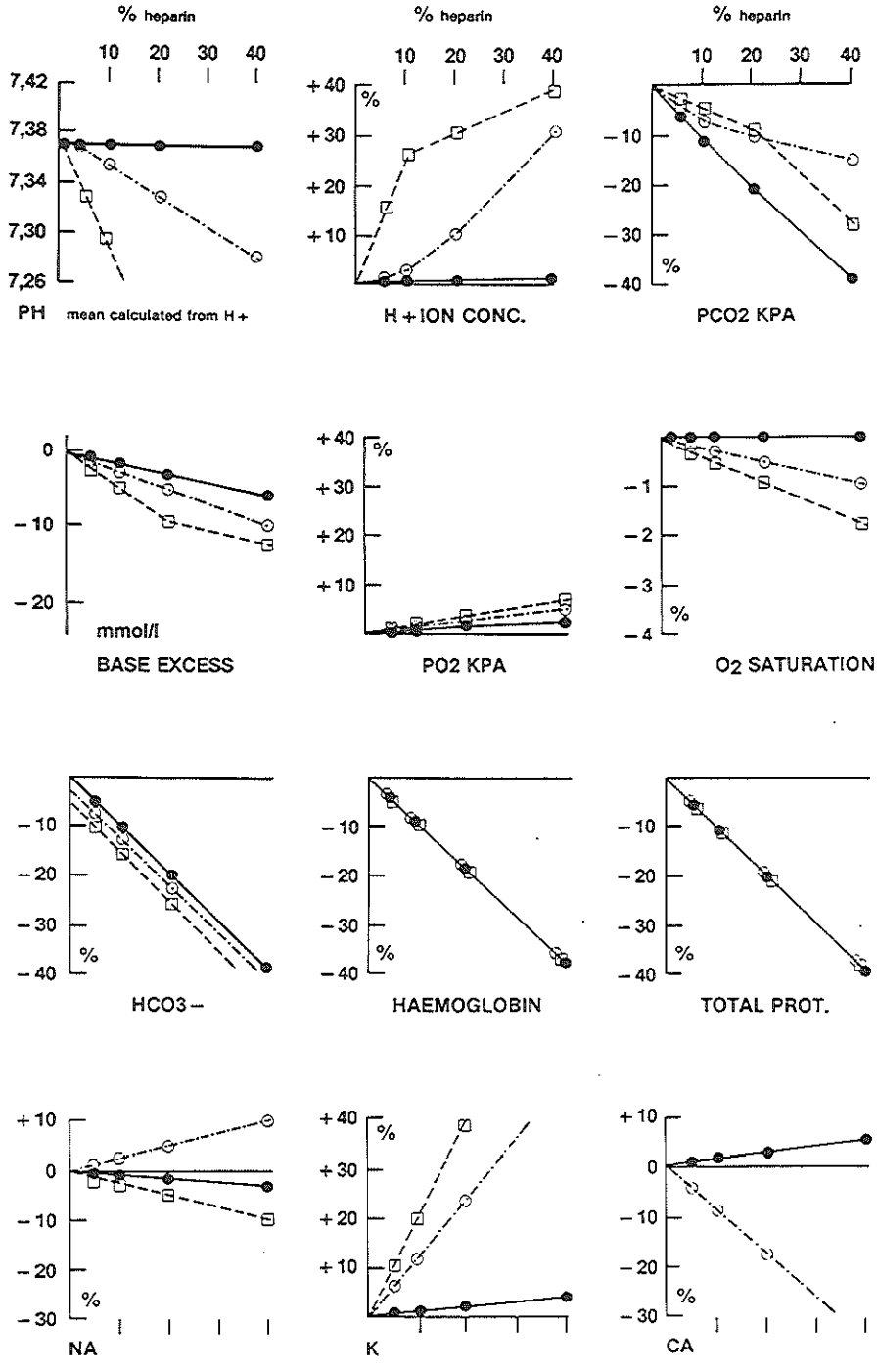

Fig. 1. These graphics give the overall effects of three different heparin solutions on the results of blood gas analysis and electrolyte estimations. – · – ○ – · – sodium heparin 5000 U/ml; ——●—— sodium heparin 1000 U/ml; · · · calcium heparin 25000 U/ml

With different heparin solutions, large variations in electrolyte compostion were found (Table I). Table II suggests a correlation between the anion concentration in the plasma sample and in the applied heparin solution. A good correlation of serum and plasma values was obtained when 1000 units/ml heparin with added anions was used, even when the dilution was up to 40 vol %. The other heparin solutions showed a poor correlation, even when low volumes of heparin were used.

Table 2. Effects of three different heparin solutions in 5, 10, 20 and 40% dilution on the electrolyte estimation in blood samples

Serum	Plasma 1% heparin 3)	1) LEO Heparin				2) Calcium heparin				3) Sodium heparin 1000 units/ml + sodium, potassium, calcium			
		5%	10%	20%	40%	5%	10%	20%	40%	5%	10%	20%	40%
M 138	138	141	145	151	158	138	137	135	133	137	138	139	139
1) SEM 0.69	1.08	1.04	0.91	1.35	2.05	1.05	1.08	0.77	1.05	0.94	0.74	0.73	0.63
p –	>0.05	NS	NS	NS	NS	>0.05	>0.05	NS	NS	>0.05	>0.05	>0.05	>0.05
M 4.37	4.20	4.46	4.75	5.34	7.05	4.62	5.18	6.62	9.78	4.42	4.41	4.48	4.65
2) SEM 0.15	0.14	0.13	0.13	0.17	0.19	0.16	0.19	0.35	0.49	0.12	0.12	0.11	0.09
p –	>0.05	>0.05	A0.05	NS	NS	0.01	NS	NS	NS	>0.05	>0.05	>0.05	0.01
						0.001							0.001
M 2.20	2.23	2.10	1.98	1.76	1.37					2.36	2.43	2.60	2.88
3) SEM 0.05	0.04	0.03	0.04	0.03	0.02					0.08	0.09	0.18	0.31
p –	0.01	NS	NS	NS	NS					0.01	0.01	>0.05	>0.05
	0.001									0.001	0.001		

1) Sodium mmol/l; 2) potassium mmol/l; 3) calcium mmol/l

The results of other biochemical tests are summarised in Table III. Statisically significant differences were found for values of inorganic phosphate, lactate dehydrogenase (LDH) and total protein. All other results showed no significant differences between the serum and plasma results (p being less than 0.05). Using the low heparin concentration in the 40 ml sample (10 units/ml), no microclots were observed during manipulation of the samples in the ABL 2 and in the Auto analyser.

Table 3. Comparison of serum versus plasma samples. Blood of the plasma samples were diluted with 1% heparin solution containing 1000 units per ml with added electrolytes

Adult normal range	Serum		Plasma		Diff. of the mean valve (%)	t	p
	mean	SD	mean	SD			
Sodium 135–143 mEq l^{-1}	138	2.49	138	2.09	0	0.52	0.05
$n = 11$							NS
Potassium 3.5–4.5 mEq l^{-1}	4.37	0.53	4.20	0.49	−4	2.41	0.05
$n = 11$							NS
Calcium 2.2–2.6 mmol l^{-1}	2.20	0.12	2.23	0.11	−1.5	3.49	0.01
$n = 10$							NS
Chloride 95–105 mEq l^{-1}	102	2.83	102	1.95	0	0.58	0.05
$n = 11$							NS
Urea 3.3 ± 6.7 mmol l^{-1}	4.23	1.32	4.15	1.30	−2	3.11	0.01
$n = 11$							NS
Creatinine 62–106 mmol l^{-1}	75.09	22.74	78.91	22.73	+5	2.74	0.01
$n = 11$							NS
PO_4^{3-} inorganic 0.65–1.30 mmol l^{-1}	1.16	0.19	1.08	0.18	−8	7.37	Significant
$n = 11$							
Alkaline phosphatase 13–120 units/l^{-1}	62.27	30.28	60.64	27.81	−3	1.26	0.05
$n = 11$							NS
LDH 114–235 units/l^{-1}	198.91	59.37	168.91	59.19	−15	4.51	Significant
$n = 11$							
OT 2–20 i. units/l^{-1}	27.00	8.38	25.20	8.20	−2	3.25	0.01
$n = 10$							NS
PT 2–15 i. units/l^{-1}	15.30	12.90	15.30	13.29	0	0	0.05
$n = 10$							NS
Serum protein 6.36–7.80 g/100 ml	60.36	5.37	63.36	2.78	+5	6.17	Significant
$n = 11$							
Albumin >3.0 g/100 ml	36.20	2.78	38.40	4.22	+5	1.40	0.05
$n = 10$							NS
Cholesterol 2.5–6.7 mmol l^{-1}	4.45	0.64	4.38	0.65	−1.5	2.69	0.01
$n = 10$							NS

Addition of the acid mucopolysaccharide heparin may simulate metabolic acidosis, according to the Henderson and Hasselbach equation :

$$pH = pK + \log \frac{HCO^-_3}{S.pCO2}$$

When less than 250 units heparin (per ml sample) are applied, there is no change in free H^+ ion concentration. More than 400 units heparin per ml sample caused a significant decrease in pH. This decrease is independent from the dilution effect. When the free H^+ concentration is increased in a closed system (syringe) it causes a simultaneous fall in bicarbonate and an increase in pCO2 (5,6,7). With 1000 units/ml heparin solution (in a 2 ml sample) no significant increase in free H^+ could be measured. When samples for blood gas analysis contain too much heparin, the results falsely indicate a metabolic acidosis.

Because carbon dioxide is distributed equally in the volume of the heparinised sample and pH does not change when the heparin concentration is low in a plasma sample, we observed a linear decrease in pCO2 when 1000 units/ml heparin solution was used. However, when pH decreases, as is the case in more concentrated heparin solutions, pCO2 values increase, as could be expected from a dilution effect. Because the bicarbonate value is calculated from both pH and pCO2 values, its value will decrease further than may be expected from dilution alone. Dilution thus causes an overall decrease in pCO2 and bicarbonate values. It is this artefact that causes the misintepretation of a respiratory compensation of the artificial metabolic acidosis.

Measurement of oxygen partial pressure showed a small increase concomitant with an increase in heparin concentration. The shift to the right of the dissociation curve, due to a lower pH, theoretically results in the liberation of oxygen from the haemoglobin. But, at the same time, an increase in pO2 was observed. This increase might be due to the low solubility of oxygen in the heparin solution, being about the same in all three solutions. The results showed significant differences for the 3 different heparin solutions.

Electrolyte estimation is possible in heparinised samples, but two factors may influence the results. Dilution may decrease the electrolyte value in plasma compared with that of serum. Contamination of heparin solutions with electrolytes may also change values accordingly. To overcome this problem, sodium, potassium and calcium ions were added to a 1000 units/ml heparin solution, so that anion concentrations were the same as the normal values used, at that time, in the hospital biochemical laboratory. This 'physiological solution' affected the results by increasing the arithmetic mean value of the normal curve. The statistical implication of this increase is that the number of samples at mean values increases and standard deviation decreases. The curve becomes higher and narrower, though the number of samples remains the same. For practical use this implies that extreme values for plasma deviate towards the normal value and seem to be less extreme than when measured in serum.

With the 'physiological solution', no significant differences between plasma and serum electrolytes were observed, even when considerable volumes of heparin were added. This is in contrast to the findings of Pannall and Rossie (8), Word et al. (9), Lum and Gambino (3). Normal values from the hospital biochemical laboratory may not be ideal for preparing physiological solution because arithmetic mean values for patients in the ICU may differ from those in other departments. However, in this study the normal value from the hospital laboratory was used to prepare the heparin solution, but 50% of the measurements were made in critically ill patients with relatively low sodium/high potassium concentrations.

Dry Lithium heparin may also introduce sodium, potassium and calcium, because some of the Lithium heparin powders are also contaminated with electrolytes. This may explain why significant differences may be found in anions when dry heparin is used (10).

Most of the enzymes and metabolites showed no significant differences because urea and bilirubin are not bound to plasma fibrogen, but part of the creatinine is. Creatinine can also be partially extracted from serum when the clot is removed. The differences between plasma and serum creatinine are not statistically significant. But, the values in plasma seem more reliable than the values obtained in serum samples. Significant difference in lactate dehydrogenase was observed when serum samples were compared with plasma samples. This may be due to platelet cell damage during the clotting process (11). Lactate dehydrogenase estimations are particu-

larly sensitive to sample manipulation and to the method of analysis.

Plasma lactate dehydrogenase therefore seems to be a more reliable estimation than serum lactate dehydrogenase. Inorganic phosphate constitutes part of the wall of the erythrocyte and escapes during the clotting process.

The results of this study show that the total protein content is 3 g/dl lower in serum estimations. Because fibrinogen forms part of the total protein content, the differences in total protein can be accounted for by the retention of fibrinogen in plasma. Sample dilution with heparin solution could be responsible for the small differences in the results of urea, alkeline phosphatase, serum glutamic-oxalacetic transaminase, serum glutamic pyruvate transaminase and cholesterol values.

CONCLUSIONS

Acidification and dilution increase in relation to the different volumes and concentration of heparin solutions in a sample. The dilution should be standardised, be as small as possible and the blood sample should not contain more than 250 units heparin per ml. Moreover, the samples should be taken and prepared for analysis according to a rigid protocol.

The electrolyte composition of heparin solutions is not constant. Therefore, it is advisable to standardise the composition and the added volume of heparin solutions when electrolyte measurements are made at the same time as blood gas analysis. A heparin solution containing 1000 units/ml with a 'physiological' elecytrolyte composition (sodium 140 $mmol/l^{-1}$, potassium 4.2 $mmol/l^{-1}$, calcium 2.5 $mmol/l^{-1}$) gives at least a similar mean value in both serum and plasma measurements. The standard deviation decreases concomitantly with the added volume of heparin solution.

It is more complicated and more expensive to perform routine biochemical tests with heparinised samples. However, because there is no disturbance from the clotting mechanism, creatinine, lactate dehydrogenase, inorganic phosphate and fibrinogen values are more reliable in plasma, than in serum samples.

Combination of blood gas analysis, electrolyte estimations and other biochemical tests is possible, saves blood and reduces the possibility of administrative error. However, the equipment used and the technique employed for sampling with heparinised blood samples should be rigidly controlled and this information should be transmitted to all personnel involved in taking and measuring samples. Scrupulous interpretation of values is necessary. The method described is very useful for paediatric cases, in neonatology wards, in laboratories using small animals and in all places where blood gas analysis is frequently performed.

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CHAPTER IV : INTENSIVE CARE

INTENSIVE CARE

Intensive care (IC) is the subdivision of Critical Care Medicine (CCM) concerned with the patient with impaired vital functions, or impending failure of vital functions, who is admitted to a specialised unit in the hospital. This chapter discusses sedation during intensive care treatment. Sedation during inhalation therapy in critically ill patients is an important field of interest for anaesthetists.

Etomidate was a potentially valuable drug as a sedative. It was a short-acting hypnotic for induction and maintenance of anaesthesia. The drug has also been investigated for its brain protection properties following resuscitation. No serious side effects were noticed before 1981.

During and after etomidate, used as a continuous drip infusion in both the operating theatre and the ICU, it was noticed that patients showed impairment of sodium and water balance, accompanied by post-operative fever. Acute Addisonian crisis was one of the possibilities. The symptoms necessitated the investigation of cortisol and the serum cortisol concentration proved to be in a pathologically low range.

During the course of these investigations it became obvious that the results could have significant implications, not only for etomidate and anaesthetists, but also for other imidazole containing drugs and for other specialities. But the results proved to be of special interest for intensive care therapy. Drugs containing imidazole structures had been enjoying a growing popularity in the ICU over the last few years.

SERUM LEVELS OF CORTISOL IN MAN DURING ETOMIDATE/FENTANYL AND AIR ANAESTHESIA, COMPARED WITH NEUROLEPT ANAESTHESIA

M.P. Boidin

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METABOLISM - hormone, cortisol

Two anaesthetic techniques, etomidate/fentanyl continuous infusion and neurolept anaesthesia (droperidol/fentanyl) were used in patients who were to undergo abdominal surgery.

Etomidate in alcohol solution (125 mg/ampule) has been widely used in Europe for total intravenous anaesthesia, together with an intravenous analgesic and automatic ventilation with an air and oxygen mixture. Its use, as a slow continuous infusion for the induction and maintenance of anaesthesia, has the advantage of causing minimal cardiovascular depression (1). Neurolept anaesthesia (droperidol/fentanyl) together with ventilation with nitrous oxide in oxygen, has also been widely used in high risk patients for its restraining effects upon the sympathetic activities in face of stress situations (2).

During infusion of etomidate and fentanyl it was observed that patients had low serum cortisol levels. The purpose of this study was to compare the cortisol levels in patients undergoing major abdominal surgery, receiving either etomidate/fentanyl anaesthesia with air ventilation, or neurolept anaesthesia with nitrous oxide in oxygen ventilation.

PATIENTS AND METHODS

Sixteen adult patients who were to undergo major abdominal surgery were selected for the study (Table I).

Table I. Demographic and anaesthetic data.

	group 1.	group 2.
Age (year, $\bar{m}\pm$SD)	60 ± 8	64 ± 6
Male (n)	6	6
Female (n)	2	2
Weight (kg $\bar{m}\pm$SD)	75 ± 14	75 ± 13
Operation time (min, $\bar{m}$/range)	380/360-480	400/360-480
ASA score ($\bar{m}$)	II	III
Etomidate (dose mg, $\bar{m}$/range	265/250-400	
Droperidol (dose mg, $\bar{m}$/range)		26/15-25
Fentanyl (dose mg, $\bar{m}$/range)	2.6/2.5-4.0	2.8/2.2-5.0

Patients who suffered from hepatic, renal or endocrinological disease, or who were using (or had recently used) corticosteroids, were excluded. For logistic reasons and because the anaesthetic techniques were totally different, we studied the patients in two successive periods, as separate groups. No selection criteria other than the above mentioned were used. Verbal consent was obtained from each patient. All patients were premedicated with oral diazepam (10 mg) one hour before surgery.

Group 1 (n=8): etomidate/fentanyl infusion + air/oxygen

250 ml infusion of dextrose was prepared containing etomidate (1 $mg.ml^{-1}$) and fentanyl (0.01 $mg.ml^{-1}$). Anaesthesia was induced by continuous infusion of the above mentioned mixture at a rate of 0.05 $mg.kg.min^{-1}$ for etomidate and 0.5 $ug.kg.min^{-1}$ for fentanyl, using a drip regulated (IVAC 531) infusion pump. The time of induction was designated as t1=0. During the first ten minutes of induction the patients breathed oxygen enriched air (FiO2 0.5) and ventilation was assisted manually. As soon as the patient was asleep, pancuronium bromide was administered (0.1 $mg.kg.min^{-1}$) and tracheal intubation was performed.

Controlled ventilation in an open circuit (Engström 300 ventilator), using an air and oxygen mixture with an FiO2 of 0.33 was maintained throughout surgery. After ten minutes the infusion rate for etomidate was reduced to 0.01 $mg.kg.min^{-1}$ and 0.1 $ug.kg.min^{-1}$ for fentanyl. The etomidate/fentanyl infusion was continued during the operation until end of surgery, after which the patient was transported (asleep) to the ICU, where controlled ventilation and postoperative care continued.

Group 2 (n=8) : droperidol/fentanyl infusion + N20

Anaesthesia in this group was induced with droperidol (0.2 $mg.kg^{-1}$) followed by fentanyl (7 $ug.kg^{-1}$) as a slow injection. Patients breathed 50% oxygen in nitrous oxide and ventilation was assisted manually when necessary. After intubation under pancuronium bromide (0.1 $mg.kg^{-1}$) the patients were ventilated with an Engström 300 ventilator at an FiO2 of 0.33, oxygen in nitrous oxide. During the course of anaesthesia the patients received one or two increments of 5 mg droperidol. Ten minutes after induction, a continuous infusion of fentanyl at a dose of 0.1 $ug.kg^{-1}.min^{-1}$ was administered.

All patients of both groups had operations lasting longer than six hours and needed invasive cardiovascular monitoring and a postoperative recovery phase necessitating ventilation (for a variety of reasons), in the ICU. Ventilation was set to maintain end tidal carbon dioxide percentage at physiological levels and this was periodically checked by arterial blood gas analysis.

Blood, plasma expanders and electrolyte solutions were given where appropriate to maintain arterial and venous pressures, peripheral circulation and diuresis. No corticosteroids were given during the course of the study.

In both groups, blood samples for serum cortisol levels were taken before induction of anaesthesia, and every two hours thereafter during surgery. On arrival in the ICU a new zero time (t2=0) was set and samples were taken at 4 and 7 hours postoperatively. The clotted samples were centrifuged and the serum was refrigerated at -20°C and stored awaiting estimation. The serum samples were assayed for plasma cortisol via a radioimmuno-assay (3), this test is highly specific for the estimation of 11 hydroxy-steroids, and the results are considered to be representative for the concentration of cortisol in serum. The variation coefficient was 10% when the cortisol levels were lower than 100 $nmol.l^{-1}$ and decreased to 5% at 200 $nmol.l^{-1}$, the sensitivity was 3 $nmol.l^{-1}$.

