A NEW APPROACH TO THE ADULT RESPIRATORY DISTRESS SYNDROME: BIOLOGICAL MODELLING AND EARLY IDENTIFICATION OF VENTILATION / PERFUSION INEQUALITIES IN THE MANAGEMENT OF PATIENTS AT RISK

BY

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ABSTRACT

The application of computer modelling and parameter identification techniques are addressed with specific reference to the adult respiratory distress syndrome and the associated mismatch in the ventilation/perfusion distribution. A literature survey and a discussion of related physiology serve as an introduction to the identification of the problem and the philosophy of its solution.

A computer model of the respiratory system is discussed followed by simulation results, including a parameter sensitivity exercise. The application of the model in the clinical environment is demonstrated and the thesis is concluded with the definition of a ventilation/perfusion index that may serve as a useful clinical indicator for both the early identification and management of patients susceptible to the adult respiratory distress syndrome (ARDS).

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

LIST OF VARIABLES AND UNITS

Variable	Description	Units
α	solubility of oxygen in blood	ml O_2/100 ml - mmHg
a/APO_2	arterial/alveolar oxygen tension ratio.	ratio
$CaCO_2$	arterial carbon dioxide content (compartment i)	ml CO_2/100 ml blood
CaG	arterial gas content	ml N_2/100 ml blood
CaN_2	arterial nitrogen content (compartment i)	ml N_2/100 ml blood
$Ca_{ID}CO_2$	ideal arterial carbon dioxide content	ml CO_2/100 ml blood
$Ca_{ID}N_2$	ideal arterial nitrogen content	ml N_2/100 ml blood
$Ca_{ID}O_2$	ideal arterial oxygen content	ml O_2/100 ml blood
CaO_2	arterial oxygen content (compartment i)	ml O_2/100 ml blood
$C\text{-}CO_2$	carbon dioxide blood content	ml CO_2/100 ml blood
Cd	dynamic compliance	ml/cm H_2O
C-G	gas content in blood	ml gas/100 ml blood
$C_{ID}G$	ideal blood gas content	ml gas/100 ml blood
$C\text{-}N_2$	blood nitrogen content	ml N_2/100 ml blood
CO	cardiac output	l/min
$C\text{-}O_2$	blood oxygen content	ml O_2/100 ml blood
Cs	static compliance	ml/cm H_2O
$C_{\bar{v}}CO_2$	mixed venous carbon dioxide content (compartment i)	ml CO_2/100 ml blood
$C_{\bar{v}}G$	mixed venous gas content	ml gas/100 ml blood
$C_{\bar{v}}N_2$	mixed venous nitrogen content	ml N_2/100 ml blood
$C_{\bar{v}}O_2$	mixed venous oxygen content	ml O_2/100 ml blood
D	diffusion constant	l/min - m - mmHg
δ	Staverman reflection coefficient	unit
DP_{50}	amount by which the P_{50} (at 37°C; pH = 7,4; PCO_2 = 40 mmHg) of the subject's blood exceeds the standard of 26,8 mmHg.	mmHg

Variable	Description	Units
F_ACO_2	fraction of alveolar carbon dioxide concentration (compartment i)	fraction
F_AG	fraction of alveolar gas concentration	fraction
F_AN_2	fraction of alveolar nitrogen concentration (compartment i)	fraction
F_AO_2	fraction of alveolar oxygen concentration (compartment i)	fraction
F_G	volumetric fraction of gas	fraction
F_ICO_2	fraction of inspired carbon dioxide concentration	fraction
F_IG	fraction of inspired gas concentration	fraction
F_IN_2	fraction of inspired nitrogen concentration	fraction
F_IO_2	fraction of inspired oxygen concentration	fraction
FRC	functional residual capacity	l
Πc	capillary oncotic pressure	mmHg
Πi	interstitial oncotic pressure	mmHg
HB	haemoglobin concentration	g/100 ml blood
HBa	arterial haemoglobin concentration	g/100 ml blood
H/blood	percentage of total pulmonary capillary perfusion to the high V_A/Q region	%
HBv	venous haemoglobin concentration	g/100 ml blood
HCO_3	bicarbonate concentration	nM/l
HCRIT	haematocrit	%
$HCRIT_a$	arterial haematocrit	%
$HCRIT_v$	venous haematocrit	%
JV	net volume (fluid) flow	l/min
KF	filtration coefficient	l/min - mmHg
L/blood	percentage of total pulmonary capillary perfusion to the low V_A/Q region.	%

Variable	Description	Units
low $\dot{V}_A/\dot{Q}$	the mean $\dot{V}_A/\dot{Q}$ ratio of the mode with the lesser mean in a bimodal ventilation/perfusion distribution.	ratio
$\bar{u}$	log mean flow/unit volume	1/min - 1
$P(A-a)O_2$	alveolar - arterial oxygen tension difference	mmHg
P_ACO_2	alveolar carbon dioxide partial pressure	mmHg
$PaCO_2$	arterial carbon dioxide partial pressure	mmHg
$PaCO_2$	arterial carbon dioxide partial pressure (compartment i)	mmHg
P_AG	alveolar gas partial pressure	mmHg
PaN_2	arterial nitrogen partial pressure	mmHg
PaN_{2_i}	arterial nitrogen partial pressure (compartmenti)	mmHg
P_AN_2	alveolar nitrogen partial pressure	mmHg
P_AO_2	alveolar oxygen partial pressure	mmHg
PaO_2	arterial oxygen partial pressure	mmHg
PaO_2	arterial oxygen partial pressure (compartment i)	mmHg
PB	barometric pressure (atmospheric)	mmHg
Pc	pulmonary microvascular pressure	mmHg
PCO_2	carbon dioxide partial pressure	mmHg
PEEP	positive end expiratory pressure	cmH_2O
P_{EF}	effective inspired gas pressure	mmHg
P_g	gas partial pressure	mmHg
pH	acid base indicator	unit
P_{H_2O}	vapour pressure at body temperature	mmHg
P_i	interstitial pressure	mmHg
$P_{ID}CO_2$	ideal carbon dioxide partial pressure	mmHg
PN_2	nitrogen partial pressure	mmHg

Variable	Description	Units
PO_2	oxygen partial pressure	mmHg
$PO_{2_{VIRT}}$	virtual oxygen partial pressure	mmHg
$P_{\bar{v}}CO_2$	mixed venous carbon dioxide partial pressure	mmHg
$P_{\bar{v}}N_2$	mixed venous nitrogen partial pressure	mmHg
$P_{\bar{v}}O_2$	mixed venous oxygen partial pressure	mmHg
$\dot{Q}$	total pulmonary capillary perfusion	l/min
$\dot{Q}i$	pulmonary capillary perfusion (compartment i)	l/min
$\dot{Q}sp/\dot{Q}t$	physiological shunt	%
$\dot{Q}t$	venous return	l/min
Re	Reynolds number	unit
RR	respiration rate	breaths/minute
RV	residual volume	l
σ	log standard deviation of flow/unit volume	unit
SO_2	haemoglobin oxygen saturation	%
SOL_{CO_2}	solubility of carbon dioxide in blood	ml O_2/100 ml blood - mmHg
SOL_{N_2}	solubility of nitrogen in blood	ml N_2/100 ml blood - mmHg
SOL_{O_2}	solubility of oxygen in blood	ml O_2/100 ml blood - mmHg
Temp	blood temperature	^oC
TLC	total lung capacity	l
$\dot{V}_A$	alveolar ventilation	l/min
$\dot{V}_{AI}$	total inspired alveolar ventilation	l/min
$\dot{V}_{AI_i}$	total inspired alveolar ventilation for compartment i	l/min
VC	vital capacity	l
$\dot{V}CO_2$	carbon dioxide output	l/min

Variable	Description	Units
V_D	anatomical dead space	%
V_{DA}	alveolar dead space	%
V_{DS}	physiological dead space	%
$\dot{V}N_2$	nitrogen exchange in the lung	l/min
$\dot{V}O_2$	oxygen consumption (supply)	l/min
V_T	tidal volume	l
$\dot{V}_T$	total ventilation (minute volume)	l/min
Xi	log flow/unit volume in a compartment	l/min/l
Yi	volume of compartment number i	l

CHAPTER 1
INTRODUCTION

The management of patients suffering from the adult respiratory distress syndrome (ARDS) presents a particularly difficult problem, as far as the assessment of the haemodynamic status and underlying patho-physiology are concerned. Patients susceptible to ARDS often present with acceptable blood gas measurements (a primary diagnostic aid in ARDS) and then suddenly (over as short a period as two hours), deteriorate to dangerously low blood oxygen tension levels; these patients then have to receive emergency treatment (i.e. ventilator and volumetric therapy) with concomitant risks.

The multiplicity of interrelated physiological variables involved (all affecting the status of the patient to a lesser or greater extent) are often confusing and could even be misleading in the process of clinical decision-making. Conventional methods of assessing patients sometimes prove to be inadequate, since these methods do not take into account that the syndrome is a complex interplay amongst several multivariate physiological variables - this is left to the good judgement of the experienced clinician.

The concept of systems physiology (i.e. the interrelating of a multitude of interdependent physiological variables) is already well established, especially in those fields where fundamental research has been undertaken. Systems analysis, applied to physiological processes, emphasises the importance of the interdependency between variables and their relation to each other; it therefore analyses the system as a whole, rather than paying attention to a few important, but isolated, variables.

Modelled on a computer, the processes are translated into a mathematical model of the preferred level of sophistication. Supplied with the necessary input variables, the model can simulate and actually predict various clinical conditions in the patient. The application of computer modelling to the actual process of clinical decision-making is, however, still a research modality and not readily applied; it can probably be ascribed to the complexity of most real life clinical situations. It is the

objective of this thesis to demonstrate how computer modelling may be applied to the management of patients susceptible to, and suffering from, ARDS.

The background respiratory physiology and patho-physiology of the syndrome is discussed, followed by the philosophy of systems physiology and computer modelling. The development of a computer model (based on equations used previously by another researcher) is explained, followed by the simulation of hypothetical conditions in the patient. It is then demonstrated how the model could be used as an aid in assessing the status of the patient.

The thesis is concluded with the extraction and definition of a diagnostic index, based on the simulation results produced by the model, which can be applied with relative ease to identify patients susceptible to the ARDS syndrome or any other patient suffering from ventilation/perfusion distribution abnormalities.

The thesis is aimed at both the engineering and medical professions, since it incorporates aspects from both these disciplines. It has the unfortunate disadvantage though that the reader may find some sections rather trivial and others lacking the necessary explanation, depending in which profession he received his training. It is nevertheless believed that although the concepts presented transcend the respective disciplines, it will be of benefit to both and may, in future, lead to closer co-operation and mutual understanding between the two professions.

CHAPTER 2
LITERATURE SURVEY

2.1 INTRODUCTION

The adult respiratory distress syndrome (ARDS) was first described as a clinical syndrome in 1967 and since then extensive research has been undertaken worldwide as evidenced by literature. This survey is biased towards those articles of a mathematical or quantitative nature, particularly those emphasizing the role of measurable physiological variables and their interrelationships pertaining to the cardio-respiratory system.

An historical perspective of ARDS was sketched in a recent review by Petty (1982) who is considered to be an expert on ARDS. ARDS was first described as a clinical syndrome by Ashbough et al. (1967). The pathological picture was almost identical to the infantile respiratory distress syndrome and was one of the major reasons why the term adult respiratory distress syndrome (ARDS) was suggested by Petty and Ashbough (1971).

Despite the fact that ARDS was described several years ago, neither the mechanism nor an established marker of the syndrome is known. The adult respiratory distress syndrome is the final common pathway of a variety of apparently unrelated but massive insults to the lung.

Petty and Fowler (1982) defined the criteria for diagnosis (which should be followed closely to prevent confusion with other acute respiratory diseases) and general principles of management, emphasizing the fact that no firmly established mechanism or common factor has been established as the common pathway. Although extensive work has been done, to date the solution, if any, is still evading us, as will be discussed in this review.

2.2 PATHOPHYSIOLOGY

2.2.1 General: The mechanism and consequences of pulmonary oedema were evaluated by Ayres (1982), who distinguished between the syndromes of cardiac lung, shock lung (ARDS) and elaborated the ventilatory principles of

shock lung. The cardiac lung; increased lung water due to left ventricular (LV) malfunction, is primarily related to an increase in LA hydrostatic back-pressure and can be considered a reflection of diffuse interstitial and alveolar transudation. The Shock lung syndrome is an example of interstitial and alveolar exudation, primarily due to changes in osmotic pressure and capillary permeability and occurs with normal left atrial (LA) pressure. In an experimental study, Lamy et al. (1976) classified patients on the basis of physiological criteria and correlated them with open lung biopsies and autopsy material. This experimental study is unique and provides useful information as regards lung pathology. Patients were divided into three groups depending on the arterial oxygen partial pressure (PaO_2) and response to venilatory therapy. They demonstrated that interstitial fibrosis is not necessarily progressive, may possibly be reversible and that the point between reversibility and irreversibility is unknown; one important aetiological factor may be oxygen (O_2) exposure at high concentration.

It is generally accepted that surfactant plays a key role in the biochemical pathophysiology of the disease; its relation to lung dynamics has been reviewed in greater detail under a subsequent heading.

A definite correlation between surfactant and alveolar permeability with subsequent changes in compliance has been demonstrated by Dauberschmidt et al. (1982) in their animal models. The major pathophysiologic mechanism now considered in human ARDS is an increased permeability of the alveolar wall, related to endothelial and epithelial damage. Ideally, treatment should also include pharmacological substances which influence the excretion of phospholipids in the alveolar wall.

The conversion of angiotensin is one of the major endothelial functions. It therefore seems likely that this function could be impaired in ARDS, so that the activity of angiotensin converting enzyme (ACE) could be an index of the extent of endothelial damage. In a recent report on its diagnostic significance in pulmonary disease (Hollinger, 1983), it appears possible that a lowered serum level of ACE may prove to have clinical significance. Fourier et al. (1983) prospectively studied ACE levels in 36 patients with ARDS and it was found that the variations of ACE levels had no prognostic value except in aseptic ARDS, where lower

levels are associated with a higher mortality.

Lamy et al. (1983) demonstrated the participation of the complement - leukocyte cascade in the increased pulmonary capillary permeability associated with ARDS.

2.2.2 Cardio-respiratory disorders: Jardin et al. (1979a) focussed on the pulmonary and systemic haemodynamic disorders in ARDS. Their measurements pointed out that pulmonary hypertension is a usual finding in ARDS and there is an associated increase in patients who died. They suggested the hypovolemia should be corrected despite the presence of pulmonary oedema.

More recently biventricular function was examined by Sibbald et al. (1983) in patients suffering from ARDS; the complex interrelationship between the various cardiac ejection fractions and arterial pressures were analysed by a combination of invasively determined pressures and concomitant radionuclide angiography.

The complex interplay between right and left ventricular function in ARDS and the effective treatment of the patient require a thorough understanding of the perplexing haemodynamic adjustments to acute illness. Laver et al. (1979) suggested that the ventricles should be viewed as if operating in parallel as well as in series; careful thought should be given when therapy is guided according to the Frank-Starling relationship.

Czer et al. (1980) and Shoemaker et al. (1980) analysed, in a retrospective study on sixty patients with sustained ARDS, the cardio-respiratory factors preceding and following the development of ARDS. They suggested that volume therapy, if at all, should be instituted early in the course of ARDS and therapy should be directed to an appropriate goal, which is not the attainment of normal values but that compensated state which affords the best possible chance of survival. A series of comprehensive measurements and statistical analysis is presented; the repeatability of which is rather doubtful.

2.3 PATIENT MONITORING AND CARDIO-RESPIRATORY MEASUREMENTS

2.3.1 Monitoring: Close monitoring of the patients with ARDS is useful and often essential for diagnostic and therapeutic reasons.

A comprehensive and up-to-date discussion on haemodynamic monitoring techniques is presented by Boysen (1982), describing techniques to measure cardiac output, mixed venous blood and the interdependence of positive-end-expiratory-pressure (PEEP), cardiac output (CO) and pulmonary wedge pressure (PWP). The response to therapy should be monitored continuously so that cardio-pulmonary function can be dynamically optimized.

Respiratory principles and techniques were discussed on a similar basis by Fallat (1982). Lung mechanics and gas exchange parameters are among the most prominent diagnostic aids, facilitating early treatment of the high risk patient and optimization of ventilation procedures.

A more general, although detailed, approach towards patient monitoring is suggested by Bone (1981), stressing the importance of intelligent observation in conjunction with the measurement of various physiological variables. The most important parameters that should be considered are: body weight, urine analysis, radiologic examination, electro-cardiogram (ECG), haematocrit and haemoglobin, arterial blood gases, variables related to gas volume and bedside measurement of lung mechanics.

A study conducted by Covelli et al. (1983) supports the use of the arterial-oxygen-to-inspired-oxygen concentration ratio (PaO_2/F_IO_2) as an accurate reflection of the physiological shunt ($\dot{Q}sp/\dot{Q}t$) in patients with ARDS; it may be used to predict the need for continuous positive airway pressure (CPAP) therapy as well as serve as a guideline for further modifying.

Shoemaker et al. (1979a) evaluated the biological importance of various haemodynamic and oxygen transport variables in post-operative patients. The analysis is based on a series of experiments conducted on post-operative patients in order to establish monitoring goals and quantitative therapeutic indices as guides to therapy (Schoemaker et al., 1979b;

Schoemaker et al., 1979c; Bland et al., 1978). A very interesting approach was followed and justifies future validation of proposed techniques in subsequent research projects.

Computer based patient monitoring will play an ever increasing role in future, providing unlimited possibilities in patient management. Prakash et al. (1982) described such a system with samples of application programs and the possibility for closed-loop control of mechanical ventilation.

2.3.2 Measurements: In order to monitor the patient, measuring equipment in conjunction with specialized transducers is utilized. Like any other form of measurement, these are susceptible to human error and technical limitations.

Pitfalls of Swan-Ganz catheterization (Backhyo et al., 1975; Backhyo et al., 1977), errors in sampling pulmonary arterial blood (Shapiro et al., 1974) and other measurement-related problems are all factors which may influence the final results.

It is unlikely that even under optimal conditions, an accuracy of more than ninety percent will be acquired with the thermodilution technique for measurement of cardiac output (Weil, 1977). Weisel et al. (1975) discussed the theory, technique and experimental validations of thermodilution cardiac output measurements in a review.

In a recent article (Stetz et al, 1982), the reproducibility and accuracy of the thermodilution (TD) method in the clinical setting has been investigated. It was shown that a minimal change of twenty-two percent is required for a single TD measurement to be clinically significant.

The effects of mechanical ventilation on the measurement of CO by TD have been investigated by Snyder and Powner (1982); they suggested the CO is best approximated by the means of values taken at regularly spaced intervals throughout the ventilation cycle.

Interpretation of pulmonary-artery wedge pressure (PAWP) when PEEP is used, has not been resolved (Roy et al., 1977; Geer, 1977; Miller, 1982).

The positioning of the tip of the Swan-Ganz catheter definitely plays a major role in this respect; temporary simultaneous discontinuation of PEEP should be considered as a possibility to solve the dilemma.

2.4 PATIENT MANAGEMENT

2.4.1 General: An integrated approach to the ARDS patient is advocated by Clemmer and Orme (1982), emphasizing the importance of a team approach consisting of specialised groups in order to integrate information into therapeutic decisions which best serve the patient as a whole. Rigid protocols and communication procedures should be established because of the complexity of the illness and the therapies administrated.

Boutros et al. (1977) compiled an algorithm for management of pulmonary complications in burn patients; the basic structure of which could be followed with adaptions in the case of ARDS patients.

Management of patients with septic shock is very difficult when acute respiratory failure is also present, Jardin et al. (1979b) studied the effects of blood volume expansion, dopamine infusion and isoproterenol infusion on blood gases in hypoxemic patients suffering from septic shock. These agents improved systemic oxygen transport although PaO_2 decreased slightly due to an increase in $\dot{Q}sp/\dot{Q}t$.

Bone (1978) evaluated the prolonged effects of diuresis and PEEP administrated throughout the course of respiratory failure. Beneficial effects of treatment with albumin and diuretics were transient and multiple doses were required to sustain the effects; he emphasized the importance of a randomised collaborative study to evaluate treatment protocols in ARDS patients.

Wood and Prewitt (1981) reviewed evidence concerning the interrelationships among pulmonary oedema formation, pulmonary blood flow distribution and how these relationships are altered by ventilator and vaso-active drug therapy.

2.4.2 Ventilatory support: The hypoxemia accompanying ARDS, may be significantly improved with sustained application of a modified form of spontaneous or mechanical ventilation. To date, PEEP in its various forms represents the most effective, but not ideal, means of treatment.

The application of the various ventilatory models and a comprehensive review on PEEP, with its cardiovascular effects, has been presented by Gong (1982). It provides a clear and instructive source of information for anybody interested in ventilation and its potential complications. Although exact mechanisms are not completely understood, it definitely decreases morbidity and mortality in patients who are hypoxemic. Survival appears related more to the maintenance of adequate tissue oxygenation, as manifested by high mixed venous oxygen, than to improved gas exchange, as reflected by an increase in PaO_2 (Springer and Stevens, 1979).

2.4.2.1 Cardiac effects of PEEP: A reduction of cardiac output tends to occur proportionally to increments of PEEP and is generally most marked with PEEP > 10 cmH_2O. However, the magnitude of the effect varies from individual to individual and results from a complex balance among several factors: the status of the cardiovascular system and intravascular volume, the compliance of the lung and the functional residual capacity at the time PEEP is applied.

Despite the widespread use of PEEP in patients with ARDS, the cardiovascular mechanisms that decrease cardiac output are not well understood. Jardin et al. (1981) studied the effects of a stepwise increase in PEEP and found that levels above 10 cmH_2O resulted in a decreased cardiac output mediated by a leftward displacement of the interventricular septum, which restricts left ventricular filling.

Cassidy et al. (1981) suggested that ventilation with increasing levels of PEEP may cause an inhibition of cardiovascular regulatory centres in the central nervous system in addition to the direct mechanical effects, and that the inability to compensate constitutes an important cause of reduced CO.

In an extensive review Pick et al. (1982) favour an impedance to systemic

venous return as the major factor in decreasing CO. Additional direct reduction of left ventricular function at high levels of PEEP is secondary to geometric changes that cause a decrease in compliance. Neural and humoral mechanisms may be operative and endocardial ischaemia at high levels of PEEP may also be a contributing cause of CO depression.

Ellman and Dembin (1982) reported in a study the lack of adverse haemodynamic effects of PEEP. The mean fall of the cardiac index (CI) was only 6% for levels of PEEP up to 20 cmH_2O. They believe it may be due to the avoidance of hypovolemia, limited use of sedative and paralytic drugs and the use of intermittent mandatory ventilation (IMV).

It was shown by Perschau et al. (1979) that PEEP promptly reduces CO during spontaneous ventilation, related to a decrease in pulmonary flow in expiration; this has a very important bearing on CO determined by indicator dilution methods, since a fundamental assumption of these techniques of measuring flow in the circulation is consistency of blood flow.

In a comparative study of the cardio-respiratory effects of continuous positive airway pressure (CPAP) and controlled positive pressure ventilation (CPPV) in ARDS by Simonneau et al. (1982), it was found that PEEP has different haemodynamic effects using these two modes; cardiac output is largely decreased with CPPV, but remains relatively constant when the CPAP or IMV mode is maintained.

2.4.2.2 Optimal PEEP: It is possible to counteract the adverse effects of PEEP on cardiac output with the institution of fluid therapy and inotropic drugs, which suggests the existence of an "optimal" combination between PEEP and haemodynamic status.

Suter et al. (1975) indicated in a study of normovolemic patients suffering from ARDS that maximum oxygen transport (CO X arterial oxygen content) correlated with the greatest total static compliance. They defined "best PEEP" and suggested that in normovolemic patients maximum total static compliance could be used as an indicator for the best gas exchange. (It resulted in settings of approximately 15 cm H_2O.)

Civetta et al. (1975) defined "optimal PEEP" as that value where the intrapulmonary shunt is minimised. Interventions, such as volume expansion and employment of inotropic agents were frequently used to counteract adverse cardiovascular effects. In some patients PEEP levels of up to 35 cm H_2O were employed.

Demers et al. (1977) defined an "optimal PEEP" as that value where the maximum mixed venous oxygen tension ($P_{\bar{v}}O_2$) is reached. In his opinion the oxygen transport does not reveal information about the oxygen demand; whereas $P_{\bar{v}}O_2$ gives a direct indication of tissue oxygenation.

Gallagher et al. (1978) confirmed the definition by Civetta and stressed the fact that if goal-directed therapy (shunt reduction to 15% or elevation of PaO_2/F_IO_2 to 300 with cardio-vascular intervention) is instituted early in the course of disease, levels of higher than 15 cm H_2O are seldomly used.

Venus et al. (1979) determined whether an optimal level of CPAP could be applied as an effective and safe method for treatment. PEEP was increased in conjunction with the infusion of fluid until the cardiovascular system showed signs of depression, at which level it was eventually maintained. They again emphasized the importance of CPAP therapy in the early stages of ARDS.

Walkinshaw and Shoemaker (1980) defined the "optimal PEEP" to occur at a level where the maximum oxygen consumption, $\dot{V}O_2$ = (arterial oxygen content - mixed venous oxygen content) X CI X 10, occurs without a significant increase of the interpulmonary shunt. They found it to be at levels of 10 cm H_2O without volume load, at levels of 15 cm H_2O with volume load (albumin was administered). They suggested that optimal PEEP must be determined in relation to optimal volume, flow and oxygen transport.

Nelson et al. (1982) investigated the effect of PEEP on oxygen consumption ($\dot{V}O_2$) in dogs. They found that $\dot{V}O_2$ does not correlate with changes in lung compliance or shunt fraction and also suggested that increased oxygen extraction comes into play as a compensatory mechanism to sustain $\dot{V}O_2$ as long as possible.

2.4.2.3 High frequency ventilation: The present status of high frequency ventilation (HFV) and future directions of research in this field were evaluated by Gallagher et al. (1982). Controlled studies of HFV and conventional techniques during ARDS are still required before any real answers are forthcoming; accompanied with standardization of delivery systems and a study of the potential detrimental aspects of HFV.

2.5 VENTILATION AND PERFUSION RELATIONSHIPS IN THE LUNG

2.5.1 Introduction: The concept of "ideal" alveolar air and the analysis of ventilation perfusion relationships in the lungs were first introduced by Riley and Cournand (1949). They derived the equations for the respiratory quotients and also the ratio of the alveolar ventilation to alveolar perfusion. A graphical solution to the "ideal alveolar air" equations with the aid of respiratory quotients lines on a PCO_2/PO_2 graph was demonstrated - presently the equations are solved by numerical techniques on the computer; the principles however remained unchanged.

In 1955 Farhi and Rahn investigated the various factors influencing the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) distribution in the lung. He concluded the alveolar-arterial O_2 difference can be attributed to three independent phenomena; diffusion impairment, venous admixture and unequal ventilation-perfusion ratios among the alveoli.

Professors J.B. West and P.D. Wagner, attached to the Department of Medicine at the University of California, are considered to be international authorities on all aspects related to ventilation - perfusion relationships.

A comprehensive and most instructive article was presented by West (1977), discussing the state-of-the-art in ventilation-perfusion relationships. The partial oxygen pressure (PO_2), partial carbon dioxide pressure (PCO_2) and partial nitrogen pressure (PN_2) in any gas-exchanging unit of the lung are uniquely determined by three major factors; the ventilation-perfusion ratio, the composition of inspired gas and the composition of mixed venous blood; illustrating the importance of the $\dot{V}_A/\dot{Q}$ factor.

A new approach towards the study of blood gas exchange in the lung was followed by King and Briscoe (1967); namely the construction of Bohr integral isopleths and ventilation-perfusion ratio isopleths superimposed on the oxygen dissociation curve. Several useful insights on oxygen transfer in the lungs are afforded by the use of these isopleths; it is however a relatively complex procedure and could be confusing if the user is not thoroughly acquainted with the method.

2.5.2 Special Conditions: Evans et al (1974) defined the properties which a gas must have for it to be possible for ventilation-perfusion inequality to enhance pulmonary elimination or uptake; this condition is however not met for any known gas under physiological steady-state conditions. It follows that any mismatching of ventilation or blood flow must reduce pulmonary elimination or uptake of any gas with a linear dissociation curve (carbon dioxide has an almost linear relationship).

Colburn et al. (1974) compared the gas exchange of a lung model with an arbitrary mismatching of blood flow and ventilation to the gas exchange of a homogenous lung with the same flow; it proved to be a function of the solubility of the gas.

The gas exchange behaviour of distributions of ventilation-perfusion ratios is elucidated in a discussion by West et al. (1974); they introduced another approach to gas exchange in the presence of inequality based on a pressure-solubility diagram.

When the inspired ventilation-perfusion ratio of a lung unit is gradually reduced, a point is reached where the expired ventilation falls to zero, such a unit will no longer eliminate gas but may continue gas uptake unless it becomes atelectatic; Dantzker et al. (1975) presented a theoretical analysis of the factors involved under these conditions.

The effect of local pulmonary blood flow control by local alveolar O_2 tension on steady-state overall pulmonary gas exchange was analysed by Grant (1982) with techniques derived from control theory. This approach lends itself to computer simulations pertaining to the ventilation-perfusion distributions in the lung and could add to the actual "physiological credibility" of such a model.

2.5.3 Estimation and evaluation of ventilation-perfusion ratios: A major descriptive problem exists in the presentation of the $\dot{V}_A/\dot{Q}$ distribution; the problem is how to handle properly multiple gas data so as to gain the greatest amount of insight into the properties of $\dot{V}_A/\dot{Q}$ distributions, without overstepping the theoretical limitations inherent in the particular technique and without discarding useful information.

A general approach to the evaluation of $\dot{V}_A/\dot{Q}$ ratios in normal and abnormal lungs was discussed by Wagner in his paper (1977). The theoretical limits and probabilistic descriptions relating to the $\dot{V}_A/\dot{Q}$ distributions were discussed by Evans and Wagner in a subsequent paper (1977), including an illustrative graphical approach.

The estimation of distributions of $\dot{V}_A/\dot{Q}$ ratios (Wagner, 1981) is a numerically complex procedure with inherent limitations and associated "sampling" problems; Wagner is considered to be the world leader on the theoretical implications of the estimation of continuous distributions of $\dot{V}_A/\dot{Q}$ ratios.

2.5.4 Experimental Investigations: Briscoe et al. (1960) assessed the distributions of ventilation within the lungs by a nitrogen washout and washin technique. They noted that when oxygen is breathed the arterial oxygen saturation rises rapidly and when after 15 minutes of O_2 breathing, air is given, the saturation falls slowly.
West et al. (1964) measured in vitro the distribution of blood flow in a dog's lung with Xe^{133}; the distribution was investigated as a function of vascular and alveolar pressures.

Lenfant and Okubo (1968) determined the pulmonary blood flow in healthy subjects and patients suffering from diffuse obstructive pulmonary syndrome based on a method whereby the F_IO_2 was increased and blood gases monitored with short intervals. These data, combined with the distribution function of lung volume determined by lung N_2 washout (Okubo and Lenfant, 1968), led to the construction of the continuous distribution of blood flow and lung volume as a function of $\dot{V}_A/\dot{Q}$.

Wagner (1972) described the multiple inert gas elimination technique, in which the distribution of $\dot{V}_A/\dot{Q}$ could be measured virtually as a

continuous function under steady state conditions. This technique was applied to determine the distribution of $\dot{V}_A/\dot{Q}$ in dogs and a few patients suffering from acute respiratory failure (Wagner et al., 1974).

Dantzker et al. (1979) determined the distribution of ventilation-perfusion ratio by the multiple inert gas elimination technique in sixteen patients with ARDS. In each case the distribution was bimodal; furthermore they concluded the hypoxemia is caused by the presence of shunts or units of very low ratio of ventilation to perfusion.

2.6 GAS EXCHANGE IN THE LUNGS

2.6.1 Introduction: West (1971) studied pulmonary gas exchange in computer models containing series inequality of ventilation; it was found that a lung region which inspires gas from an adjacent region usually has a high alveolar PCO_2 and a grossly impaired CO_2 output; its O_2 uptake is much less affected.

The alveolar/arterial oxygen tension difference $P(A-a)O_2$ is extensively applied as an index of gas exchange; it reflects the effects of the diffusion gradient, ventilation-perfusion imbalance and true shunt. Unfortunately the difference is sensitive to changes in the F_IO_2.

Gilbert (1974) suggested another way of expressing the difference between alveolar and arterial oxygen partial pressures, namely the arterial/alveolar oxygen tension ratio (a/APO_2); it proved to be more stable with changing values of F_IO_2.

Piiper and Scheid (1982) presented models for a comparative functional analysis of gas exchange organs in vertebrates. They followed an interesting "lateral" approach towards a better understanding of the underlying gas exchange principles in biological systems.

2.6.2 Gas transfer in ARDS: The rise in PO_2 in response to graded increases in F_IO_2 in dogs before and after the creation of a shunt was studied by King et al. (1974). They concluded that patients with shock lung do not necessarily need to have shunting and that hypoxemia may be ascribed to

areas with a very low diffusing capacity; a finding which has some very important therapeutic and prognostic implications. It followed out of a discussion held on this article that there might still be some confusion as regards the exact definition of the term "shunt".

The relationship between delivery and uptake of O_2 was evaluated in twenty patients with ARDS by Danek et al. (1980). They concluded that in patients with ARDS there is a direct relationship between delivery of O_2 and uptake of O_2. Changes in $P_{\bar{v}}O_2$ may not reflect changes in O_2 delivery, cardiac output or the adequacy of tissue oxygenation.

Ralph and Robertson (1981) examined the physiologic abnormalities in ARDS gas exchange and how it may be related to the observed pathologic changes. They concluded that increased shunt is the predominant mechanism of arterial hypoxemia; many patients may also have low $\dot{V}_A/\dot{Q}$ regions, although these may not be apparent clinically if a high F_IO_2 is used. A definite pathologic correlate of the regions of low ventilation to perfusion has not been determined; furthermore the pathology could not be predicted by any single physiological test, but the information obtained by altering the F_IO_2 or PEEP level could be used to predict the predominant underlying pathology.

In an extensive review published by Dantzker (1982) the following facts concerning gas exchange in the ARDS emerged :

(a) The acute abnormalities of pulmonary function, in all cases, result from the progressive accumulation of extravascular fluid in the lung.

(b) The progression of events is similar irrespective of the aetiology of the oedema, be it increased hydrostatic pressure or increased capillary permeability.

(c) Flooded alveoli are scattered throughout the lung, with filled alveoli lying adjacent to uninvolved ones.

(d) Hypoxemia of ARDS is primarily due to pulmonary oedema which results in a right to left shunt.

(e) In addition, hypoxemia may be caused by the presence of regions with very low (0,02 - 0,1) ventilation-perfusion ratios as well as the possibility of diffusion abnormality; this has however been ruled out by experiments performed by Dantzker.

They applied the technique of multiple inert gas estimation to evaluate abnormalities of gas exchange and it was found that while units with very low ventilation-perfusion ratios do sometimes exist; no diffusion impairment could be detected.

It followed, from results, that in ARDS, blood flow is distributed mainly to two types of lung units; those normally ventilated and those unventilated. Any diffusion impairment which may have been induced by the pulmonary oedema did not appear to contribute significantly to the development of hypoxemia.

The finding in some patients that a significant rise in PaO_2 may be seen as the F_IO_2 is increased, was explained by intermittent ventilation of some flooded alveoli leading to the presence of lung units with very low but finite $\dot{V}_A/\dot{Q}$ ratios.

Finally, it should be noted that alterations of non-pulmonary variables ($P_{\bar{v}}O_2$, CO, anaemia, increased metabolic rate) can dramatically alter the arterial blood gases; it is possible to misinterpret a fall in PaO_2 due to one of these factors as a worsening of the underlying ARDS.

2.7 LUNG MECHANICS

2.7.1 Surfactant and Compliance: The mechanical properties of the lung, especially the compliance and accompanying surface tensions in the alveoli, are of great relevance in the pathogenesis of ARDS. It is a generally accepted fact that a definite correlation exists between the decrease in lung compliance and the onset of ARDS (Bone, 1976a, 1976b; Petty et al., 1979).

Bone (1976a) introduced a method based on lung compliance for a simple non-invasive determination that assists in the evaluation of acute respiratory failure, it basically involves the evaluation of the pressure-volume curves and associated "shifts" that occur.

In a prospective study by Bone (1976b) of the value of pressure-volume curves in seven patients suffering from acute respiratory failure; the following facts emerged : those conditions associated with predominantly

airway disease altered dynamic compliance measurements, whereas those associated with loss of lung volume generally altered both dynamic and static pressure-volume measurements.

Petty et al. (1977) studied the characteristics of pulmonary surfactant in one patient suffering from ARDS and concluded that definite biochemical changes took place in the surfactant layer, associated with an irreversible loss of surface elasticity. They suggested that the rheologic and kinetic properties of pulmonary surfactant may be more relevant to physiologic function than the absolute value of compliance.

In a subsequent study, Petty et al. (1979) examined lungs from five patients who died with ARDS. The alveoli displayed increased surface compressibility which they considered to be the primary factor contributing to the stiffness of the lungs of ARDS patients.

Massaro et al. (1980) suggested that a physical alteration in surfactant may lead to, or contribute to, the development of some forms of ARDS. They hypothesized that shallow breathing leads to the aggregation of surfactant into a less functional form resulting in increased alveolar surface tension and atelectasis. The increase in surface tension would also contribute to the oedema found in these conditions. This is an interesting hypothesis and surely justifies further experimental investigation.

2.7.2 Pulmonary Oedema: Staub et al. (1967) induced pulmonary oedema in anaesthetized dogs by transfusion of dextran and alloxan, followed by extensive cardio-pulmonary monitoring to ascertain the sequence of fluid accumulation in lungs. They found the mechanisms of oedema in the two groups to be different; fluid appears first in the interstitial connective tissue around the large blood vessels and airways, followed by independent and rapid alveolar filling after the interstitial compartment is well filled.

An extensive review covering the subject of pulmonary oedema was presented by Staub (1974) and is probably the most comprehensive report on this subject.

The possibility that surface tension may effect the hydrostatic transmural pressure of pulmonary vessels and the development of pulmonary oedema was studied by Albert et al. (1979) in anaesthetized dogs. They concluded that increased surface tension favours fluid leakage, presumably because it increases the microvascular transmural pressure.

The Starling equation relates the hydrostatic forces and colloid oncotic pressures to the net volume movements across the semi-permeable capillary membrane. Civetta (1979) discussed the methodology and limitations behind the application of this equation; it is clearly subject to various factors not directly stated in the equation and should, as such, be applied with caution.

It follows that increased alveolar capillary membrane permeability on the one hand and changes in the lung alveolar surfactant on the other seem to be of great importance in the pathogenesis of ARDS. Kuckelt et al. (1981) investigated the validity of a model of ARDS based on repeated pulmonary lavage in LEWE-mini-pigs; from their results a primary damage of surfactant could be identified.

A series of experiments in anaesthetised rabbits were conducted by Egan (1982), suggesting that hyperinflation of the lung alone could produce a protein permeable lung epithelium and accumulation of liquid in the alveolar space; the results were however not conclusive.

Wiener et al. (1983) developed a mathematical model that integrates the various processes that affect fluid and protein transport in the lung. The model is useful in following the course of patients with pulmonary oedema, and could be a valuable addition to existing mathematical gas exchange models.

2.8 PROGNOSIS AND PREDICTION IN PATIENT MANAGEMENT

2.8.1 General: Beneken et al. (1979) conducted a survey to elucidate the state-of-the-art in trend prediction as a basis for optimal therapy, emphasizing quantitative prognostic techniques, the detection and use of trends in the patients state and the use of models in prediction and their possible use for deciding which therapy is optimal for a specific

patient. An extensive list of centres working in these fields, as well as a comprehensive reference list, were included. It serves as a valuable review of the various techniques employed and possible applications to patients suffering from ARDS.

In a series of studies by Schoemaker et al. (1973, 1974a, 1974b, 1977) a quantitative approach was followed towards the early prediction of death and survival in post-operative patients suffering from circulatory shock. They based their analysis on nonparametric analysis and frequency distributions of cardio-respiratory variables, measured in these patients. Usually the objective in therapy of most diseases is to restore normal physiological values; they suggested that the bodily response to injury and illness are compensatory and have survival value, therapeutic goals should rather be directed towards installing cardio-respiratory patterns similar to those seen in previous survivors.

2.8.2 ARDS Patients: Bartlett et al. (1975) suggested a method for retrospective and prospective data collection in ARDS patients, based on a graph of an alveolar-arterial gradient against time - based on this graph he defined a pulmonary insufficiency index which correlated well with mortality in the series being investigated (45 patients were evaluated).

Shimada et al. (1979) selected 14 patients who developed acute hypoxemia and monitored pulmonary physiologic values on a daily basis. The data was correlated with the progress and prognosis of the ARDS patients. They remarked that the method employed by Bartlett et al. (1975) could sometimes be misleading, as it represents intrapulmonary shunting or ventilation-to-perfusion inequality, which are present in the potentially reversible pulmonary pathology of interstitial or alveolar oedema. Combining the alveolar dead space, pulmonary vascular resistance and dynamic compliance with the $P(A-a)O_2$ serves as a more accurate method for prediction of prognosis.

A method whereby the arterial oxygen pressure was measured for values of 40% and 100% F_IO_2 was suggested by Weigelt et al. (1981). By this method eighty-two percent of the 22 patients monitored were identified as being at risk more than 12 hours before the onset of hypoxemia.

A retrospective study was carried out on a group of 50 ARDS patients by Jardin et al. (1982) (article in French). The predictive value of a severity index (derived from arterial and alveolar oxygenation) was tested.

The diagnostic value of different respiratory function tests in the respiratory distress syndrome was investigated by Guillot et al. (1982) (article in French); the majority of the measurements consisted of expiratory flow variables.

Fowler et al. (1983) studied 936 patients over a period of 1 year to identify predispositions and associated risk in ARDS patients. They identified patients who had one or more of eight conditions thought to predispose to respiratory failure. It followed that the highest incidence rates occur after direct pulmonary injury such as aspiration of gastric contents, rising dramatically when more than one predisposing event occurred. This study serves as a valuable measure to select high risk patients for close clinical observation and future research projects.

2.9 MODELLING AND COMPUTER PROGRAMS

2.9.1 Models:

Author	Title	Comments
Petersen (1981)	A survey of applications of modeling to respiration	The true expansion in the application of system analysis to physiology took place after the Second world war; with the largest increase of papers during the last two decades. This paper is an invaluable document discussing the methodology behind modelling as well as the various models specifically for the respiratory system.
West (1969)	Ventilation - Perfusion inequality and overall gas exchange in computer models of the lung	The $\dot{V}_A/\dot{Q}$ distribution is one of the most important issues in the understanding of gas exchange in the lungs. This model lends itself to a thorough investigation of the $\dot{V}_A/\dot{Q}$ distribution, as well as other respiratory related variables, and its effect on gas exchange in the lungs.
Lutchen et al. (1982)	A non-linear model combining pulmonary mechanics and gas concentration dynamics	A multi-compartment model relating pulmonary mechanics and gas concentration dynamics in the lungs.
Barbini (1982)	Non-linear model of the mechanics of breathing applied to the use and design of ventilators	Investigated optimum wave patterns for specific categories of patients on ventilators to optimize gas exchange in the lungs. (An electrical analogue of the mathematical model of the mechanics of breathing was presented.)
Dickinson et al. (1979)	Macpuf - version 79.2	This is a "holistic" computer model developed to simulate overall physiologic and pathologic behaviour in transient and steady states. (Contains only three compartments for $\dot{V}_A/\dot{Q}$ matching.)
Hinds et al. (1982)	Self-instruction and assessment in techniques of intensive care using a computer model of the respiratory system.	Macpuf linked up to a computer-assisted instructional driver and provides an effective instructional tool.

Author	Title	Comments
Voigt et al. (1982)	O_2-CO_2-Diagram and Iso-shunt lines for assessment of pulmonary gas exchange during artificial respiration	The O_2-CO_2 diagram is an invaluable aid in the understanding and interpretation of gas exchange in the lungs. The computer program is based on the O_2-CO_2 diagram, the iso-shunt lines and the arterio-venous acid base state. (Clinical applications are illustrated by two examples.)
Miller & Granger (1982)	A Block diagram, graphical and microcomputer analysis of the O_2 transport system	The O_2 transport system has been formulated on the basis of the conventional three-compartmental model for pulmonary gas exchange. (Steady state mode.) It is valuable as an instructive tool.
Gardner et al. (1982)	Computer-based ICU data acquisition as an aid to clinical decision making	Discusses the application of a computer system to optimize medical care for the acutely ill. The emphasis is placed on data processing and advocates the development of more quantitative medical methods which could be transferred into computer protocols.

2.9.2 Programs and sub-routines:

Kelman & Nunn (1966) Severinghaus (1966) Kelman (1966) Olszowka & Farhi (1968)	A series of digital computer sub-routines developed by the authors for blood gas calculations	Sub-routines for the conversion of gas saturation, gas partial pressures and other biochemical factors related to blood content; for application in computer models of the respiratory system.

Author	Title	Comments
Winslow et al. (1983)	Simulation of continuous blood O_2 equilibrium curve over physiological pH, DPG and PCO_2 range	Nomograms and equations have been developed to estimate the O_2 dissociation curve; this approach is probably more accurate than the equations used by Kelman & Nunn (1966); Kelman (1966).
Kelman (1968)	Computer program for the production of O_2-CO_2 diagrams	This represents the first approach to "computerise" the O_2-CO_2 diagram of Rahn and Fenn in 1955, and is in principle similar to the program suggested by Voigt et al. (1982).
Olszowka & Fahri (1969)	A digital computer program for constructing vent-perf lines	This program starts with a specific $\dot{V}_A/\dot{Q}$ value and proceeds to calculate the corresponding alveolar gas composition.
Siegel et al. (1979)	An improved program to calculate intra-pulmonary shunting	Developed for the TI 59 calculator.
Powles & Jones (1982)	A pocket calculator program for non-invasive assessment of cardio-respiratory function	Developed for the HP 41 calculator and is actually dedicated to the evaluation of physiological variables at rest and during exercise.

CHAPTER 3
RESPIRATION PHYSIOLOGY

A brief introduction to respiration physiology is presented in the following chapter, supplemented with a rather philosophical discussion of systems physiology and its application to respiration.

Respiration physiology is a complex and diverse field, impinging on the fields of circulation and renal physiology. The objective of this discussion is not an in-depth analysis of the relevant physiology; instead elucidation of the most important issues and their interrelationships has been attempted.

3.1 STRUCTURAL APPROACH

This section deals with a structural approach towards respiration physiology, and the discussion is guided by the anatomical layout of the various structures involved in respiration.

Respiration refers to the complete process of ventilation of the alveoli, gas exchange in the lungs, transport of gas towards and from the cells, as well as gas exchange on cellular level. The structures involved are the airways, lungs, heart, blood vessels and the cells.

3.1.1 Functional Anatomy: The gas delivery apparatus consists of a collection of branching ducts, which finally lead into the alveoli; the area where actual gas exchange is effected.

The trachea, which opens into the larynx, divides into two bronchi, which further sub-divide into a system of ducts (transitional zone) leading into the alveolar ducts lined with the alveoli (respiratory zone).

The gas delivery ducts do not partake in the gas exchange process and therefore constitute the so called anatomical dead space. (Approximately 150 ml in the average man of 70 kg.) The concept of an anatomical dead space is of relevance when the actual amount of fresh air reaching the respiratory zone, i.e. the alveolar ducts lined with alveoli, is calculated.

The alveoli resemble minute bubbles divided by the alveolar septa, attached to the alveolar ducts. It is estimated that the respiratory zone consists of approximately 300 million alveoli, with an average diameter of 0,3 mm. In between the alveoli an intricate network of capillaries ensure direct contact of the blood and the alveolar wall; a capillary is actually believed to be comprised of a "sheet of blood" encapsulated between shared alveolar walls and reinforced by pillar-like structures, keeping the walls apart.

Blood supply to the lung capillaries is sustained through the pulmonary artery, which conveys de-oxygenated blood from the right ventricle of the heart; the returning oxygenated blood is conveyed through the four main pulmonary veins to the left atrium of the heart. A diagrammatic representation of the anatomy of the respiratory system is presented in Fig. 3.1, with the numerical values of a respiratory zone model for an average adult in Table 3.1.

3.1.2 Ventilation: Inspiration is the process of gas delivery from the atmosphere to the alveoli; whereas expiration signifies the reverse process. Ventilation refers to a combination of these two processes.

The static volumes involved in the process of breathing (or ventilation) are defined as follows:

Tidal volume (V_T)	:	Normal breathing volume per breath.
Vital capacity (VC)	:	The volume of expired air after a maximal inspiration, followed by a maximal expiration.
Residual volume (RV)	:	The volume of gas that remains in the lungs after a maximal expiration.
Functional residual capacity (FRC)	:	The volume of gas that remains in the lungs after a normal expiration.
Minute volume	:	The total volume leaving the lung each minute.

$$\text{Minute volume} = RR \times V_T \qquad (3.1)$$

RR = Respiration rate

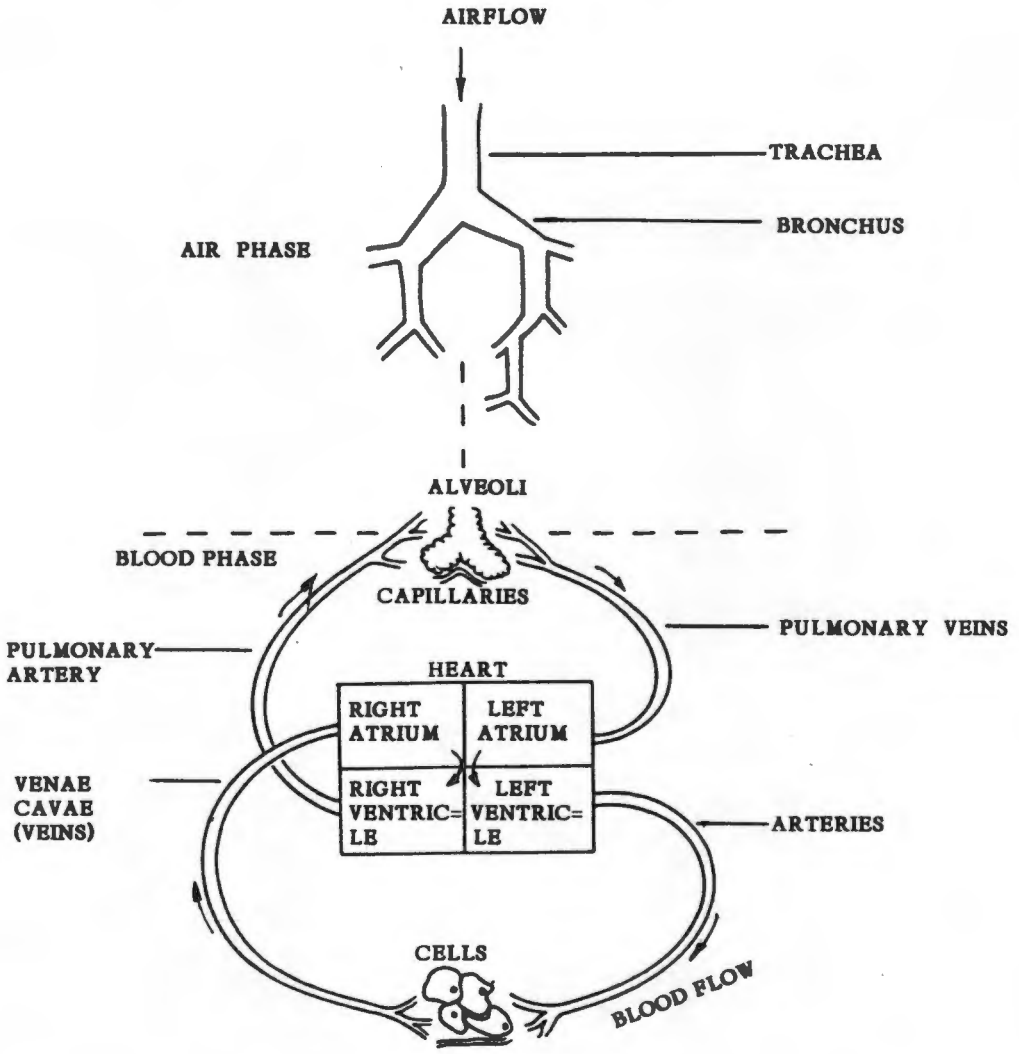


Figure 3.1 Diagrammatic representation of the anatomy of the respiratory system and circulation.

Component	Value
Volume of model lung	4800 ml
Volume of respiratory zone	3150 ml
Volume of capillary network	140 ml
Number of alveoli	$300 \cdot 10^6$
Air-tissue interface	95 m^2
Tissue-blood interface	90 m^2
Radius of alveolus	140 μm
Volume of alveolus	$10.5 \cdot 10^{-6}$ cm^3
Surface of alveolus	$30 \cdot 10^{-4}$ cm^2
Number of capillary segments per alveolus	1800
Capillary blood volume per alveolust	$4.7 \cdot 10^{-7}$ cm^3
Capillary surface per alveolust	$28 \cdot 10^{-4}$ cm^2
Radius of capillary segments	$4 \cdot 10^{-4}$ cm
Mean length of capillary segments	$10.3 \cdot 10^{-4}$ cm

Table 3.1 Numerical values of Respiratory Zone (model for average adult) - from E.R. Weibel (1963). Morphometry of the Human Lung. Academic Press Inc.

The various volumes involved in ventilation are exemplified in Fig. 3.2. The functional residual capacity is analogous to parallel electrical capacitance in the ventilatory system; it damps small and rapid changes in the gas concentration of alveolar air.

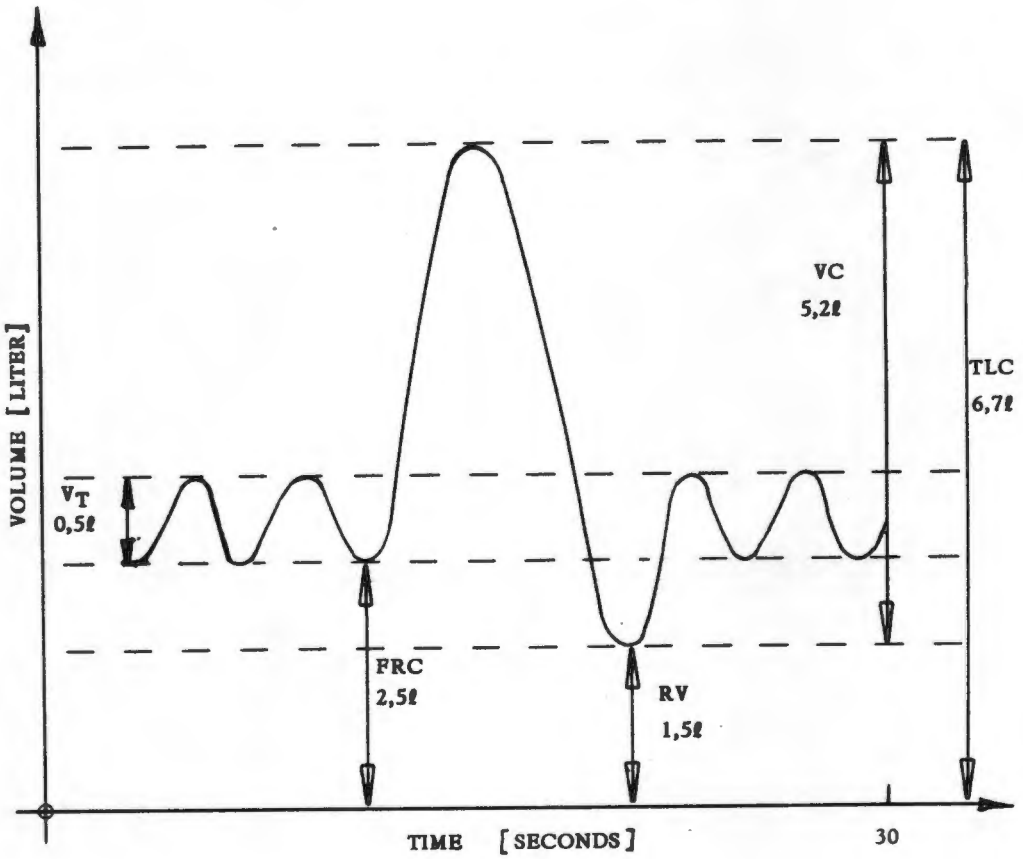


Figure 3.2 Lung volumes with typical values for a healthy young adult male (70 kg).

Alveolar ventilation ($\dot{V}_A$) represents the total amount of new air entering the alveoli each minute. On inspiration, a certain amount of fresh air must fill the airways before reaching the alveoli; this volume signifies the anatomical dead space (V_D). It follows that alveolar ventilation equals:

$$\dot{V}_A = RR.(V_T - V_D) \qquad -(3.2)$$

A typical value would be:

$$\dot{V}_A = 12.(0,5 - 0,15)$$
$$= 4,2 \text{ l/min}$$

The physiological dead space (V_{DS}) represents the total volume of inspired air that does not participate in gas exchange; in normal subjects it nearly equals the anatomical dead space; however, in the case of lung disease it may increase considerably due to abnormalities in the alveoli or capillaries.
Airflow through the airways is a combination between laminar flow (stream lines parallel to the sides of the tubes) and turbulent flow. Whether local flow will be laminar or turbulent depends to a large extent on the Reynolds number (Re).

$$Re = \frac{2.r.v.d.}{N} \qquad -(3.3)$$

r : radius of tube [m]
v : average velocity of medium [ms^{-1}]
d : density of medium [$kg.m^{-3}$]
N : viscosity of medium [Nsm^{-2}]

Turbulence is probable when the Reynolds number exceeds 2000.

Flow resistance (R) for laminar flow equals:

$$R = \frac{8.N.l}{r^4} \qquad -(3.4)$$

l : length of section over which resistance is measured. [m]

Note that if the radius is halved, the resistance increases sixteen-fold; this is of importance in, for instance asthmatic patients where a narrowing of the airways occurs. The airflow in the bronchi is usually a combination of laminar and turbulent profiles. It is furthermore noteworthy that the chief site of airway resistance occurs at the larger airways and not at the narrow alveolar ducts; this is due to the fact that the total cross sectional area of the alveolar ducts by far exceeds that of the larger airways and because Re never exceeds 2 000 in the alveolar ducts. The radius of an alveolar duct is typically 0,1 mm, compared to 0,5 mm for a bronchiole; it follows from equation 3.4 the ratio of resistance to laminar air flow of an alveolar duct compared to a bronchiole is 640 : 1. This implies that the total cross-sectional area of the alveolar ducts must be more than 640 times that of the bronchioli.

Dalton's Law

In a mixture of gases the total pressure is equal to the sum of the pressures exerted by its component gases; the individual gas pressures are referred to as the partial pressures of the components. The partial pressure of a respiratory gas may be calculated as follows:

$$P_G = F_G \cdot P_{EF} \qquad -(3.5)$$

P_G : partial pressure of the gas
F_G : volumetric fraction of the gas present in a unit volume
P_{EF} : effective pressure exerted by the gas mixture

It is important to note that inhaled gas is actually saturated with water vapour (also considered as a gas) in the airways; the maximum partial pressure of water in a wet gas at a given temperature equals the vapour pressure of water at that temperature.
(Vapour pressure at $37^{o}C$ equals 47 mm Hg.)
The total pressure (B_T) exerted by the respiratory gas mixture therefore equals:

$$P_{EF} = P_B - P_{H_2O} \qquad -(3.6)$$

P_B : barometric pressure (atmospheric)
P_{H_2O} : water vapour pressure at a specific temperature

Henry's Law

When a liquid and gas are in equilibrium, the amount of gas in solution is directly proportional to the partial pressure of the gas, provided temperature is constant. This is of relevance in the case of alveolar gas dissolved in capillary blood; it does not, however, account for the respiratory gas that is chemically bound to compounds in the blood.