As no stress-induced increase in cortisol levels were found at awakening of 2 preceding patients (treated as in Group 1), it was decided to stimulate the adrenal cortex during the study with synthetic adrono-cortico-trope-hormone, $ACTH^{1-24}$, Synacthen (0.25 mg i.m.). Four patients received $ACTH^{1-24}$ three hours after etomidate/fentanyl infusion was started and the infusion rate was kept constant during the test until the end of the operation. The remaining four patients (Group 1) received $ACTH^{1-24}$ four hours after the end of the operation. As the serum cortisol levels increased during and after droperidol/fentanyl anaesthesia, these patients were not subjected to $ACTH^{1-24}$ stimulation to avoid possible adverse reactions. The differences between the two groups were evaluated using the Student's t test for unpaired values. Changes within one group were evaluated with the standard Student's t test, these values were compared with the initial value at t1=0.

RESULTS

In the etomidate/fentanyl patients (Group 1), a considerable and significant decrease ($p < 0.05$) of serum cortisol levels was observed after two hours of infusion, and later. Consistently low values were measured four hours postoperatively, but seven hours after the operation the serum cortisol levels equalled the initial concentration. In the droperidol/fentanyl group (Group 2), no decrease in serum cortisol levels occurred during anaesthesia. In contrast, there was a postoperative significant increase ($p < 0.001$) in cortisol concentration (fig 1). Intergroup differences were found to be significant (p maximally < 0.05) at all sampling times.

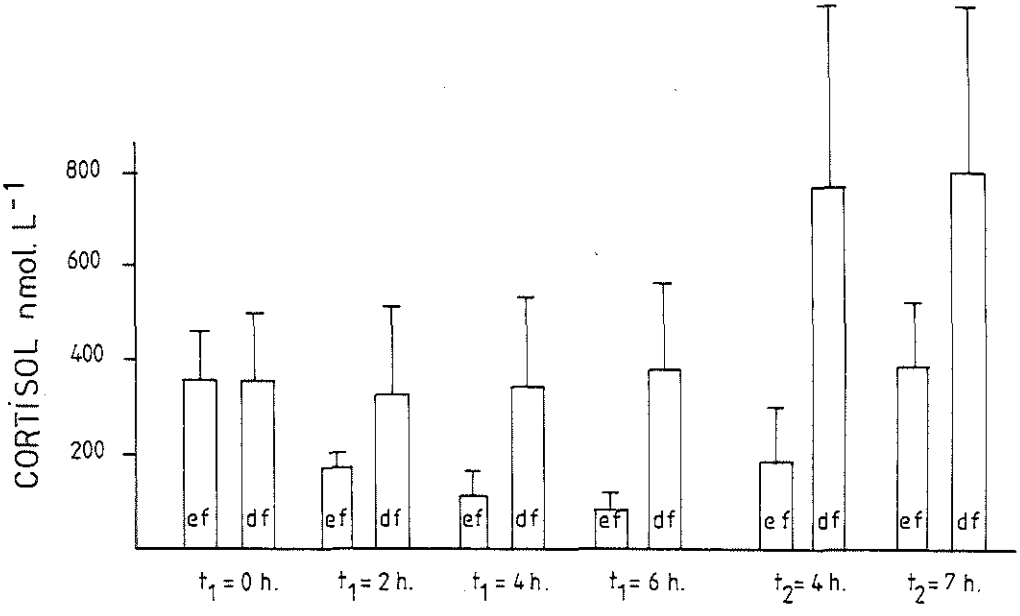

Figure 1. Cortisol concentration in serum measured in 2 groups. (ef = etomidate/fentanyl/air anaesthesia; df = droperidol/fentanyl/air anaesthesia; t1 = intraoperative time in hours; t2 = postoperative time in hours).

When the adrenal cortex was stimulated with $ACTH^{1-24}$ during etomidate/fentanyl infusion there was a slight increase in serum cortisol concentration. When $ACTH^{1-24}$ was administered 4 hours after the operation, a small increase in serum cortisol level could be measured, but this increase was insufficient to call the ACTH stimulation test positive i.e. an increase of at least 100 $nmol.l^{-1}$, 30 min after Synacthen i.m. (fig. 2).

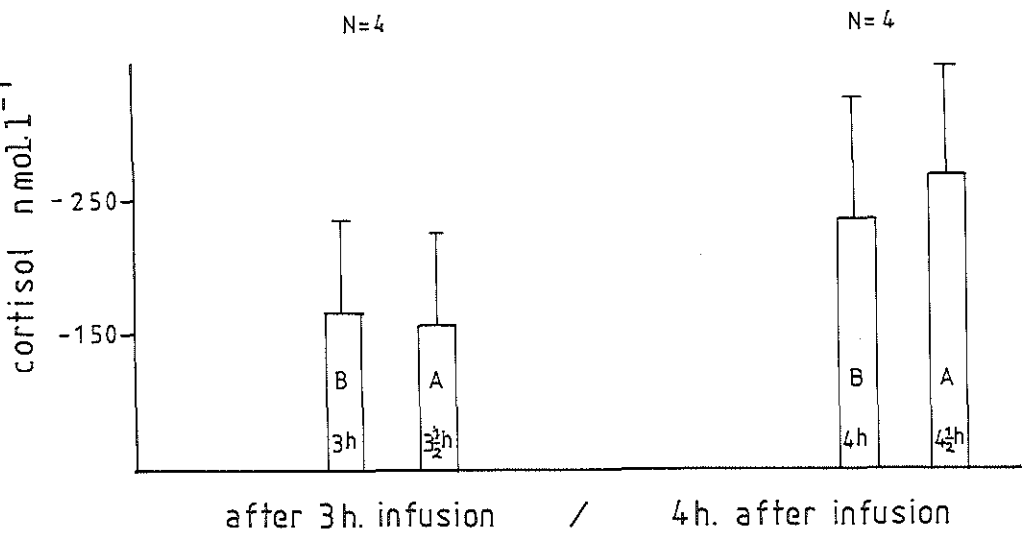

Figure 2. Serum cortisol concentrations:
B = before and A = after administration of ACTH$^{1-24}$ (0.25 mg i.m.)

DISCUSSION

It was tempting to infer from the results that etomidate could be held responsible for the decrease in serum cortisol levels measured in Group 1. Indeed, Hall and co-workers (4) reported that, even after a dose of 70 ug.kg^{-1} fentanyl, the response to ACTH$^{1-24}$ remained within normal range and a similar decrease in serum cortisol concentration was observed during and after etomidate infusions given to patients under regional anaesthesia. However, from this single study it was not possible to conclude that etomidate alone was responsible for the decrease in serum cortisol level. This decrease could also be due to the combination of etomidate and fentanyl. The serum cortisol concentration in patients receiving droperidol/fentanyl and nitrous oxide (Group 2) were similar to those that Oyama (5,6,) observed in his studies, but higher than those observed by Hall (4) and Stanley (7), both using high doses of fentanyl.

The negative response to ACTH$^{1-24}$ stimulation indicated insufficiency of the adrenal cortex. During etomidate/fentanyl infusion serum cortisol levels even decreased, despite stimulation with ACTH$^{1-24}$. Because the reaction was negative, the sampling of patients in Group 1 was continued. It was assumed that the stimulation test did not interfere with the study results.

The question remained as to whether or not this decrease in serum cortisol concentration had any clinical significance. The most notable effect of low cortisol levels was the altered sodium homeostasis (8), which may consequently lead to fever, low arterial blood pressure and rapid pulse rate. When these symptoms were treated with intravenous infusions, there was a positive fluid and sodium balance. The latter parameter was sufficiently characteristic of adrenal insufficiency that it could be used as a diagnostic criterion (9). These symptoms were identified in most of the patients receiving etomidate/fentanyl as a continuous infusion (Table II). Therefore, all patients were given parenteral corticosteroids after the sampling was completed. Complete recovery was achieved within three hours, the excess of sodium and water were excreted and the temperature decreased to normal postoperative levels.

Table II. Postoperative data indicating that a corticosteroid depletion could be possible.

	group 1.	group 2
Cumulative fluid balance ($\bar{m} \pm$ SD, l, per- + postop.)	4.3 ± 1.5	2.3 ± 1.1
Cumulative sodium balance ($\bar{m} \pm$ SD, nmol, per-+postop.)	320 ± 150	90 ± 100
Core temp. 4 hrs postop. ($\bar{m} \pm$ SD, ^{o}C)	38.4 ± 0.4	37.0 ± 0.6
Core temp. 7 hrs postop. ($\bar{m} \pm$ SD, ^{o}C)	38.7 ± 0.8	37.4 ± 0.6

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ETOMIDATE AND ACTH INDUCED STEROIDOGENESIS IN ISOLATED ADRENAL CELLS OF RATS

H.J.M Goverde, M.P. Boidin, D.F. Zandstra, S. Agoston

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KEY WORDS : ANAESTHESIA - etomidate, side effects
METABOLISM - endocrinology
hormones
corticosteroids

During the last few years the use of etomidate and fentanyl infusions in fixed-dose mixtures for total intravenous anaesthesia, or for long-lasting analgesia and sedation in intensive care patients, has gained wide popularity. The above technique has been used successfully as a routine procedure in cardiac anaesthesia and in patients undergoing vascular surgery. Postoperative complications including fever, low arterial blood pressure and increased heart rate, sometimes associated with delayed wound healing, were repeatedly observed but not initially related to the anaesthesia technique. This was due to the fact that most of the above complications could be explained by a multiplicity of factors originating from the underlying pathology. The patients, however, often showed altered sodium homeostasis and responded well to intravenous physiologic sodium solutions but not to dextrose 5%. This prompted investigations into the adrenal function in these patients by determining plasma cortisol levels during and after operations. The subsequent pilot study (1), which focused on changes in plasma cortisol levels in patients receiving either the etomidate/fentanyl mixture or neurolept anaesthesia with droperidol/fentanyl, revealed that there was a greater decrease in serum cortisol in patients receiving etomidate and fentanyl than in the neurolept group. Moreover, in the former group the serum cortisol levels remained low (postoperatively) despite adrenal stimulation with synthetic adreno-cortico-trope-hormone ($ACTH^{1-24}$).

The above clinical findings suggested an etomidate-mediated inhibition of adrenal function. In order to substantiate this blockade the effects of this intravenous anaesthetic agent on ACTH-induced steroidogenesis in vitro using isolated adrenal cells of rats was investigated.

METHODS

The preparation of isolated rat adrenal cells has already been extensively described (2). Adrenals of 5 male Wistar rats were freed of fat, cut into 10 pieces and incubated at 37°C for 10 min under 95% O_2, 5% CO_2 in a solution of 10 ml KRBG containing 32 mg crude collagenase (Sigma type I) and 400 mg BSA (OHRD, Hoeschst). After disruption of the tissue by pipetting, the suspension (without the large remaining particles) was transferred to a cold 100 ml polyethylene tube. 2 ml KRBG containing 0.5% BSA and 7.65 mM Ca (KRBGACa) were added to the large particles and the material was again disrupted. Both supernatants were combined and centrifuged at 100 G for 10 min. (4°C). The supernatant was

discarded and the pellet was washed twice in 10 ml KRBGACa. After the final centrifuge, the cells were re-suspended in 40 ml KRBGACa. The cells were purified by layering 1 ml supernatant upon 8 ml 5% BSA (Sigma, fraction CV, A 6003) in KRBGCa. After 30 min the upper layer was removed by suction and the 5% BSA layers (which by then contained the purified cells) were combined and diluted appropriately. 0.8 ml aliquots of this suspension were pre-incubated for 1 hr at 37°C under an atmosphere of 95% O_2 and 5% CO_2. Synthetic $ACTH^{1-39}$ (Ciba-Geigy Ltd, Basel) in diluent (0.9% NaCl + 0.5% BSA, pH adjusted to 3.5 with 0.1 N HCL) with or without etomidate diluent (KRBG) was added to a total volume of 1 ml. The cells were incubated for two hours under the same conditions. Corticosterone production was measured fluorometrically as described by Goverde et al. (2). All samples were tested in duplicate and the mean values are expressed in figure 2 and Table I.

NOTES : KRBG = Krebs Ringer Bicarbonate Glucose
KRBGCa = Krebs Ringer Bicarbonate Glucose + Calcium
KRBGACa = Krebs Ringer Bicarbonate Glucose Albumin + Calcium
BSA = Bovine Serum Albumin

Table I. Inhibition capacity of etomidate at different levels of $ACTH^{1-39}$ stimulation. The values were expressed as a percentage of the production of corticosterone without etomidate. This value given in pg ml^{-1}.

	induction by $ACTH^{1-39}$ pg ml^{-1}		
	?	25	50
etomidate ml^{-1}			
1.25 mg	-	100	-
125 ug	-	100	-
20 ug	100	100	100
12.5 ug	-	100	-
2.0 ug	100	100	100
200 ng	100	86.5	82
20 ng	47.5	28	36
2.0 ng	12.5	-	14
200 pg	0.0	-	0.0
20 pg	0.0	-	0.0
	corticosterone production pg ml^{-1}		
	150	280	340

Figure 1 shows a standard dose-response curve to ACTH stimulation in the isolated rat adrenal cell system. Figure 2 shows the effect of different doses of etomidate after corticosterone induction with 25 pg ACTH.

It was observed (fig. 2) that doses of more than 0.2 µg per ml almost completely inhibited steroidogenesis in vitro. Etomidate solvent was also tested separately, but no blocking effect could be measured in these tests (results not shown). Because the results in the first investigation were difficult to quantify, a new series of tests were performed with increasing ACTH stimulation on increasing concentrations of etomidate. In this series, the blockade was expressed as a percentage of the stimulation of the corticosterone production in a sample without etomidate (Table I). Doses of 200 pg or lower did not affect steroidogenesis in vitro. 50% inhibition in the three experiments occurred at a mean dose of 33.3 ± 10.3 ng etomidate/ml suspension (approximately 1.5×10^{-7}M).

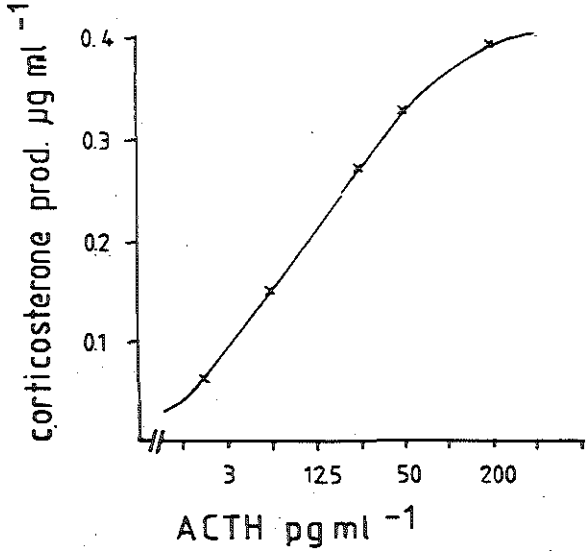

Figure 1

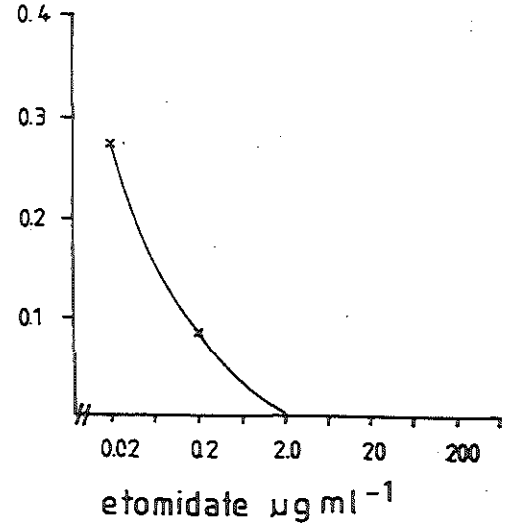

Figure 2

Figure 1. Corticosterone production in vitro in relation to ACTH stimulation.

Figure 2. Corticosterone production in vitro in relation to various concentrations of etomidate, stimulated by 25 pg ACTH ml^{-1}.

DISCUSSION

This study demonstrates that etomidate inhibits ACTH-induced steroid production in isolated adrenal cells of rats. Concentrations of 200 ng etomidate/ml (and higher) resulted in an almost complete blockade of steroidogenesis. Such concentrations were also present in the circulation of patients during etomidate anaesthesia (3,4). Therefore, the results of this study in vitro supports the observations of Boidin (1), and those of Ledingham and Watt (5), indicating a direct inhibitory effect of etomidate on adrenocortical tissue.

However, definite conclusions regarding the mechanism of the interaction between etomidate and ACTH in adrenal tissue cannot yet be drawn. It is conceivable that ACTH-receptors might be blocked by etomidate, but it is more likely that specific enzymes involved in steroidogenesis, or general intracellular activity, are inhibited by this intravenous anaesthetic. The 50% blocking concentration of etomidate (1.5×10^{-7}M) is comparable with the blocking effect of specific steroid enzyme inhibitors. Comparable assays were performed for Trilostane (10^{-6}M), metopyrone (5×10^{-6}M) (6) and aminoglutethimide (5×10^{-5}M) (7). This supported the idea that etomidate could be an inhibitory substance specific for adrenocortical tissue. In order to support this hypothesis further experiments are now in progress concerning the mode of action of etomidate, with special attention being given to the reversibility of the inhibition phenomenon.

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MODIFICATION OF CORTICOSTEROID SYNTHESIS BY ETOMIDATE/FENTANYL AND AIR ANAESTHESIA

M.P. Boidin

In press : Acta Anaesth Belgica

KEYWORDS : ANAESTHESIA - etomidate, side effects
METABOLISM - hormone, corticosteroids

Etomidate (R-(+)-ethyl-1(phenyl)-1H-imidazole-5-carboxylate) is a potent and short-acting hypnotic when given as a bolus injection (0.3 $mg.kg^{-1}$) for the induction of anaesthesia (1,2). The same drug may also be used in concentrated form in an alcohol solvent (125 mg per 1 ml ampule) for maintenance of anaesthesia (3). This anaesthetic technique is normally complemented with analgesics and muscle relaxants.

A recent pilot study showed that etomidate/fentanyl anaesthesia caused a decrease in serum cortisol concentration (4). Adreno-corticotropic-hormone (ACTH) stimulates the synthesis of corticosteroids in the adrenals. This synthesis begins with hydroxylation of cholesterol at the 20 and 22 positions (fig. 1). Side chain cleavage occurs and isocaproaldehyde and pregnenolone are the metabolites. Pregnenolone is the main precursor of all steroid hormones, apart from sex hormones. These hormones have androstene-dione as a precursor and can be synthesized de novo, or via pregnenolone (5). The present investigation was designed to explore the precise mechanism behind this decrease.

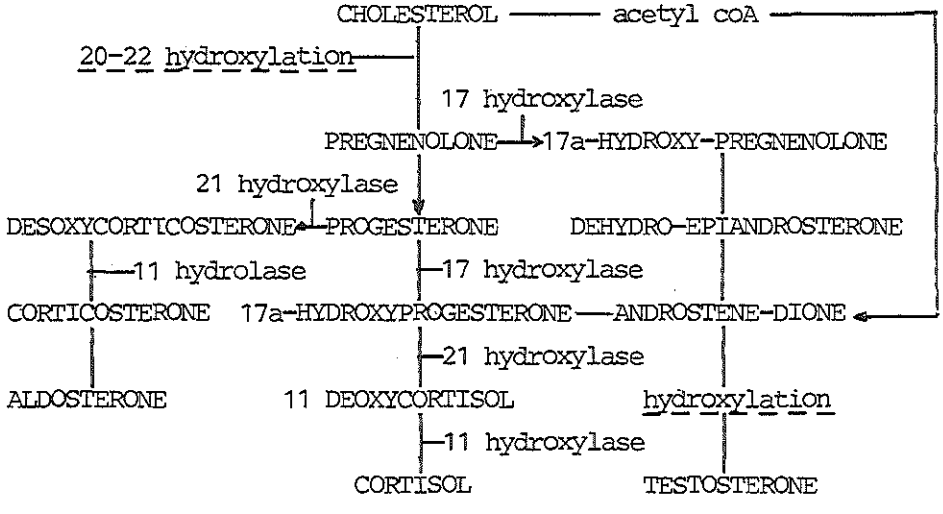

Figure 1. General overview of steroid synthesis.

METHODS

Seven adult patients who were to undergo major abdominal surgery were selected for the study. Patients who suffered from hepatic, renal or

endocrinological disease, and those who were using (or had recently used) corticosteroids, were excluded (Table I).