Fick's Law

The rate of transfer of a gas through a sheet of tissue is proportional to the tissue area and the difference is gas partial pressure between the two sides, and inversely proportional to the tissue thickness.

$$V \propto \frac{A.D.\Delta P}{T} \qquad -(3.7)$$

V	:	gas flow through sheet	[l/min]
D	:	diffusion constant	[l/min-m-mmHg]
A	:	area of sheet	[m^2]
T	:	thickness of sheet	[m]
ΔP	:	pressure difference	[mmHg]

$$D \propto \frac{\text{Solubility}}{\sqrt{\text{molecular weight}}} \qquad -(3.8)$$

The diffusion constant is directly proportional to the solubility of the gas in the medium and inversely proportional to the square root of the molecular weight of the gas. (CO_2 diffuses about 20 times more rapidly than O_2 through the alveolar septa - it does not, however, imply the absence of possible diffusion limitations in the case of CO_2.)

3.1.3 Elastic Properties of the Lung: The combined elastic properties of the individual components constituting the lung and thorax are conveniently described by a pressure - volume curve. The curve is non-linear with a sigmoid shape, it also exhibits hysteresis properties, i.e. the pressure - volume relation is different for the inspiration and expiration cycles. A typical curve is displayed in Fig. 3.3.

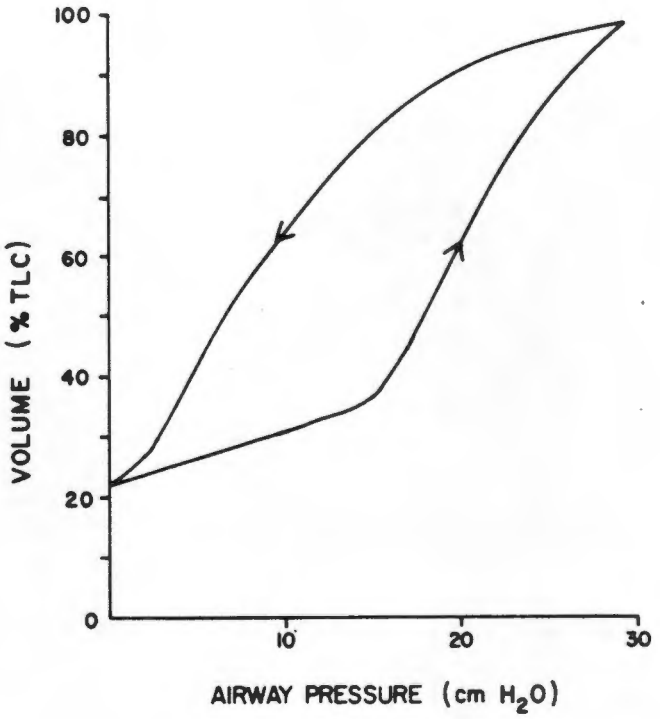


Figure 3.3 Representative static volume-pressure relationship of lung for a cycle from 0 to 30 cm H_2O - from D.H. Glaister et al. (1973). Bulk elastic properties of exised lungs and the effect of a transpulmonary pressure gradient. Resp. Physiol., 17; 347-364.

The slope of the pressure - volume curve, or the volume change per unit pressure change, is known as the compliance. If measured at a specific volume on a pressure - volume curve, it is referred to as the static compliance (Cs):

$$Cs = \frac{\Delta VL}{\Delta PA}\Big|_{VL} \qquad -(3.9)$$

ΔVL : change in lung volume [ml]
ΔPA : change in airway pressure [cm H_2O]

The dynamic compliance (Cd) can be estimated by taking the ratio of the change in lung volume (ΔVL) and the change in airway pressure (ΔPA) at zero airflow conditions:

$$Cd = \frac{\Delta VL}{\Delta PA} \Big| \dot{V} = 0 \qquad -(3.10)$$

It is important to note that the compliance as measured in (3.9) and (3.10) represents either the lumped thoracic and pulmonary compliance, or only that of the lung, depending on which experimental procedure has been followed. Furthermore the reader should realise that during inspiration a negative pressure is generated within the chest cavity by contraction of the respiratory muscles (especially the diaphragm), causing the lung to expand by air flowing from a atmospheric pressure to a lower pressure in the lungs. This is in contrast with the lungs of a patient connected to a ventilator and sealed off from the environment, in which case the lungs are distended by the higher pressure generated within the ventilator and air being forced into the airways, resulting in a raised average pleural pressure.

Alveolar surface tension

One of the factors contributing towards the pressure generated within the lung when inflated, is that of surface tension in the alveolar wall. The fluid lining the alveolar wall generates a tension in the wall, favouring total alveolar collapse. If a spherical shape were assumed for a single alveolus, the pressure generated within the alveolus can be predicted by Laplace's law:

$$\text{Pressure} = \frac{4 \times \text{surface tension}}{\text{alveolar radius}} \qquad -(3.11)$$

It is evident from equation (3.11) that an alveolus with a smaller radius will generate a higher pressure and therefore attempt to inflate other alveoli with a larger radius. According to Laplace's law, the collection of alveoli within the lung is a highly unstable system and would alternately expand and collapse. In practice this does not, however, occur and was one of the observations that lead to the discovery of surfactant.

Pulmonary surfactant is a lipoprotein excreted by cells in the alveolar wall which dramatically reduces the surface tension in the alveolar wall; it also has the effect of making the tension directly dependant on the

alveolar surface area. Stability is not perfect and occasionally alveoli do collapse (atelectasis); a deep breath will, however, normally reinflate collapsed units.

The preceding discussion is a gross simplification of alveolar stability; the factors involved are numerous (mechanical and physiological) and are all, by nature, interrelated.

3.1.4 Transport of respiratory gases

3.1.4.1 Circulation: The pulmonary circulation begins at the main pulmonary artery which receives the mixed venous blood pumped by the right ventricle. It sub-divides until it finally supplies the capillary bed lining the alveolar walls. The oxygenated blood is collected by the small pulmonary veins which eventually unite to form the four pulmonary veins which drain into the left atrium. A major pressure difference exists between the pulmonary and systemic circulation and consequently in the structure of the vessel walls. A comparison of pressures in the two circulatory systems and typical values are displayed in Fig. 3.4.

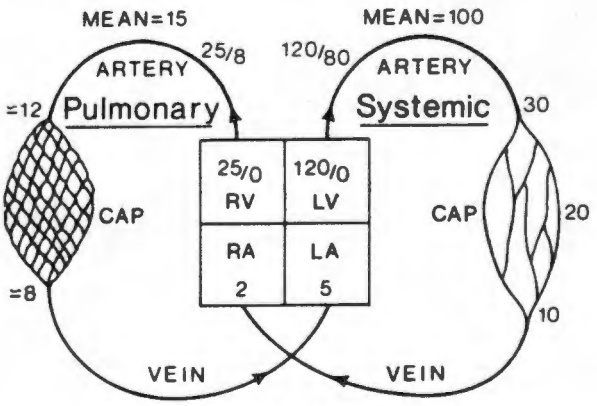


Figure 3.4 Comparison of pressures (mmHg) in the pulmonary and systemic circulations - from J.B. West (1979). Respiratory Physiology. Williams and Wilkins Company; 33

The distribution of blood in the pulmonary capillaries is affected by gravity (change in posture) and active physiological responses causing the capillaries to constrict (i.e. reduction of alveolar PO_2, low blood pH). It is however a highly non-linear response.

Starlings Law

The alveoli containing the respiratory gas, are separated by thin septa (approximately 0,5 um) from the blood in the capillaries; fluid balance between these two units is extremely delicate and in case of pathology the alveoli can easily be flooded with fluid (pulmonary oedema). The net fluid flow can be described by Starling's equation:

$$JV = KF \; [\; (Pc - Pi) - \delta.(\pi c - \pi i) \;] \qquad -(3.12)$$

JV	:	net volume flow	[l/min]
KF	:	filtration coefficient	[l/min-mmHg]
Pc	:	pulmonary microvascular pressure	[mmHg]
Pi	:	interstitial pressure	[mmHg]
δ	:	Staverman reflection coefficient	
πc	:	Capillary oncotic pressure	[mmHg]
πi	:	Interstitial oncotic pressure	[mmHg]

The earliest form of pulmonary oedema is characterised by accumulation of fluid in the interstitial space and is known as interstitial oedema. The practical use of Starling's equation is unfortunately limited, because of our ignorance of many of the variables. Because Starling's law appears so simple, it is common practice to measure a few variables involved, substitute "commonly accepted values" for the unmeasured variables, and create any physiological state to prove a point. It can however be assumed with reasonable certainty that alveolar oedema could at least partially be explained by this equation; especially if accompanied with a change in the Staverman reflection coefficient, related to the permeability of the alveolar wall.

Respiratory gases are transported in the blood, which acts as an intermediate medium between the gas exchange apparatus and the tissue. In fact the prime function of blood is that of transport, not only the

respiratory gases, but also various other substances. It follows logically that blood physiology has evolved in such a way to optimize the transport of O_2 and CO_2.

3.1.4.2 Oxygen transport: A small percentage of O_2 (about 3%) is dissolved in the water of the plasma and cells, according to Henry's law; the remainder of the oxygen is carried in loose chemical combination with haemoglobin in the red blood cells. When the PO_2 is high (as in the pulmonary capillaries) oxygen binds with the haemoglobin, a drop in PO_2, as experienced in the tissue capillaries, causes the oxygen to be released from the haemoglobin.

The relationship between the PO_2 and amount of oxygen bound to the haemoglobin, i.e. the percent saturation of the haemoglobin, is not linear. The exact relationship is conveniently described by the oxygen haemoglobin dissociation curve, it is sigmoidal, the exact shape of which is determined by various blood-chemical factors. A typical oxygen dissociation curve is displayed in Fig. 3.5.

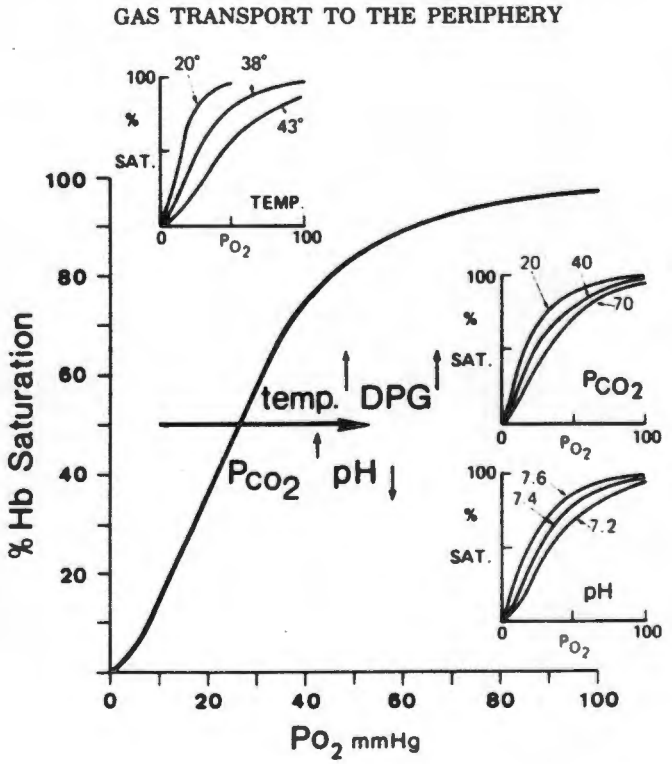


Figure 3.5 Shift of the O_2 dissociation curve by pH, PCO_2 and Temp - from J.B. West (1979). Respiratory Physiology. Williams and Wilkins Company; 73.

Note that the following blood-chemical factors cause the curve to "shift" towards the right.

a. increased hydrogen ion content (decreased pH).
b. increased CO_2 content (Bohr effect).
c. increased temperature.
d. increased 2,3 diphosphoglycerate (DPG); a phosphate compound normally present in blood.

Inherent to the shape of the curve and the factors influencing it, are various physiological advantages and safeguards. The flat shape in the upper region renders the O_2 content less sensitive for PO_2 changes in that region, whereas the steep portion implies that the tissue can withdraw large amounts of O_2 without major changes in capillary PO_2.

The blood of a normal person contains approximately 15 grams of haemoglobin in each 100ml of blood, and each gram of haemoglobin can bind with a maximum of approximately 1,34ml of oxygen when 100% saturated. It follows that 100ml of fully saturated blood contains approximately 20ml of oxygen.

3.1.4.3 Carbon Dioxide Transport: Transport of carbon dioxide in the blood is not as critical as transport of oxygen; it can be transported in far greater quantities than in the case of oxygen. Carbon dioxide has, however, a profound influence on the acid-base balance of the body fluids and its control is therefore just as critical.

An average of 10% CO_2 is transported in the dissolved state, the remainder is carried as plasma bicarbonate (70%) in combination with plasma proteins bound to haemoglobin (20%).

The carbon dioxide dissociation curve (Fig. 3.6) depicts the dependence of the total blood CO_2 content (in all the forms) on the PCO_2. The lower the saturation of Hb with O_2, the larger the CO_2 content for a given PCO_2; this phenomenon is referred to as the Haldane effect.

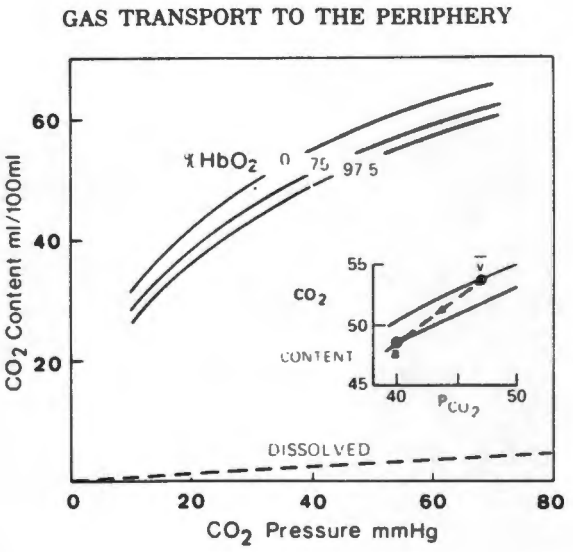


Figure 3.6 CO_2 dissociation curves for blood of different O_2 saturations. Note that oxygenated blood carries less CO_2 for the same PCO_2. The "physiological" curve between arterial and mixed venous blood is also shown - from J.B. West (1979). Respiratory Physiology. Williams and Wilkins Company; 77

3.1.5 Acid-Base Status: The hydrogen ion concentration $[H^+]$ of arterial blood is normally kept very close to 38,9 nM/l corresponding to a pH of 7,41. This normal value is protected by a combination of passive (chemical) and active (physiological) buffering reactions. The respiratory system and kidneys are most important in the case of physiological buffering. The lungs excrete a hundred times as much acid per day compared to the kidneys; it follows that the lungs play a major role in the control of the acid-base balance of the body fluids.

The Henderson-Hasselbach equation defines the relative bicarbonate (HCO_3) and CO_2 ratios to produce a given blood pH:

$$pH = 6,1 + \log \frac{[HCO_3^-]}{0,03.PCO_2} \qquad -(3.13)$$

$[HCO_3^-]$: concentration in nM/l or mEq/l

PCO_2 : mmHg

The bicarbonate concentration is determined chiefly by the kidneys and the PCO_2 by the lung; as long as the ratio $[HCO_3^-]/(PCO_2 \cdot 0,03)$ remains equal to 20:1 the pH will remain at 7,4.

This ratio can be disturbed either by an increase or decrease in $[HCO_3^-]$ or by an increase or decrease in blood PCO_2; each one of these disturbances gives rise to a characteristic acid-base balance.

The Davenport diagram (Fig. 3.7) depicts the relationship between $[HCO_3^-]$ pH and PCO_2 and possible deviations from the norm.

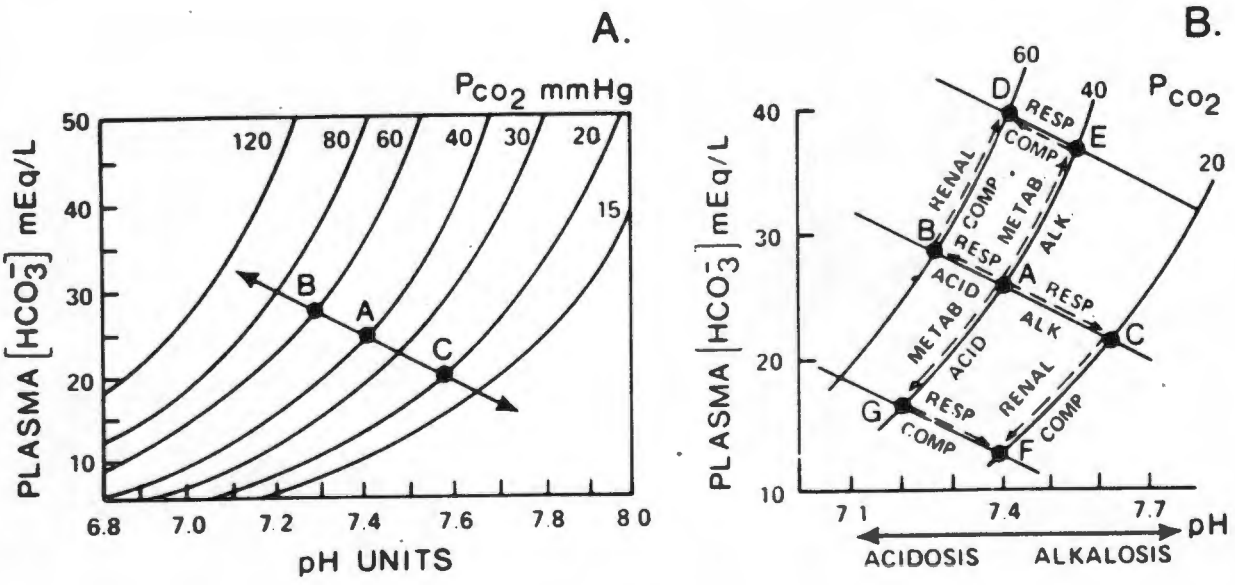


Figure 3.7 Davenport diagram showing the relationships between HCO_3^-, pH and PCO_2. A shows the buffer line BAC. B shows the changes occurring in respiratory and metabolic acidosis and alkalosis - from J.B. West (1979). Respiratory Physiology. Williams and Wilkins Company; 81.

a. Respiratory acidosis: Caused by an increase in PCO_2 and consequently a decrease in pH. (Can be caused by hypoventilation or ventilation-perfusion inequality.)

If this condition persists, the kidneys will respond by conserving HCO_3 and the condition is then referred to as compensated respiratory acidosis. The extent of the renal compensation can be determined from the standard bicarbonate value (plasma bicarbonate when the blood is equilibrated at the normal PCO_2 of 40 mmHg).

Another way of expressing the compensation is by calculating the base excess (BE); i.e. the amount that the plasma $[HCO_3^-]$, measured at a pH of 7,4 exceeds that of the normal value (24 mEq/l).

b. Respiratory Alkalosis: It is caused by a decrease in PCO_2 and an elevation of the pH (may be a result of hyperventilation). Renal compensation occurs as an increased excretion of HCO_3^-, resulting in a negative base excess or base deficit.

c. Metabolic Acidosis: A decrease in the HCO_3^- concentration (due to a primary cause) followed by a decrease in the pH (loss of sodium bicarbonate through diarrhoea could be a cause).

Respiratory compensation occurs as an increase in ventilation which lowers the PCO_2. A base deficit is measured.

d. Metabolic Alkalosis: An increase in $[HCO_3^-]$ due to a primary cause, followed by an increase in the pH. Loss of acid gastric juice (excessive vomiting) may give rise to this condition.

Respiratory compensation may occur by a reduction in alveolar ventilation, raising the PCO_2. A base excess is measured.

Respiratory gas transport is summarized in Fig. 3.8.

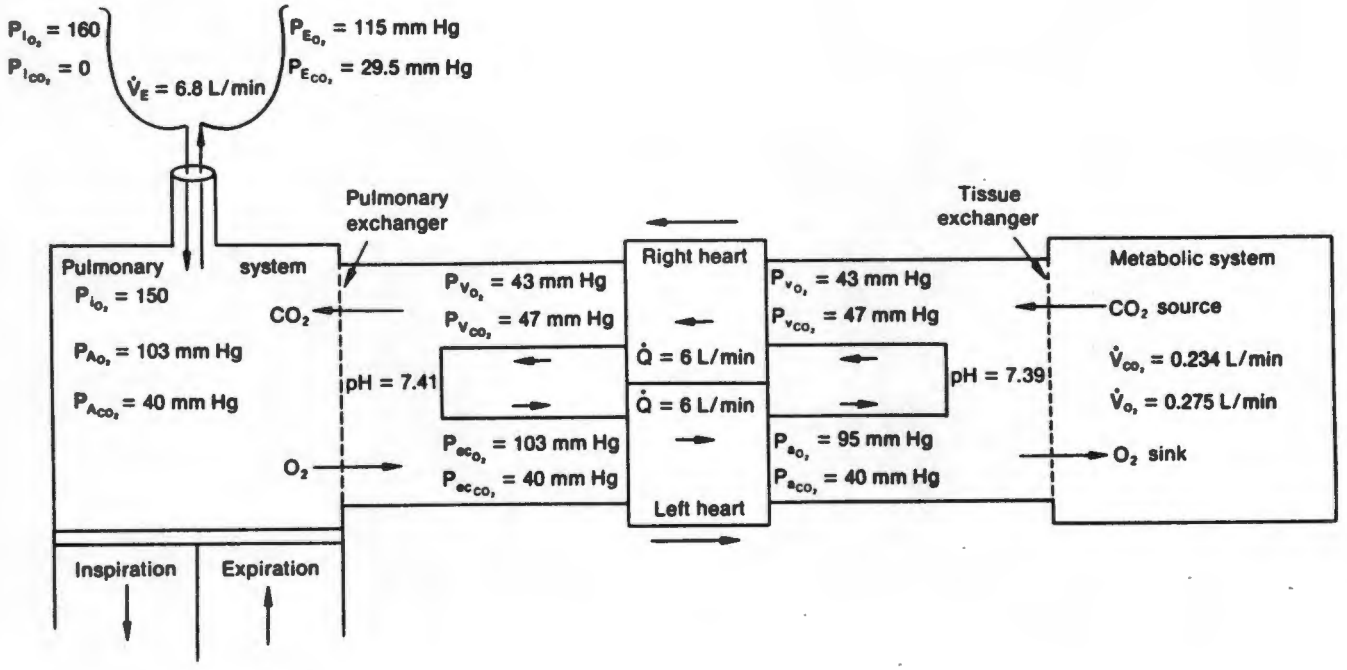


Figure 3.8 Diagrammatic representation of the respiratory gas transport system - from F.S. Grodins and S.M. Yamashiro (1978). Respiratory function of the lung and its control. Macmillan Publishing Co.; 5.

3.2 A SYSTEMS APPROACH

3.2.1 Introduction: Historically, physiology originated primarily from anatomy and histology, which resulted in a sub-division of physiology into various so-called physiological "systems"; i.e. respiratory, circulatory, nervous, endocrine. These "systems" are, however, closely related to the individual functional anatomical components, with the emphasis placed on analysis of the function and interaction of these individual components, i.e. lungs, heart, brain, glands, etc.

In recent years a new approach has emerged, with the emphasis placed on analysis of the so-called individual unit process followed by a synthesis of the complete system. The overall behaviour of a complex system is

studied in terms of interacting unit processes as well as interaction with other systems. The unit process is chosen to contribute to useful understanding and may not be directly related to the anatomy of the unit (Grodins, 1978).

It is believed that the functioning of the complete system, as synthesized from the individual unit processes, is far more complex than the sum total of the individual unit processes. In order to study the dynamic response of the system and its detailed functioning, a qualitative approach proved to be unsatisfactory; instead the response should be studied in terms of a well-developed scientific method.

Engineering control system theory and related mathematical principles lend themselves to such an application. It is in this field that the engineer with a thorough understanding of related biology, referred to as a bio-engineer (sub-division of biomedical engineering), can contribute towards a better understanding of biological systems.

The terms 'systems analysis' and more specifically 'systems physiology', are recognised as referring to this new approach; they should not, however, be confused with the physiological "systems" referred to in the introductory paragraph.

3.2.2 Biological Processes: The majority of organisms, depending on their level of sophistication can be sub-divided into the following major processes (Jaros, 1982a):

a. Cellular Processes: The cell is the building block of any living organism, in fact it could be regarded as the primarily requirement to sustain life as we know it. It represents a unit process, although we rather tend to analyse a specialised collection of cells, structured to perform a specific function. The majority of the chemical processes, forming the basis of life, are initiated and completed within the cell.

b. Homeostatic Processes: For the cell to survive, it requires a very specialised internal environment (milieu interne), maintained at

relatively constant values. The various ion concentrations and osmolality of extracellular fluid are typical requirements to ensure the continuation of the living cell. Homeostasis means the maintenance of constant conditions in the internal environment; i.e. the region in direct contact with the living cell. Various organs and tissues contribute towards the homeostatic processes, playing a major part in the maintenance of favourite conditions for the cells and consequently life.

c. Defence Processes: The organism under discussion must act against the intrusion of hostile organisms and therefore needs a defence system. Whereas the homeostatic processes ensure the maintenance of a favourite internal milieu, the defence processes ensure the continuation of the living organism in a hostile external environment. The defence processes, if functioning correctly, act on behalf of the complete organism and ensure survival in the long term; e.g. the immune processes.

d. Reproductive Processes: Once survival of the organism itself has been secured in the existing environment, it is essential that the organism replaces obsolete cells and finally reproduces itself, in order to ensure its future existence as well as that of the species. It involves continuous reproduction on a cellular level and, in case of multi-cellular organisms, that of the whole organism.

e. Orientation Processes: In order to survive and perform the functions related to the previously mentioned processes, it is often necessary for the organism to orientate itself in response to either internal or external stimuli. The organs involved in higher organisms are mainly the various receptors, musculo-skeletal system and nervous system.

The sub-division of the various life processes is merely an artificial exercise and it must be emphasized that all the processes are interrelated; it is often rather the interaction between the various processes that is under investigation in systems physiology. A diagrammatic representation of the various processes is presented in Fig. 3.9.

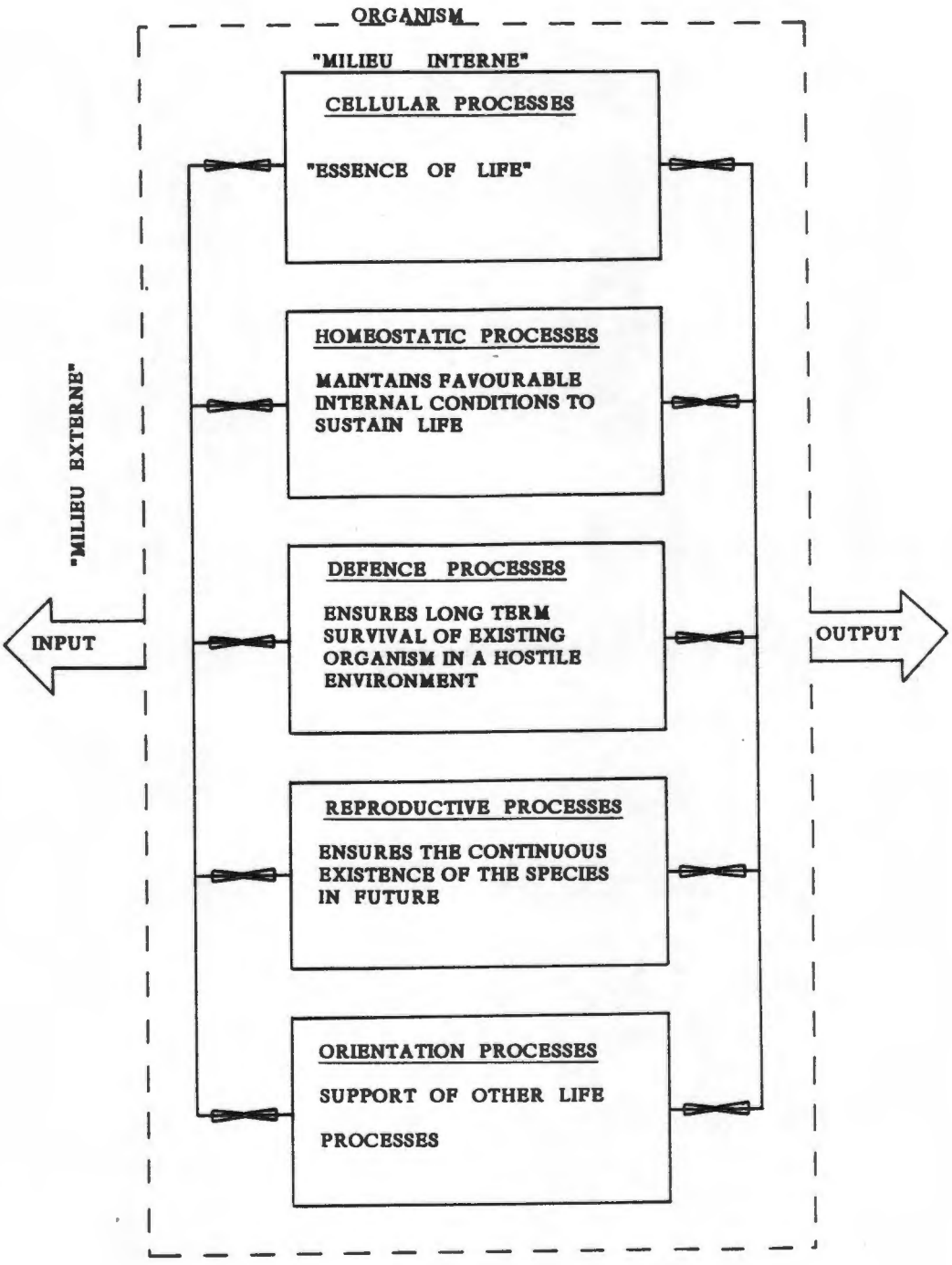


Figure 3.9 Diagrammatic representation of the various life processes.

Homeostatic processes are of particular importance in so far as this thesis is concerned, especially the process responsible for the control of PCO_2, PO_2 and pH in the extracellular fluid. It is with this in mind that the homeostatic process will now be analysed in more detail.

3.2.3 Homeostasis: A homeostatic process always involves the control of a specific entity and as such it presents itself for the application of engineering control system theory. Homeostatic processes can be further sub-divided into a collection of sub-systems (Jaros, 1982b).

a. Terminal System: The terminal system forms the basis of contact with the external environment of the organism and is involved in the exchange of information and solid substances. Examples are the lungs, alimentary canal and the kidneys.

b. Intermediate System: This system acts as a store for the substances being controlled and, in some instances, alteration or filtering of the substances occur within the intermediate system. Examples are the liver, bone, adipose tissue and the reticulo-endothelial system.

c. Control System: Homeostasis requires the maintenance of various parameters within very small tolerances under extreme conditions. It follows logically that a control system is required, in order to co-ordinate and monitor the activity of the other sub-systems. Control in biological systems always relies on negative feedback mechanisms to maintain the variables within the acceptable limits; an irreversible state of shock would be an example of a condition where positive feedback exists in the control loop. Control is usually a combination of the following processes:

i. Autoregulation: Local control of the variable; for instance, vaso-constriction in the case of pulmonary capillaries.

ii. Endocrine control: Hormonal control of the variables; the hormones are excreted by the various glands in response to hormonal and nervous stimuli and are then distributed in the blood to their target organ(s).

iii. Autonomic nervous control: The autonomic nervous system controls the activity of various organs and glands (e.g. lungs, circulation, digestive system and interaction with endocrine system) via the nerve tracts.

d. Transport System: The transport system ensures the distribution of the entity being controlled, from the terminal systems, via the intermediate system, to the cells and vice versa. Distribution could be either via the blood, lymph or nerve tracts. It is important to note that the transport system also acts as a communication link (conveying of information) and not only the distribution of substances. A diagrammatic representation of the homeostatic sub-systems is displayed in Fig. 3.10.

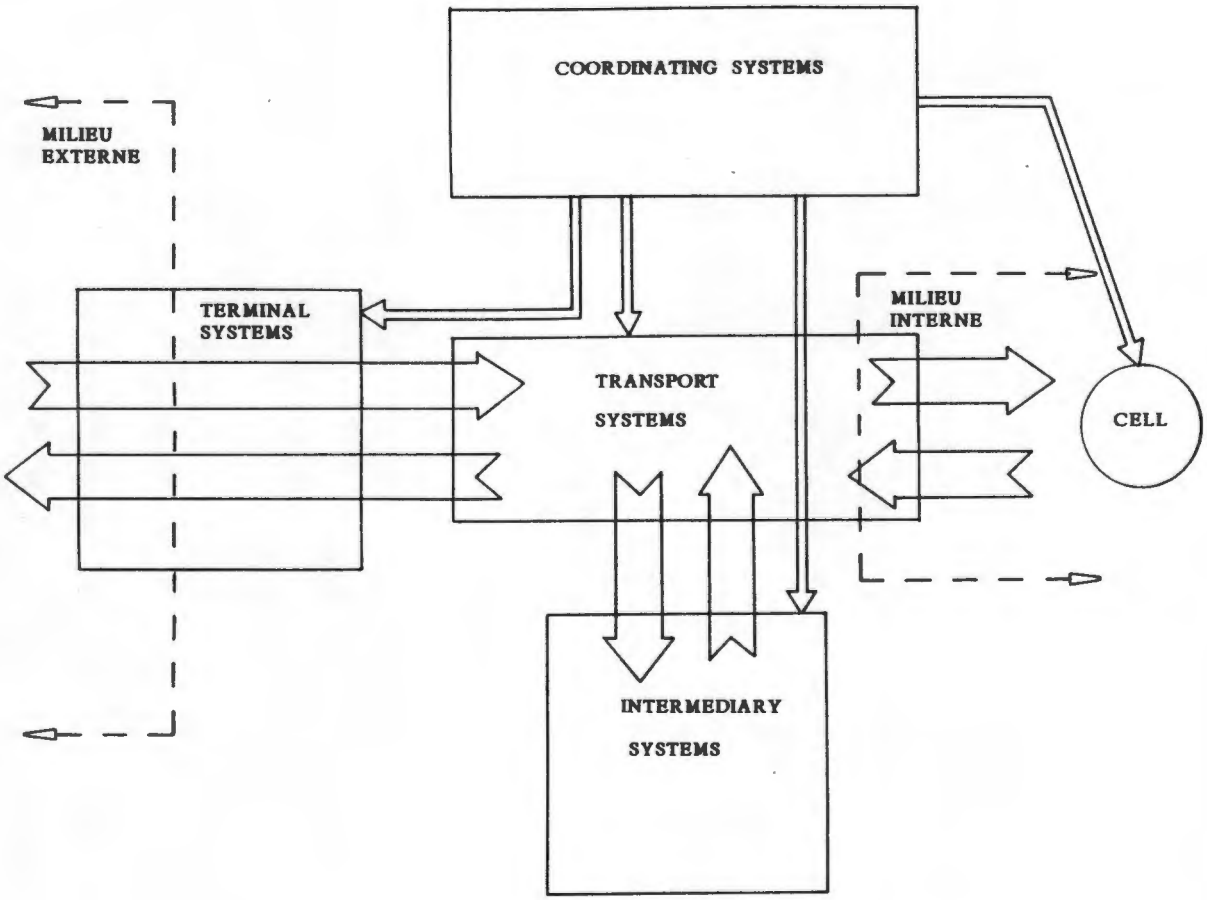


Figure 3.10 Diagrammatic representation of the homeostatic sub-systems.

On completion of this rather lengthy introduction to systems physiology, the respiratory system should be referred to as [pH, PO_2, PCO_2] homeostasis. For convenience the process will be referred to as respiration homeostasis in subsequent discussions.

3.2.4 Respiration Homeostasis

3.2.4.1 Terminal System: The function of the terminal system in respiration homeostasis is fulfilled by the lungs and kidneys. As mentioned in the previous paragraph, three variables are being controlled, namely the pH, PO_2 and PCO_2. The kidneys fulfil a direct function in the regulation of pH, although the lungs dominate also in that respect (the pH and PCO_2 are closely related as demonstrated in equation 3.13.

The concept of a continuous ventilation-perfusion ratio distribution in the lungs is of vital importance in the successful understanding of gas exchange in this region.

Intuitively it should be clear that there exists an optimum ratio of the air flow in a specific alveolus to the blood flow in the capillaries supplying it. A redundancy or shortage in either one of these entities will cause a "mismatch" between the gas and blood phase, causing insufficient or non-optimal gas transfer for that specific unit. The ventilation-perfusion ratio distribution is discussed in greater detail in a subsequent chapter.

3.2.4.2 Transport System: The systemic and pulmonary circulation play a major role in respiration homeostasis and any defect in its operation may have a profound influence on the variables being controlled.

The respiratory gases either dissolve in, or combine with, the blood and its chemical constituents; of relevance are the oxygen and carbon dioxide dissociation curves and how it may influence the concentration of the respective gases.

3.2.4.3 Intermediate System: There is no significant intermediate system present for any one of the controlled variables; i.e. respiratory gases are not stored in significant quantities over an extended period

(blood may be considered to act as an intermediate system, although the volume of gases stored is sufficient only for a very short period). This has important physiological consequences; the best that could be done in case of a lack of oxygen for instance, would be for the oxygen rich blood to be diverted to the most critical regions; i.e. the brain and heart.

3.2.4.4 Control System: Control of respiration homeostasis should be analysed in terms of its influence on the various sub-systems; i.e. terminal and transport. It involves control of circulation, ventilation and renal function. The ideal would be to combine the various units into a mathematical model, depicting all the unit processes, feedback mechanisms and interrelating pathways; output variables would be pH, PCO_2 and PO_2 in the blood.

This is a formidable task and progress has been made in the fields of circulation, respiration (Dickinson, 1979) and renal function (acid-base balance) individually; a holistic model of respiration homeostasis has not been sucessfully completed to date.

Fig. 3.11 is analogous to Fig. 3.10 but has been adapted to respiration homeostasis. It is believed that the kidney plays a minor role in the regulation of pH, compared to the lungs; its function is probably more relevant in the control of blood pressure and fluid balance.

A diagram of the "metabolic servomechanism" as designed by Grodins et al. (1978) is presented in Fig. 3.12. This diagram conforms in pattern and purpose to a simplified approach towards respiration homeostasis. In constructing it, they have assumed that the respiratory system comprises a metabolic servomechanism designed to match pulmonary and metabolic gas exchange ratios over a wide range with little change in arterial composition.

They have further assumed that $\dot{V}_A$ (alveolar ventilation) varies in direct proportion to $\dot{V}CO_2$ (carbon dioxide output).

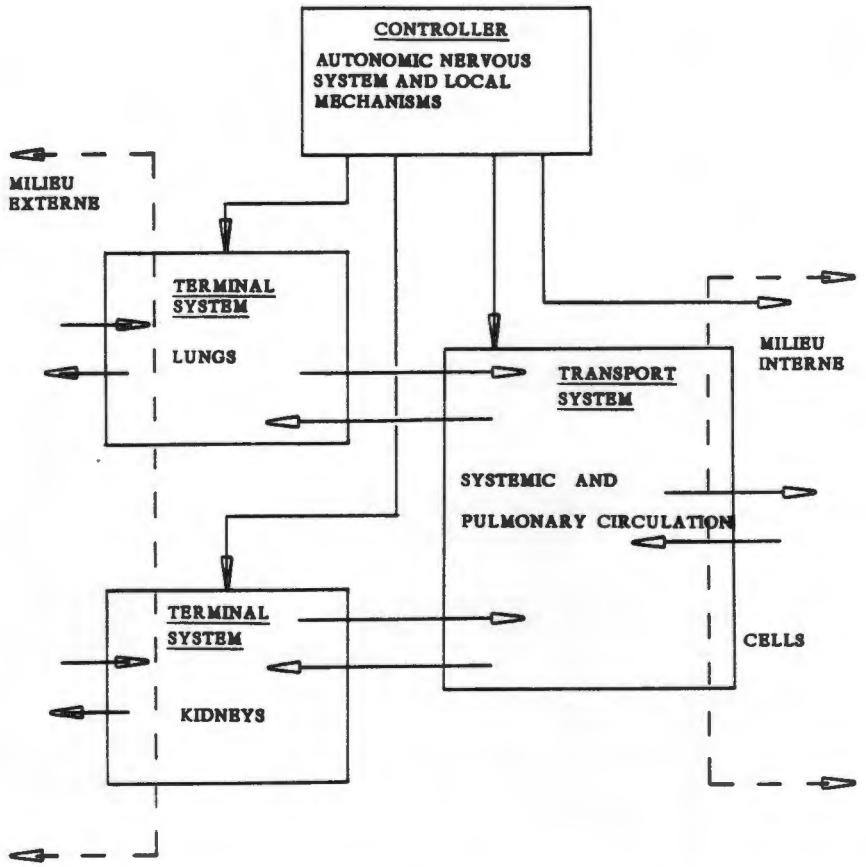


Figure 3.11 Diagrammatic representation of respiration homeostasis.

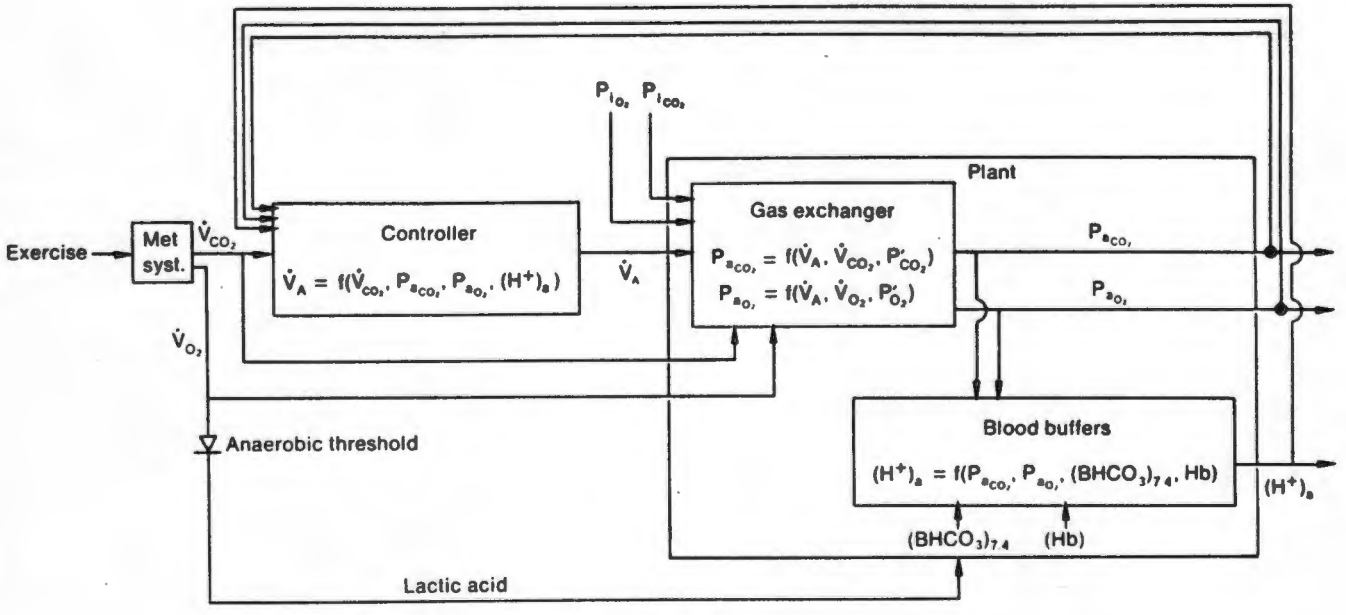


Figure 3.12 Block diagram of the modified respiratory chemostat (i.e. the metabolic servomechanism) including a dual role of VCO_2 (information flow to controller, material flow to gas exchanger) - from F.S. Grodins and S.M. Yamashiro (1978). Respiratory function of the lung and its control. Macmillan Publishing Co.; 118.

CHAPTER 4
ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

4.1 INTRODUCTION

The adult respiratory distress syndrome (ARDS), so called because of similarities with the infantile respiratory distress syndrome, was first described as a clinical syndrome in 1967 by Ashbough et al. Advanced evacuation and resuscitation techniques of military patients during the Vietnam war allowed patients to be observed over extended periods in hospital, highlighting the occurrence of ARDS in patients suffering from severe trauma (Petty, 1982).

The syndrome is characterized by hypoxaemia, bilateral pulmonary infiltrates, severe dyspnoea and a reduction in lung compliance. It is preceded by a variety of catastrophic insults or risk factors (Petty & Fowler, 1982). The clinical signs become evident only after a period of approximately 12 to 48 hours following the initial insult; a positive diagnosis is very difficult to make before the onset of severe hypoxaemia. The mortality rate may be as high as 80% and usually varies from 30% to 80% in the case of patients diagnosed according to the severity criteria laid down by Petty & Fowler (1982).

The exact mechanism of ARDS is, to a large extent, unknown. Based on a systems approach (vide infra) it can however be stated that the secondary cause is to be found in the terminal system, especially the lungs, where impairment of gas exchange occurs as a direct result of ventilation - perfusion inequalities (King et al., 1974; Ralph & Robertson, 1981; Dantzker, 1982).

The primary cause is believed to be biochemical in nature and is believed to act upon the terminal system via the circulatory system (Dauberschmidt et al., 1982; Lamy et al., 1983; Petty & Fowler, 1982). Surfactant function seems to be of profound importance and depletion might eventually prove to be a primary mechanism of the syndrome (Bone, 1976b; Petty et al., 1977; Petty et al., 1979; Massaro et al., 1980).

Changes in the haemodynamic status should be viewed as a result of de-

fects in the terminal system and are not to be confused with the primary causes (Ayres, 1982; Jardin et al., 1979a; Shoemaker et al., 1980; Czer et al., 1980; Laver et al., 1979; Sibbald et al., 1983).

Early prophylactic treatment and close monitoring is essential to reduce the risk of patients who are potential candidates for ARDS and increases the chances of survival in ARDS patients; intelligent interpretation of the various physiological variables should ideally be integrated towards a goal directed therapy (Boysen, 1982; Bland et al., 1978; Czer et al., 1980; Gong, 1982; Schoemaker et al., 1980).

4.2 DIAGNOSIS

There is no single "marker" of the syndrome which can be incorporated into a single diagnostic test for the diagnosis of ARDS; instead one must rely on a description of the clinical syndrome as a definition.

Criteria for diagnosing ARDS have been described by Petty & Fowler (1982) and serve as a quantifiable diagnostic technique.

4.2.1 Criteria for diagnosis (Petty & Fowler, 1982):

a. Clinical history of catastrophic event :
   (i) Pulmonary (e.g. aspiration, massive infection, contusion)
   (ii) Non-pulmonary (e.g. shock, multisystem trauma)
   exclude :
   chronic pulmonary disease
   left ventricular failure (wedge pressure > 12 cm H_2O)

b. Must have clinical respiratory distress :
   (i) tachypnoea > 20 breaths/minute
   (ii) laboured breathing

c. With chest radiograph showing :
   (i) diffuse pulmonary infiltrates (early interstitial, followed by alveolar)

d. And physiological measurements of :

(i) PaO_2 < 50 mm Hg when F_IO_2 > 0,6

(ii) total dynamic respiratory compliance < 50 ml/cm H_2O (usually 20 to 30)

(iii) increased shunt fraction and deadspace ventilation

4.2.2 Clinical states associated with ARDS (Petty & Fowler, 1982):

a. Shock

(i) Septic

(ii) Haemorrhagic

(iii) Cardiogenic

(iv) Anaphylactic

b. Trauma

(i) Direct pulmonary contusion

(ii) Non-pulmonary, multisystem

c. Infection

(i) Viral pneumonia

(ii) Bacterial pneumonia

(iii) Miliary tuberculosis

(iv) Legionnaire's pneumonia

d. Disseminated intravascular coagulation

e. Fat emboli

f. Amniotic fluid emboli

g. Aspiration : especially of highly acidic gastric contents (pH < 2,5)

h. Near drowning

i. Inhaled toxic agents

(i) Smoke

(ii) Phosgene

(iii) oxides of nitrogen

j. Pancreatitis

k. Oxygen toxicity

l. Narcotic drug abuse
   (i) Heroin
   (ii) Methadone
   (iii) Propoxyphene

m. Radiation pneumonitis

n. Drugs
   (i) Ethchlorvynol
   (ii) Salicylates

4.3 PATHOPHYSIOLOGY

4.3.1 Pulmonary Oedema: While the underlying pathology associated with ARDS is myriad and not clearly understood in all cases, acute abnormalities of pulmonary function result from the progressive accumulation of extravascular fluid (Dantzker, 1982). Hypoxaemia of ARDS is primarily due to pulmonary oedema which results in a right to left shunt; the concept of a physiological shunt is however often confused and should actually be regarded as the integration of the effect of ventilation - perfusion inequalities in the lung (West, 1977; King et al., 1974), combined with the anatomical shunt.

Two forms of pulmonary oedema have been described : haemodynamic or cardiogenic oedema, in which fluid accumulates secondary to changes in hydrostatic and oncotic pressures and permeability oedema, which is characterised by functional or anatomical damage of the pulmonary microvascular membrane (Wiener et al., 1983). It appears, however, that a protein-permeable epithelium alone does not induce alveolar oedema, but usually a combination of both effects (Egan, 1982), although the mechanisms differ (Staub et al., 1967).

Dantzker (1982) concluded from experimental data that blood flow in ARDS is distributed mainly to two types of lung units; those normally ventilated and those unventilated. This all-or-none phenomenon is consistent with a theory that alveolar flooding is either complete or absent.

The mechanism of pulmonary oedema could be described by employing Starling's equation (Staub, 1974); it has, however, given rise to controversy and is by no means a clear cut-approach (Civetta, 1979).

The sequence of pulmonary oedema can be sub-divided into a few distinct phases (Staub et al., 1967): Fluid appears first in the interstitial connective tissue around the large vessels and airways, followed by alveolar wall thickening, and finally rapid and independent alveolar filling after the interstitial compartment is well filled. Increased surface tension favours fluid leakage, presumably because it increases the microvascular transmural pressure (Albert et al., 1979).

4.3.2 Surfactant Abnormalities: Abnormalities in pulmonary mechanics are characterised by reduced lung compliance, and morphologically the lungs are congested and atelectatic.

Surface compressibility, or its reciprocal which is surface elastance, is an expression of the resistance of the surface film to compression at any given area. In a study conducted by Petty et al. (1979), the films from ARDS lungs had a high value of compressibility which demonstrates that these films are unable to adjust rapidly to stress, in contrast to the normal films with low values of compressibility.

Surfactant abnormalities are believed to be a result and not a primary cause of ARDS, which begins as a result of a catastrophic insult (Petty et al., 1977). It does, however, remain a reasonable hypothesis that surfactant abnormalities in ARDS play a secondary but vital role in the pathogenenis of the clinical syndrome through the mechanism of encouragement of further intra-alveolar fluid sequestration, further alteration in lung mechanics, and reduced functional residual capacity resulting in a vicious circle leading to shunting and refractory hypoxia (Petty et al., 1979).

It has been hypothesized (Massaro et al., 1980) that shallow breathing leads to the aggregation of surfactant into a less functional form resulting in increased alveolar surface tension and atelectasis.

Whatever the situation may be, it appears as if a definite correlation exists between changes in lung compliance and the onset of ARDS (Bone, 1976a;Bone, 1976b; Petty et al., 1979).

4.3.3 Haemodynamic Disorders: As a result of defects in the respiratory terminal system in ARDS patients, combined with the effects of the initial insult, the function of the circulation is altered primarily by the control system as a compensatory measure. Therapy, for instance ventilatory support, may also influence its functioning.

The patient with post-traumatic ARDS has circulatory and metabolic demands which are greater than normal values defined from healthy unstressed volunteers and also somewhat greater than haemorrhage and trauma patients without ARDS (Czer et al., 1980). A universal finding in all groups of ARDS patients is pulmonary hypertension and also a progressive increase in the mean pulmonary arterial pressure (MPAP) in patients who eventually died (Jardin et al., 1979; Czer et al., 1980).

Pulmonary hypertension has two important haemodynamic consequences :

a. It causes an elevated afterload for the right ventricle with an excessive right ventricular stroke - work index (Jardin et al., 1979) which can produce right heart failure (Sibbald et al., 1983). However, straightforward application of the Frank - Starling principle to an analysis of right ventricular and left ventricular function after an extensive acute destruction of pulmonary vasculature architecture may be inappropriate (Laver et al., 1979).

b. It is probably in part responsible for an abnormally low systemic arterial pressure due to reduction in systemic arterial resistance (Jardin et al., 1979).

Whatever the interpretation may be, management of systemic haemodynamic disturbances complicating the early state of ARDS, such disorders as a

hyperkinetic state, myocardial failure, hypovolemia or overperfusion can enhance hypoxaemia and myocardial failure or hypovolemia may be worsened by the use of mechanical ventilation with positive end expiratory pressure (PEEP) (Ellman et al., 1982; Jardin et al., 1981; Cassidy et al., 1981; Pick et al., 1982; Perschau et al., 1979).

A block diagram of the pathophysiology is given in Fig. 4.1.

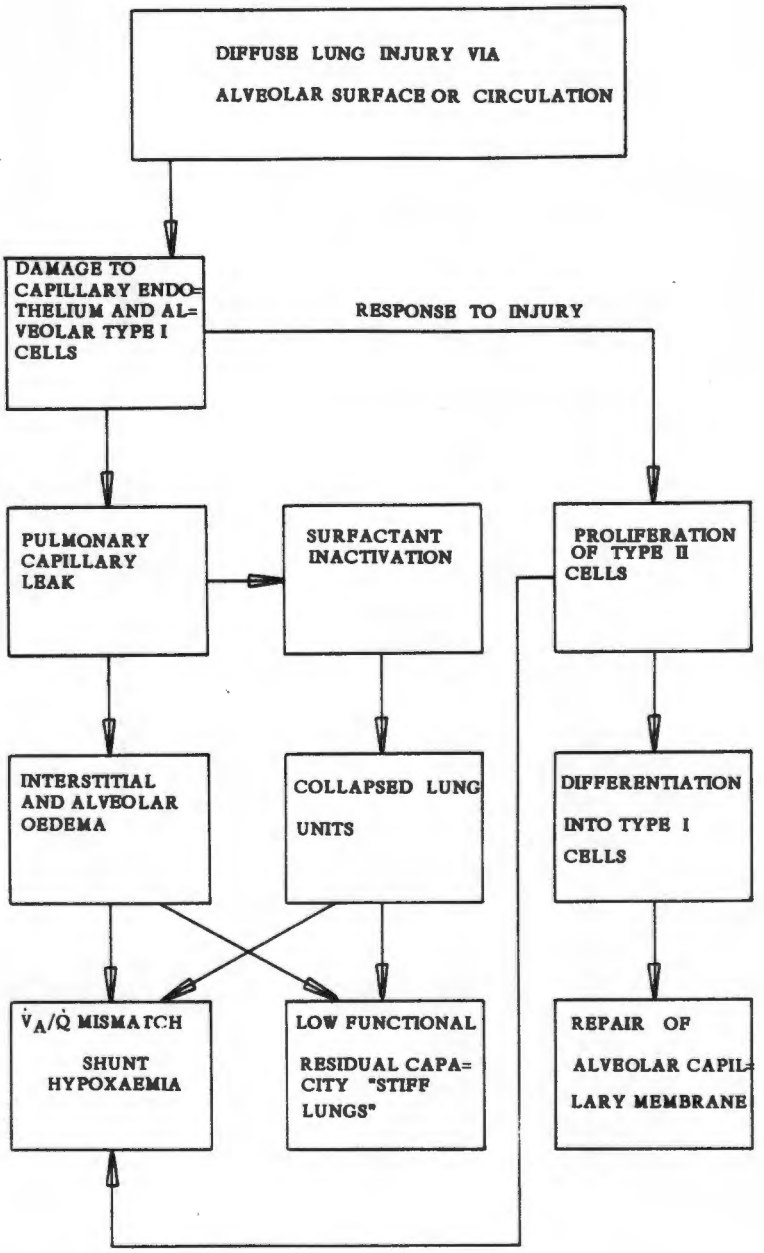


Figure 4.1 Pathophysiology of ARDS - data from T.L. Petty (1982). Another look at ARDS. Chest, 82; 99.

4.4 VENTILATION/PERFUSION RELATIONSHIPS AND GAS EXCHANGE IN THE LUNGS

Gas exchange in the lungs occurs at the level of the alveoli; to be more exact, at the interface between the air and the blood phases of ventilation and perfusion respectively. A few concepts as regards the gas and blood phases are noteworthy and should be thoroughly understood before an attempt can be made to analyse optimum gas exchange in the lungs.

The inspired air is distributed amongst the individual alveoli; after diffusion has occurred and a state of equilibrium has been reached within each one of the alveoli, the individual expired alveolar air concentrations are summed in the airways, finally to produce the expired air concentration measured at the mouth.

Individual alveolar air concentrations vary and do not necessarily resemble the (mixed) inspired or mixed expired air concentrations at the mouth.

By analogy, the mixed venous blood of the blood phase corresponds to the inspired air and the pulmonary capillary blood gas content to the alveolar air concentrations.

An optimum ratio of the alveolar gas and pulmonary capillary blood flow exists; i.e. air flow represents a specific oxygen supply and the blood flowing in the capillary has a limited capacity to absorb a specific volume of oxygen - for optimum gas transfer these two gas delivery and carrying capacities should be equal. The ratio of the alveolar air flow (ventilation) and capillary blood flow (perfusion) at this point, is the optimum ventilation-perfusion ratio for that specific alveolus.

It must be emphasized that it is the ratio of the ventilation to perfusion in an individual alveolus that determines the effectiveness of the gas transfer in that alveolus and not the absolute value of any one of the two entities. The air and blood flowing to two separate alveoli may differ drastically but both will operate at the optimum point, as long as the ratios are equal and optimal.

The "ideal" alveolar and arterial gas concentration points are obtained when the mixed alveolar air concentrations and mixed pulmonary capillary (arterial) gas concentrations are derived at the average ventilation-perfusion ratio for a specific lung, which does not necessarily equal the optimal ratio.

Since a situation where all alveoli function at the ideal point does not exist in real life, the concept of a statistical distribution of $\dot{V}_A/\dot{Q}$ fractions in the alveoli was introduced (Riley & Courand, 1948; West, 1977; Evans et al., 1974).

Due to the fact that all the alveoli do not function at the ideal point, gas is not exchanged up to a point where the oxygen content is depleted, although a state of equilibrium does exist. This gives rise partially to the alveolar-arterial oxygen tension difference [$P(A-a)O_2$] and is a direct result of a combination of three independent phenomena: diffusion impairment, venous admixture (anatomical) and unequal ventilation-perfusion ratios among the alveoli, including true shunt (Farhi & Rahn, 1955). A state of diffusion impairment could be present in, for instance, some patients suffering from chronic pulmonary disease.

A different approach towards the study of blood gas exchange in the lung was followed by King & Briscoe, 1967; namely the construction of Bohr integral isopleths and ventilation - perfusion ratio isopleths superimposed on the oxygen dissociation curve.

4.4.1 Presentation and measurement of ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$): A major description problem exists in the presentation of the $\dot{V}_A/\dot{Q}$ distribution; the problem is how to properly handle multiple gas data so as to gain the greatest amount of insight into the properties of $\dot{V}_A/\dot{Q}$ distributions, without overstepping the theoretical limitations inherent in the particular techniques and without throwing away useful information (Wagner, 1976; Evans & Wagner, 1977; Wagner, 1981). The data are normally displayed with the $\dot{V}_A/\dot{Q}$ on the abscissa and the ventilation and perfusion values respectively on the ordinate.

Continuous $\dot{V}_A/\dot{Q}$ distributions have been measured in patients by combining the nitrogen washout technique with varying values of F_IO_2 (Briscoe et

al., 1960; Okubo & Lenfant, 1968; Lenfant and Okubo, 1968). A typical distribution for a healthy subject is displayed in Fig. 4.2.