Table I. Demographic description of the patients included in this study.

Age (years, $\bar{m}$ / range)	66 / 54-72
Weight (kg, $\bar{m}$ / range)	63 / 56-73
Length (cm, $\bar{m}$ / range)	176 / 164-188
Operation time (hrs, $\bar{m}$ / r)	5.7 / 4.2-7.3
Sex ratio male/female	5 / 2
ASA risk factor.	4 pat II / 3 pat III

All patients were scheduled for operations lasting four hours or more, and all needed invasive cardiovascular monitoring with postoperative ventilation in the ICU. Informed consent was obtained in all cases and 10 mg diazepam was prescribed for night sedation prior to the operation. No further drugs were administered except for 1 g ampicillin/cloxacillin (Ampiclox).

250 ml infusion of dextrose was prepared containing etomidate (1 $mg.ml^{-1}$) and fentanyl (0.01 $mg.ml^{-1}$). Anaesthesia was induced by continuous infusion of the mixture at a rate of 1 drip = 0.05 ml/kg/min using a drip regulated infusion pump (IVAC 531). This administration rate resulted in a dose of 0.05 $mg.kg.min^{-1}$ for etomidate and 0.5 $\mu g.kg.min^{-1}$ for fentanyl. Two minutes after intubation, the infusion rate was reduced to 20% of the induction rate and maintained throughout surgery (in all cases). Ventilation was set to maintain end tidal carbon dioxide percentage at physiological levels, which was periodically checked by arterial blood gas analysis. Blood, plasma, electrolyte solutions and plasma expanders were given, as appropriate, to maintain parameters within physiological limits. No corticosteroids were administered until the sampling was completed. Serum and plasma samples were taken before anaesthesia and at 30, 60, 120 and 180 minutes after induction. Within 20

min after sampling, the samples were centrifuged and refrigerated at -40°C to await estimation. 180 min after induction of anaesthesia, synthetic $ACTH^{1-24}$ (Synacthen) 0.25 mg was given by deep intramuscular injection. The sample taken at 180 min was used as a control and compared with the samples taken at 210 and 140 min after induction.

Serum ACTH and $ACTH^{1-24}$ was determined in unextracted serum using a commercially available radio-immunoassay kit (CIS, Italy) with a sensitivity of 20 $nmol.l^{-1}$ and a variation coefficient of 15% at 300 $nmol.l^{-1}$. Serum cortisol was estimated using radio-immunoassay according to the method of Pratt (6). Sensitivity was 15 $nmol.l^{-1}$ and the interassay variation coefficient was 8% at 50 $nmol.l^{-1}$. Serum compound S (11 deoxycortisol) was extracted (7) and assayed by competitive protein binding using dog serum as a binder, ^{3}H corticosterone as a tracer and Florisol for separation, with a sensitivity of 20 nmol per l and a variation coefficient of 5% at physiological values. Androstene-dione was measured in plasma by radio-immunoassay after extraction with 5% ethyl acetate in pentane. The antisera were raised in rabbits to an androstene-dione-7 alpha-carboxyethyl-thioether bovine thyroglobulin conjugate, sensitivity 0.8 $nmol.l^{-1}$ and a variation coefficient of 7% above 2 $nmol.l^{-1}$ (8).

The results of each sample were calculated for mean and standard deviation and were compared with the pre-anaesthestic level using a paired Student's t test. The values obtained at 180 min served as a control for the $ACTH^{1-24}$ stimulation test. The value at 180 min was compared with the values obtained at 210 and 240 min using the Student's t test for paired values. The overall response of the cortisol, androstene-dione and compound S may be expressed as the cortisol/ACTH ratio, being the quotient of the serum cortisol concentration and the serum ACTH + $ACTH^{1-24}$ concentration. This method was repeated for the other hormones.

RESULTS (figs. 2,3,4,5)

ACTH and $ACTH^{1-24}$ (fig. 2)

After induction there was a significant decrease in serum ACTH concentration which remained stable until Synacthen was injected. When $ACTH^{1-24}$ was administered there was a significant increase in the ACTH concentration. Mean and standard deviations also increased at 180 min after induction. This is because one value increased five times the mean of the other six concentrations (reason unknown). When this value is disregarded, mean and standard deviations are the same as the value measured at 120 min after induction.

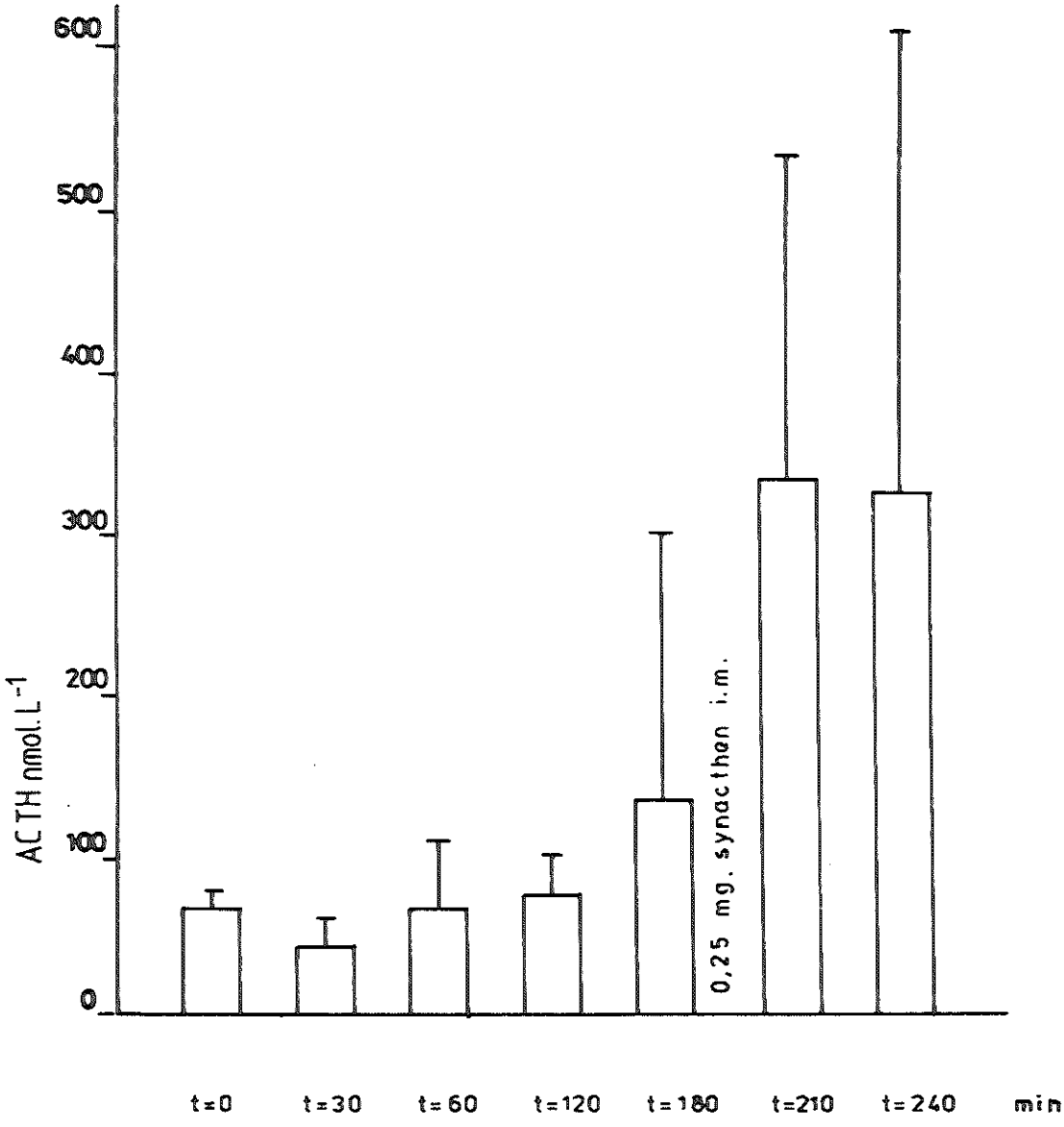

Figure 2. ACTH serum concentrations during etomidate/fentanyl anaesthesia

Compound S (fig. 3)

The serum concentration of compound S decreased significantly directly after induction ($p \leq 0.05$) and remained constant until ACTH was administered. As the ACTH concentration increased, there was a small but insignificant rise in compound S concentration. When the relationship between ACTH and compound S was considered, it became apparent that less compound S was secreted than would be expected from the ACTH concentration. This reduction was progressive throughout the course of the study. When $ACTH^{1-24}$ was administered, this relationship seemed to totally disappear.

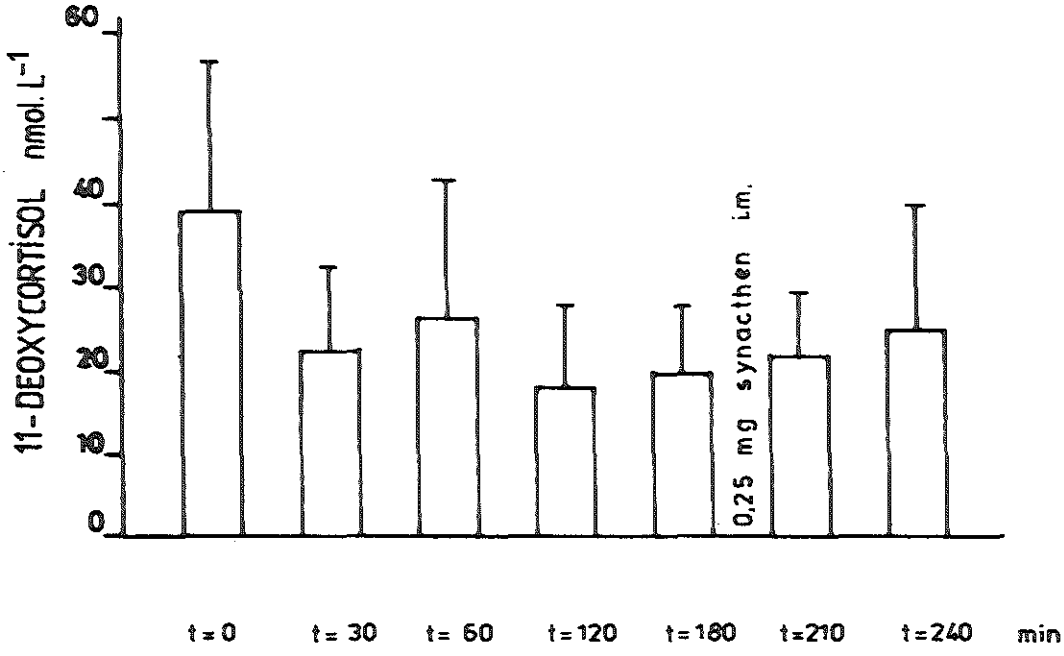

Figure 3. 11-deoxy cortisol concentrations during etomidate/fentanyl anaesthesia

Cortisol (fig. 4)

The serum concentration of cortisol decreased immediately after induction of anaesthesia. This decrease was progressive throughout the study. Administration of $ACTH^{1-24}$ was not capable of significantly increasing the cortisol concentrations. The relationship between the effector hormone and the tropic hormone was stable in the first hour after induction and subsequently decreased. The relationship lost significance at 180 min after induction and did not recur after $ACTH^{1-24}$ administration.

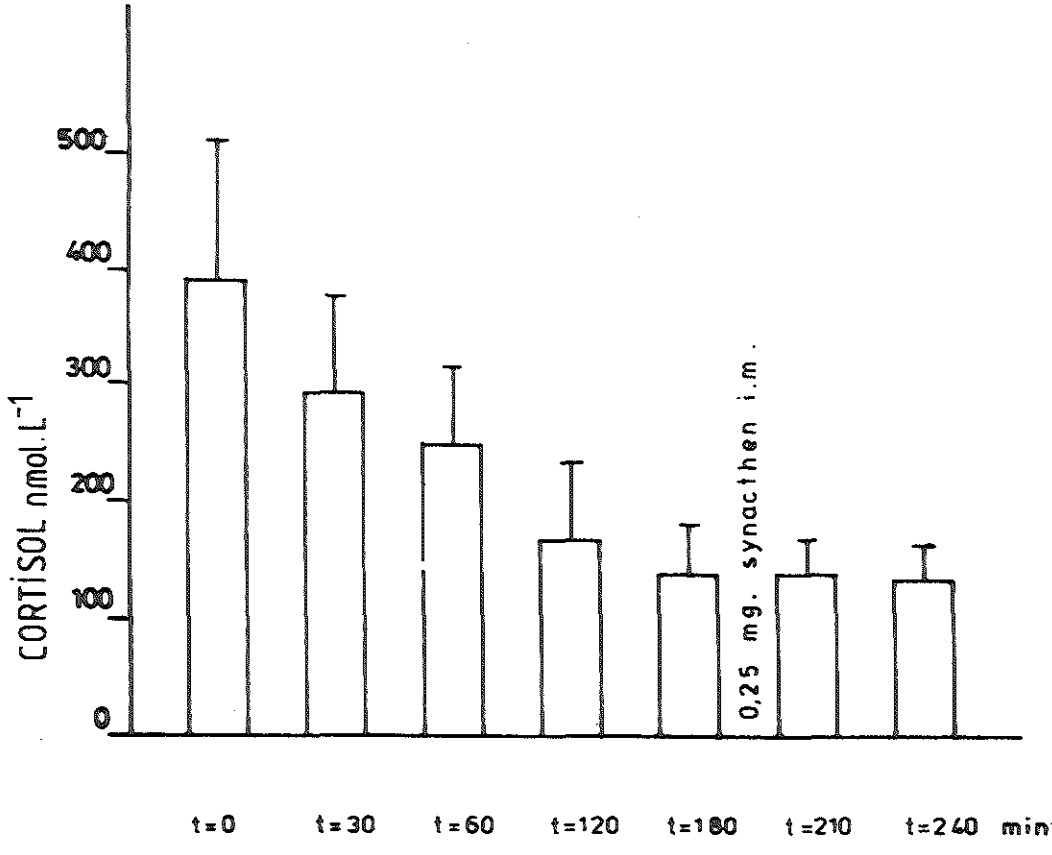

Figure 4. Cortisol serum concentrations during etomidate/fentanyl anaesthesia.

Androstene-dione (fig. 5)

The plasma concentration of this hormone precursor decreased proportionate to the reduction of ACTH concentration and remained so until the end of the study. When the $ACTH^{1-24}$ stimulation test was performed, the relationship between adrostene-dione and ACTH was preserved, evidenced by the rise in plasma concentration after administration of $ACTH^{1-24}$.

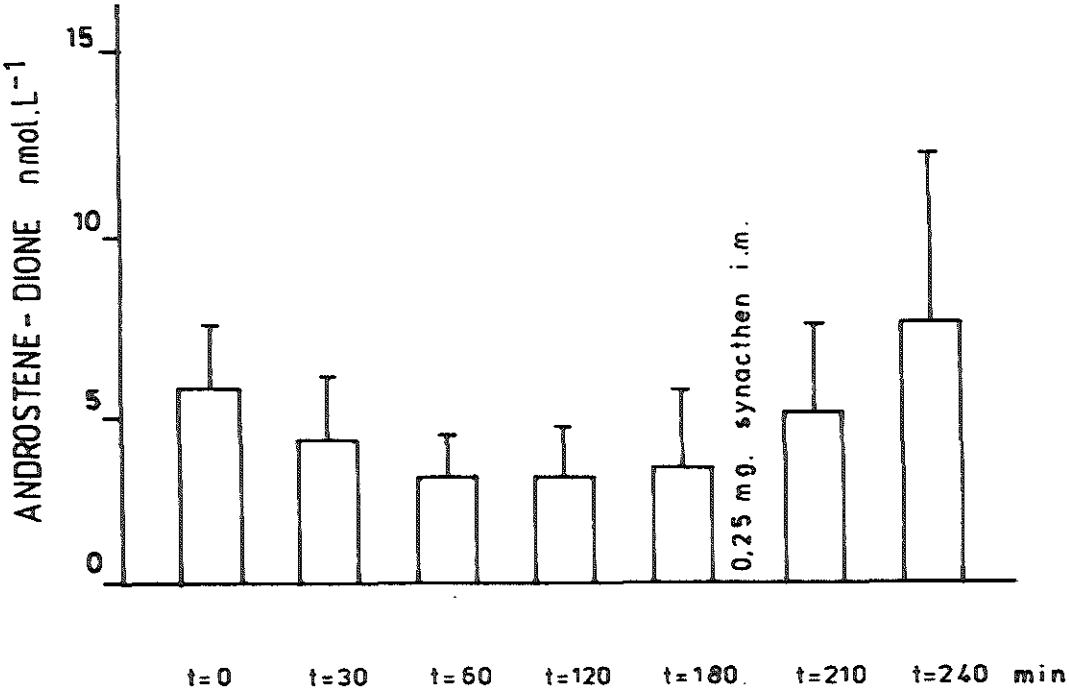

Figure 5. Androstene-dione concentrations during etomidate/fentanyl anaesthesia.

DISCUSSION

The ability of morphine to inhibit the plasma ACTH concentration under stress conditions was first described by McDonald et al. (9) in 1959. George et al. (10) observed that large doses of morphine (4 mg. kg^{-1}) abolished the reaction of cortisol and growth hormones in response to cardiac surgery. Hall et al. found the same quenching effect on the hypothalamic adrenal axis with high doses of fentanyl (50 $mg.kg^{-1}$). They tested the reaction of the adrenals during halothane, nitrous oxide, fentanyl anaesthesia with synthetic $ACTH^{1-24}$ and found a normal reaction of the adrenal cortex after stimulation. This suggested that the blockade of cortisol secretion in their study was due to depression of the tropic hormone secretion from the hypophysis. Their findings could be confirmed in four patients treated with the same technique (11).

From the data presented in this article it is obvious that the reduction in corticosteroid hormone of the serum is due to a blockade of the production within the adrenals. Androstene-dione may have a different metabolic pathway and is not necessarily synthesized in the same manner as cortisol and compound S. Details concerning the mechanism of this blockade are not yet fully explored. A severe depression of steroid synthesis was described for aminoglutethimede (Doriden) (12). The cortisol concentrations were depressed to levels comparable to that of patients with total surgical adrenalectomy. The data in this article indicates that the cortisol level decreased to comparable values, namely 50-100 $nmol.l^{-1}$. Uzgiris et al. found that the molecule of aminoglutethimide binds to the cytochrome P 450 complex to block several steps in the steroid synthesis (13). This same binding was demonstrated for cimetidine, an imidazole structure similar to etomidate (14). In the synthesis of corticosteroid hormones from cholesterol, the function of cytochrome P 450 is still believed to be the main rate limiting factor (15). The questions therefore arose as to whether etomidate could bind to this cytochrome complex and what could be the possible role of this complex in hydroxylation. Biochemical and animal studies are now required to elucidate the exact mechanism of the blockade of cytochrome P 450 in adrenal hormone synthesis.

CONCLUSIONS

This study could not conclusively show whether etomidate or fentanyl was responsible for the blockade in the adrenals. But, when fentanyl was used in other anaesthetic techniques, no blockade of corticosteroid synthesis could be measured. This study might have been more valid if the possible influence of the operation itself could have been eliminated.

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CAN ETOMIDATE CAUSE AN ADDISONIAN CRISIS?

M.P. Boidin

In press : Acta Anaesth Belg

KEYWORDS : ANAESTHESIA - etomidate
DRUGS - side effects
METABOLISM - hormones

INTRODUCTION

It has recently been shown that etomidate can cause a significant decrease in serum cortisol concentration (1,2,3). Cortisol concentrations did not respond to the administration of $ACTH^{1-24}$ during anaesthesia or thereafter (3). Sudden occurrence of low serum cortisol concentrations can cause an acute Addisonian crisis in stress situations (4). The classic symptoms of Addisonian crisis include : arterial and venous hypotension, increased pulse rate, a fall in peripheral temperature and a rise in core temperature, impaired diuresis, reduction of the renal clearance, hypoglycaemia, an increase in serum potassium and a fall in serum sodium and chloride. In the conscious patient nausea, vomiting, drowsiness, catatonia and diarrhoea may occur.

When these clinical phenomena occur during anaesthesia, the anaesthetist will automatically take steps to prevent these abnormalities from progressing further. Therefore, symptoms may be minimised in the anaesthetic records, making the interpretation and diagnosis of side effects extremely difficult. Even routine biochemical tests are not very helpful as sodium and other fluids may be administered during anaesthesia to compensate for fluid shifts which may occur due to the operation, the ventilatory assistance or the infusion therapy.

The purpose of this study was to assess whether it was possible to discover the side effects of etomidate earlier, using different combinations of parameters routinely measured during anaesthesia.