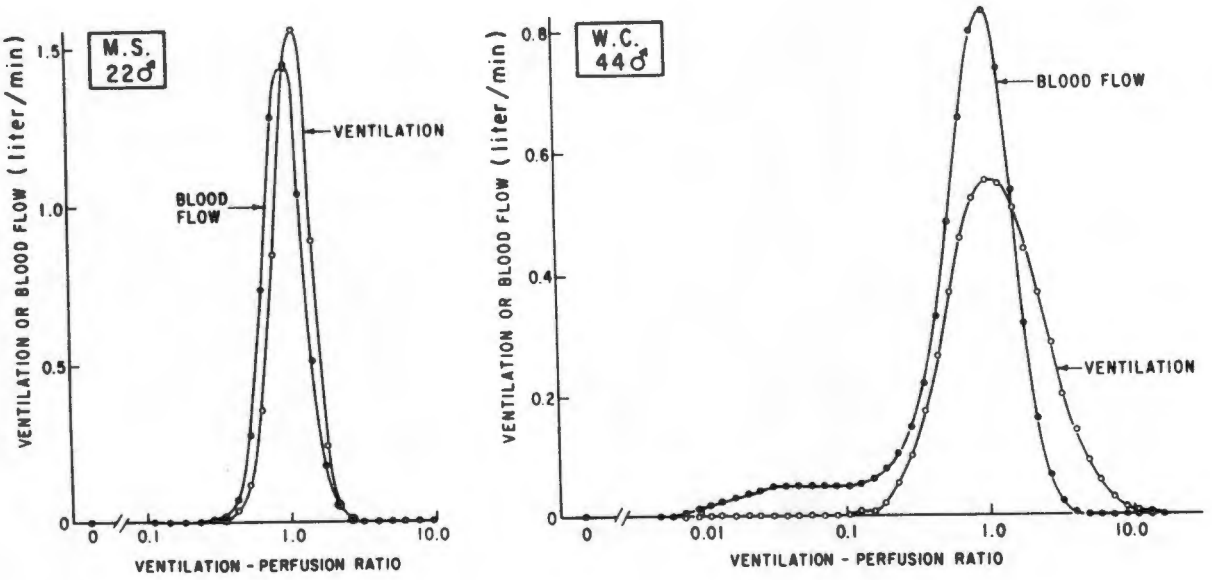


Figure 4.2 Examples of ventilation/perfusion distributions in normal subjects. The left panel shows the result in a young subject and the right panel the results in an older man - from J.B. West (editor) (1977). Bioengineering aspects of the lung. Marcel Dekker, Inc.; 405.

The $\dot{V}_A/\dot{Q}$ distribution in subjects suffering from ARDS tends to be bimodal, with regions of very low $\dot{V}_A/\dot{Q}$ participating in the overall gas exchange; no single unique pattern has however emerged from measurements performed in these subjects (Wagner et al., 1974; Dantzker et al., 1979). The concomitant change in the $\dot{V}_A/\dot{Q}$ distribution presents itself as an attractive method of early diagnosis and prediction of the onset of ARDS in traumatic patients. The nucleus of this thesis is, in fact, based on this hypothesis and will be elucidated in the subsequent chapter. An example of a $\dot{V}_A/\dot{Q}$ distribution in an ARDS patient is presented in Fig. 4.3.

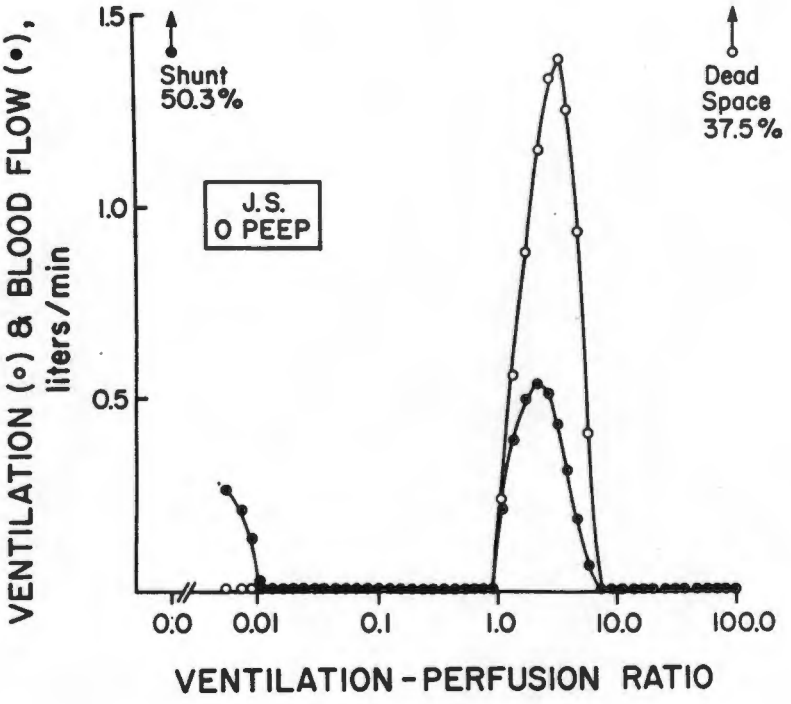


Figure 4.3 Venilation/Perfusion distribution in a patient with the adult respiratory distress syndrome - from R.D. Dantkzker (1979). Am. Rev. Resp. Dis., 120; 1039.

4.4.2 Gas transfer in ARDS patients: A decrease in blood oxygen content and unresponsiveness to oxygen administration characterise the diagnostic syndrome of ARDS (Petty, 1982; Petty & Fowler, 1982).

Carbon dioxide retention has also been observed in ARDS patients (Ralph & Robertson, 1981); very few studies are clear about this aspect and usually expired CO_2 is not measured.

The possible determinants of altered gas exchange in the lung are believed to be threefold:

a. A "true shunting" of blood; blood passing totally unventilated alveoli.
b. The perfusion of regions with very low $\dot{V}_A/\dot{Q}$.
c. A diffusion impairment in the functional alveoli.

In ARDS patients, it appears as if a "true shunt" is the predominant mechanism of hypoxaemia, accompanied by regions with very low $\dot{V}_A/\dot{Q}$ (Ralph & Robertson, 1981; Dantzker et al., 1979). It has been estimated with a mathematical model of the gas exchange process that diffusion impairment does not contribute significantly towards hypoxia (Dantzker et al., 1979); it cannot be ruled out with any certainty, however (Ralph & Robertson, 1981).

Although the gas exchange abnormalities (King et al., 1974; Danek et al., 1980; Dantzker, 1982; Ralph & Robertson, 1981), pulmonary mechanics (Petty et al., 1979; Petty et al., 1977; Bone, 1976a,b) and pathologic findings (Ayeres, 1982; Lamy et al., 1976) in ARDS have been well described, correlations between these measurements and the evaluation of histologic alterations in the injured lung remain mostly a matter of speculation. The only study that extensively correlated observed pathologic changes with measurements of gas exchange and prognosis in humans with ARDS is that of Lamy et al. (1976).

The following facts concerning gas exchange in ARDS patients may, however, be assumed with reasonable certainty (Dantzker, 1982):

a. The acute abnormalities of pulmonary function, in all cases, result from the progressive accumulation of extravascular fluid in the lung.
b. The progression of events is similar irrespective of the aetiology of the oedema; viz. increased hydrostatic pressure or increased capillary permeability.
c. Flooded alveoli are widely scattered throughout the lung, with filled alveoli often adjacent to uninvolved ones.
d. Hypoxaemia of ARDS is primarily due to pulmonary oedema which results in right to left "true shunt".
e. In addition, hypoxaemia may be caused by the presence of regions with low (0,02 - 0,1) $\dot{V}_A/\dot{Q}$'s as well as the possibility of diffusion impairment, although is unlikely to be so.

The regions with low $\dot{V}_A/\dot{Q}$'s are especially noteworthy, since it actually implies a bimodal $\dot{V}_A/\dot{Q}$ distribution in the lungs with a concomitant increase in the physiological shunt.

4.5 PATIENT MANAGEMENT

4.5.1 Introduction: Skillful management of fluids is essential in maintaining an adequate circulation and avoiding further complications (Petty & Fowler, 1982; Bone, 1978; Gallagher et al., 1978; Venus et al., 1979; Walkinshaw & Schoemaker, 1980). Whereas aggressive fluid therapy was the rule in management of shock before the characterization of ARDS, it subsequently became clear that fluid overload is an important complicating factor in ARDS (Wood & Prewitt, 1981; Jardin et al., 1979).

The use of corticosteroids in the treatment of ARDS patients is widespread but controversial (Petty & Fowler, 1982). If given early, they can reduce lung injury and maintain alveolar stability and prevent damage of the capillary epithelium. Unfortunately, they may also reduce lung macrophage antibacterial defences.

F_IO_2 should always be kept as low as possible (preferably less than 0,5) in order to reduce the risk of atelectasis and oxygen toxicity (Dantzker et al., 1974; Ayeres, 1982). In severe cases of ARDS it may however be necessary to maintain levels of 100% oxygen supply over extended periods in order to ensure an acceptable level of PaO_2 (Lamy et al., 1976).

The hypoxaemia accompanying ARDS is significantly improved with sustained application of a modified form of spontaneous or mechanical ventilation, combined with positive end-expiratory pressure (PEEP). To date, PEEP in its various forms represents the most effective, but not ideal (vide 2.4.2.1), means of treatment.

4.5.2 Ventilatory Support: Intermittent mandatory ventilation (IMV) with PEEP offers a few advantages over a rigidly controlled mode of ventilation. IMV reduces the mean intra-thoracic pressure and therefore reduces the risk of barotrauma and other mechanical deleterious effects, especially if used in conjunction with PEEP (Gong, 1982; Bone, 1978). Tidal volume and respiratory rate are determined by the state of the patient (tidal volume is usually set between 10 and 12 ml per kilogram of body weight) (Petty & Fowler, 1982). Fig. 4.4 depicts a typical pressure waveform of an IMV mode with PEEP on the ventilator.

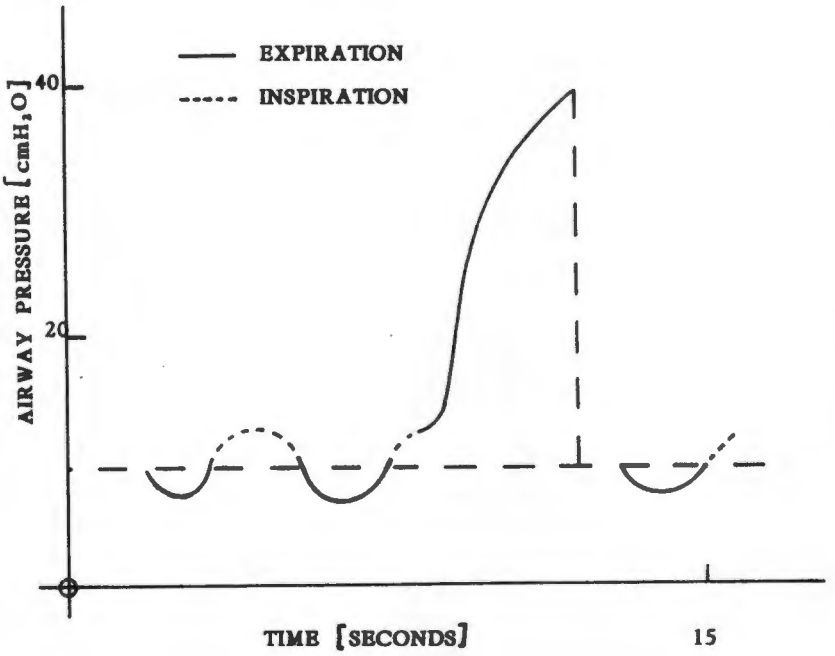


Figure 4.4 Intermittent mandatory venilation with PEEP

It is possible to determine the ideal ventilatory pattern with a simulation of lung mechanics and optimal ventilation parameters (Barbini, 1982). In practice an ideal ventilator neither exists nor can it be designed (due to conflicting physiological interests); it could, however, be utilized in such a way as to optimize the parameters which, in each case, are considered the most important.

High frequency ventilation (HFV) offers another possibility for ventilatory support, it seems as if it might be superior to other ventilatory techniques. Controlled studies of HFV in ARDS are still required before any real answers will be forthcoming (Gallagher et al., 1982).

A controversy exists over the exact amount of PEEP that should be applied to optimize gas transfer to the tissue. A reduction of cardiac output tends to occur proportional to increments of PEEP and is generally most marked with PEEP > 10 cm H_2O. The magnitude of the effect varies from individual to individual and results from a complex balance among several factors; the most important of which are: the status of the

cardiovascular system, lung compliance and the functional residual capacity (FRC) (Jardin et al., 1981; Cassidy et al., 1981; Pick et al., 1982; Ellman and Dembin, 1982; Perschau et al., 1979; Simonneau et al., 1982).

An "optimal" combination exists between the level of PEEP administered and the cardiovascular status; the exact combination and parameters that should be optimized are, however, still controversial (Suter et al., 1975; Civetta et al., 1975; Demers et al., 1977; Gallagher et al., 1978; Venus et al., 1979).

The various physiological parameters involved in oxygen delivery to the tissue, with their interaction, are shown in Fig. 4.5. Therapy should be directed towards the optimization of oxygen delivery to the tissue ($\dot{V}O_2$).

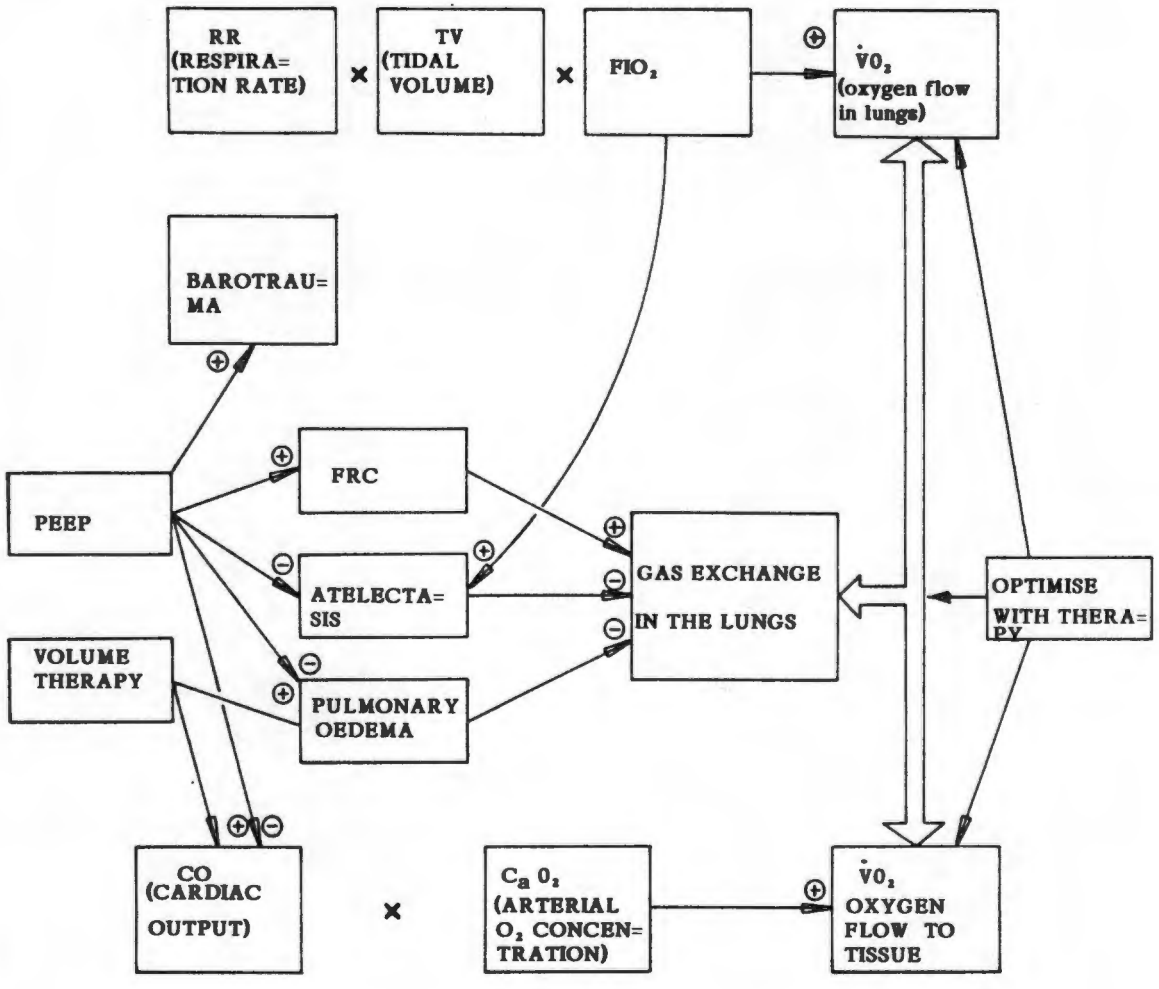


Figure 4.5 Schematic representation of the therapeutic goals in ARDS patients

4.5.3 Monitoring: Monitoring of the patient with ARDS is essential and should be guided by a strict protocol in order to encourage goal-directed therapy. Measurements should, however, always be accompanied by intelligent observations performed by experienced personnel. The basic methods of physical diagnosis and radiologic examination techniques are of prime importance and should not be replaced by advanced monitoring techniques; they should rather supplement the fundamental techniques.

For a detailed discussion of monitoring techniques the reader is referred to: (Bone, 1981; Fallat, 1982, Boysen, 1982).

Blood gases probably represent the most important physiological variables in patients suffering from ARDS; they give, in conjuntion with the cardiac output, a direct indication of the oxygen supply to the tissue. Ideally the arterial as well as the mixed venous blood gas content should be monitored. Various methods of presenting the data have been suggested (Covelli et al., 1983; Bone, 1981; Giovannini, 1983); the most popular configurations are the physiological shunt ($\dot{Q}sp/\dot{Q}t$), arterial oxygen partial pressure and fraction of inspired oxygen ratio (PaO_2/F_IO_2), the alveolar-arterial oxygen tension difference [$P(A\text{-}a)O_2$] and the mixed venous oxygen tension $P_{\bar{v}}O_2$.

Blood gases should always be judged in conjunction with haemodynamic and ventilatory variables and a diagnostic or therapeutic decision should not be made on the basis of the blood gas content alone.

The cardiac output, combined with systemic and pulmonary vascular pressures constitute the quintessence of haemodynamic monitoring. Vascular resistance calculations and haemodynamically derived parameters related to cardiac function have evolved over the years, assisting in therapy directed towards haemodynamic stability (Boysen, 1982; Schoemaker et al., 1979a; Bland et al., 1978).

Interpretation of the data and directing therapy present a major difficulty. In the past, correlation of derived indices with the underlying pathology has been attempted (Schoemaker et al., 1979a, 1979b, 1979c); methods relying on observing a trend or analysing a series of measurements appear to be the most reliable.

Integration of the most important physiological variables into a quantitative (mathematical) model is one way of overcoming the problem of interpretation of multivariable physiological measurements. The following chapter deals with such an approach towards respiration physiology.

CHAPTER 5
MATHEMATICAL MODELLING

5.1 INTRODUCTION

Modelling is the process of building and listing a mathematical description of a system in close co-ordination with complementary experimental studies.

Two basic approaches to the modelling of physiological systems can be distinguished; models with unit processes directly related to the physiology of the system that is being modelled and those models that follow a "black box" approach, attempting only to model the relation between the input and output variables of the system, i.e. the "transfer function". In practice, mathematical models of physiological systems are a combination of these two approaches.

It can be stated with certainty that formal mathematical modelling, including forcing techniques and analytical techniques adopted from engineering, is by now firmly established in physiology and will contribute to a large extent towards future progress in the field of biological sciences (Petersen, 1981).

Identification of redundant components in a complex biological system or of unwanted information in a mathematical problem is one of the major problems confronting the modeller. In the words of Richard Bellman on the limitations of mathematics: **"We require methods for extracting the essential information from the sea of data in which we float. This is an extraordinarily difficult problem, or class of problems. We can assert that the ability of the human being that is remarkable is not so much the ability to handle large amounts of information as the ability to discard large amounts and to concentrate upon the essentials".**

A mathematical model of a biological system may assist in the evaluation of the quantitative value of experimental data, to plan the most relevant experimental protocol and can contribute towards the identification of gaps in our theoretical knowledge of the physiology, which may determine the direction of future research projects (Coleman, 1978).

The philosphical implications of applying conventional mathematical principles to biological systems has been a matter of dispute in the past (Brown et al., 1973); the trend seems to be in the direction of thermodynamics of general systems (Stear, 1973).

The vigour of physics as a theoretical as well as an experimental science has been manifested in the persistence of metaphysical arguments in philosophy that have interacted with work in physics itself to give it new direction. Brown et al. (1973) suggested that perhaps biology will be mature when a "metabiology" develops and similarly interacts with biology which so far is rich in content but poor in concept.

Whatever future developments may take place in the field of modelling, it can be asserted that it will make an ever increasing contribution towards the advancement of the biological sciences.

5.2 MATHEMATICAL MODEL OF THE GAS EXCHANGE PROCESS IN THE LUNGS

Respiration homeostasis involves various interrelating physiological and mechanical mechanisms; when attempting to model a system of such complexity, it invariably follows that certain aspects will be favoured and modelled in more detail, neglecting some of the other mechanisms involved.

The objective of this thesis is to gain more knowledge about the pathophysiology involved in ARDS and to apply this knowledge to the treatment of these patients. Considering the fact that ventilation - perfusion inequalities occur in these patients, presumably related to the pathophysiology of the syndrome, it was decided that this aspect of respiration homeostasis should be emphasized in the mathematical model. The $\dot{V}_A/\dot{Q}$ distribution should be regarded as a sub-section of the terminal system of the respiration homeostasis process; this particular sub-section of respiration homeostasis, therefore, guided the modelling process.

The decision was also influenced, however, by the fact that $\dot{V}_A/\dot{Q}$

inequalities can be detected by performing measurements on relatively accessible physiological variables, i.e. blood flow, gas flow and their various concentrations combined with blood physiology measurements.

The options were either to model one of the other systems in more detail (e.g. the transport system, co-ordinating system) or to adopt a mechanical approach towards the terminal system, emphasizing the role of, for instance, surfactant deficiencies on lung mechanics and consequently on gas exchange in the lungs. It is, however, difficult to attach a unique quantitative value of, for instance, alveolar elastance to a specific set of physiological variables.

Although the primary cause of ARDS is probably biochemical in nature, it is difficult to perform those biochemical measurements involved and also to model the processes - it was thus ruled out as a possible basis for the model.

In developing the model, the co-ordinating system has been ignored completely with the transport system featuring only in the interface with the terminal system, i.e. the gas dissociation curves and cardiac output values. It is believed that changes in the co-ordinating system in ARDS patients are primarily a result of either changes in the terminal system or transport system (vide 4.3); it could not, therefore, contribute significantly towards the understanding of the fundamental pathophysiology of the syndrome.

Ideally the model should incorporate the co-ordinating system and a detailed analysis of the transport system; in this specific application the knowledge gained would not, however, justify the effort of such an undertaking.

The lines of thought and sequence of analytical procedures followed during the design of a mathematical model are depicted in Fig. 5.1. An appropriate hypothesis of ARDS pathophysiology was first decided on, after which the model design was guided by this hypothesis.

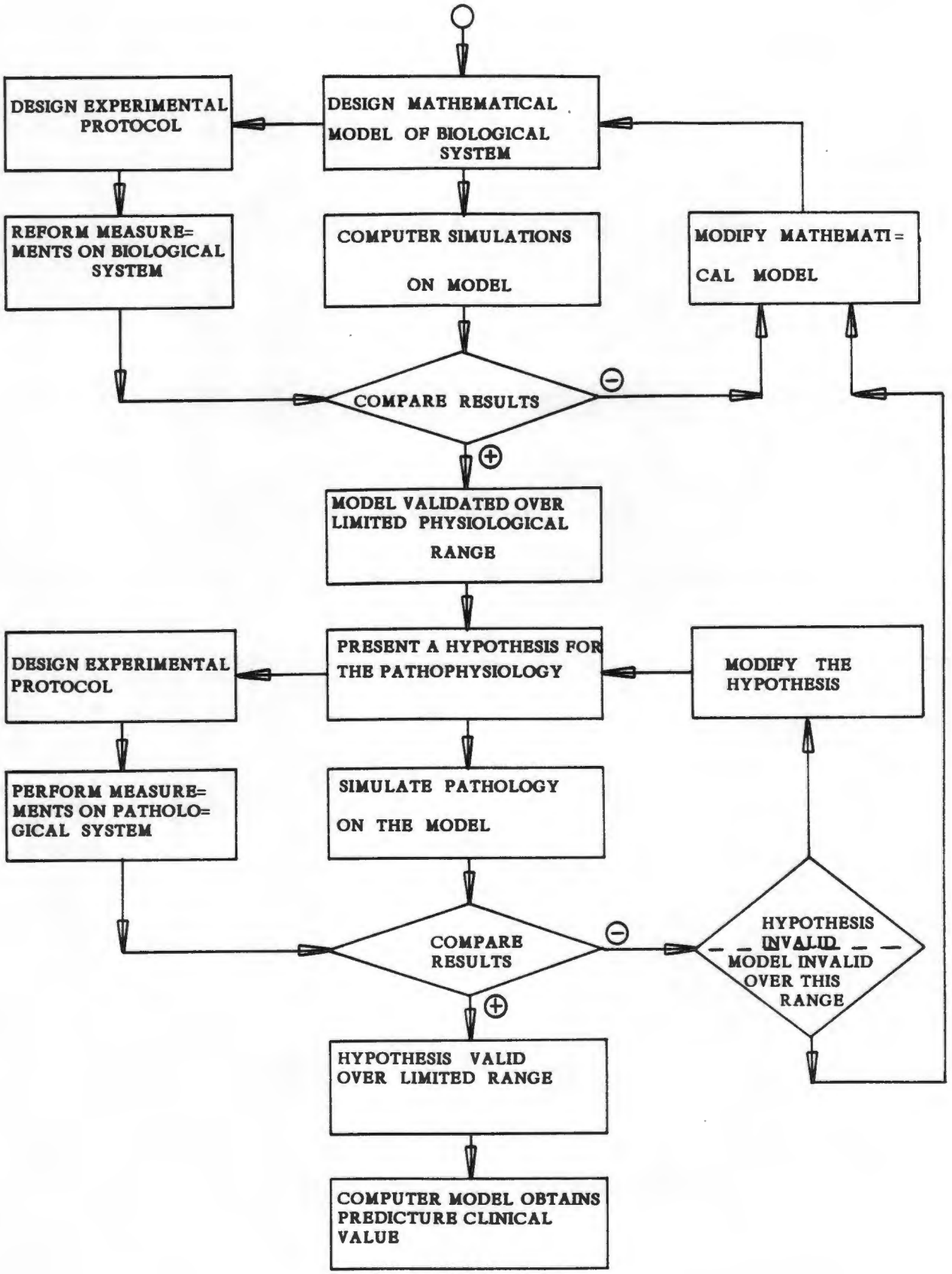


Figure 5.1 Diagrammatic representation of the modelling and simulation process for biological systems.

Hypothesis 1

A correlation exists between the onset and severity of ARDS in human beings and the nature or shape of the ventilation/perfusion distribution in the lung.

A diagramatic representation of the model developed for simulating gas exchange in a single compartment in the lungs is presented in Fig. 5.2.

$\dot{V}_I$: inspired air flow [l/min]
P_I : partial pressure of inspired gasses [mmHg]
$\dot{V}_A$: alveolar air flow [l/min]
P_A : alveolar partial pressure [mmHg]
$\dot{V}_E$: expired air flow [l/min]
P_E : partial pressure of expired gasses [mmHg]
$\dot{Q}_V$: venous blood flow [l/min]
$\dot{Q}_c$: pulmonary capillary blood flow [l/min]
$\dot{Q}_a$: arterial blood flow [l/min]
C_a : arterial gas concentration [ml/100 ml blood]
C_v : venous gas concentration [ml/100 ml blood]
C_c : pulmonary capillary blood concentration [ml/100 ml blood]
DP_{50} : amount by which the P_{50} (at 37°C, pH = 7,4, PCO_2 = 40 mmHg) of the subject's blood exceeds the standard of 26,8 mmHg.
PB : Barometric pressure [mmHg]
PH_{20} : Vapour pressure [mmHg]

The model depicted in Fig. 5.2 can be combined in a multi-compartmental gas exchange model according to the ventilation-perfusion distribution in the lungs. Fig. 5.3 depicts the complete model, representing N compartments of the gas exchange units, with ventilation and perfusion supplies according to the ventilation-perfusion distribution for N compartments.