PATIENTS AND METHODS

Twelve adult patients who were scheduled for major abdominal surgery were selected for the study. Patients who suffered from hepatic, renal or endocrinological disease, and those who were using (or had recently used) corticosteroids, were excluded (Table I). Because the anaesthetic techniques were totally different, the patients were studied during two successive periods, as separate groups. No selection criteria other than the above mentioned were used. Verbal consent was obtained from each patient. All patients were premedicated with oral diazepam (10 mg) one hour before surgery.

Table I. Demographic and anaesthetic data of the patients of the study.

	group 1.	group 2.
Number of patients	6	6
Age (years, $\bar{m} \pm SD$)	57 ± 12	64 ± 6
Weight (kg, $\bar{m} \pm SD$)	75.8 ± 13	73.3 ± 14
Sex male/female	4 / 2	4 / 2
ASA	2 pat I	1 pat I
	3 pat II	3 pat II
	1 pat III	2 pat III
Etomidate (dose, mg, $\bar{m} \pm SD$)	265 ± 42	
Droperidol (dose, mg, $\bar{m} \pm SD$)		21 ± 4.2
Fentanyl (dose, mg, $\bar{m} \pm SD$)	2.65 ± 0.4	2.78 ± 0.4
Duration of operation (min)	380 ± 60	400 ± 55

Group 1 etomidate/fentanyl infusion, air + oxygen ventilation (n=6)

An infusion of dextrose 5%, containing etomidate (1 $mg.ml^{-1}$) and fentanyl (0.01 $mg.ml^{-1}$) was prepared. Anaesthesia was induced by continuous infusion of the mixture, at a rate of 0.05 $mg.kg^{-1}min^{-1}$ etomidate and 0.5 $\mu g.kg^{-1}min^{-1}$ fentanyl, using an automatic drip regulator (IVAC 531). During the first ten minutes of the induction, patients breathed oxygen enriched air (FiO2 0.5) and ventilation was assisted manually. As soon as the patient was asleep, pancuronium bromide was administered (0.1 $mg.kg^{-1}$) and tracheal intubation was performed. Controlled ventilation was established using an Engström 300 ventilator in open circuit, with an air and oxygen mixture. FiO2 0.33 was then maintained throughout surgery. The infusion rate of the anaesthetic mixture (etomidate + fentanyl) was reduced to 20% of the induction dose and this dose was continued until the end of surgery. Afterwards, the patients were transfered (still asleep) to the ICU, where controlled ventilation and postoperative care continued.

Group 2 droperidol/fentanyl infusion, N2O (n=6)

Anaesthesia in this group was induced with droperidol (0.2 $mg.kg^{-1}$) followed by fentanyl (7 $\mu g.kg^{-1}$) as a slow injection. Patients breathed 50% oxygen in nitrous oxide and ventilation was manually assisted when necessary. After intubation under pancuronium bromide (0.1 $mg.kg^{-1}$),

the patients were ventilated with an Engstrom 300 ventilator in open circuit at an FiO2 of 0.33, oxygen in nitrous oxide. Ten minutes later, a continuous infusion of fentanyl (0.1 $\mu g.kg^{-1}$) was started at the same rate as in the etomidate group. The patients received 1 or 2 increments of droperidol during anaesthesia.

All patients of both groups were scheduled for operations lasting six hours or more and all needed invasive cardiovascular monitoring with postoperative ventilation in the ICU. Ventilation volumes were set to maintain end tidal carbon dioxide at physiological levels, which was periodically checked by arterial blood gas analysis. Blood, plasma, electrolyte solutions and plasma expanders were given, as appropriate, to maintain arterial and central venous pressure and diuresis. No corticosteroids were given during surgery, or in the first seven hours thereafter. The medical history of all patients was studied with special attention given to preoperative evaluation, duration of surgery, the first seven hours of the postoperative period and later complications occurring during the postoperative admission period.

The medical history included: identification, age, sex, baseline vital signs and ASA score. The intraoperative data included : continuous measurement of arterial and central venous blood pressure via indwelling catheters, peripheral and core temperatures measured in the oesophagus and the thenar region at the base of the thumb. The anaesthetic records included drugs administered, intravenous infusions, urine output and end tidal carbon dioxide levels. Every two hours, samples were analysed for arterial blood gases, haemoglobin content, serum electrolytes, total protein content, serum cortisol and urine electrolytes. These samples were also taken 4 and 7 hours after surgery. At the end of this period the patient received a general physical examination, including a chest X-ray. A record was also made as to whether the patient was still intubated, ventilated, or needed any other support of the vital functions.

The data were expressed as mean $\pm$ SD. The two groups were compared using the Student's t test for unpaired values. Differences within one group were compared using the Student's paired t test, using the pre-anaesthetic level as control. Time of induction was designated t1=0 and time of arrival in the ICU was designated t2=0. The cumulative fluid and cumulative sodium balances were obtained by deducting the urine output

and the urinary sodium output from the fluid and sodium intake, assuming that perspiration rate in both groups was equal.

RESULTS

No significant changes in pulse rate could be measured during surgery in either group. However, the pulse rate showed a small but significant increase after the operation in both groups, as compared to the pre-induction pulse rate ($p < 0.05$). The central venous pressure increased only during intermittent positive pressure ventilation. After correction of this factor, there were no significant differences within, or between, each group. Systolic, diastolic and mean arterial pressure showed no significant differences within or between each group.

Core temperature decreased significantly ($p < 0.01$) during the operation, but recovered towards the end of surgery (fig. 1).

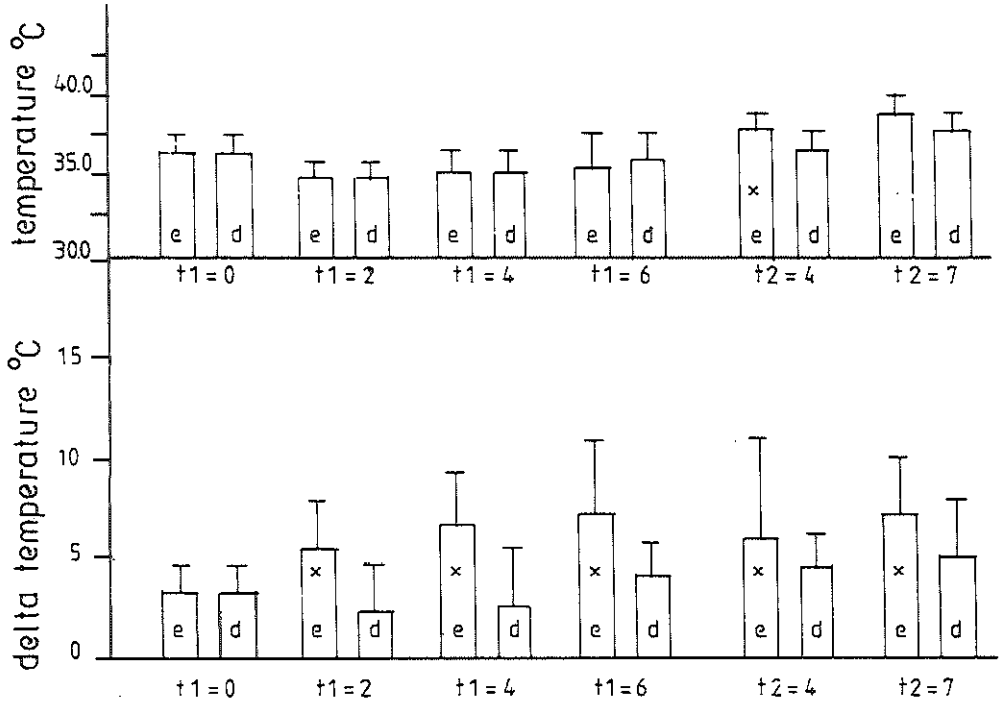

Figure 1. Core and delta temperature in two groups.
x Significant intergroup differences are indicated.

In the postoperative period (t2=4), the core temperature in Group 1 increased significantly as compared to the initial temperature and also as compared to Group 2 ($p < 0.001$ for both comparisons). At t2=7,

temperatures in both these values showed no significant intergroup difference. Differences between core and peripheral temperature (delta temperature) were registered separately. In Group 1 there was a significant increase ($p < 0.01$) after induction of anaesthesia, rising throughout the observation period. On the other hand, Group 2 showed a gradual but not significant increase in delta temperature during surgery and thereafter. Intergroup comparison demonstrated significantly higher values of delta temperatures for Group 1 ($p < 0.01$) at all times, except for the pre-induction period and the values at t2=7 (fig. 1).

The cumulative fluid balance was assessed at the times specified (fig. 2).

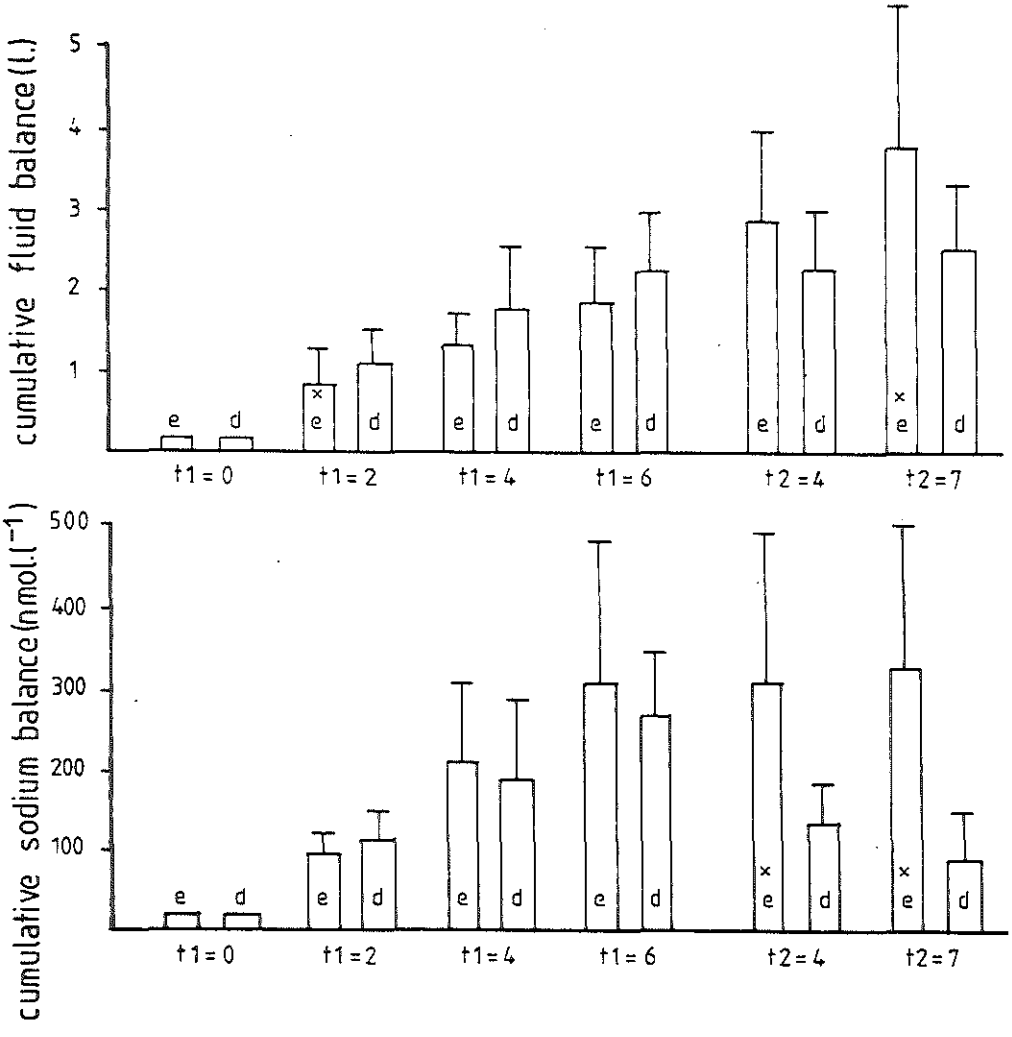

Figure 2. Cumulative fluid balances and cumulative sodium balances in two groups. [x]Significant intergroup differences are indicated.

In Group 2, there was a higher net fluid supply in the first two hours of surgery as compared to Group 1 ($p < 0.01$). In the pre-operative period there was a tendency for the net fluid intake to increase but in the post-operative period there was a balance between fluid intake and fluid output and no increase in the cumulative fluid balance occurred. In Group 1 however, postoperative fluid intake was significantly higher ($p < 0.01$) than the values assessed in Group 2. The cumulative fluid balance increased in Group 1 to 4.1 ± 1.4 liters at t2=7, in contrast to the cumulative fluid balance in Group 2, which rose to 2.7 ± 1.2 liters at t2=7 (fig.2).

The two groups also differed in their cumulative sodium balances. Group 2 showed a greater intake of sodium in the first two hours of surgery. After this period there was a slight increase in the sodium intake, towards the end of the operation. The differences were not significant at the end of surgery. In the postoperative period, however, there was a decrease in the cumulative sodium balance measured in Group 2, indicating that the excess sodium was excreted. In Group 1 there was no change at the end of the operation and sodium intake equalled sodium output. The differences were highly significant ($p < 0.01$) and considerable, amounting to 320 ± 260 nmol for Group 1 and 90 ± 90 nmol for Group 2, at the end of the study period (fig. 2).

The electrolyte estimations from serum and blood gas analysis did not indicate any significant differences between the two groups. Inter- and intra-group differences in cortisol serum concentrations were significantly different in both groups (fig. 3).

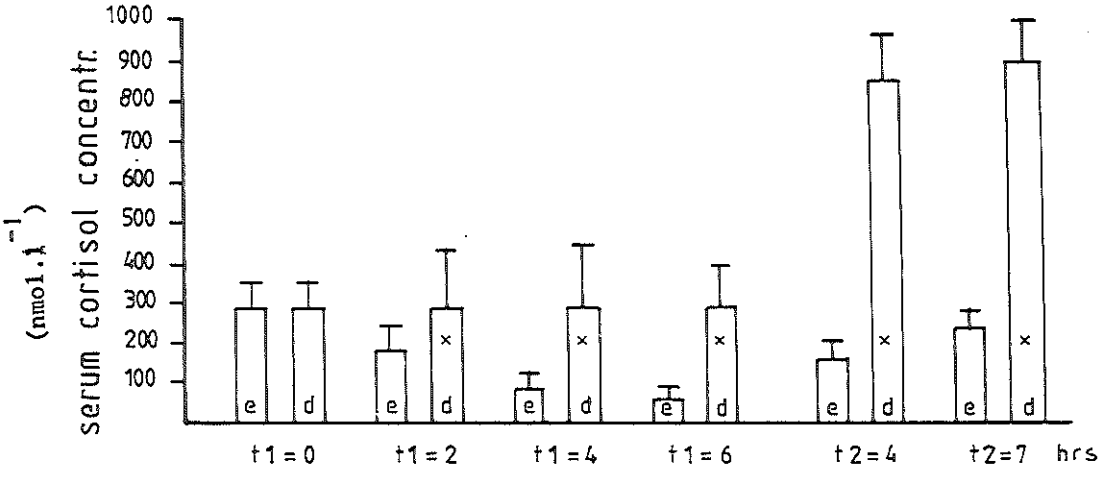

Figure 3. Serum cortisol concentrations in two groups.
x Significant intergroup differences are indicated.

The clinical evaluation at the end of the first seven hours of the postoperative period in the ICU also showed differences between the two groups. Table II shows that a larger number of patients in Group 1 (etomidate) were more often ventilated and intubated, had more cardiotonics and diuretics, needed more tranquilisers, sedatives and analgesic drugs, and showed more evidence of interstitial fluid deposits on chest X-ray.

Table II. Postoperative complications, drugs needed and the results of physical examinations.

	group 1	group 2
Cardiotonics given (n)	7	4
Anti-arrhythmics given (n)	5	1
Diuretics given (n)	6	2
Analgesics (nr of adminstrations)	15	8
Sedatives (nr of administrations)	13	7
End of study:		
Intubated	5	1
Ventilated	5	1
Responsive	1	6
Indication for corticosteroids	4	0
Interstitial fluid on X-ray	4	2
Nr of survivors	6	6

Table III shows the postoperative complications in the period from the end of the study until discharge.

Table III. Postoperative complications from the end of the study period until discharge.

	group 1	group 2
Detubation after (time in hrs)	23 $\pm$ 16	11 $\pm$ 5
Indication for steroids (n)	6	1
Wound dehiscence (n)	2	0
Subcutaneous bleeding (n)	3	0
Clotting disturbances (n)	3	1
Days until discharge ($\bar{m} \pm$ SD)	19 $\pm$ 7	14 $\pm$ 5

None of the patients died, but 4 out of 6 patients in Group 1 (etomidate) had serious complications, such as wound dehiscence, subcutaneous bleeding and 2 patients showed clotting anomalies even after the administration of corticosteroids. In Group 2 (droperidol), none of these complications occurred. All patients were treated on the surgical ward according to a standard protocol which remained constant throughout the study period.

DISCUSSION

The incidence of corticosteroid depletion after surgery is not yet fully documented. However, it is possible that it occurs with severe stress or during the course of specific diseases (4). Low serum cortisol concentrations, as in the etomidate group, are not necessarily the result of stress-free anaesthesia. Stress-free anaesthesia implies that the stress to the patient is minimised by use of anaesthetic agents, in turn keeping the serum cortisol concentrations low (3). But etomidate blocked the corticosteroid production (2), inducing an incapacity of the adrenals to secrete cortisol.

This prospective study had the aim of showing that it could have been possible to discover the side effects of etomidate at an earlier stage, using the routine parameters of anaesthesia. The results showed fluid and sodium retention after surgery, a significantly different delta temperature during and after surgery and postoperative fever. But there were also concomitant increases in the interstitial fluid deposits in the lung, together with intensified use of cardiotonics, diuretics and antiarrhythmic agents, all indicating a certain state of shock. Later, this shock was shown to be due to the low serum cortisol concentration.

The absence of significant changes in pulse rate, arterial and central venous pressures is due to the vigilant monitoring and correcting of these parameters by the anaesthetist. This may in turn mask the early signs of an impending Addisonian crisis. Changes in delta temperature could have been an early indication of the onset of hypovolemic shock. But, when adequate amounts of sodium-containing infusion fluids were administered, the arterial and central venous pressures and pulse rate remained unchanged. Thus, when only cardiovascular parameters were considered, the possibility of diagnosing an impending Addisonian crisis could be missed. The global clinical picture could have been masked because of

the effects of both anaesthesia and surgery. Even clinical signs might have been overlooked during surgery. But in the postoperative phase, however, the need for sodium containing infusions, the occurrence of cold extremities and pyrexia (which was effectively treated with dexamethasone) all indicated a state of low serum cortisol concentration.

Table III presents details of incidence of some complications that occurred postoperatively. The data indictes that patients in the etomidate group (Group 1) had a slower recovery. In addition, other phenomena were observed even after most of the patients had received high doses of corticosteroids. Thus, the possibility that other biochemical disturbances may exist, has to be considered.

CONCLUSION

From appraisal of several parameters during routine anaesthesia, together with measurements of cumulative fluid/sodium balances and delta temperatures, it should have been possible to detect steroid blockade, due to etomidate, in an earlier stage of its clinical introduction. This study does not claim to prove that the inhibition of corticosteroid synthesis is solely due to etomidate.

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STEROID RESPONSE TO ACTH AND TO ASCORBIC ACID DURING INFUSION OF ETOMIDATE IN GENERAL SURGERY

M.P. Boidin

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KEYWORDS : METABOLISM - corticosteroids
imidazole
cytochrome P450
ascorbic acid

Etomidate is an intravenous hypnotic which causes a blockade of cytochrome P 450 (1). But the effect on cytochrome P 450 (by free or substituted imidazole groups) and on corticosteroid synthesis is not yet clear.

Ascorbic acid plays a crucial role in steroid synthesis (2). As it is a relatively harmless drug, available for clinical use, it was administered to patients in whom corticosteroid synthesis was blocked by a continuous infusion of etomidate (1). Effects of ascorbic acid and ACTH administration were compared in two groups of five patients. Because of the differences in individual treatment during surgery it was not possible to conduct a double blind clinical trial.

METHODS

Ten adult patients who were to undergo major abdominal surgery were studied (Table I).

Table I. Demographic and anaesthetic data.

Age (year, $\bar{m}$/range)	66/54-72	63/47-75
Weight (kg, $\bar{m}$/range)	67/56-73	64/59-69
Operation time (hrs, $\bar{m}$/range)	5.7/4.2-7.3	6.3/5.2-8.2
Sex ratio (f/m)	2/3	1/4
ASA classification.	1 pat. I	
	2 pat. II	3 pat. II
	2 pat. III	2 pat. III

Patients who suffered from hepatic, renal or endocrinological disease, and those who were using (or had recently used) corticosteroids, were excluded. All patients were scheduled for operations lasting four hours or more, and all needed invasive cardiovascular monitoring with postoperative ventilation in the ICU. Informed consent was obtained in all cases on the day before operation and 10 mg diazepam was prescribed for night sedation. No further drugs were administered except for 1 g ampicillin/cloxacillin (Ampiclox).