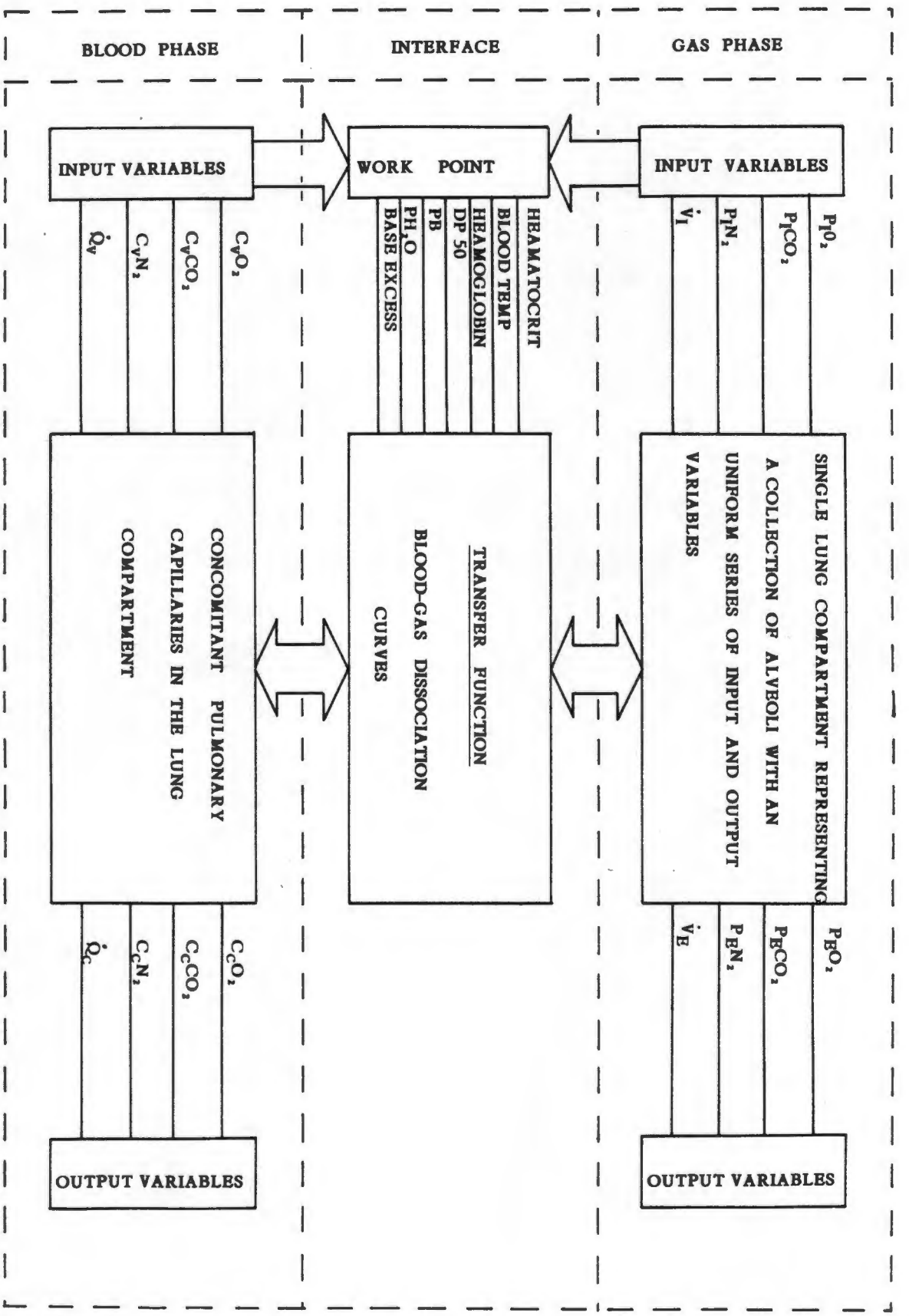


Figure 5.2 Block diagram of a gas exchange model for a uniform compartment in the lung.

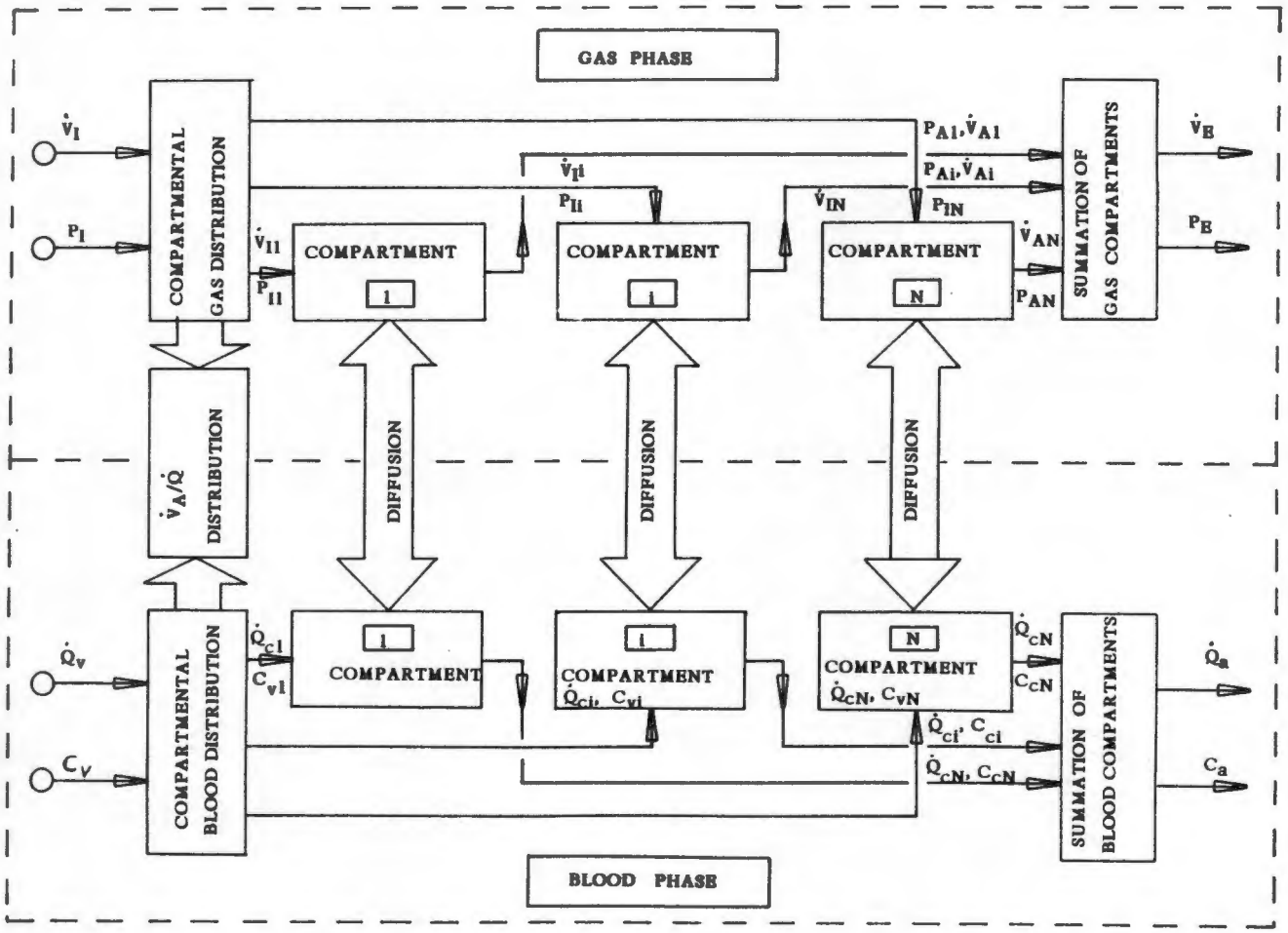


Figure 5.3 Block diagram of a N-compartmental pulmonary gas exchange model.

Model Assumptions

a. The model is time invariant and therefore represents a steady state condition of gas exchange in the lungs, i.e. no cyclical variations in air or blood flow are considered.

b. The functional gas exchange units (i.e. the alveoli and pulmonary capillaries) are represented as a series of N different compartments within the lungs, with varying ventilation-perfusion ratios.

c. The alveoli, capillaries and the respective blood and air flow to a single compartment are uniform.

d. A state of equilibrium between the blood and gas phase is reached instantaneously, disregarding possible diffusion impairments and time dependant biochemical reactions in the blood.

e. The alveolar and end-capillary partial gas pressures are assumed to be equal in a specific compartment.

The model is non-linear with multi-variable inputs and outputs, with a working point that is a function of various physiological variables, i.e. the "transfer function" is a function of the model variables. With this in mind, it is possible to adopt the model for a specific biological system and therefore create a unique model for a specific patient under investigation.

5.2.1 Model equations: The lung was sub-divided into N different compartments, with respective air and blood supplies, each compartment is solved according to the Fick principle (the conservation of mass in a system), the compartments being finally summed to obtain a picture of the resultant gas exchange in the lungs.

The equations used in the model developed by the author to study gas exchange in the lung were acquired from a model originally designed by West (1969).

Similar to West's model, the exchange of nitrogen was incorporated, which adds considerably to its complexity; the resulting error when neglecting nitrogen gas exchange increases under conditions of a high fraction of inspired oxygen as well as in regions of very low ventilation-perfusion ratios (both conditions which are simulated with the model).

The system equations pertaining to gas transfer in the lungs are based on the Fick principle, i.e. the conservation of mass of the individual respiratory gases (Olszowka and Farhi, 1969; West, 1977).

5.2.1.1 System Equations:

$$\dot{V}_{AIi} \cdot F_IO_2 - \dot{V}_{Ai} \cdot F_AO_{2i} = K.\dot{Q}_i.[CaO_{2i} - C_{\bar{V}}O_2] \quad (5.1)$$

$$\dot{V}_{AIi} \cdot F_ICO_2 - \dot{V}_{Ai} \cdot F_ACO_{2i} = K.\dot{Q}_i.[CaCO_{2i} - C_{\bar{V}}CO_2] \quad (5.2)$$

$$\dot{V}_{AIi} \cdot F_IN_2 - \dot{V}_{Ai} \cdot F_AN_{2i} = K.\dot{Q}_i.[CaN_{2i} - C_{\bar{V}}N_2] \quad (5.3)$$

- Fick principle

$$F_AO_{2i} + F_ACO_{2i} + F_AN_{2i} = 1,0 \quad (5.4)$$

$$F_IO_2 + F_ICO_2 + F_IN_2 = 1,0 \quad (5.5)$$

- Daltons Law

The systems equations are elucidated in Fig. 5.4.

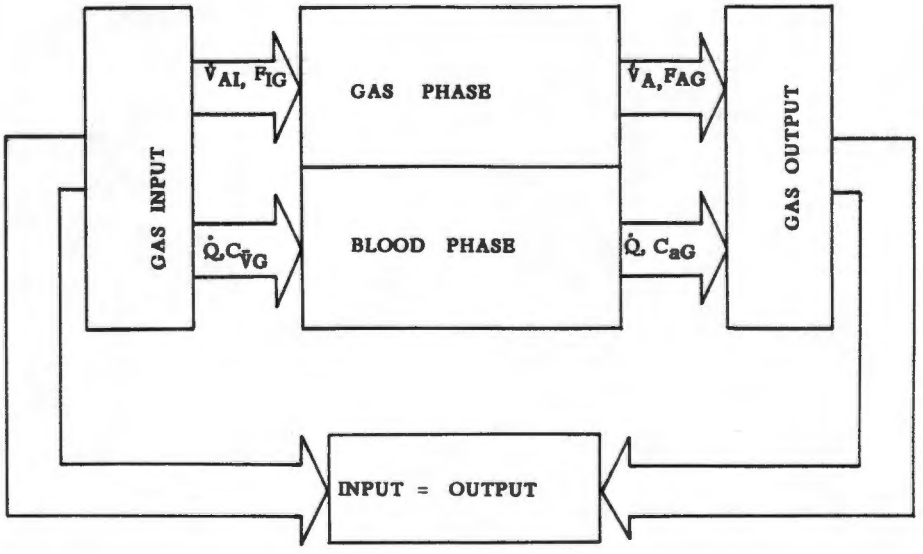


Figure 5.4 Block diagram of the systems equations.

Equilibrium with no gas concentration difference is assumed between the gas and blood phases for a single compartment; furthermore the mass input of a specific respiratory gas into the compartment equals the mass output (i.e. no significant storage compartment for the respiratory gases exists).

$\dot{V}_{AI}$: inspired alveolar ventilation
$\dot{V}_{A}$: alveolar ventilation (resultant)
F_{IG} : fraction of inspired gas concentration
F_{AG} : fraction of alveolar gas concentration
$\dot{Q}$: pulmonary capillary perfusion
CaG : arterial gas content
$C_{\bar{v}}G$: mixed venous gas content + (pulmonary artery)
i : refers to compartment number (total number of compartments = N)
K : BTPS to STPD conversion factor (0,0121)

The resultant gas exchange in a gas exchange unit equals the difference between the arterial gas content and the mixed venous gas content (Fick's principle). The sum total of the respiratory gas exchanged equals the sum total of the gas exchanged in the individual compartments; this is also valid for the total perfusion (cardiac output) and total ventilation (minute volume).

$$\sum_{i=1}^{N} \dot{Q}_i.[CaO_{2i} - C_{\bar{v}}O_2] = \dot{V}O_2 \qquad (5.6)$$

$$\sum_{i=1}^{N} \dot{Q}_i.[CaCO_{2i} - C_{\bar{v}}CO_2] = \dot{V}CO_2 \qquad (5.7)$$

$$\sum_{i=1}^{N} \dot{Q}_i.[CaN_{2i} - C_{\bar{v}}N_2] = \dot{V}N_2 \qquad (5.8)$$

$$\sum_{i=1}^{N} \dot{Q}_i = \dot{Q} \qquad (5.9)$$

$$\sum_{i=1}^{N} \dot{V}_{Ai} = \dot{V}_A \qquad (5.10)$$

$\dot{V}O_2$: total oxygen consumption

$\dot{V}CO_2$: total carbon dioxide output

$\dot{V}N_2$: total nitrogen exchange

$\dot{Q}$: total pulmonary perfusion (cardiac output - anatomical shunts)

$\dot{V}_A$: total alveolar ventilation (minute volume - anatomical dead space)

The arterial and mixed alveolar gas concentrations are the weighted average of the individual gas exchange compartments in the lungs :

$$CaO_2 = \sum_{i=1}^{N} \frac{\dot{Q}_i . CaO_{2i}}{\dot{Q}} \qquad (5.11)$$

$$CaCO_2 = \sum_{i=1}^{N} \frac{\dot{Q}_i . CaCO_2}{\dot{Q}} \qquad (5.12)$$

$$CaN_2 = \sum_{i=1}^{N} \frac{\dot{Q}_i . CaN_2}{\dot{Q}} \qquad (5.13)$$

$$P_AO_2 = \sum_{i=1}^{N} \frac{\dot{V}_{Ai} . P_AO_{2i}}{\dot{V}_A} \qquad (5.14)$$

$$P_ACO_2 = \sum_{i=1}^{N} \frac{\dot{V}_{Ai} . P_ACO_{2i}}{\dot{V}_A} \qquad (5.15)$$

$$P_AN_2 = \sum_{i=1}^{N} \frac{\dot{V}_{Ai} . P_AN_{2i}}{\dot{V}_A} \qquad (5.16)$$

The ideal gas point is calculated by assuming one uniform gas exchange compartment:

$$C_{ID}G = C\text{-}G \,\big|\, \dot{V}_A/\dot{Q} \qquad (5.17)$$

C-G : gas content

C_{ID} : gas content at ideal gas point

CaG : arterial gas content

P_AG : alveolar partial gas pressure.

5.2.1.2 Blood - Gas interphase (transfer function)

(a) Oxygen - Haemoglobin dissociation curve

The blood oxygen concentration ($C\text{-}O_2$) is a function of the oxygen partial pressure (PO_2) and other related physiological variables :

$$PO_2 = f\ (TEMP,\ pH,\ PCO_2,\ DP50)$$
$$SO_2 = f\ (PO_2)$$
$$C\text{-}O_2 = f\ (SO_2,\ HB,\ SOL_{O_2})$$

SO_2 : haemoglobin oxygen saturation

SOL_{O_2} : solubility of oxygen in blood

Various sets of curve fitting equations have been described for the oxygen - haemoglobin dissociation curve (Severinghaus, 1966; Olszowka & Farhi, 1968; Kelman, 1966, 1968) and more recently Winslow et al. (1983), incorporating in more detail the effect of DPG.

The equations described by Kelman in 1966 have been applied in this model:

$$PO_2virt_1 = PO_2 . 10^{\,[0,024.(37-TEMP)+0,4.(pH-7,4)+0,06.(\log 40-\log PCO_2)]} \qquad (5.18)$$

This equation compensates for acid-base and temperature disturbances from the standard PO_2 which would have been obtained at a pH of 7,4 and a PCO_2 of 40 mm Hg.

$$PO_2\ virt_2 = \frac{PO_2\ virt_1\ .\ 26,8}{26,8 + DP50} \qquad (5.19)$$

Equation (5.19) was subsequently added in West (1977) to compensate for additional shifts such as caused by an increased red cell concentration of 2,3 DPG.

DP50 : the amount by which the P50 of the subjects blood exceeds the P50 of the standard dissociation curve (26,8 mm Hg). The P50 of the patient must be known at :

TEMP = 37°C pH = 7,4 PCO_2 = 40 mm Hg

X = $PO_2\ virt_2$

IF X > 10 mm Hg then: (5.19a)

$$SO_2 = 100.(a_1x + a_2x^2 + a_2x^3 + x^4)/(a_4 + a_5x + a_6x^2 + a_7x^3 + x^4) \quad (5.20)$$

$a_1 = -8,53222\ 89 \times 10^3$
$a_2 = 2,12\ 14010 \times 10^3$
$a_3 = -6,707\ 3989 \times 10^1$
$a_4 = 9,359\ 6087 \times 10^5$
$a_5 = -3,1346258 \times 10^4$
$a_6 = 2,396\ 1674 \times 10^3$
$a_7 = -6,7104406 \times 10^1$

$$C\text{-}O_2 = 1,39.HB.SO_2/100 + {}^{SOL}O_2.PO_2 \quad (5.21)$$

IF X < 10 mm Hg then:

$$SO_2 = 0,003683.\ X + 0,000584.X^2 \quad (5.22)$$

These equations (5.21, 5.22) have subsequently been added by Kelman (1968) to describe the region of the curve below a PO_2 of 10 mm Hg.

PO_2 virt	:	virtual oxygen partial pressure	[mm Hg]
SO_2	:	haemoglobin oxygen saturation	[%]
$C\text{-}O_2$	:	blood oxygen content	[$ml O_2$/100 ml blood]
HB	:	haemoglobin concentration	[g/100 ml blood]
$^{SOL}O_2$	:	solubility of oxygen in blood normal value : 0,003	[$ml O_2$/100 ml - mm Hg]
TEMP	:	blood temperature	[°C]

(b) Carbon Dioxide dissociation curve

The carbon dioxide blood content is dependant on the PCO_2 and other related physiological variables :

$$C\text{-}CO_2 = f\ (PCO_2,\ pH,\ SO_2,\ HCRIT,\ TEMP)$$

An algorithm for the conversion of PCO_2 into blood CO_2 content, developed by Kelman (1967), was used in the model design :

$$P = 7,4 - pH \quad (5.23)$$

$$pK = 6,086 + 0,042.P + (38-TEMP).(0,00472 + 0,00139.P) \quad (5.24)$$

$$TEMP = 37 - TEMP \quad (5.25)$$

$$SOL_{CO_2} = 0{,}0307 + 0{,}00057 \cdot TEMP + 0{,}00002 \cdot TEMP^2 \quad (5.26)$$

$$DOX = 0{,}590 + 0{,}2913 \cdot P - 0{,}0844 \cdot P^2 \quad (5.27)$$

$$DR = 0{,}664 + 0{,}2275.P - 0{,}0938 \cdot P^2 \quad (5.28)$$

$$D = DOX + (DR-DOX) \cdot (1 - SO_2/100) \quad (5.29)$$

$$CP = SOL_{CO2}.PCO_2 \cdot [1 + 10^{(pH - pK)} \quad (5.30)$$

$$CC = D \cdot CP$$

$$C\text{-}CO_2 = [HCRIT \cdot CC + (1 - HCRIT) \cdot CP] .2{,}22 \quad (5.31)$$

$C\text{-}CO_2$: blood carbon dioxide content [ml O_2/100 ml blood]

SOL_{CO2} : solubility of carbon dioxide in blood [mlCO_2/100 ml blood - mm Hg] Normal value = 0,0017

HCRIT : heamatocrit

(c)<u>pH - pCO_2 relationship</u>

$$\Delta pH = 0{,}003 \cdot HB \cdot (1 - SO_2/100) \quad (5.32)$$

ΔpH compensates for the shift of the blood buffer line which occurs when the haemoglobin is reduced (Kelman, 1968).

$$pH = 7{,}59 + \Delta pH - 0{,}2741 \log (PCO_2/20) \quad (5.33)$$

The pH is obtained from the Siggard-Anderson pH-log PCO_2 diagram (West, 1977).

(d) <u>Nitrogen - blood dissociation</u>

The amount of nitrogen dissolved in blood is in accord with Henry's law :

$$C\text{-}N_2 = SOL_{N_2} \cdot PN_2 \quad (5.34)$$

$C\text{-}N_2$: nitrogen blood content [mlN_2/100 ml blood]

SOL_{N_2} : solubility of nitrogen in blood [mlN_2/100 ml blood - mm Hg]

5.2.2 Ventilation-Perfusion ratio distribution: The ventilation and perfusion to each one of the individual gas exchange compartments in the model must be specified in order to solve the systems equations; a log normal distribution for both the ventilation and perfusion distributions was assumed.

The major considerations were "physiological compatibility" and sufficient freedom to manipulate the distributions in order to simulate pathological conditions, especially those related to ARDS (vide 4.4).

As for the physiological considerations, a similar distribution function was chosen by Farhi and Rahn (1955) for their theoretical analysis of the alveolar-arterial oxygen pressure difference (P(A-a) O_2). More recently, in experiments determining the blood flow and ventilation in the lungs (Lenfant & Okubo, 1968; Okubo & Lenfant, 1968; Wagner et al., 1974; Dantzker et al., 1979), it appears that the actual distribution in the lungs broadly resembles that of a log normal distribution.

It should be noted, however, that the distribution function remains only a theoretical representation of the actual lung physiology; furthermore, direct anatomical parallels should be attempted with caution since the measuring process does not always contain information related to the spatial distribution of blood and air in the lungs.

Mathematical model: The respective distributions are derived from the standard equation for a log normal statistical distribution, i.e.

$$Yi = \frac{1}{\sigma \cdot \sqrt{2 \cdot \pi}} \cdot e^{[-0,5 \, (\frac{Xi - \bar{u}}{\sigma})^2]} \qquad (5.35)$$

Yi = volume of compartment number i

Xi = log flow/unit volume in compartment i

$\bar{u}$ = log mean flow/unit volume

σ = log standard deviation of flow

$$Flow_i = 10^{Xi} \cdot Yi \qquad (5.36)$$

$$\sum_{i=1}^{N} Flow_i = \text{total flow } (\dot{Q}, \dot{V}_A) \qquad (5.37)$$

Remarks:

(a) The flow represents either the ventilation or perfusion.

(b) The distributions are modified such that the total ventilation or perfusion equals that specified for the model.

(c) The lung compartments are spaced equidistantly on the log X-axis.

(d) Both sets of compartments (ventilation and perfusion) are numbered from left to right on the X-axis and matched accordingly to obtain the $\dot{V}_A/\dot{Q}$ for a specific compartment.

(e) A bimodal distribution may be specified for either the ventilation or perfusion distributions or both, in which case the resultant distribution is the arithmetic sum of two separate log normal distributions (the flow ratio of the two distributions is specified).

(f) The total number of compartments is specified and is always equal for both the ventilation and perfusion distributions.

(g) The distributions are discrete and contain discrete points (either ventilation or perfusion) for each one of the compartments. (Whenever represented as a continuous curve it is for aesthetic reasons only).

5.2.3 Physiological Shunt and Dead Space: The concept of a shunt in the pulmonary circulation has been firmly established in physiological reviews and clinical practice. However, it is not always appreciated for what it is and sometimes unduly contributes towards confusion in the process of clinical decision making.

Various shunts have been defined in the past which further contributes towards the confusion. For the purpose of this thesis, the physiological shunt or venous admixture is defined as that percentage of venous blood mixed with the arterial blood that would cause the measured difference

between the actual arterial oxygen content and the ideal arterial oxygen content. The ideal arterial oxygen content would be obtained when all gas exchange units within the lung have a ventilation-perfusion ratio equal to $\dot{V}_A/\dot{Q}$ and no diffusion impairment exists, i.e. the optimum gas exchange is affected for a specific combination of total alveolar ventilation and pulmonary perfusion.

The physiological shunt can be calculated as follows :

$$\dot{Q}_{SP}/\dot{Q}_t = \frac{C_{ID}O_2 - CaO_2}{C_{ID}O_2 - C_{\bar{v}}O_2} \qquad (5.38)$$

$\dot{Q}_{SP}$: blood flow that is shunted
$\dot{Q}_t$: total venous return or cardiac output
$C_{ID}O_2$: ideal arterial oxygen content

The physiological shunt can be ascribed to two major effects :

(a) That portion of venous blood that never has any contact with the alveolar septum and consequently does not partake in the gas exchange process, not even in the case of the completely healthy lung. This percentage is due to the blood flow in the Thebesian and bronchial veins and is usually referred to as the anatomical shunt.

(b) The other factor contributing towards the physiological shunt is the effect of ventilation - perfusion mismatch in the gas exchange units. The concept of ventilation - perfusion mismatch is illustrated in Fig. 5.5.

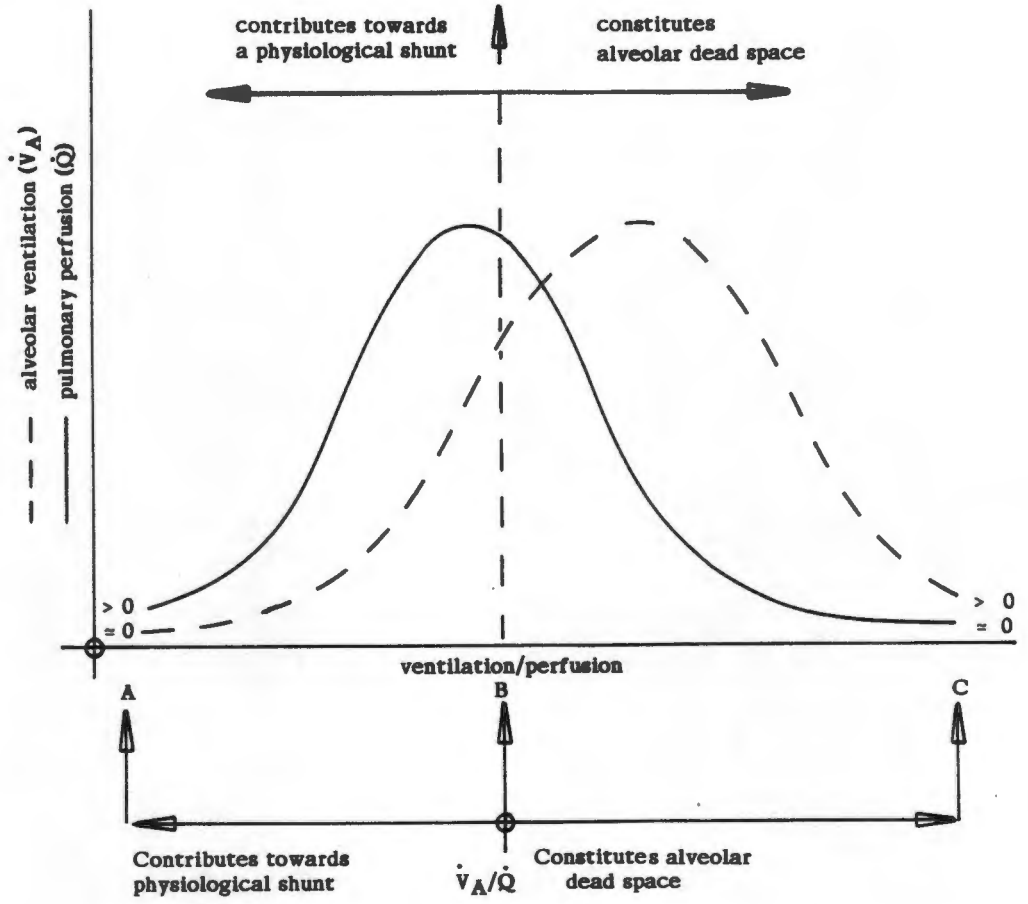


Figure 5.5 Illustration of a ventilation/perfusion mismatch

Point (A) represents atelectatic alveoli (unfortunately this is sometimes also referred to as part of the anatomical shunt) and point (C) represents total pulmonary capillary occlusion or constriction. The ideal ventilation-perfusion ratio for a specific lung would be $\dot{V}_A/\dot{Q}$; any ratio less than it would contribute towards shunt-like effects due to a ventilation-perfusion mismatch. It is of the utmost importance to realise that the actual ventilation-perfusion distribution in the lung resembles a continuous distribution and all the gas exchange units with a ventilation-perfusion ratio less than the ideal ratio will contribute towards the physiological shunt.

The concept of the physiological dead space is analogous to the physiological shunt, except that in this case the transport medium is the ventilatory gas and all the gas exchange units with ventilation-perfusion

ratios greater than the ideal ratio, contribute towards the physiological dead space.

Physiological Dead space = Anatomical dead space + dead space due to $\dot{V}_A/\dot{Q}$ inequalities (alveolar dead space). (5.39)

The physiological dead space percentage can be calculated with the Bohr equation :

$$\dot{V}_{DS}/\dot{V}_T = \frac{P_ACO_2 - P_ECO_2}{P_ACO_2} \quad (5.40)$$

$\dot{V}_{DS}$: airflow through the physiological dead space
$\dot{V}_T$: total ventilation (minute volume)
P_ECO_2 : expired carbon dioxide patial pressure
P_ACO_2 : alveolar carbon dioxide partial pressure

The alveolar dead space percentage can be calculated with the following equation :

$$\dot{V}_{DA}/\dot{V}_A = \frac{P_{ID}CO_2 - P_ACO_2}{P_{ID}CO_2 - P_ICO_2} \quad (5.41)$$

$P_{ID}CO_2$: ideal alveolar carbon dioxide partial pressure
P_ACO_2 : mixed alveolar CO_2
P_ICO_2 : inspired CO_2 partial pressure
$\dot{V}_{DA}$: air flow through the alveolar dead space
$\dot{V}_A$: total alveolar ventilation

5.2.4 Computer Simulation Program: The software was developed as an experimental package exclusively and not for general use or educational purposes. Software was written in TURBO PASCAL (VERSION 3) and simulations were performed on an Olivetti M24 microcomputer with a floating point co-processor.

The program flow chart, combined with the detailed sequence of calculations (program algorithm) provided in Table 5.1, should however facilitate development of a similar software package in any other computer language.

The complete program should be treated as a subroutine with input and output parameters as specified in Appendix A. A master simulation program was used to change the input variables of the subroutine in order to simulate specific physiological conditions in the respiratory system.

Fig. 5.6 represents the general program flow chart and should be read in conjunction with Table 5.1, describing the sequence of program calculations. The system of non-linear simultaneous equations as depicted in Table 5.1 is solved employing the Newton Raphson method (Appendix B); this technique was favoured due to its inherent matrix structure and ease of operation once the equations are simplified and configured in the appropriate matrix structure.