250 ml infusion of dextrose was prepared containing etomidate (1 mg. ml^{-1}) and fentanyl (0.01 $mg.ml^{-1}$). Anaesthesia was induced by continuous infusion of the mixture at a rate of 1 drop 0.05 ml/kg/min using a

drip regulated infusion pump (IVAC 531). This resulted in an administration rate of 0.05 $mg.kg.min^{-1}$ for etomidate and 0.5 $\mu g.kg.min^{-1}$ for fentanyl. Before intubation patients breathed oxygen enriched air (FiO2 0.5) and ventilation was assisted manually, when required. As soon as the patient was asleep (± 5 min) pancuronium bromide (0.1 mg/kg) was administered and 3 minutes later intubation was performed. Controlled ventilation was established with air and oxygen (FiO2 0.33) in an open circuit, using an Engström 300 ventilator.

Two minutes after intubation, the infusion rate was reduced to 20% of the induction rate. This regime was maintained throughout surgery. Ventilation was set to maintain end tidal carbon dioxide percentage at physiological levels, which was periodically checked by arterial blood gas analysis. Blood, plasma, electrolyte solutions and plasma expanders were given, as appropriate, to maintain cardiovascular parameters within physiological limits. No corticosteroids were administered until the sampling was completed.

Serum and plasma samples were taken before anaesthesia and at 60, 120 and 180 minutes after induction. Within 20 min after sampling, the samples were centrifuged and refrigerated at -40°C awaiting estimation. Serum ACTH and $ACTH^{1-24}$ was determined in unextracted serum using a commercially available radio-immunoassay kit (CIS, Italy) with a sensitivity of 20 $nmol.l^{-1}$ and a variation coefficient of 15% at 300 $nmol.l^{-1}$. Serum cortisol was estimated using radio-immunoassay according to the method of Pratt (3). Sensitivity was 15 $nmol.l^{-1}$ and the interassay variation coefficient was 8% at 50 $nmol.l^{-1}$. Serum compound S (11 deoxycortisol) was extracted and assayed by competitive protein binding using dog serum as a binder, H^3-corticosterone as a tracer and Florisol for separation (4). The sensitivity of this method is 20 $nmol.l^{-1}$ and the variation coefficient is 5% at physiological values. Androstene-dione was measured in plasma by radio-immunoassay after extraction with 5% ethylacetate in pentane. The antisera were raised in rabbits to an androstene-dione-7 alpha-carboxyethyl-thioether bovine thyroglobulin conjugate. This method has a sensitivity 0.8 $nmol.l^{-1}$ and a variation coefficient of 7% above 2 $nmol.l^{-1}$ (5).

In five patients the adrenal cortex was stimulated 3 hours after induction of anaesthesia by $ACTH^{1-24}$, synacthen Ciba (0.25 mg i.m.). Ascorbic acid was administered without $ACTH^{1-24}$ to five other

patients. Three hours after induction these patients received 1000 mg ascorbic acid in 100 ml dextrose over a period of 5 minutes. In both groups, the sample at 180 minutes after induction was used as the control for the stimulation test. This sample was compared with the samples taken at 210 and 240 min after induction of anaesthesia.

The results at each specified time were calculated for mean and standard deviation and they were compared with the control at t=0 using the Student's t test for paired values. The values obtained at t=210 and t=240 were compared with the value at t=180 using the same method. The phenomena in each group were only compared qualitively because the study was not double blind. No quantitative intergroup comparison was attempted after the stimulation tests.

RESULTS (Figs. 1 and 2)

Adreno-cortico-trophic-hormone (ACTH)

After induction of anaesthesia there was a significant decrease in serum ACTH concentration which remained constant until synacthen ($ACTH^{1-24}$) was administered. When $ACTH^{1-24}$ was given there was a significant increase in serum ACTH concentration. The ACTH serum concentration in the ascorbic acid group did not change significantly at t=180 and later.

11 deoxy-cortisol (compound S)

The serum concentration of compound S decreased significantly directly after induction of anaesthesia and remained constant until $ACTH^{1-24}$ was administered. When ACTH concentration increased, there was a small but insignificant increase in compound S concentration. When ascorbic acid was administered, there was a significant increase in serum concentration of 11 deoxy-cortisol.

Cortisol

The serum concentration of cortisol decreased immediately after induction of anaesthesia. The decrease was significant and progressive during the first 3 hours of anaesthesia. $ACTH^{1-24}$ was not capable of significantly increasing the serum concentration of cortisol. When the

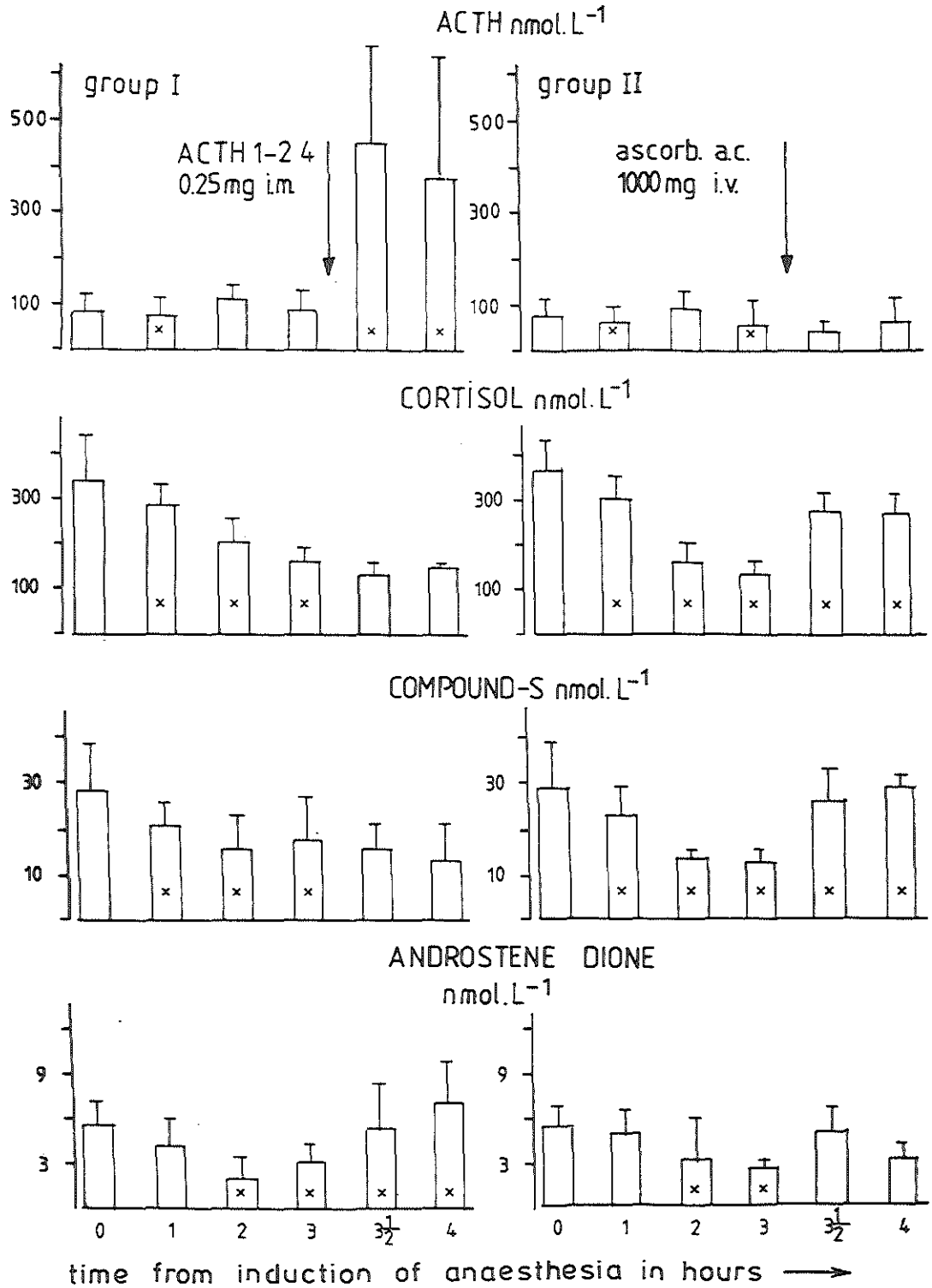

Fig. 1: ACTH, cortisol, 11 deoxy cortisol and androstene-dione concentrations in two groups.

Significant differences compared to t=0 and t=3 are indicated.

relationship between the trophic hormone and the effector hormone was calculated, it was apparant that the cortisol/ACTH ratio decreased during the first 3 hours of anaesthesia. The relationship appeared to be lost after administration of $ACTH^{1-24}$. In the group of patients receiving ascorbic acid, the same reaction was observed in the first 3 hours after induction of anaesthesia. After ascorbic acid had been administered there was a considerable and significant increase in serum cortisol concentration. The relationship between cortisol and ACTH returned to pre-anaesthetic levels.

Androstene-dione

The plasma concentration of this hormone precursor decreased in proportion to the reduction in ACTH concentration. When $ACTH^{1-24}$ was administered there was an increase in plasma concentration and the relationship between the trophic hormone and androstene-dione appeared to be preserved. This was also the case in the group of patients receiving ascorbic acid.

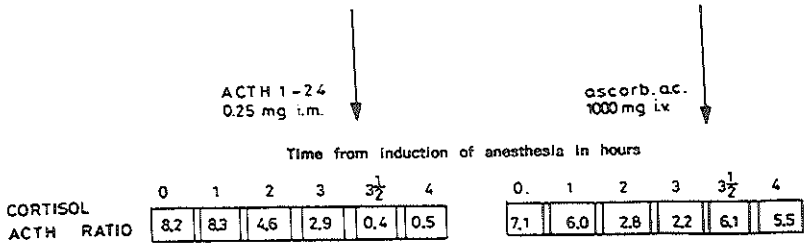

Fig. 2 : Modification of the etomidate blockade of cortisol synthesis by ACTH and ascorbic acid.

DISCUSSION

It is known that guinea pigs and primates cannot convert alpha-keto--gulonic acid into ascorbic acid (2). Thus, these species depend on digested vitamin C and resynthesis from dehydro-ascorbic acid, for the restoration of their ascorbic acid pool. As ascorbic acid is essential for cortisol synthesis and because guinea pigs and primates have a surprisingly low ED 50 and LD 50 compared with all other species (6), it has been administered therapeutically to patients with etomidate-induced cortisol synthesis blockade.

In cases where ascorbic acid was given, there was an increase in serum cortisol concentration. This moderate increase may be due to the fact that the serum ACTH concentration did not significantly increase in this group of patients. However, when the cortisol/ACTH ratio was studied, there proved to be a restoration to pre-operative levels. This was interpreted as indicating that the adrenals are capable of synthesizing cortisol, without a significant blockade, in the cases where ascorbic acid was administered.

Wagner et al. (1) have shown that etomidate, in common with all drugs with a free imidazole radical, blocks the mitochondrial cytochrome P 450. However, since ascorbic acid can overcome this blockade it implies that cytochrome P 450 is only peripherally involved in cortisol synthesis. From the presented data it appears that cytochrome P 450 may be an intermediary for the reconversion of dehydro-ascorbic acid into ascorbic acid. It is assumed that cytochrome P 450 transfers electrons and/or hydrogen ions from the mitochondria to dehydro-ascorbic acid to resynthesize ascorbic acid. Thus, when the cytochrome is blocked, the pool of ascorbic acid will become exhausted and cortisol synthesis ceases. When ascorbic acid is administered, cortisol synthesis will recover.

If this assumption proves correct, it should have significant implications for other hydroxylation processes. Indeed, Wagner (1) predicted that sex hormone synthesis is also blocked by etomidate. During this study, it was observed that, in 3 cases, testosterone synthesis was blocked. When ascorbic acid was administered, the testosterone concentration in serum increased markedly, indicating that the same mechanism applies to this chemical reaction (author's unpublished data).

CONCLUSIONS

Because the study was undertaken as a clinical trial, it is difficult and risky to draw definite conclusions. The study should be repeated in a double blind study under laboratory conditions. These investigations can best be carried out in guinea pigs or primates, because of their exceptional ascorbic acid metabolism.

It appears that ascorbic acid, and not $ACTH^{1-24}$, increases serum cortisol concentration in patients in whom cortisol synthesis was blocked by etomidate infusion. Ascorbic acid restores the relationship between

serum cortisol and serum ACTH/$ACTH^{1-24}$ concentration. If these conclusions prove to be correct, the toxicological studies of all drugs containing free imidazole radicals will be invalidated.

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THE ROLE OF ASCORBIC ACID IN ETOMIDATE TOXICITY

M.P. Boidin, W. Erdmann, N.S. Faithfull

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Keywords : ANAESTHESIA - imidazole, side effects

METABOLISM - corticosteroid synthesis
ascorbic acid
cytochrome P 450

Etomidate, R-(+)-ethyl-1-(phenylethyl)-1H-imidazole-5-carboxlate is a potent, short acting hypnotic, which is clinically employed for the induction of anaesthesia. Janssen et al.,(1) following toxicology studies concluded that : "The duration of hypnosis with etomidate is dose dependent and the safety margin will therefore be widened when sleep of short duration is aimed at". These studies, investigating chronic toxicity following both long and short term administration, were performed using rats and dogs. Investigations into teratogenic and embryotoxic effects were performed in rabbits and rats. However, no significant changes related to the drug were noted. A striking feature of these toxicity studies was the relatively low LD50 in guinea pigs, death occurring 20 to 120 minutes following administration of 7.13 mg per kg of etomidate. The concentrated form of this drug etomidate, in alcohol solvent (125 mg per ml), has been used since 1978 for induction and maintenance of total intravenous anaesthesia. This drug is easy to administer and causes minimal cardiovascular depression. A further advantage is that pollution of the operating theatre by gaseous anaesthetic agents is avoided (2).

Etomidate is rapidly hydrolised in the liver to form carboxylic acid. Elimination is rapid and 76% of the administered dose is recovered as metabolites in the urine in 24 hours - 78% is recovered in 4 days. No accumulation of drug was observed in animals or man (3). At that time, the only reports of adverse reactions were the occurrence of pain at the injection site and epileptiform movements during rapid injection of an induction bolus - 0,2 mg per kg (4). Recently however (5), the occurrence of fever has been noted following the use of high doses of etomidate (3 mg/kg over a period of 6 hours) used as a continuous drip infusion during major abdominal surgery. Moreover, positive fluid and sodium cumulative balances were observed.

Thus, serum cortisol concentrations were estimated in order to exclude the presence of an acute Addisonian crisis. The results showed that steroid levels were very low and, after 6 hours administration of etomidate, the serum cortisol concentration had decreased from a mean pre-operative value of 380 nmol per litre (SEM 102) to a mean value of 91 nmol per litre (SEM $\pm$ 29). The low concentration of cortisol was not increased by stress and was not changed by the administration of synthetic adenocorticotropic hormone (ACTH 1-24). Similar changes (unpublished observations) in the serum cortisol concentrations were measured when etomidate was used as an hypnotic agent in a continuous infusion

technique, during local anaesthesia. In another group of patients (5), anaesthetised with neurolept anaesthesia, though decreases in cortisol concentrations of up to 30% of the pre-operative value were observed, these cases reacted normally to ACTH administration and to stress.

A follow up study (6), in which six patients received a continuous infusion of etomidate, measurements revealed a decrease, not only in the levels of all steroid hormones, but also in their precursors. Neither stress nor stimulation by ACTH was able to increase the measured concentrations of any of these hormones, with the exception of androstenedione. This was confirmed by Wagner and coworkers in 1983 (7). Post-operative abnormalities were also observed and in some patients poor wound healing was to be seen between three and six days after operation. Occasional spontaneous subcutaneous bleeding also occurred at this stage, but was not seen in patients who were receiving a normal diet or were on a total parenteral nutrition regime. Administration of corticosteroids did not prevent these late complications (8).

It is known that no storage of steroids occurs in the adrenal glands (9). When ACTH reaches the surface of the cell in the adrenal cortex, it activates adenyl-cyclase. Adenosine-tri-phosphate (ATP) is converted to adenosine-mono-phosphate and inorganic phosphate. This reaction is followed by a reduction of intracellular ascorbic acid, a reduction in triphopho-pyridine-nucleotide, NADPH, increased molecular oxygen consumption and increased levels of serum cortisol (10). The rate limiting factor in the synthesis of steroid hormones by the body is the hydroxylation of cholesterol to 20-22 hydroxypregnenolone, the progenor of many other steroids (11). The mechanism of cortisol synthesis is blocked by several drugs. For example, glutethimide is presently used to depress steroid hormone synthesis in cases of oestrogen dependant mammary carcinoma, with the aim of producing remissions of both the primary tumor and also its metastases (12). Other drugs, such as cimetidine and ketokonazole may also cause chemical adrenalectomy. The degree of suppression of the adrenal cortex following the administration of these drugs may be as much as that caused by surgical adrenalectomy (13,14). Wagner et al.,(7) recently provided strong evidence that etomidate blocks cytochrome P450 similar to other drugs with free imidazole radicals. This was confirmed by the Janssen Research Laboratories who proved that imidazole groups indeed bind to this cytochrome (15).

Ascorbic acid plays a crucial role in hydroxylation processes (10) as in the formation of hydroxyproline, an amino acid involved in connective tissue synthesis, as well as in the formation of thyrosin (16) and of prostaglandins such as PGE 1 (17). It also plays a role in the hydroxylation processes of steroid synthesis and sex hormone synthesis (18). It might be suggested that ascorbic acid acts as an electron donor. It is postulated that two electrons are donated to atomic oxygen, which together with a hydrogen ion, received from NADPH, forms a hydroxyl group. This reaction does not consume energy, on the contrary, it produces energy and may be initiated by an increase in pH within the cell. This has been illustrated by von Dippe et al., (19) who have shown that the rate of synthesis depends on the intracellular pH. Ascorbic acid can bypass the effect of the blockade of cytochrome P 450 on the cortisol synthesis (20). Guinea pigs and primates, lacking the enzymes for de novo synthesis of ascorbic acid, are the only species with a low ED50 and a low LD50 for etomidate and show an impairment of hydroxylation processes. Moreover, imidazole structures can block the action of cytochrome P450. Therefore it must be concluded that cytochrome P450 is an intermediary in the reconversion of dehydro-ascorbic acid to ascorbic acid. The cytochrome probably transfers electrons and/or hydrogen ions from the mitochondria to dehydro-ascorbic acid to form ascorbic acid. The electrons and hydrogen ions are produced within the mitochondria of the adrenal cortical cells in response to ACTH. Mitochondrial activity restores the pools of ATP, cholesterol, NADPH and ascorbic acid. Drugs containing free imidazole radicals and drugs such as metapyrone and aminoglutethimide specifically prevent the restoration of the ascorbic acid pool and, as a consequence, there is a blockade of all hydroxylation reactions proceeding via mono-oxygenase reactions.

As a proposal, it has been suggested to the Janssen Pharmaceutical Company that the imidazole radical in etomidate should be changed for a furane group. A similar substitution in the case of cimetidine has led to the development of ranitidine - a drug with similar pharmacological action but with less side effects than cimetidine (21). An alternative could be that patients treated with imidazole group containing drugs are simultaneously treated with ascorbic acid, when normal serum cortisol and sex hormone concentrations are preferred. In contrast, when low hormone levels are preferred, as might be desirable in treatment of malignancy, it would seem wise to withhold ascorbic acid.

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PHOSPHATE ACTING AS A SECOND MESSENGER IN STEROIDOGENESIS

Hypothesis and suggestions for further investigations.

M.P. Boidin

Keywords : METABOLISM - steroidogenesis
- inorganic phosphate
- pH
- ascorbic acid

Steroid hormone synthesis depends largely on a hydroxylation process, involving a mono-oxygenase system. Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidation, and oxidation of ascorbic acid occur concomitant with the synthesis of corticosteroids (1). No steroid hormones are stored in the adrenals, but ascorbic acid and cholesterol are available in large quantities. The same metabolic pathway as in steroidogenesis also plays an important role in the synthesis of Testosterone, Serotonin, Hydroxyproline (1) and Thromboxane (2).

It was observed that ascorbic acid, and not ACTH, could increase the serum cortisol concentration in patients whose steroidogenesis was blocked by etomidate which was administered for the maintenance of anaesthesia during surgery. In the molecular structure of etomidate there exists an imidazole radical which binds to cytochrome P 450 (3). Because ascorbic acid can increase the serum cortisol of patients it is not likely that cytochrome P 450 is directly involved in steroidogenesis. It is more likely that cytochrome P 450 is involved in the ascorbic acid metabolism.

Therefore, it was concluded (4) that ascorbic acid is the main electron and/or hydrogen ion donor in the formation of hydroxyl groups via a mono-oxygenase system.

The acidity of ascorbic acid is due to the hydrogen ion carbon-3 (pKa = 4.17). The most prominent chemical property of vitamin C is its ready oxidation to dehydro-ascorbic acid (1). Ascorbic acid is a dietary necessity for man, other primates and the guinea pig. These species depend on re-synthesis of ascorbic acid from dehydro-ascorbic acid for the restoration of their vitamin C pool. By this process, the ascorbic acid pool is sufficient for a period of approximately six months in a diet without ascorbic acid. Ascorbic acid is stable at low pH and dissociates at high levels. It has been shown that steroidogenesis is related to the free hydrogen ion concentration in the cell (5). When ascorbic acid dissociates, it produces energy and re-synthesis will consume energy. This energy is obtained from the Krebs' cycle, together with the electrons and the hydrogen ions, as the mitochondria are activated by the same stimulus as for steroid synthesis (1). The function of cytochrome P 450 is to transfer electrons and/or hydrogen ions to dehydro-ascorbic acid to form ascorbic acid. This mechanism seems to be specifically blocked by imidazole radicals (3).

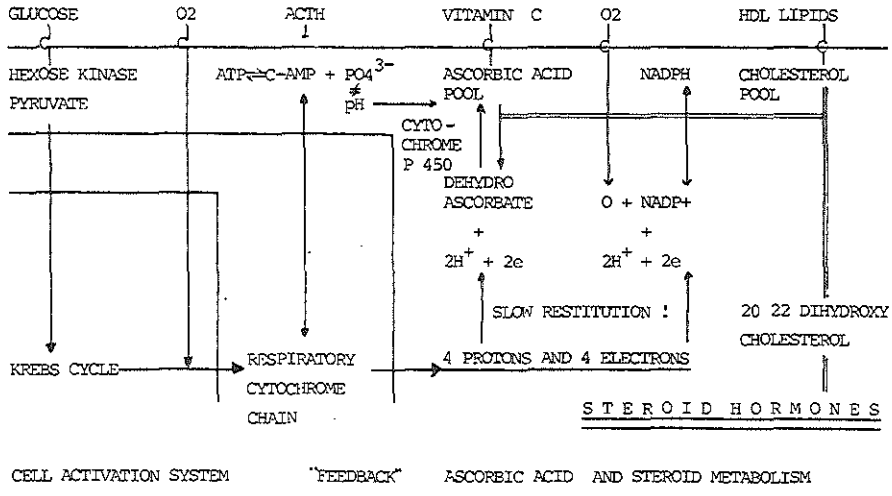

Fig. 1 : Biofeedback mechanism of steroid hormone synthesis by ascorbic acid and cholesterol.

When ACTH makes contact with the cell membrane, adenylcyclase is activated. Adenosine Tri Phosphate (ATP) is converted to cyclic Adenosine Mono Phosphate (c-AMP). The ATP loses its energy and its inorganic phosphate (5). This inorganic phosphate may act as a buffer substance for the pH and the free hydrogen ion concentration will decrease. Ascorbic acid starts to dissociate when the pH of the cytoplasma increases and dehydro-ascorbic acid appears in the venous outflow of the adrenals (6). Normally, the cell will restore its ascorbic acid pool simultaneously with the restoration of its energy pool. As the ATP pool is restored, the inorganic phosphate will disappear from the cytoplasma. The pH will decrease and the ascorbic acid pool will be restored. The cell will then be ready for a new production phase (fig. 1). When etomidate is used to block the cytochrome P 450, no restoration of the ascorbic acid pool occurs. In this case there is no available ascorbic acid to initiate the hydroxylation of cholesterol (5).

The data presented suggests that inorganic phosphate may act as a trigger for the spontaneous oxidation of ascorbic acid. Oxidation of ascorbic acid initiates steroidogenesis by starting the process of cholesterol hydroxylation via a mono-oxygenase system. In this manner, inorganic phosphate acts as a second messenger for ACTH.

Thus, the instability of the ascorbic acid pool at high pH, the facts that steroid production is pH dependent, that no steroid hormones are stored in the adrenal cells (only ascorbic acid and cholesterol are

available), the vigorous onset of steroid synthesis with a very short production time, and the fact that ascorbic acid can bypass the imidazole blockade of the cytochrome P 450 - all tend to support this hypothesis.

It is therefore suggested that further investigations should be oriented towards intracellular pH measurements during stimulation of the adrenals of live guinea pigs. Starvation studies, with and without adrenal blockade with imidazoles, and ascorbic acid turnover and resynthesis rate may prove to support this hypothesis. Ultimate proof will be obtained when it can be demonstrated that changes in intracellular pH, caused by inorganic phosphate only, can induce corticosteroid synthesis.

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S U M M A R I E S

OF THE ARTICLES

CHAPTER II, 1

AIRWAY PATENCY IN THE UNCONSCIOUS PATIENT

Airway patency was explored in patients breathing spontaneously with deep halothane anaesthesia. Opening and closing of the airway was observed with a flexible bronchoscope looking caudally from the nasopharynx at the epiglottis and the tongue. With the occiput elevated at various angles, the smallest angle of retroflexion of the neck necessary to open the airway was measured. The influence of adjuncts for free airway on this angle of retroflexion of the neck was also measured. Cadaveric preparations of the upper airway were studied to assess the mechanisms involved in airway patency. The results indicate that the epiglottis and not the tongue is the main cause of obstruction of the upper airway. Adjuncts for the establishment of the free airway do not affect the angle of retroflexion. This angle is only affected by the elevation of the occiput above the level of the operation table. When methods were applied to displace the hyoid anteriorly the airway was, in most cases, cleared.

CHAPTER II, 2

CONTROLLED ADMINISTRATION OF OXYGEN WITH SELF-INFLATING RESUSCITATION BAGS

Resuscitation bags were originally developed to ventilate patients under emergency conditions. Under circumstances where oxygen is available one should make full use of it. The problem of air-enrichment has not yet been satisfactorily solved. A new system has therefore been designed which can supply controlled delivery of FiO_2 with a self-inflating resuscitation bag. A stable FiO_2 was achieved via a venturi device connected to the air inlet of a manual resuscitation bag. FiO_2's delivered to patients from a self-inflating bag were tested for values of 0.24, 0.30, 0.40 and 0.50 oxygen delivery. The new system proved to be capable of delivering exact FiO_2's, in contrast with previously applied methods of oxygen delivery where a stable FiO_2 could not be achieved.

CHAPTER II, 3

PROTOTYPE OF AN INTAKE VALVE FOR RESUSCITATION BAGS

Self-inflating resuscitation bags were originally designed for ventilation with air. The modification to permit additional oxygen delivery was readily introduced but failed to fulfil the requirements for a stable inspired oxygen concentration in combination with a low medical oxygen consumption.

This manuscript is concerned with a new design for an air-intake valve for resuscitation bags. The percentage of the inspired oxygen had to become independent from the inspiratory minute volume. The consumption of medical oxygen should be considerably reduced. This could be achieved by using a downflow (second stage) demand valve which admits oxygen via a venturi. Oxygen was admitted to the venturi only when the bag filled with the fresh gas mixture. Air enrichment with this system will function as long as medical oxygen is available but, when oxygen supply fails, the bag may be used for air ventilation without further adjustment. The safety provisions of the resuscitator are not affected using this prototype of an intake valve.

CHAPTER III, 1

A PORTABLE PEEP VALVE FOR 0-20 cm H2O

Positive End Expiratory Pressure (PEEP) ventilation is a valuable method in modern critical care therapy. Nevertheless, it is often necessary to take patients off the ventilator for routine physiotherapy as well as for special investigations and transport. Portable ventilators, or manual bag ventilators, are used during the off-ventilator periods. In order to keep the expiratory pressure within the therapeutic range, it is desirable to have a portable PEEP valve available. This valve has to be lightweight, small, easy to use, cheap and stable.

AMBU Danmark has designed such a PEEP valve which fits onto adult and paediatric non-return valves. The latest design is a PVC spring-type valve with a pressure range of 0-20 cm H2O. This valve was tested in the laboratory for different flows, temperatures, humidity and position. A further evaluation was made under clinical conditions. The AMBU PEEP valve was found to be accurate and easy to use, with a stable performance, meeting all requirements for Emergency Medical Care.

CHAPTER III, 2

MECHANICAL VENTILATORS FOR EMERGENCY MEDICAL CARE USING A MANUAL RESUSCITATION BAG

It is possible to construct a mechanical ventilator from the parts of a self-inflating bag in combination with a magnetic valve. These ventilators prove to be very helpful for the transport of critically ill patients of all categories and under varying conditions. The ventilators can be used by medical and paramedical personnel, but experience in ventilation of patients with this device is mandatory.

The ventilators are cheap and reliable with a stable performance, but more sophisticated patterns of ventilation necessitate the use of volume and pressure monitoring. The mode of action of the ventilator, the compliance of different reservoir bags and the place of the monitor devices are discussed in this article.

CHAPTER III, 3

INFLUENCE OF DIFFERENT HEPARIN SOLUTIONS UPON BLOOD GAS ANALYSIS AND BIOCHEMICAL VALUES MEASURED IN PLASMA.

Blood gas analysis in adults was usually carried out using relatively large blood samples, which could be detrimental to the patient. In paediatric cases, smaller samples were taken for blood gas analysis and other biochemical tests, but the results were frequently disturbed by dilution and acidification. This could lead to false values and subsequent therapy was sometimes based on these false laboratory results. To overcome this problem, a new heparin solution was produced which is discussed in this article.

Three types of heparin solutions and their effect on blood gas analysis were investigated in 4 series of dilutions. The addition of heparin solution caused changes in pCO2, bicarbonate and pH, and these changes simulated respiratory compensation of a metabolic acidosis. The effects of addition of different volumes and types of heparin solution were investigated.

The accuracy of other routine biochemical values were also assessed in plasma compared with serum for : sodium, potassium, calcium, chloride, urea, creatinine, inorganic phosphate, alkaline phosphatase, lactate dehydrogenase, serum glutamic-oxalate transaminase, serum glutamic-pyruvate transaminase, total protein, albumin and cholesterol. Differences in lactate dehydrogenase, inorganic phosphate and total protein could be demonstrated. These differences could be due to the clotting process in the serum samples.

CHAPTER IV, 1

SERUM LEVELS OF CORTISOL IN MAN DURING ETOMIDATE, FENTANYL AND AIR ANAESTHESIA, COMPARED WITH NEUROLEPT ANAESTHESIA

A study was carried out in sixteen patients who were to undergo major abdominal surgery. The effects of etomidate and fentanyl (given as a mixture in a continous infusion) and of classical neurolept anaesthesia with droperidol and fentanyl, on the serum cortisol levels were compared during and after anaesthesia. The results showed that the postoperative increase in serum cortisol levels, which occurred in the neurolept group, was absent in the group receiving etomidate and fentanyl infusion. During anaesthesia there was a more significant decrease in serum cortisol in the patients receiving etomidate and fentanyl and no rise in serum cortisol levels occurred 30 min after injection of synthetic ACTH.

Etomidate and fentanyl, given as a continuous infusion during major abdominal surgey, blocks the adrenal mechanism to secrete endogenous cortisol in response to stress and increased levels of adreno-corticotrope hormone in the serum of patients.

CHAPTER IV, 2

ETOMIDATE AND ACTH INDUCED STEROIDOGENESIS IN ISOLATED ADRENAL CELLS OF RATS

The effects of intravenous anaesthetic etomidate have been investigated on ACTH-induced steroidogenesis in vitro, using isolated rat adrenal cells. It was found that doses of etomidate 200 ng, or greater, almost completely blocked corticosterone production induced by 25 pg of ACTH. The mean etomidate concentrations resulting in 50 percent inhibition approximated 1.5×10^{-7} M which is in the range of concentrations measured after clinical doses of etomidate.

CHAPTER IV, 3

MODIFICATION OF CORTICOSTEROID SYNTHESIS BY ETOMIDATE/FENTANYL AND AIR ANAESTHESIA

Characteristics of cortisol synthesis blockade by an etomidate/fentanyl combination was explored in a group of 7 patients undergoing major abdominal vascular surgery. Cortisol, androstene-dione, 11-deoxy cortisol (compound S) and ACTH were measured during surgery for three hours. In the fourth hour an $ACTH^{1-24}$ stimulation test was performed and the reaction of the corticosteroid synthesis was assessed.

ACTH and adrostene-dione showed a stable concentration during the study, the reaction of androstene-dione to $ACTH^{1-24}$ was blunted but normal. Compound S and cortisol concentrations decreased during anaesthesia and showed no significant increase after stimulation with $ACTH^{1-24}$.

These results indicate that the infusion of etomidate and fentanyl may cause a blockade of the corticosteroid synthesis. The blockade is situated at the site where conversion of cholesterol to pregnenolone occurs. Because the study was performed in a clinical setting the results should be interpreted carefully. The experiment should be repeated under laboratory conditions to obtain more conculsive scientific results.

CHAPTER IV, 4

CAN ETOMIDATE CAUSE AN ADDISONIAN CRISIS?

The purpose of this study was to assess, prospectively, the side effects of etomidate given by infusion, using the routine parameters of daily anaesthetic practice. The study included 12 patients scheduled for major abdominal vascular surgery. The effects of etomidate/fentanyl and air anaesthesia were compared with those of neurolept anaesthesia. Arterial blood pressure, central venous blood pressure, pulse rate, peripheral and core body temperature were recorded continuously. Blood samples were taken every two hours during anaesthesia for the estimation of arterial blood gases, cortisol, sodium, potassium and chloride.

contd....

Significant differences were seen in : the peripheral and core temperatures, and the cumulative sodium and cumulative fluid balance, from which the diagnosis of an Addisonian crisis could have been deduced. There were also differences in the incidence of early and late complications, and in the recovery rate of the patients after receiving etomidate infusions.

CHAPTER IV, 5

STEROID RESPONSE TO ACTH AND TO ASCORBIC ACID DURING THE INFUSION OF ETOMIDATE FOR GENERAL SURGERY

The characteristics of the steroid response during an etomidate/fentanyl combination were explored in 2 groups of five patients undergoing major abdominal vascular surgery. Cortisol, androstene-dione, compound S and ACTH were measured during surgery for three hours. In the fourth hour, an $ACTH^{1-24}$ stimulation test was performed in one group and the steroid response was assessed. The other group received ascorbic acid intravenously and the reaction of the adrenals was measured in the same way.

The results indicated that etomidate causes a blockade of the adrenal corticosteroid synthesis at the site of the hydroxylation of cholesterol. It appeared that the blockade was due an interaction of the imidazole structure of etomidate with the cytochrome P 450. Ascorbic acid, however, was able to overcome this blockade, indicating that cytochrome P 450 was involved in the ascorbic acid metabolism, rather than in the corticosteroid synthesis.

CHAPTER IV, 6

THE ROLE OF ASCORBIC ACID IN ETOMIDATE TOXICITY

Etomidate, a short-acting hypnotic used in anaesthesia, has been shown to block steroidogenesis in humans. The free imidazole radical in the structure of etomidate binds to cytochrome P 450. Serious side effects have only been observed in guinea pigs and man. These species rely upon resynthesis and the daily intake of vitamin C to restore the ascorbic acid pool. It has been shown that ascorbic acid and not ACTH increases serum corisol concentration during etomidate infusion. Ascorbic acid even restores the ACTH/cortisol ratio to preoperative values.

It was thus concluded that etomidate blocks the ascorbic acid metabolism rather than the steroid metabolism. It appears that depletion of the ascorbic acid pool then causes an inhibition of steroidogenesis in the case of etomidate. This phenomenon occurs only in guinea pigs and primates, all other species can synthesize their own ascorbic acid.

CHAPTER IV, 7

PHOSPHATE ACTING AS A SECOND MESSENGER IN STEROIDOGENESIS : Hypothesis and suggestions for future investigations.

Etomidate, a short-acting hypnotic for anaesthetic use, blocks the cytochrome P 450 and ascorbic acid can bypass this blockade. Administration of this vitamin increases the serum cortisol concentration when given during continuous infusion of etomidate. This in contrast to Adreno-Cortic-Trope-Hormone (ACTH). Therefore, it has been suggested that ascorbic acid dissociation initiates the steroidogenesis. The steroid synthesis is pH dependent. It seems that inorganic phosphate, released when adenylcyclase is activated by ACTH, can act as a second messenger for ACTH. Inorganic phosphate disappears from the cytoplasma of the cell when Adenosine Tri Phospahte is restored. The pH within the cell will therefore decrease and the ascorbic acid pool will be restored and become stable again. This process provides a bio-feedback mechanism, a trigger and an explanation for the phenomena of steroidogenesis.

GENERAL DISCUSSION

The goal of this thesis was to illustrate, rather than to prove, that anaesthesia and CCM are interactive and that the quality of care in these two specialities are interdependent. All investigations had in common that they concerned anaesthetic problems in the field of CCM. Because it was extremely difficult to investigate these problems in the ICU, the studies were performed in the operating theatre, or in the experimental laboratories. Patients in the ICU were often seriously ill. Multiple organ failure, Adult Respiratory Distress Syndrome (ARDS) and/or circulatory failure made these patients unsuitable for most of the clinical studies. The patients who were to undergo general surgery possessed more physical reserves and the experimental conditions were generally better in the operating room, despite the somewhat unstable conditions for the investigations. Nevertheless, the population could be defined by relatively standard criteria and the procedures were generally performed in a standardised manner. Moreover, the studies could be conducted in a more convenient and less distressing way, for both the patients and the investigating team. Therefore it is clear that, for most of the studies, the results obtained in the operating room were of a higher standard than could be achieved elsewhere.

Chapter IV : Intensive Care

The most appropriate subject to illustrate the interaction between anaesthesia and CCM appears to be the etomidate investigations. Etomidate was developed as a short-acting hypnotic for induction of anaesthesia. After it proved to be a rather successful drug it was used in a continuous infusion technique for long-lasting operations. Anaesthetists transferred use of this drug to the ICU, for sedation during ventilation. This technique showed some unwanted side effects. The origin of these effects could not be found, but the side effects were effectively treated with corticosteroid administration. During pilot investigative studies in the ICU, no conclusive results were obtained. A comparable experimental protocol was carried out in the operation room and results showed pathological serum cortisol concentrations. These results gave motivation for the investigation outlined in Chapter IV, 1. The results proved that etomidate blocked cortisol production in the adrenals. The third experiment proved that cortisol synthesis was blocked at the site of cholesterol hydroxylation. This posed the question as to why ICU patients did not suffer from this phenomenon to the same extent as patients in the

operating room. One of the differences was that patients in the ICU received total parenteral nutrition containing ascorbic acid. When it was discovered that ascorbic acid was essential for corticosteroid synthesis, it was tested in the operating room using the same protocol that was used during the third part of Chapter IV. It was then proved that ascorbic acid could increase serum cortisol concentration. It then became obvious that investigations in the ICU could not have been successful.

The subject matter contained in Chapter IV could have formed a possible basis for a separate thesis. But, as it was decided to combine all the published articles of the author, the subjects have constituted one chapter of this book. The articles in this chapter illustrate :

- discovery of the etomidate toxicity problem
- initiation of the investigation
- initial proof of etomidate side effects
- location of the biochemical site of action
- evaluation of the clinical symptoms
- theoretical background of cortisol synthesis
- related problems of other drugs and metabolites
- development of a therapy for etomidate toxicity
- conclusions and discussion of the phenomena
- formulation of a new hypothesis
- suggestions for future investigations

As the technical aspects of these subjects are fully discussed in Chapter IV and in order to avoid diversion from the major topic of this thesis (the interaction between anaesthesia and CCM) it did not seem appropriate to duplicate this information here.

Chapter III : Emergency Medical Care

Another example of interaction between the two specialities was the study of heparin solutions. The initial idea was that it would be useful to take samples from resuscitated patients in the street. Because it is very difficult to take several samples under these conditions, it was decided to study the possibility of taking one heparinised sample for the estimation of blood gas analysis (BGA) and other biochemical estimations at the same time. One of the first observations was that the potassium values had a poor correlation. This gave rise to a deeper investigation into the different kinds of heparin solutions and their influence on BGA

and electrolyte estimations.

Until recently it was very difficult to guarantee a sophisticated ventilatory support during transport of critically ill patients. For this purpose it was considered necessary to develop a transport ventilator for use in all circumstances and for all purposes. The study began with the Mini-Vent magnetic valve ventilator and ended with the ventilator described in Chapter III, 2. As patients in the ICU frequently do not have the physical reserve to enable changing their ventilatory patterns, the investigation was performed in the operating theatre where PEEP ventilation could be given for short periods without damage to the patient. As the patient did not really require the PEEP ventilation no harm could ensue when the PEEP was failing. But, if a critically ill patient were subjected to such a test with a failing PEEP valve, the outcome could be disasterous. The ventilator described in this thesis enables transport of patients everywhere, under all conditions, as long as electricity (< 12 volts), or pressurised medical gas sources are available.