A detailed discussion of the software and problems encountered during the development phase is not justified; these are usually specific to the computer system or the numeric techniques employed and would not elucidate any of the simulation equations or underlying physiology.
It must, however, be stated that a considerable amount of time, in proportion to the total time invested in the thesis, was spent on the software development.

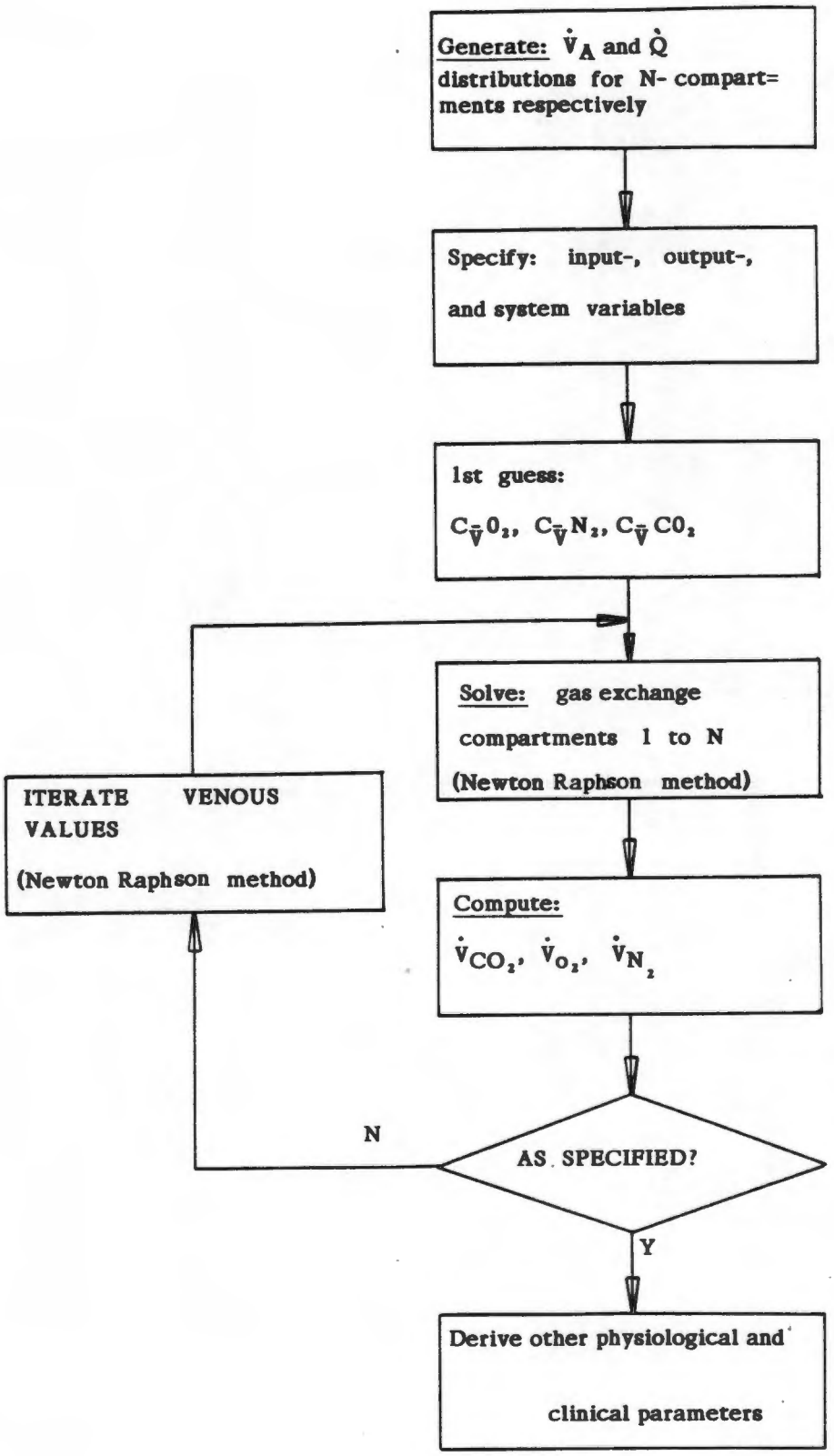


Figure 5.6 Simplified flow chart for the simulation program

TABLE 5.1

Line Sequence	Parameters Specified	Parameters Solved	Equations	Method	Comment
1	Generate $\dot{V}_a$ and $\dot{Q}$ distributions				
1.1	Bimodal Ventilation Distribution?	N	(5.35)		The distributions are adjusted to equal the total ventilation and perfusion as specified in the model.
1.2	Bimodal perfusion Distribution?	$\sum_{i=1}$ $\dot{V}_{AIi}$	(5.36)		
1.3	Number of Compartments?		(5.37)		
	Ventilation Distribution Parameter				
1.4	Ventilation Range				
1.5	LOG u_1 VENT				
1.6	LOG u_2 VENT (if bimodal)				
1.7	LOG σ_1 VENT				
1.8	LOG σ_2 VENT (if bimodal)				
1.9	Volume ratio of two distributions (if Bimodal)				
1.10	Total alveolar ventilation ($\dot{V}_A$)				
	Perfusion Distribution Parameters				
	Similar to ventilation distribution	N $\sum_{i=1}$ $\dot{Q}i$	(5.35) (5.36) (5.37)		
2	Solve series of lung gas exchange compartments				
2.1	F_IO_2	F_AO_{2i}	(5.1)		
2.2	$F_I\overline{CO}_2$	$F_A\overline{CO}_{2i}$	(5.2)		
2.3	F_IN_2	F_AN_{2i}	(5.3)		
2.4	$\dot{Q}i$		(5.4)	(1)(2)	

TABLE 5.1

Line Sequence	Parameters Specified	Parameters Solved	Equations	Method	Comment
2.5	$\dot{V}_{AIi}$	$\dot{V}_{AI}$	(5.5)	Newton Raphson (numerical partial derivatives)	
2.6	$C_{\bar{v}}O_2$	CaO_{2i}			
2.7	$C_{\bar{v}}O_2$	$CaCO_{2i}$			
2.8	$C_{\bar{v}}N_2$	CaN_{2i}			
2.9	$C\text{-}O_2$ --- PO_2	PO_2 --- $C\text{-}O_2$	(5.18) to (5.22)	Newton Raphson (algebraic partial derivatives)	
2.10	$C\text{-}CO_2$ --- PCO_2	PCO_2 --- C_{CO2}	(5.23) to (5.31)		
2.11	$C\text{-}N_2$ ---PN_2	PN_2 --- $C\text{-}N_2$	(5.34)		
2.12	pH --- PCO_2	PCO_2 --- pH	(5.32) to (5.33)		
	Calculate Venous Point			(1) (2)	
2.13	$\sum_{i=1}^{N}$ CaO_{2i}, $C_{\bar{v}}O_2$	$\dot{V}O_2$	(5.6)		Correct venous point if $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}N_2$ do not equal specified values (Newton Raphson method)
2.14	$\sum_{i=1}^{N}$ $CaCO_{2i}$, $C_{\bar{v}}CO_2$	$\dot{V}CO_2$	(5.7)		
2.15	$\sum_{i=1}^{N}$ CaN_2, $C_{\bar{v}}N_2$	$\dot{V}N_2$	(5.8)		

TABLE 5.1

Line Sequence	Parameters Specified	Parameters Solved	Equations	Method	Comment
3	Calculate Ideal Gas Point		(5.17)	Newton Raphson (numerical partial derivatives)	
	(Solve variables for one "ideal" compartment)				
3.1	F_IO_2		(5.1) to (5.5)		
3.2	F_ICO_2				
3.3	F_IN_2				
3.4	$\dot{Q}$				
3.5	$\dot{V}_A$				
3.6	$C_{\bar{v}}O_2$	$Ca_{ID}O_2$		(3)	Venous values as calculated
3.7	$C_{\bar{v}}CO_2$	$Ca_{ID}CO_2$			in previous routine
3.8	$C_{\bar{v}}N_2$	$Ca_{ID}N_2$			
3.9	$C\text{-}O_2$ --- PO_2	PO_2 --- $C\text{-}O_2$	(5.18) to (5.22)		
3.10	$C\text{-}CO_2$ --- PCO_2	PCO_2 --- $C\text{-}CO_2$	(5.23) to (5.31)		
3.11	$C\text{-}N_2$ --- PN_2	PN_2 - $C\text{-}N_2$	(5.34)		
3.12	pH --- PCO_2	PCO_2 --- pH	(5,32) to (5.33)		

TABLE 5.1

Line Sequence	Parameters Specified	Parameters Solved	Equations	Method	Comment
4	Arterial Gas Concentrations				
4.1	$\sum_{i=1}^{N} \dot{Q}_i$, CaO_{2i}, $\dot{Q}$	CaO_2	(5.11)		
4.2	$\sum_{i=1}^{N} \dot{Q}_i$, $CaCO_{2i}$, $\dot{Q}$	$CaCO_2$	(5.12)		
4.3	$\sum_{i=1}^{N} \dot{Q}_i$, CaN_{2i}, $\dot{Q}$	CaN_2	(5.13)		
5	Mixed Alveolar Partial Gas Pressures				
5.1	$\sum_{i=1}^{N} \dot{V}_{AIi}$, P_AO_{2i}, $\dot{V}_{AI}$	P_AO_2	(5.14)		
5.2	$\sum_{i=1}^{N} \dot{V}_{AIi}$, P_ACO_{2i}, $\dot{V}_{AI}$	P_ACO_2	(5.15		
5.3	$\sum_{i=1}^{N} \dot{V}_{AIi}$, P_AN_{2i}, $\dot{V}_{AI}$	P_AN_2	(5.16)		

TABLE 5.1

Line Sequence	Parameters Specified	Parameters Solved	Equations	Method	Comment
6	<u>Arterial Parial Gas Pressures</u>			(numeric Partial Derivatives) Newton Raphson (4)	
	CO_2 --- PO_2	PO_2 --- CO_2	(5.18)		
6.1	CaO_2	PaO_2	to (5.22)		
	C_{CO2} --- P_{CO2}	P_{CO2} --- C_{CO2}	(5.23) to (5.31)		
6.2	$CaCO_2$	$PaCO_2$	to (23.9)		Use a similar routine as venous routine (5).
	C_{N2} --- P_{N2}	P_{N2} ---C_{N2}			
6.3	CaN_2	PaN_2	(5.34)		
6.4	pH --- pCO_2	pCO_2 --- pH	(5.32) to (5.33)		
7	<u>Venous Partial Gas Pressures</u>			(numeric Partial Derivatives) Newton Raphson (5)	
	$C\text{-}O_2$ --- PO_2	$P_{\bar{v}}O_2$	(5.18) to (5.22)		
7.1	$C_{\bar{v}}O_2$				
	$C\text{-}CO_2$ --- PCO_2		(5.23) to (5.31)		
7.2	$C_{\bar{v}}CO_2$	$P_{\bar{v}}CO_2$			
	$C\text{-}N_2$ --- PN_2				
7.3	$C_{\bar{v}}N_2$	$P_{\bar{v}}N_2$	(5.34)		
7.4	pH --- PCO_2	PCO_2 --- pH	(5.32) to (5.33)		

TABLE 5.1

Line Sequence	Parameters Specified	Parameters Solved	Equations	Method	Comment
8	Shunt				
8.1	$C_{ID}O_2$				
8.2	CaO_2	$\dot{Q}_{sp}/\dot{Q}_t$	(5.38)		
8.3	$C_{\bar{v}}O_2$				
9	Dead Space				
9.1	$P_{ID}CO_2$	$\dot{V}_{DA}/\dot{V}_A$	(5.41)		
9.2	P_ACO_2				
10	Other derived physiological parameters are calculated at this point.				

CHAPTER 6
COMPUTER SIMULATIONS

6.1 INTRODUCTION

The mathematical model as discussed in the previous chapter was applied as an iterative subroutine in a master simulation program to generate a series of simulations.

Different solutions for the bloos gas pressures (i.e. PaO_2, $P\bar{v}O_2$, $PaCO_2$, $P_{\bar{v}}CO_2$, PaN_2, $P_{\bar{v}}N_2$) exist for each set of model parameters. It is rather obvious that through structured variation of the model parameters, the respective solutions can be obtained and the effect on the blood gas pressures observed.

The number of combinations by which a set of model parameters can be selected is limited only by the physiological range of the respective parameters. In practice selection is biased by the prospective clinical application of simulations.

6.2 SIMULATION METHOD

A series of simulations was completed according to the flow chart presented in fig. 6.1. The respective model parameters (correlating in most instances with actual physiological variables) as well as the $\dot{V}_A/\dot{Q}$ distribution parameters were specified and held constant for the duration of a single simulation procedure.

For each of the simulation procedures, two or three of the above-mentioned parameters were however varied iteratively over a limited range; producing a set of solutions in either two or three dimensions.

The $\dot{V}_A/\dot{Q}$ distributions generated as an input for the model were altered by equating a distribution parameter with one of the parameters varied in the simulation program. The actual shape of the ventilation/perfusion distribution is in fact the entity that bears the most clinical significance (as discussed in 4.4) and therefore deserves further discussion.

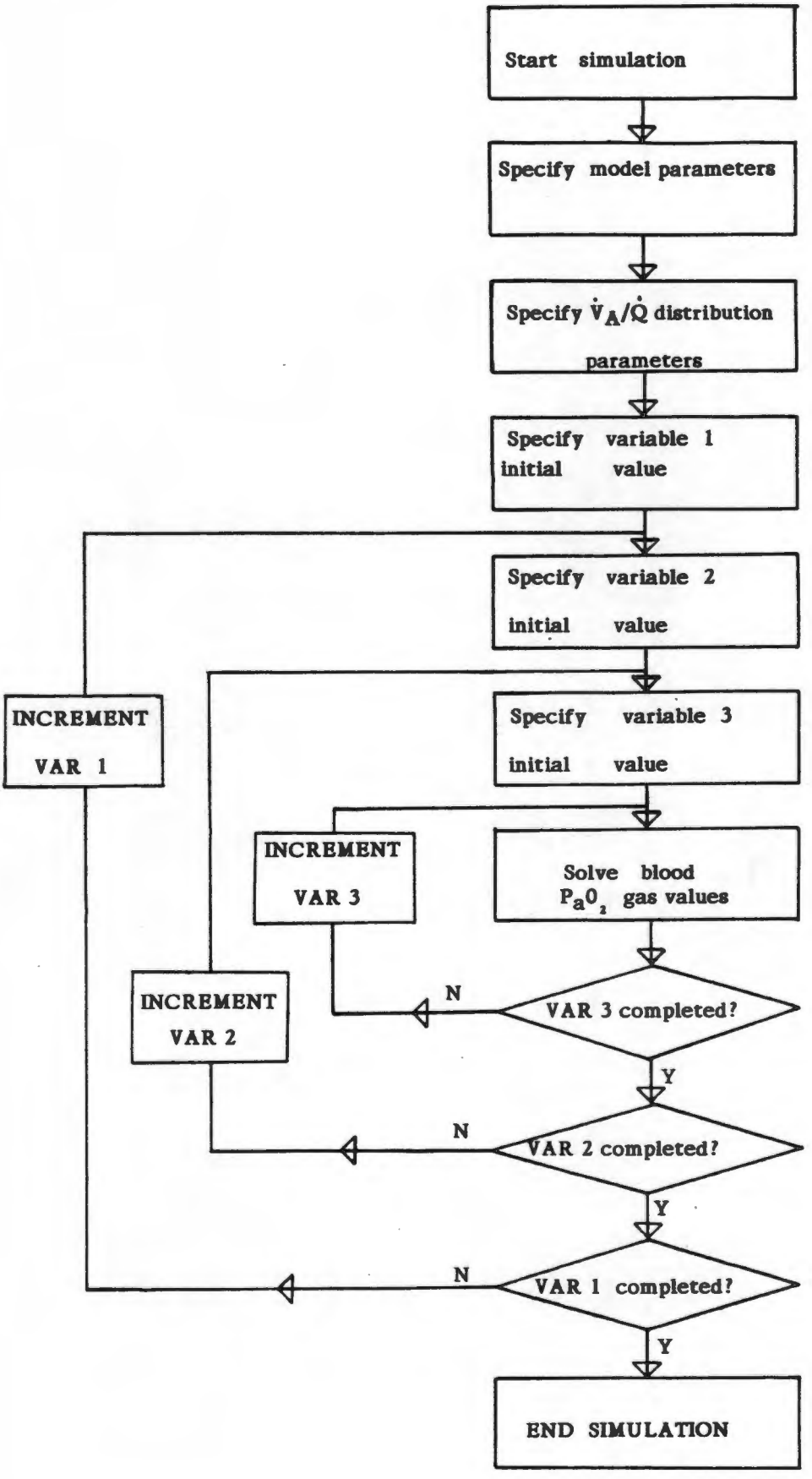


Figure 6.1 Flow chart for master simulation program

6.2.1 $\dot{V}_A/\dot{Q}$ Distributions: $\dot{V}_A/\dot{Q}$ distributions were generated at discrete intervals between two extreme cases; i.e. a distribution with a single mode represented by a mean $\dot{V}_A/\dot{Q}$ of 0,85 and the state of an additional mode with a mean $\dot{V}_A/\dot{Q}$ that is markedly lower. (The mean $\dot{V}_A/\dot{Q}$ value of the lesser mode is subsequently referred to as the low $\dot{V}_A/\dot{Q}$ value.)

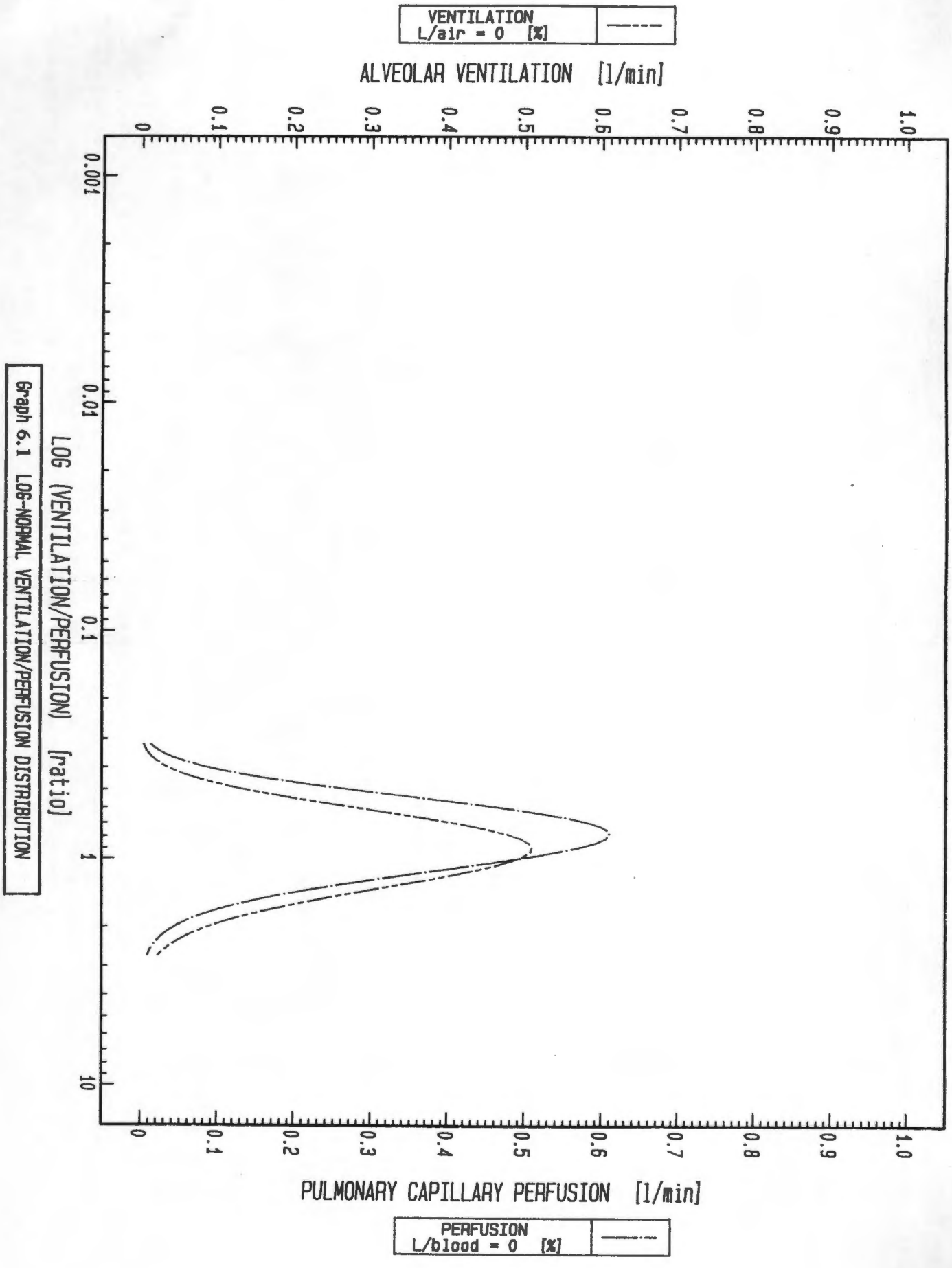
The intermediate distributions were generated by increasing the amount of blood and air flow to the low $\dot{V}_A/\dot{Q}$ region, starting at zero. The mean $\dot{V}_A/\dot{Q}$ values for the two modes were held constant, as well as the combined pulmonary perfusion to the two regions.

In order to realise these conditions it is inevitable to tolerate a small decrease in the total alveolar ventilation with a concomitant increase of perfusion to the low region. (The low $\dot{V}_A/\dot{Q}$ value would otherwise change as a result of the perfusion change in this region.) The decrease in alveolar ventilation is nevertheless physiologically justifiable, as it is analogous to increased pulmonary oedema, resulting in an effective decrease in ventilation to these regions and a percentage increase in perfusion.

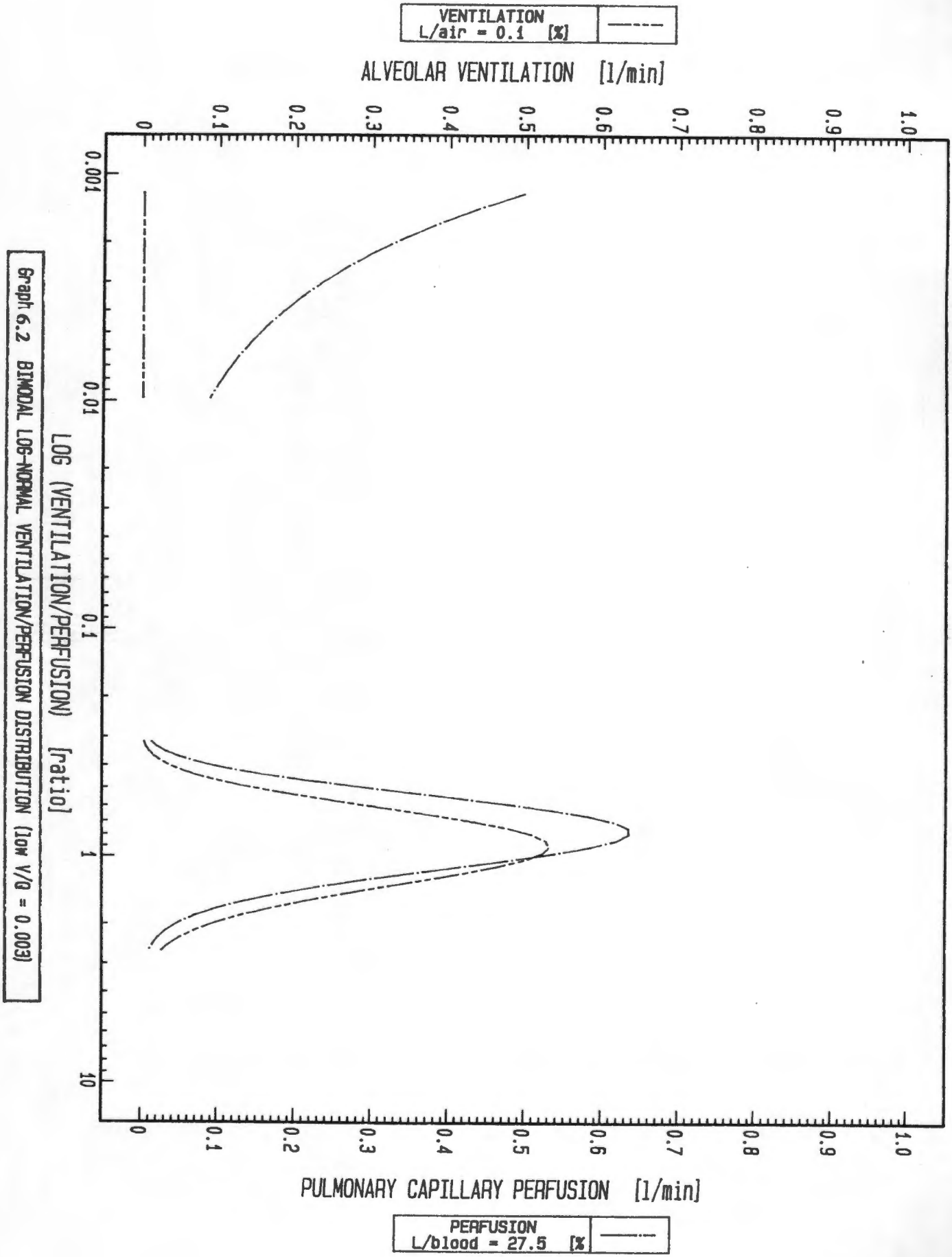
Two separate series of distributions were considered with respective low $\dot{V}_A/\dot{Q}$ values of 0,124 and 0,003 and a veriation of the blood and air supply (as discussed) for both cases. Although variations inbetween the two low $\dot{V}_A/\dot{Q}$ values were not explicitly addressed, it is assumed that the majority of distributions for ARDS patients, or those susceptible to ARDS, will be within the boundaries represented by these two series (i.e. a perfusion to the low $\dot{V}_A/\dot{Q}$ region of 0 to 55% of total pulmonary perfusion and a low $\dot{V}_A/\dot{Q}$ value of inbetween 0,003 and 0,124). This assumption will be elucidated in the discussion pertaining to graph 7.2.

Three of the distributions in the series with a low $\dot{V}_A/\dot{Q}$ value of 0,003 are represented in graphs 6.1, 6.2 and 6.3; with respective percentages of total pulmonary perfusion to the low region of 0%, 27,5% and 55%.

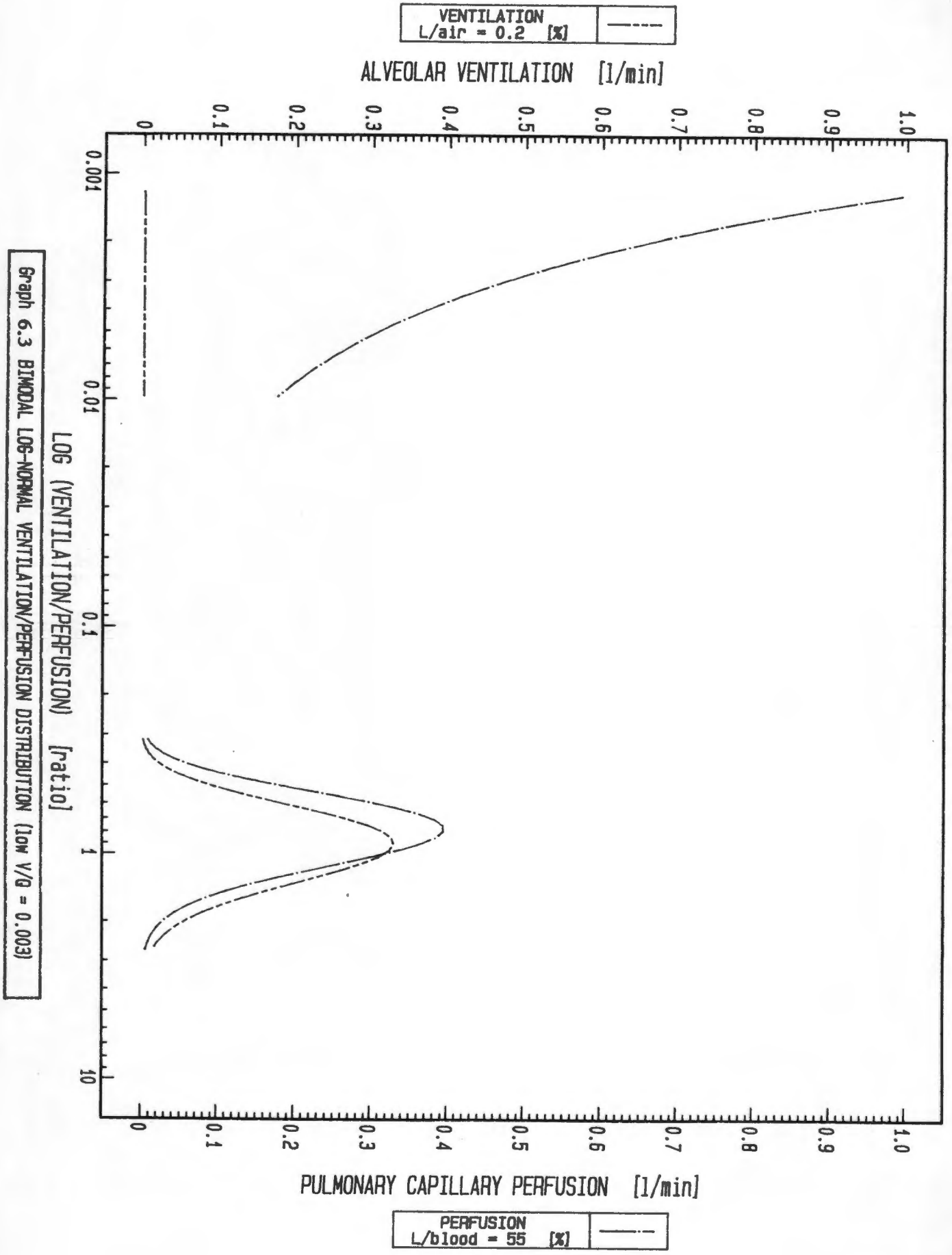
Graphs 6.1, 6.4 and 6.5 represent the corresponding distributions in the series with a low $\dot{V}_A/\dot{Q}$ value of 0,124.