Chapter II : Resuscitation

The air intake systems and air enrichment studies illustrate the contribution anaesthetists have made in the improvement of resuscitation techniques. Before 1980 it was impossible to ventilate patients with a resuscitation bag with a known FiO2. However, by application of a venturi system to the air intake valve of the resuscitator, this problem could be solved. This technique was later improved and is described in Chapter II, 3. The improved inhalation apparatus is not only important for basic resuscitation, but also for intensive care procedures. With this device it is possible to maintain critically ill patients with the same ventilatory support during manual ventilation periods as under mechanical ventilation. It was also possible to maintain the same PEEP level, the same FiO2 and the same frequency and tidal volume as can be achieved with the most sophisticated ventilators of this decade.

The subjects discussed in Chapter II, 2 and 3 and Chapter III, 1 and 2, could have formed a possible basis of a separate thesis concerning inhalational equipment. These articles offer a series of improvements in ventilation devices for CCM. The subjects include :

- an overview of the existing resuscitation bags

- descriptions of the problems with intake valves
- innovation of the air intake valve
- tests with the newly developed resuscitator
- updating of a transport ventilator
- clinical tests of the new transport ventilator
- combination of a resuscitator and transport ventilator
- description of complete inhalational equipment for resuscitation/EMC
- discussion and conclusions
- implications for disaster medicine and Third World countries

The technical discussion and conclusions concerning these topics are presented in their respective chapters. Therefore, in order to maintain emphasis on the main subject of this thesis (the interaction between anaesthesia and CCM), the detailed technical information has not been duplicated here.

The investigations into airway patency (Chapter II, 1) were motivated out of theoretical interest. The basic methods of maintaining an open airway remained unchanged, but a broader understanding of the mechanisms of the free airway had positive consequences for the clinical situation. It gave a better insight as to why conscious patients are more suitable for the performing of a successful bronchoscopy than patients under anaesthesia. It was shown that adjuncts for a free airway do not guarantee a free airway. It was also shown that adjuncts do not change the angle of retroflexion of the head to open the airway. A slight elevation of the occiput makes it easier to open the airway of the patient during out-of-hospital situations. This means that the head of the patient should be elevated instead of being lowered during resuscitation. This study puts an end to the 'story' that the tongue is the main object of obstruction in the airway.

The investigations in this thesis show that anaesthesia and CCM do indeed mutually support the quality of medical care in both specialities. The articles demonstrate that these specialities are interactive and interdependent. It appears that when one of the two specialities is less well developed in one hospital, or when one of the two offers too little service compared with the other, it can lead to deterioration of the patients' condition. The articles published in this thesis have already proved to have made a positive contribution towards improving the quality of medical care in both fields.

Knowledge concerning the mechanism of the free airway has improved management of the airway in the unconscious patient in the ICU and during recovery, as well as during resuscitation in the street. Thanks to the improvement of resuscitation bags, the rescuer is able to ventilate resuscitation patients with more 'know how', with better safety features and with a more reliable instrument. The transportation of critically ill patients is no longer a hazardous option, but can now be achieved with the same quality of ventilatory care as exists in the ICU. The newly developed heparin solution is now used by most of the manufacturers of pre-fabricated arterial bloodgas sample syringes. The adverse effects of the sedative etomidate are still being generally publicised, so it is expected that many patients in both anaesthesia and the ICU will benefit from the latest biochemical and pharmacological knowledge.

The above mentioned improvements could only be realised by an anaesthetist who was working in anaesthesia and in CCM at the same time. This shows that it is necessary for anaesthetists to work in both fields. Had the author not been working in both specialities, it would have been impossible to detect most of the problems discussed in this thesis. It would have been impossible to study the problems and it would have been impossible to solve the problems in the ways described in these articles. Thanks to the general improvement of anaesthetic care, and the concomitant improvement of anaesthetic care in CCM, it is now possible to treat and save patients who would certainly have died a few years ago. Thus, it may be assumed that the life expectancy of patients who are attended to by anaesthetists has been improved, not only due to better care in the theatre but also in the wider field of Critical Care Medicine.

The quality of care in CCM, and all of its subdivisions, must respond to the most sophisticated demands of this decade. Thus, efforts in this area are only rewarding if all the components of CCM are provided and maintained in a well-balanced way. This thesis deals with most of the components of CCM (as described by Safar in 1974). It shows the diversity as well as the complexity of this area of activity. Experience has shown that the best approach for CCM management and operation is a multidisciplinary approach in which the anaesthetist is an essential team member. The anaesthetist has therefore to learn to function as a team member by working in an ICU, effectively cooperating with residents from other specialities. Mutual respect and knowledge of each others skills, expertise and potentials could be a good basis for this common venture.

The anaesthetic resident has to learn to cope with discussions in the ICU, he has to learn how to communicate his ideas to other specialists and he has to learn the level of his restrictions. It is also important to have a compassionate feeling for patients and be interested in them as total human beings. Last but not least, the anaesthetist should develop not only his practical skills but also develop himself as broadly as possible. Modesty and self-discipline may well prove to be necessary virtues for everybody planning to be an effective member of the ICU.

CONCLUSIONS

The goal of this thesis could be achieved by demonstrating the interaction of Critical Care Medicine and Anaesthesia through use of examples and situations drawn from the various components of CCM.

This thesis illustrates, rather than proves, that the combination of simultaneous expertise in both anaesthesia and CCM can be of great advantage to the anaesthetist. In fact, it improves and enriches the expertise and quality of care in both fields. All the propositions contained in this thesis are sustained and supported by the evidence and facts presented in the various articles.

CURRICULUM VITAE

The author was born on September 30th 1947 in Oostburg, Zeeland. He lived there until 1965 then left for boarding school in Leeuwarden where he finished the HBS-B at the Rijks HBS. In September 1967 he started medical training in the Medical Faculty of the Erasmus University in Rotterdam. These studies were completed in 1974 and were followed by military service in the Mathijssen Military Hospital in Utrecht. In 1975 the author began anaesthesia training in Dijkzigt Hospital Rotterdam, under the supervision of Professor dr. D.H.G. Keuskamp. In 1978 the author went to the University Hospital in Groningen to continue further specialisation in Intensive Care Medicine under supervision from Professor dr. D. Langrehr and Professor dr. W. Erdmann. He completed his anaesthesia training in 1979 and remained in Groningen for several years, as a staff member, in the Department of Anaesthesia. Since November 1983 the author has been working as an anaesthetist in the St. Ignatius Hospital in Breda.

HOOFDSTUK VI : NEDERLANDS TALIGE SAMENVATTING VAN HET PROEFSCHRIFT

INLEIDING

De aanleiding voor het schrijven van dit proefschrift is een publicatie van Professor P. Safar (Pittsburgh, USA). Deze wetenschapper is een van de pioniers van Dringende Medische Hulp Verlening (DMHV). Hij publiceerde in 1974, het jaar waarin de auteur van dit proefschrift zijn medische opleiding voltooide, een boek getiteld "Public Health aspects of Critical Care Medicine and Anesthesiology". Dit boek,, met name het eerste hoofdstuk "Health Care Delivery, Problems and Goals : A personal Philosophic Appraisal" beïnvloedde de carrière van de auteur in grote mate. Het bepaalde voor een goed deel de samenstelling van zijn opleiding, zijn visie op en de benadering van het probleem van DMHV. Uiteindelijk bepaalde het artikel van Safar ook het onderwerp en dus de titel van dit proefschrift.

Het doel van dit proefschrift is om aan te tonen, meer dan dat het wil bewijzen, hoe anesthesiologie en DMHV elkaar wederzijds kunnen ondersteunen, dat er raakgebieden te herkennen zijn en hoe over en weer de kwaliteit van de zorg van elkaar afhankelijk kan zijn. Omdat in de spoedeisende geneeskunde van DMHV weining situaties denkbaar zijn voor een rustig en gedegen onderzoek kan de anesthesioloog deze in de operatiekamer nabootsen en zodoende een verbetering aanbrengen in de zorg voor DMHV. Omgekeerd kan een situatie in de anesthesie al jarenlang goed voldoen, terwijl de gebreken van het gehanteerde systeem pas blijken als het wordt toegepast in DMHV. In Nederland is het begrip DMHV (CCM), haar indeling in componenten en de gebruikte terminologie, nog weining algemeen bekend. Daarom zal eerst aandacht besteed worden aan de inhoud van de begrippen en het systeem van DMHV. De auteur houdt zich daarbij aan de inhoud en indeling zoals die ook door de Wereld Gezondheids Organisatie gehanteerd worden.

Dringende Medische Hulp Verlening

DMHV is dat deel van de gezondheidszorg wat zich bezig houdt met het opsporen, de behandeling en de bewaking van patienten met falende vitale functies. Vitale functies zijn bloedsomloop en ademhaling. Het doel van DMHV is om invaliditeit te voorkomen. De anesthesioloog is in dit verband met name geïnteresseerd in het voorkomen van cerebrale beschadiging door zuurstoftekort. Daarnaast gaat zijn zorg uit naar het vermijden van beschadiging van die organen die de vitale functies

binnen hun fysiologische grenzen dienen te houden. Soms kunnen preventieve maatregelen voldoende zijn, maar als de vitale functies (onontbeerlijk voor het verder leven) buiten hun normale grenzen dreigen te raken, moet handelend worden opgetreden. Een bijkomend voordeel is dat een aantal patienten door deze maatregelen uit een schijnbaar dode toestand weer tot leven kunnen worden gewekt. Dat laatste is natuurlijk alleen dan gewenst als de patient met redelijk normale hersenfuncties verder zal kunnen leven.

Naar de locatie wordt het systeem wel in drie fases ingedeeld, te weten : Resuscitatie, Emergency Medical Care (EMC = vervoer van resuscitatie patienten) en Intensive Care Unit (ICU = de afdeling van het ziekenhuis waar de resuscitatie patient verpleegd wordt). Om nu een adequate hulpverlening tot stand te kunnen brengen dient binnen de gezondheidszorg aan een aantal voorwaarden te worden voldaan.

1. De grondbeginselen van resuscitatie door leken dienen gemeengoed te worden.
2. Er moet een adequate werkwijze overeengekomen worden om de organisatie voor DMHV te alarmeren.
3. Liefst onder leiding van een medicus zal de resuscitatie patient (op straat) eerst voor transport gereed gemaakt dienen te worden.
4. De ambulance dient geschikt te zijn voor het vervoer van de meest ernstig zieke patienten.
5. Poliklinieken moeten 24 uur per dag, 365 dagen per jaar deze patienten te kunnen opvangen met gelijke kwaliteit.
6. De patient moet daarna door hetzelfde team volledig verder behandeld kunnen worden.
7. Preventieve maatregelen, onderzoek van het systeem van DMHV en onderwijs aan alle groepen die in DMHV werkzaam zijn, vormen de taken voor het medische team dat het systeem van DMHV moet besturen.

Resuscitatie

Resuscitatie is een symptomatische behandeling van falende vitale functies. Zij is er op gericht deze functies zo nodig op kunstmatige wijze binnén fysiologische grenzen te houden of te brengen.Resuscitatie door leken, die een basiscursus resuscitatie hebben gehad is de eerste fase van DMHV. Bewusteloosheid wordt vastgesteld door aanspreken of

aanraken. Daarna wordt snel begonnen met het vrij maken van de ademweg. Er wordt gekeken of de patient nog ademt. Zo niet dan wordt snel tweemaal mond op mond beademd. De pols wordt gevoeld en bij afwezigheid van polsslag wordt direct met hartmassage begonnen. Het systeem van DMHV dient te worden gewaarschuwd. De behandeling gaat door tot professionele hulpkrachten zijn aangekomen. Deze hulpkrachten (liefst vergezeld van een arts) zullen met eenvoudige hulpmiddelen de behandeling overnemen.

Emergency Medical Care

EMC is het begeleiden van een patient met falende vitale functies door een team (onder leiding van een medicus of eventueel een speciaal getrainde vepleegkundige) van de plaats van het incident tot in het ziekenhuis. De taak van het team is het voorbereiden van de patient op het vervoer, het vervoer zelf en de opvang in de poliklinische voorziening van een ziekenhuis. Daar het om zeer ernstig zieke patienten gaat die tot de moeilijkste ziektegevallen gerekend kunnen worden verdient het aanbeveling dat een medicus deel uit maak van het behandelende EMC team.

Intensive Care

Intensive Care Unit (ICU) is het laatste station in de reeks van voorzieningen van DMHV. Het is de verpleegafdeling waar de patienten met falende vitale functies worden opgenomen totdat ze zelf hun vitale functies binnen fysiologische grenzen kunnen houden. Zodra de vitale functies niet meer ondersteund behoeven te worden gaat de patient naar een conservatieve vepleegafdeling. De bemanning van de Intensive Care Unit houdt tevens de resultaten bij van het hele systeem van DMHV voor een bepaalde regio. Zij onderwijst, bestuurt en beheert het hele pakket van maatregelen in oveleg met de betrokkenen. Voorts bestudeert de ICU bemanning nieuwe technieken, materialen, middelen en medicamenten. Deze taak dient uit te gaan van de ICU omdat deze de gehele lijn van voorzieningen kan overzien. De definitieve behandeling van de patienten van DMHV vindt namelijk steeds op de ICU plaats.

Anesthesie

Anesthesie is het medische specialisme dat zich bezig houdt met :

1. procedures die de patient behoeden voor pijn of schade gedurende een chirurgische ingreep
2. het ondersteunen van de vitale functies tijdens een chirurgische ingreep of bij andere bronnen van fysieke stress
3. klinische verzorging van de vitale functies bij de bewusteloze patient
4. pijnbestrijding in teamverband
5. resuscitatie binnen en buiten het ziekenhuis
6. beademing van patienten
7. behandeling van vloeistof-, electrolyt- en voedings balansen van patienten die beademd worden.

Omdat in het verleden anesthesisten vaak minder actief waren op het gebied van DMHV konden patienten niet ten volle profijt trekken van de aanwezige ansthesiologische kennis. Dankzij intensivering van het anesthesieonderwijs wordt het nu allengs meer bekend dat anesthesisten zich niet alleen met 'intubatie' en 'in slaap maken' bezighouden. Als de details van de volledige anesthesiologische expertise (1-7 als boven) aan de andere medische specialisten meer bekend worden, is het niet onmogelijk dat anesthesiologie als specialisme in de toekomst nog aanzienlijk aan belang kan winnen.

Het is aangetoond dat opleiding in DMHV voor anesthesisten kan leiden tot een verbetering van de anesthesiologische kwaliteiten. Mede daarom is het onverstandig dat anesthesisten alleen op de operatiekamers werken. In DMHV is nog enorm veel te doen. De mortaliteit is nog relatief hoog en misschien te verlagen door vergrote anesthesiologische inzet. Anesthesisten die werkzaam zijn in DMHV dienen hun anesthesiologische vaardigheden en kennis niet te verwaarlozen. De anesthesiologische vaardigheden en kennis vormen namelijk de basis voor hun functioneren binnen DMHV.

Het proefschrift heeft als basis een dertiental door de auteur gepubliceerde artikelen. Twee van de onderwerpen hadden ook afzonderlijk als uitgangspunt kunnen dienen voor een proefschrift. Enerzijds is daar het deel met de problemen van beademing tijdens het transport van ernstig zieke patienten. De auteur heeft meegewerkt aan de ontwikkeling

van een volledig assortiment van beademingshulpmiddelen. Anderzijds is daar het deel met de problemen van de toxiciteit van het slaapmiddel etomidate. De auteur heeft daarvoor de bijwerkingen opgespoord, nagemeten en geduid. Mede op wens van de promotor werden alle dertien artikelen onder één noemer gebracht. De nadruk is hierdoor komen te liggen op DMHV. De indeling van de hoofdstukken in het proefschrift is gemaakt volgens de hoofdindeling van DMHV zoals die door Safar in 1974 werd voorgesteld.

SAMENVATTINGEN VAN DE ARTIKELEN

HOOFDSTUK II, 1

HET MECHANISME VAN DE VRIJE ADEMWEG BIJ DE BEWUSTELOZE

Het mechanisme van de vrije ademweg werd onderzocht bij spontaan ademende patienten in diepe halotaan narcose. Het openen en sluiten van de luchtweg werd geobserveerd met een flexibele bronchoscoop die naar caudaal gericht was en van achter uit de neus in de richting van de epiglottis keek. Door het achterhoofd van de patient tot verschillende hoogtes van de onderlaag te heffen, werd bestudeerd wat de kleinste hoek van retroflexie van het hoofd was waarbij de ademweg net open was. De invloed van diverse hulpmiddelen voor de vrije-ademweg werd gemeten. Om het mechanisme vast te stellen wat noodzakelijk is voor het in stand houden of voor het tot stand brengen van een vrije ademweg, werden kadaver studies gedaan van het bovenste deel van de luchtwegen.

De resultaten duiden erop dat de epiglottis de luchtweg afsluit ter hoogte van de hypopharynx. De tong is zelden de oorzaak van een afgesloten luchtweg bij de bewusteloze patient. Hulpmiddelen voor het tot stand brengen van een vrije ademweg hoeven slechts op bijzondere indicatie gebruikt te worden.

HOOFDSTUK II, 2

GECONTROLEERDE TOEDIENING VAN ZUURSTOF MET ZELFVULLENDE RESUSCITATIE BALLONNEN.

Resuscitatie ballonnen werden oorspronkelijke ontworpen voor Dringende Medische Hulp Verlening om met lucht te kunnen beademen. Onder omstandigheden waar zuurstof beschikbaar is moet daar ook gebruik van gemaakt worden. Het probleem van de zuurstof toediening met resuscitatie ballonnen werd nooit geheel naar wens opgelost. Daarom werd een nieuw systeem ontworpen waardoor een stabiele zuurstoffractie kon worden toegediend met resuscitatie ballonnen.

De stabiele zuurstoffractie (FiO2) werd bereikt via een venturi-systeem gekoppeld aan de inlaatklep van de resucitatie ballon. De FiO2's werden getest voor waarden van : 0.24, 0.30, 0.40 and 0.50. Met het nieuwe systeem kon worden bewezen dat het mogelijk is om de patient een stabiele zuurstoffractie te leveren.

PROTOTYPE VAN EEN LUCHTINLAAT VOOR RESUSCITATIE BALLONNEN

Half-automatische resuscitatie ballonnen werden ontworpen voor beademing met lucht. Mogelijkheden om de beademingslucht met zuurstof te verrijken werden al snel toegepast, maar voldeden niet aan de gestelde eisen voor extra-murale Dringende Medische Hulp Verlening. Met name een stabiele zuurstofconcentratie van de inademingslucht en een laag zuurstof verbruik behoorden niet tot de verworvenheden.

In dit artikel wordt het proto-type van een inlaatklep voor resuscitatie ballonnen beschreven welke in de bovenstaande omissies voorziet. Met dit systeem is het mogelijk een stabiele zuurstof concentratie toe te dienen aan een patient. De FiO_2 is onafhankelijk van het minuut volume wat toegediend wordt. Daarnaast is het mogelijk om de consumptie van medische zuurstof tot een minimum te reduceren door gebruik te maken van down-flow-demand valve.

Dit type ballon kan overal gebruikt worden, de veiligheid van de patient is gegarandeerd en de prijs hoeft niet hoog te zijn. De verrijking met zuurstof kan gebeuren zolang de voorraad strekt. Is de zuurstof voorraad op, dan kan de beademing worden voortgezet zonder de ballon te veranderen. In zo'n geval wordt alleen buitenlucht toegediend.

HOOFDSTUK III, 1

EEN PEEP KLEP VOOR 0 tot 20 cm H20

Positieve Eind Expiratoire druk (PEEP) beademing is een waardevolle methode in de moderne zorg voor de Intensive Care patient. Het is echter dikwijls nodig om een patient van de beademingsmachine te ontkoppelen voor routine fysiotherapie, bij bijzondere onderzoeken en voor transport. Draagbare beademings machines of half-automatische resuscitatie ballonnen worden tijdens deze periodes gebruikt. Teneinde de expiratoire druk op de therapeutisch gewenste waarde te houden is het noodzakelijk te beschikken over een eenvoudige PEEP klep. Deze klep dient van gering gewicht te zijn, klein van omvang, gemakkelijk te gebruiken, stabiel en goedkoop.

AMBU (Denemarken) heeft een dergelijke PEEP klep ontwikkeld die past op de éénrichting kleppen voor volwassen en voor kinderen. De laatste ontwikkeling betref een groene PVC klep van het veertype met een drukwaarde van 0 tot 20 cm H20. Wij onderzochten deze klep in het laboratorium bij verschillende debieten, temperaturen, vochtigheidsgraden en posities. In de kliniek werd de klep gebruikt onder verschillende omstandigheden. De conclusie luidde dat de AMBU PEEP klep accuraat was, eenvoudig te bedienen, met een stabiele werking welke aan alle eisen voor dringende medische hulpverlening tegemoet kon komen.

HOOFDSTUK III, 2

MECHANISCHE VENTILATOREN VOOR EMERGENCY MEDICAL CARE OP BASIS VAN EEN RESUSCITATOR BALLON

Het bleek mogelijk om een beademingsmachine te maken door de onderdelen van een half-automatische resuscitatie ballon te combineren met een magnetische klep. Deze beademingsmachines bleken in de praktijk goed te voldoen bij het beademen van intensive care patienten in het ziekenhuis, tijdens het vervoer er naar toe, of bij onderzoeken buiten de ICU. De beademingsmachines zijn echter ook toepasbaar in extramurale situaties voor alle categorieen patienten.

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De beademingsmachine kan bediend worden door zowel medisch als door paramedisch personeel. Het gebruik van een dergelijke machine moet dan echter wel geleerd worden. Dat kan gebeuren tijdens het normale chirurgische programma, op de operatiekamer. De beademingsmachine blijkt goedkoop en betrouwbaar, zij heeft een stabiel prestatievermogen, zij is robuust en veilig in het gebruik. De meer geavanceerde beademingstechnieken die met dit apparaat mogelijk zijn, maken het gebruik van ademhalingsbewaking noodzakelijk. Het werkingsmechanisme en de plaatsing van de manometer en de volumemeter worden in dit artikel besproken.

HOOFDSTUK III, 3

DE INVLOED VAN VERSCHILLENDE HEPARINE OPLOSSINGEN OP DE BLOEDGAS ANALYSE EN ANDERE BIOCHEMISCHE TESTS DIE GEMETEN WERDEN IN PLASMA

Bloedgas analyse bij volwassenen wordt vaak verricht in grote monsters. In de pediatrie is het echter noodzakelijk om kleine monsters te nemen. Hierdoor treedt, als er heparine oplossing aan het monster worden toegevoegd, verdunning en verontreiniging op. Er kunnen valse waarnemingen gedaan worden welke tot schade voor een patient kunnen leiden.

Om één en ander te voorkomen werd een nieuwe heparine oplossing samengesteld welke in dit artikel besproken wordt. Drie types heparine oplossingen werden bestudeerd voor hun effecten op de bloedgas analyse, electrolyten, haemoglobine en totaal eiwit. Bicarbonaat, pCO_2 en pH vertoonden afwijkingen door heparine toevoeging en die veanderingen simuleren een respiratoire compensatie van een metabole acidose. Het haemoglobine en het totaal eiwit werden alleen verdund door de vloeistof. De waarde van andere biochemische tests, die in plasma werden verricht werd vergeleken met bepalingen in serum. Significante veranderingen konden alleen aangetoond worden voor LDH, fosfaat en voor totaal eiwit. De oorzaak hiervoor moet waarschijnlijk worden gezocht in de stolling die optreedt in het serum monster.

HOOFDSTUK IV, 1

SERUMSPIEGELS VAN CORTISOL BIJ MENSEN TIJDENS EEN ETOMIDATE/FENTANYL EN LUCHT NARCOSE VERGELEKEN MET EEN NEUROLEPT ANESTHESIE

Het effect van etomidate/fentanyl en lucht narcose werd vergeleken met de klassieke neurolept anesthesie, voor wat betreft de serum spiegels van cortisol. Gedurende en na een operatie werden zestien patienten, welke een grote vaatoperatie moesten ondergaan, bemonsterd voor cortisol bepalingen. De resultaten lieten een postoperatieve stijging zien voor de neurolept groep. Intra-operatief werden de waarden wel iets kleiner maar daalden niet tot een pathologisch niveau. De dalingen in de etomidate groep waren significant groter en bereikten het niveau waarop klinische verschijnselen van een laag cortisol te verwachten zijn (lager dan 150 nmol l^{-1}). Postoperatief bleven de waarden relatief te laag, zeker als men die vergelijkt met de postoperatieve waarden in de andere groep. Een stimulatie proef met $ACTH^{1-24}$ bleek, zowel tijdens als na de operatie, negatief te zijn in de etomidate groep. Etomidate en fentanyl narcose bleek een verlaging van het serum cortisol ten gevolge te hebben met een blokkade op het niveau van de bijnier zelf.

HOOFDSTUK IV, 2

ETOMIDATE EN ACTH GEINDUCEERDE STEROIDOGENESE IN GEISOLEERDE BIJNIER CELLEN VAN DE RAT

De effecten van het intraveneus inleidingsmiddel etomidate werden bestudeerd op een door ACTH geinduceerde steroïdogenese in vitro, door gebruik te maken van geïsoleerde rattecellen. Als de dosis van etomidate 200 ng l^{-1} bedroeg, dan werd de steroïdogenese, gemeten aan de corticosteron productie, onder stimulatie met 25 pg ACTH, compleet geblokkerd. De gemiddelde etomidate concentratie die 50% inhibitie vertoonde was ongeveer 1.5×10^{-7} M. Dit is in de zelfde orde van grootte als klinische werkzame en toegepaste concentratie.

HOOFDSTUK IV, 3

MODIFICATIE VAN DE CORTICOSTEROID SYNTHESE DOOR ETOMIDATE/FENTANYL EN LUCHT ANESTHESIE

De karakteristiek van de blokkade van de cortisol synthese door een etomidate/fentanyl combinatie werd onderzocht in een groep van zeven patienten tijdens grote vaatoperaties. Cortisol, androsteen-dion, 11-deoxycortisol (compound S) en ACTH concentraties werden gemeten gedurende drie uur peroperatief. In het vierde uur van de operatie werd een $ACTH^{1-24}$ stimulatieproef gedaan en de reactie op de corticosteroïd synthese werd bepaald. ACTH en androsteen-dion vertoonden een stabiele concentratie tijdens de studie, de reactie op $ACTH^{1-24}$ van het androsteen-dion was zwak maar normaal. Compound S en cortisol spiegels daarentegen werden steeds lager en vertoonden geen significante verhoging na het toedienen van $ACTH^{1-24}$.

De resultaten duiden er op dat de infusie van etomidate en fentanyl een blokkade van de corticosteroid synthese kan veroorzaken. De plaats van de blokkade lijkt gesitueerd op de plaats waar het cholesterol wordt omgezet in pregnenolon.

HOOFDSTUK IV, 4

VEROORZAAKT ETOMIDATE INFUUS EEN ADDISONSE CRISIS?

Het doel van deze studie was om vast te stellen of het mogelijk zou zijn geweest om de bijwerkingen van etomidate in een vroeger stadium van de introductie op de markt te achterhalen door gebruik te maken van de routine gegevens die in de alledaagse anesthesiologische praktijk verzameld werden. De studie werd verricht bij twaalf patienten die opgenomen waren voor een grote vaatoperatie. Het effect van een etomidate/fentanyl en lucht anesthesie werden vergeleken met het effect van een neurolept anesthesie. De arteriële bloeddruk, de centraal veneuse bloeddruk, pols frequentie, de perifere en centrale temperatuur werden continu geregistreerd. Bloedmonsters werden elke twee uur afgenomen voor de bepaling van de arteriële bloedgas waarden, cortisol, natrium, kalium en choloride.

contd

Significante verschillen werden gevonden voor de centraal, perifere temperatuur verschillen, de cumulatieve natrium balans en vocht balans. Door deze verschillen te registeren en te interpreteren had de diagnose 'addisonse crisis' gesteld kunnen worden. Verder werden verschillen gevonden voor vroege en late complicaties na een etomidate infuus en ook in de tijd voor herstel na een dergelijke anesthesie.

HOOFDSTUK IV, 5

DE STEROID RESPONS OP ACTH EN OP ASCORBINEZUUR GEDURENDE EEN INFUSIE VAN ETOMIDATE VOOR ALGEMENE ANESTHESIE

De corticosteroïd synthese gedurende een etomidate/fentanyl narcose werd bepaald in twee groepen patienten tijdens grote vaatoperaties. Bij twee keer vijf patienten werd cortisol, androsteen-dion, compound S en ACTH bepaald gedurende drie uren. In het vierde uur kreeg de ene groep een stimulatie test met synthetisch $ACTH^{1-24}$, de reactie van de bijnier daarop werd bepaald. De andere groep kreeg een intraveneuse bolus met ascorbinezuur toegediend en de reactie van de steroïd synthese werd op gelijke manier verricht.

Het resultaat duidde er op dat etomidate een blokkade van de corticosteroïd synthese veroorzaakt op de plaats waar de hydroxylatie van het cholesterol plaatsvindt. De blokkade van deze reactie is het gevolg van de interactie van de imidazol structuur van het etomidate met cytochrome P-450. Ascorbinezuur is in staat om deze blokkade te breken. Dat wil waarschijnlijk zeggen dat cytochrome P-450 betrokken is bij de stofwisseling van ascorbine zuur en niet direct bij de cortisol synthese.

HOOFDSTUK IV, 6

DE ROL VAN ASCORBINEZUUR IN DE TOXICITEIT VAN ETOMIDATE

Etomidate, een kortwerkend anestheticum, blokkeert de steroïdogenese bij mensen. De vrije imidazol radicaal in etomidate bindt zich aan cytochrome p 450. De ernstige bijwerkingen van etomidate werden alleen gezien bij guineese biggen en bij primaten. Deze species varen voor wat betreft hun ascorbinezuur pool op de dagelijkse opname en op de resynthese van vitamine C. Het is aangetoond dat ascorbinezuur en niet ACTH de serum cortisol concentratie tijdens een etomidate infuus kan verhogen. Vitamine C herstelt zelfs de cortisol/ACTH ratio tot preoperatieve waarden. De conclusie luidt : "etomidate blokkeert het ascorbinezuur metabolisme". Depletie van ascorbinezuur veroorzaakt direkt een inhibitie van de steroïdogenese. Dit is alleen het geval bij primaten en guineese biggen, alle andere species kunnen hun eigen vitamine C maken uit alpha-keto-gulonzuur.

HOOFDSTUK IV, 7

Uit dit artikel en de bijhorende conclusies vloeide een hypothese voort : Fosfaat is een 'second messenger' voor ACTH.

De hypothese wordt ondersteund door bovengemelde feiten en door het feit dat ascorbinezuur spontaan dissocieert bij een hogere pH. Het is dan ook de vraag of fosfaat dat vrijkomt bij de omzetting van ATP naar cAMP de pH in de cel zodanig kan beïnvloeden dat ascorbinezuur dissocieert en of dat een inductie kan geven van de steroïdogenese. Verder onderzoek zal dit moeten aantonen.

DISCUSSIE OVERZICHT

Het was de bedoeling van dit proefschrift om aan te tonen dat anesthesiologie en DMHV elkaar wederzijds kunnen ondersteunen en te illustreren hoe de kwaliteit van de zorg onderling van elkaar afhankelijk kan zijn. In het eerste hoofdstuk van het proefschrift wordt nader ingegaan op de probleemstelling en de indeling van DMHV. Voorts wordt daarin aandacht besteed aan het hoe en waarom van de onderzoeken die door de auteur zijn gedaan. Hoe de onderzoeken geïnitieerd werden en waarom zij in dit proefschrift zijn opgenomen.

Resuscitatie

Het tweede hoofdstuk van dit proefschrift is gewijd aan de resuscitatie fase van DMHV. Het eerste deel betreft het vrijmaken van de ademweg. Het probleem heeft een duidelijk DMHV karakter, het werd echter bestudeerd gedurende kleine chirurgische ingrepen onder narcose. Vervolgens kwam het weer ten goede aan de resuscitatie fase van DMHV. Maar ook voor het onderwijs in de anesthesiologie wordt er dankbaar gebruik van gemaakt.

Het tweede en derde deel van dit hoofdstuk gaan over het verbeteren van beademingsballonnen voor resuscitatie. Het bleek namelijk tot voor kort onmogelijk om met deze ballonnen een constante zuurstof concentratie aan de patient toe te dienen. Het is thans mogelijk om ook buiten het ziekenhuis met een gecontroleerde-, constante FiO2 met de hand te beademen. Het bleek met één bepaalde methode mogelijk om zuurstof te besparen. Dat is in het veld van vitaal belang. Er werd een constructie bedacht die het mogelijk maakt om zowel 100% als 40% zuurstof toe te dienen. Op de operatiekamer werden de instrumenten ontwikkeld, getest, aangepast en weer getest, in DMHV vinden zij hun toepassing.

Emergency Medical Care

In het derde hoofdstuk van het proefschrift wordt het eerste deel gewijd aan een nieuwe voorziening voor transport beademingssystemen. Tot dusver was het schier onmogelijk om tijdens het transport van ernstig zieke patienten PEEP beademing te geven. Geen enkele andere voorziening kan deze beademingsvorm vervangen. Daarom is het essentieel dat PEEP ook tijdens het vervoer gecontinueerd kan worden. Het

onderzoek van de betreffende klep werd volledig op de operatiekamer verricht. Daarna werd de klep op de ICU gebruikt. Weer later, nadat gebleken was dat er geen problemen waren te verwachten, werd hij toegepast in EMC.

In het tweede deel wordt een beademingsautomaat beschreven die geschikt is voor alle patienten, voor alle gebieden van DHMV alsmede voor alle randgebieden. De anesthesiologische beademingsmachines werden geschikt gemaakt voor DHMV. De tests werden gedaan op de operatiekamer tijdens eenvoudige chirurgische ingrepen en de anesthesiologie kon zodoende de kwalitieit van DMHV verbeteren. Door het materiaal te testen in het veld, tijdens actuele patientenzorg werden weer tekortkomingen geconstateerd. Aanpassingen werden bedacht die daarna hun weerslag hadden op delen van reeds in gebruik zijnde anesthesiologische apparatuur. Een bijkomend voordeel van de beschreven EMC beademingsmachines was dat zij uitermate geschikt bleken om er een voorraad mee aan te leggen voor rampen en andere onvoorziene omstandigheden. De beademingsmachine is zeer goedkoop en onderhouds ongevoelig. Daarnaast leent de beademingsmachine zich ook heel goed voor het gebruik in derde-wereld landen. De kwaliteit van de beademing met deze machine kan concurreren met de meeste apparatuur die vandaag de dag als routine op de operatiekamer en op de ICU gebruikt wordt.

Het derde deel van hoofdstuk III betreft een manier om bloed af te nemen voor laboratorium bepalingen. Het oospronkelijke idee was om bloed af te nemen van patienten die op straat geresusciteerd werden. Bij aankomst in het ziekenhuis zouden dan de bepalingen verricht worden. Om ook geïnformeerd te zijn over de arteriële bloedgas status, werd gepoogd om geheparinïseerde monsters af te nemen in een plastic spuit. Dit gaf aanleiding tot heel wat problemen. Deze werden opgelost in het anesthesiologische spoedlaboratorium met bloed van operatie patienten. Achteraf bleken de resultaten van groot belang voor de bemonstering op de ICU, speciaal bij de bemonstering van kleine kinderen. Het onderzoek naar de biochemie van patienten op straat heeft nog steeds niet plaatsgevonden, maar het zou thans, met de resultaten van dit onderzoek, wel mogelijk zijn.

Intensive Care

Het vierde hoofdstuk van dit proefschrift betreft een bijwerking van een geneesmiddel. Dit deel van het proefschrift toont ook zeer duidelijk de interactie van DMHV en Anesthesiologie.

Het slaapmiddel etomidate werd eerst gebruikt als kortwerkend slaapmiddel bij de inleiding van de narcose. Op het eerste gezicht vertoonde dit medicament weinig bijwerkingen. Het zou goed zijn voor oude mensen omdat het de bloedsomloop bijna niet beïnvloedde. Dat was ook de reden om het continu te gaan gebruiken bij langdurig operaties. Er hoefde dan geen lachgas gebruikt te worden. Deze methode werd vooral toegepast in de hartchirurgie en de neurochirurgie. Omdat zij daar goed voldeed werd deze techniek overgenomen op de ICU om patienten aan de beademing langdurig te laten slapen. Hier kwam echter een bijwerking te voorschijn die niet goed geduid kon worden. Het probleem werd teruggespeeld naar de operatiekamer. De anesthesist kreeg de opdracht uit te zoeken wat de bijwerkingen van dit medicament waren. Toen deze anesthesie techniek in een andere context werd gebruikt bleek al heel spoedig dat er een tekort aan bijnierschors hormonen was. Er ontstond dus een 'addisonse crisis' omdat in de hartchirurgie en in de neurochirurgie vaak gebruik werd gemaakt van corticosteroïden werd daar deze bijwerking niet opgemerkt.

Het probleem werd terug gespeeld naar de ICU maar de metingen aldaar konden de resultaten met de lage cortisol spiegels niet echt bevestingen. Bij de bestudering van dit onderwerp in de literatuur bleek dat vitamine C essentieel was voor de steroïd productie. Omdat ascorbinezuur een relatief onschuldig medicament is, werd het in een nieuwe serie operatie patienten getest. Nu bleek dat ascorbinezuur wèl en Adreno-Cortico-Troop Hormoon (ACTH) niet de cortisol spiegel in het serum kon verhogen. Daarmee was de oorzaak van de negatieve bevingdingen op de ICU geduid. De uitkomst van de studie opent een nieuw onderzoeksterrein op het gebied van steroïd synthese. Omdat de auteur in de zelfde periode zowel in de anesthesiologie als in de ICU werkzaam was, kon deze bijwerking ontdekt en geduid worden.

Alle onderwerpen in dit proefschrift hebben gemeen dat zij één der componenten van DMHV tot onderwerp hadden. Alle onderwerpen zijn uitgevoerd of in het laboratorium of op de operatiekamer, door een anesthesist, tijdens het electieve chirurgische programma. Elke keer als er een vooruitgang was geboekt kon direct daarna een praktische test worden uitgevoerd in het gebied van DMHV. He grote voordeel van deze methode was dat er gebruik gemaakt kon worden van de relatief grote fysiologische reserve van de 'gezonde' operatie patient. Bij patienten op de ICU kon vaak geen onderzoek plaatsvinden omdat die patienten te ziek waren. Door een beperking van de reserve door 'multiple organ failure' waren de meeste proefnemingen zelfs onmogelijk uit te voeren binnen DMHV. Bovendien zijn er gebieden van DMHV waar zulke hectische situaties bestaan dat de tijd ontbreekt voor een rustige waarneming. De operatiekamer biedt deze beperking niet. Hoewel er gedurende een operatie vaak een instabiele situatie is welke de meetresultaten kan beïnvloeden, zijn de meeste ingrepen toch zo gestandaardiseerd dat vrijwel steeds van een identieke situatie gesproken kan worden.

Om bovenstaande reden is het dan ook wenselijk dat een anesthesist tegelijkertijd werkzaam is in anesthesiologie en in DMHV. Hij kan de verworvenheden uit de DMHV meenemen in zijn dagelijkse routine van zijn anesthesiologische praktijk. Voorts kan hij zijn ervaring in de anesthesiologie meenemen in het veld van DMHV. Het is mogelijk om een onderzoek dat in DMHV onmogelijk uitgevoerd kan worden op de operatiekamer te doen. Nieuwe methoden kunnen ontwikkeld worden op de operatiekamer en ingebracht worden in DMHV. Daarnaast is het vaak mogelijk om technieken van DMHV toe te passen op ernstig zieke operatie patienten. Patienten uit DMHV kunnen na hun resuscitatie begeleid worden door hetzelfde anesthesiologische team. Dit heeft als voordeel dat er geen onderbreking in de behandeling hoeft te onstaan. Het is echter noodzakelijk dat anesthesisten opgeleid worden in het gebied van DMHV zodat ze als een teamgenoot tussen andere specialisten kunnen functioneren.

LEVENSLOOP

De auteur werd geboren op de 30-ste dag van september in 1947 te Oostburg. Hij woonde daar tot 1965 waarna hij naar kostschool ging in Leeuwarden. Hij behaalde daar ook zijn einddiploma HBS-B aan de Rijks HBS. In september 1967 begon zijn medische opleiding aan de Medische Faculteit van de Erasmus Universiteit te Rotterdam. Deze studie kon in 1974 afgerond worden en werd gevolgd door de militaire dienst in het Mathijssen hospitaal te Utrecht. Daarna werd de opleiding in de anesthesiologie aangevangen in het Dijkzigt Ziekenhuis te Rotterdam onder leiding van Professor dr. D.H.G. Keuskamp in 1975. In 1978 ging de auteur naar Groningen om daar een verdere specialisatie te ondergaan in Intensive Care Medicine onder leiding van Professor dr. D. Langrehr en Professor dr. W. Erdmann. Hij voltooide zijn opleiding in 1979 in Groningen in het instituut voor anesthesiologie. Hij bleef vijf jaar verbonden als staflid aan die afdeling van de universiteit. Sinds 1 november 1983 is hij als anesthesioloog werkzaam in het St. Ignatius Ziekenhuis te Breda.