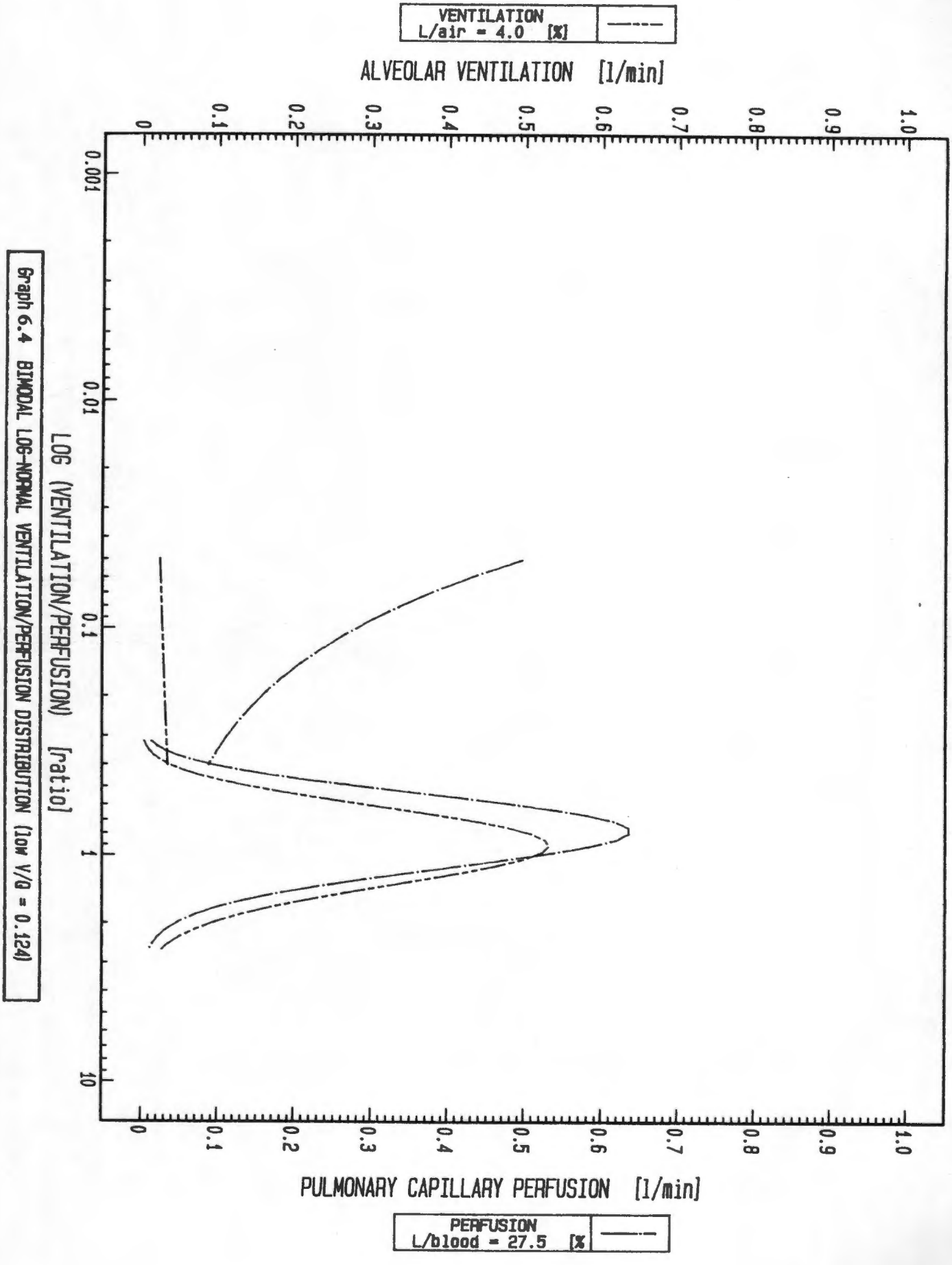
Graph 6.1 LOG-NORMAL VENTILATION/PERFUSION DISTRIBUTION



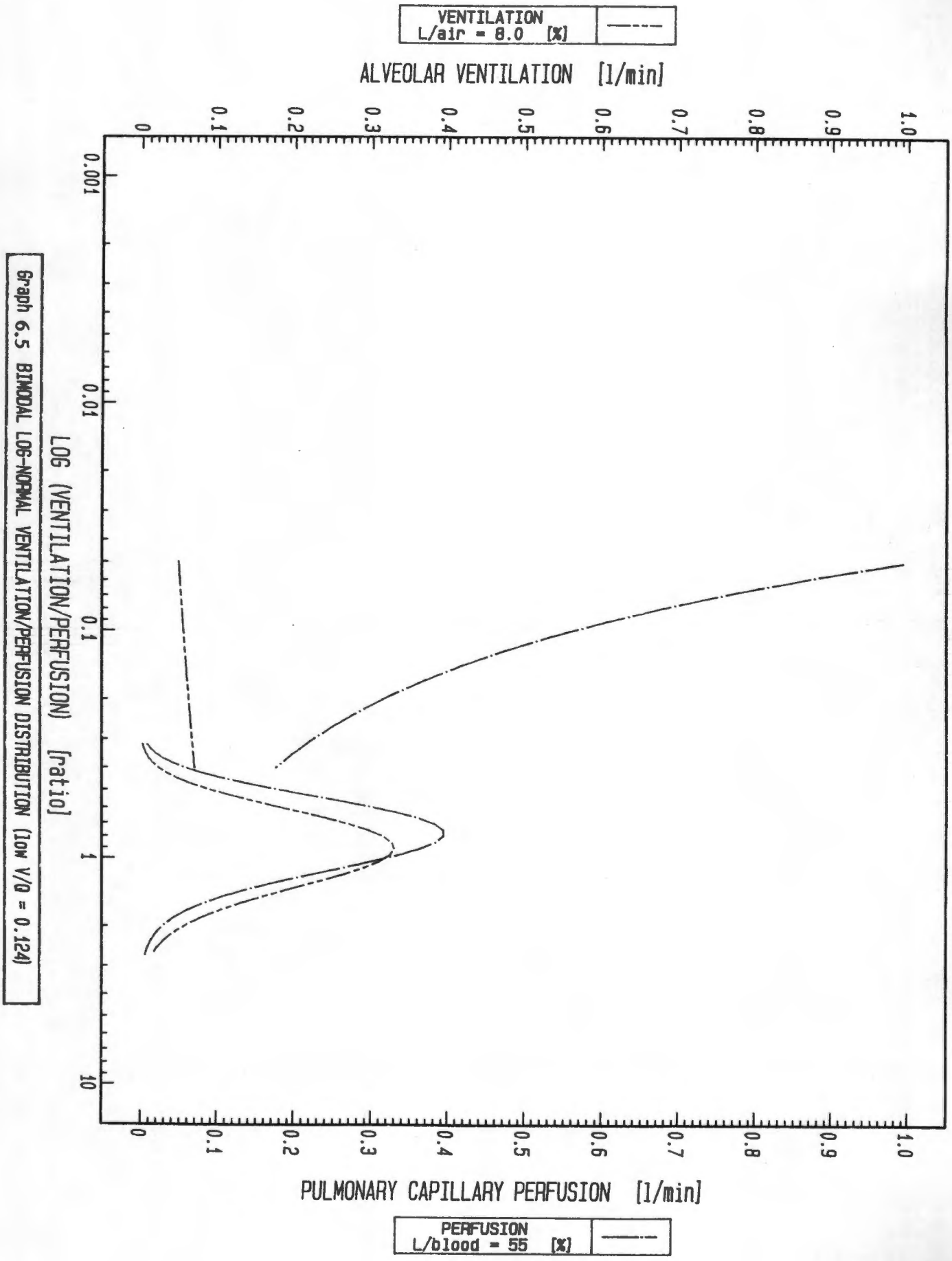
Graph 6.2 BIMODAL LOG-NORMAL VENTILATION/PERFUSION DISTRIBUTION (low V/Q = 0.003)



Graph 6.3 BIMODAL LOG-NORMAL VENTILATION/PERFUSION DISTRIBUTION (low V/Q = 0.003)



Graph 6.4 BIMODAL LOG-NORMAL VENTILATION/PERFUSION DISTRIBUTION (low V/Q = 0.124)



Graph 6.5 BIMODAL LOG-NORMAL VENTILATION/PERFUSION DISTRIBUTION (low V/Q = 0.124)

6.2.2 Simulation Strategy: The simulations are divided into two major categories, namely those pertaining to a low $\dot{V}_A/\dot{Q}$ value of 0,003 and 0,124 respectively. (The low $\dot{V}_A/\dot{Q}$ value is specified as one of the model parameters.)

Furthermore the percentage of total pulmonary perfusion to the low $\dot{V}_A/\dot{Q}$ region is varied between 0% and 55% and is, with reference to fig. 6.1, represented by variable 2.

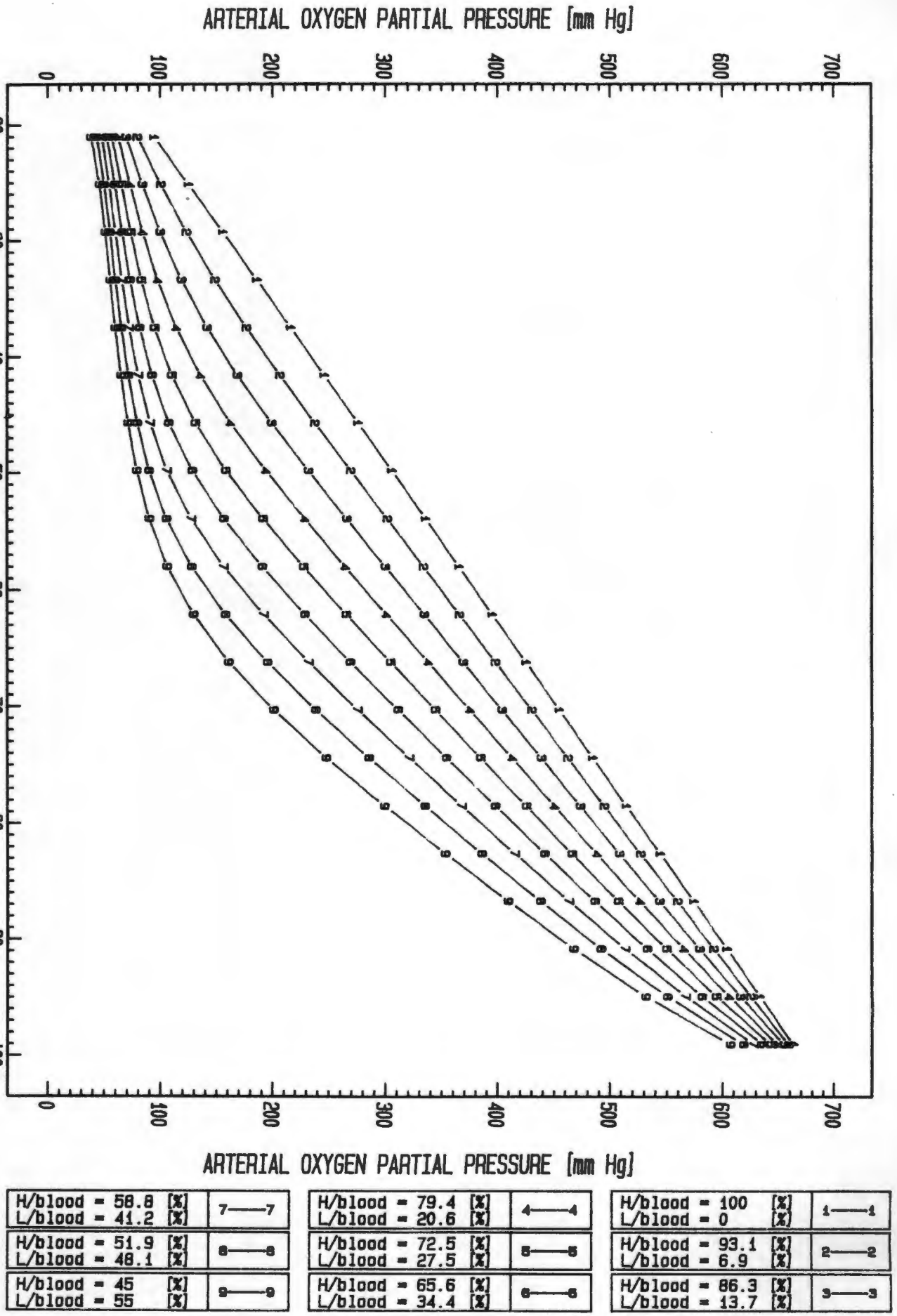
In all instances, the fraction of inspired oxygen is varied from 0,21 to 0,99 and is, with reference to fig. 6.1, represented by variable 3.

The data series representing the arterial oxygen partial pressure as a function of both the fraction of inspired oxygen and the percentage of total pulmonary perfusion to the respective low $\dot{V}_A/\dot{Q}$ regions, are considered to be the model outputs bearing the most useful information. (In these cases variable 1, with reference to fig. 6.1, is held constant.)

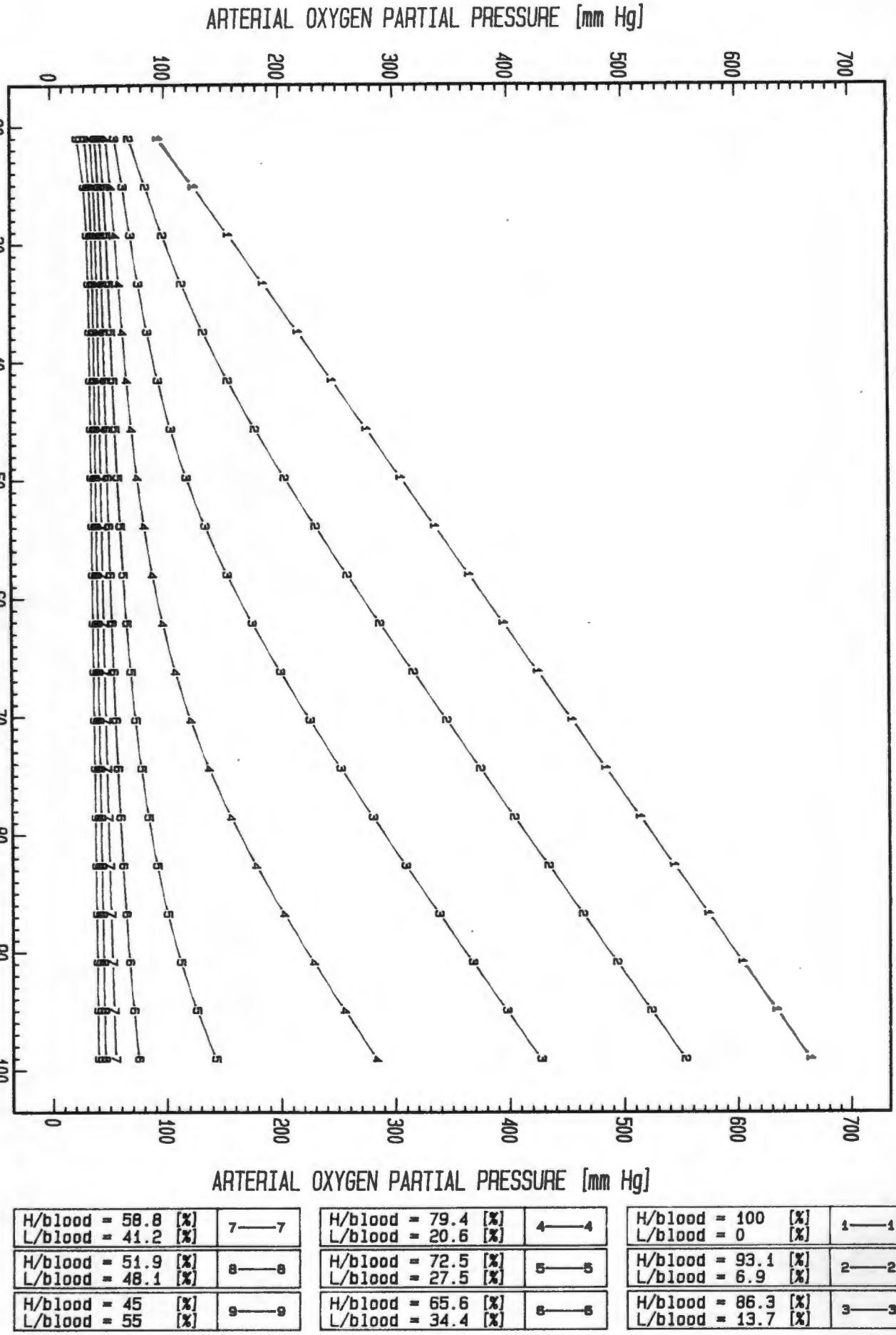
The following values were assigned to the various model parameters and were kept constant for each simulation (except for the sensitivity analysis, in which case one parameter was varied at a time). Simulations resulting from these "standard" values, are considered to be the norm in subsequent discussions.

	Parameter	Value	Inits
i)	F_ICO_2	0,0	[fraction]
ii)	F_IN_2	1 - F_IO_2	[fraction]
ii)	Solubility of O_2 in blood	0,003	[mlO_2/100ml - mmHg]
iv)	Temp	37,0	[^oC]
v)	HB (venous and arterial)	15,5	[g/100ml blood]
vi)	Solubility of N_2 in blood	0,0017	[mlN_2/100ml - mmHg]
vii)	DP50	0,0	[mmHg]
viii)	K (BTPS to STPD factor)	0,0121	-
ix)	HCRIT	0,47	-
x)	P_{EF} (effective gas pressure)	713,0	[mmHg]
xi)	$\dot{V}O_2$	0,275	[l/min]
xii)	$\dot{V}CO_2$	0,234	[l/min]
xiii)	$\dot{V}N_2$	0,0	[l/min]
xiv)	$\dot{V}_A$	5,0	[l/min]
xv)	$\dot{Q}$	5,9	[l/min]
xvi)	number of lung compartments	13,0	-
xvii)	FIO_2	0,21 to 0,99	[fraction]
xviii)	$\dot{V}_A/\dot{Q}$ distribution parameters	as discussed	

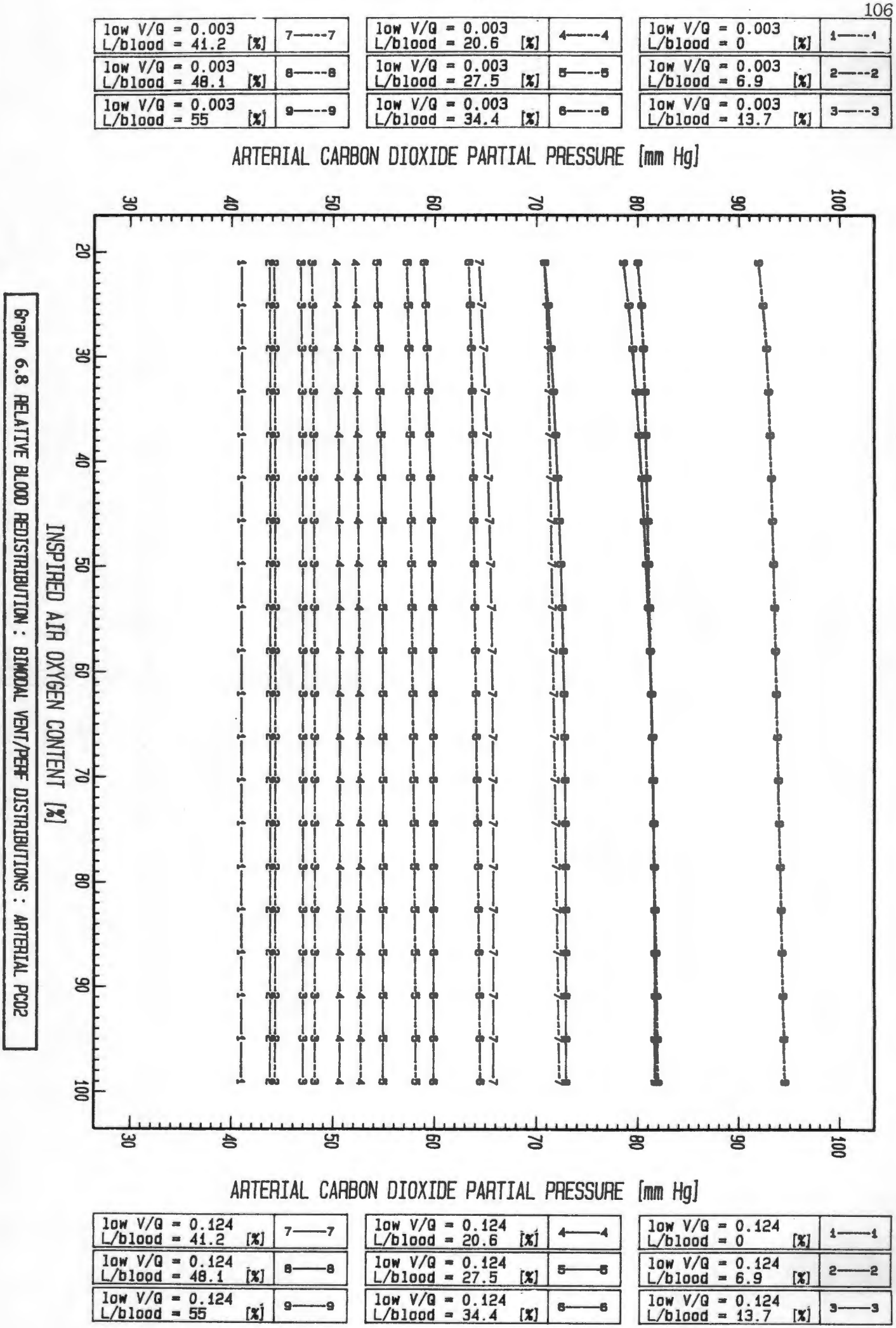
Graphs 6.6 to 6.9 were generated by the model with the abovementioned techniques.



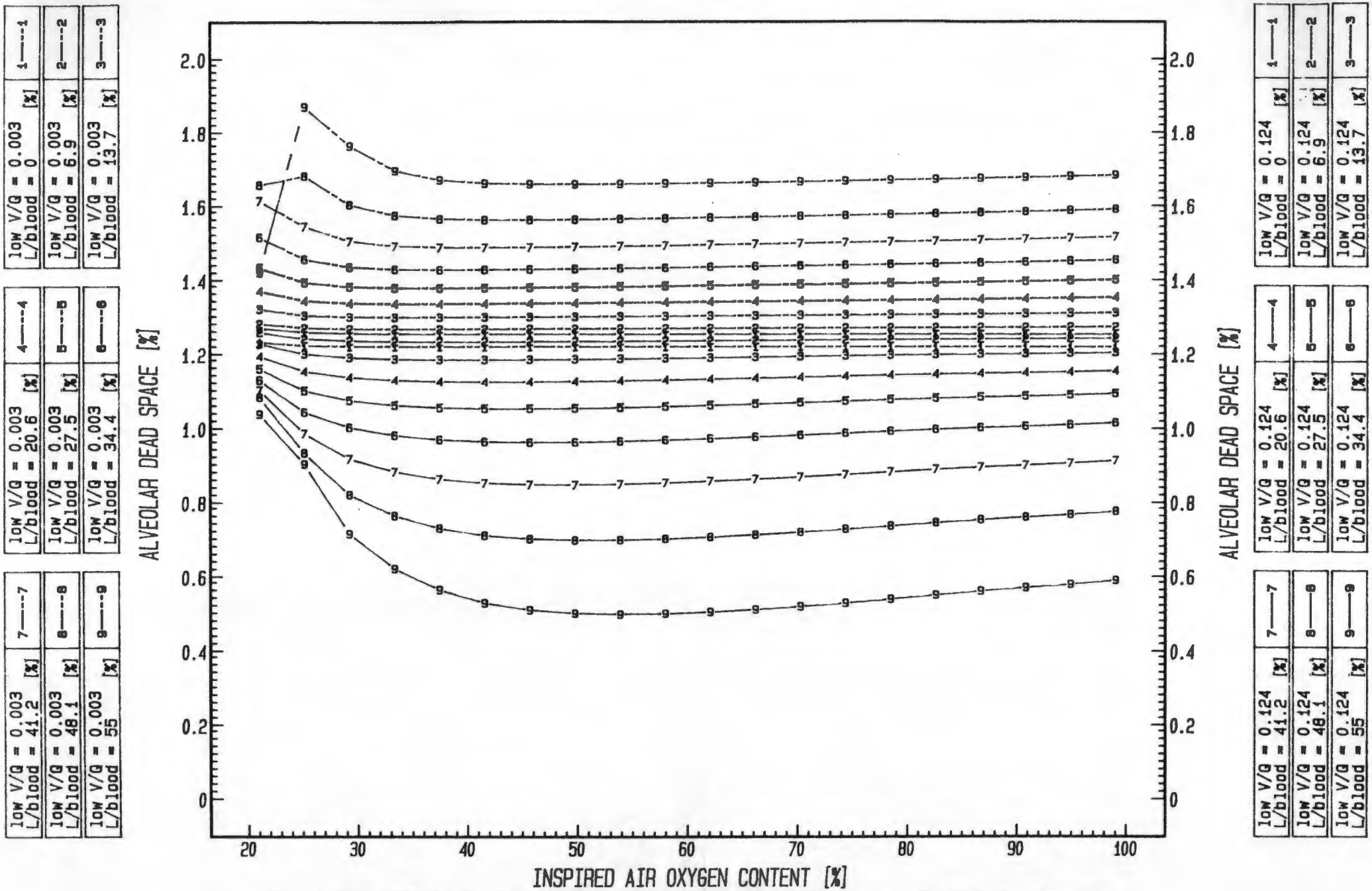
Graph 6.6 RELATIVE BLOOD REDISTRIBUTION : BIMODAL VENT/PERF DISTRIBUTION (low V/Q = 0.124)



Graph 6.7 RELATIVE BLOOD REDISTRIBUTION : BIMODAL VENT/PERF DISTRIBUTION (low V/Q = 0.003)



Graph 6.8 RELATIVE BLOOD REDISTRIBUTION : BIMODAL VENT/PERF DISTRIBUTIONS : ARTERIAL PCO2



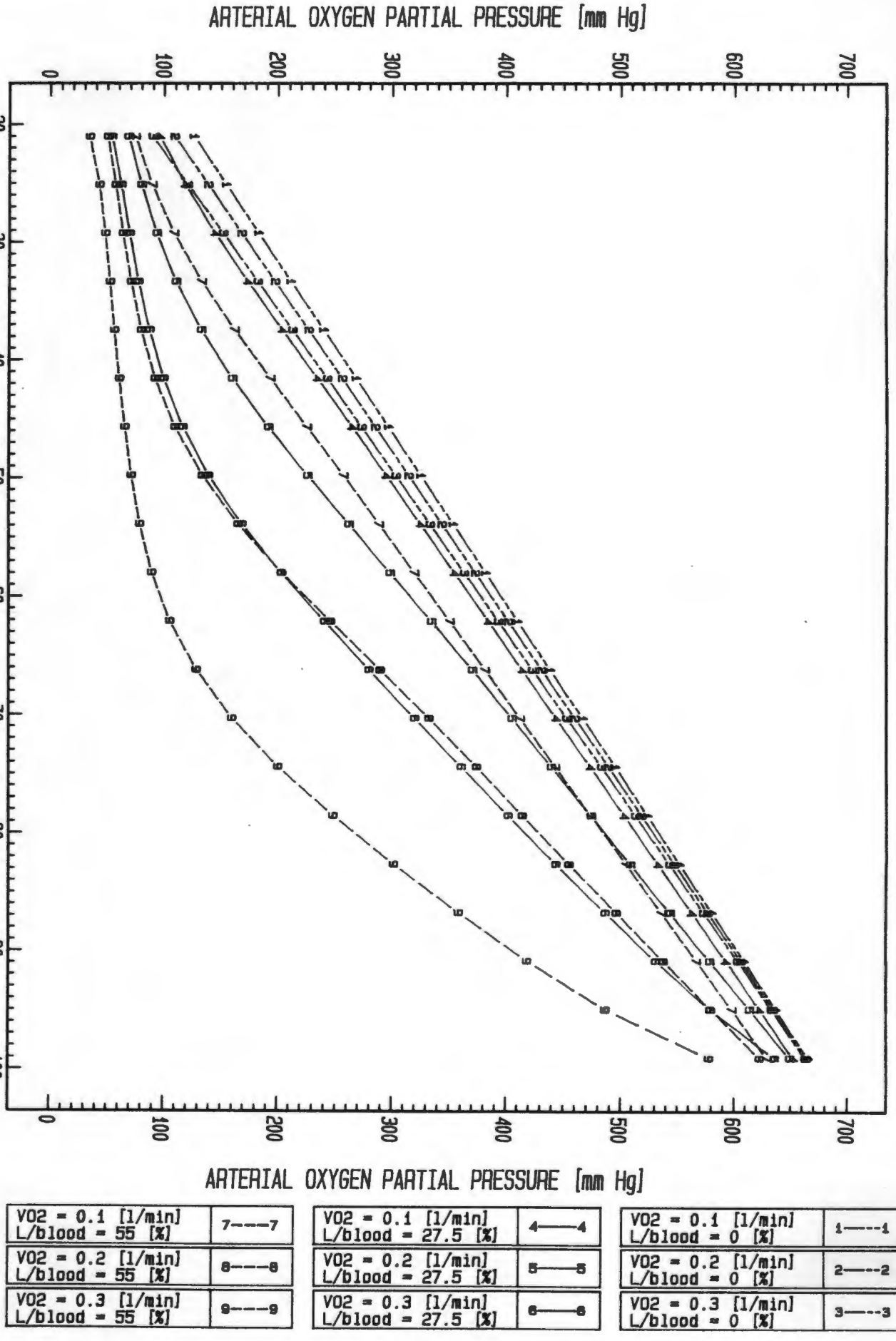
Graph 6.9 RELATIVE BLOOD REDISTRIBUTION : BIMODAL VENT/PERF DISTRIBUTIONS : ALVEOLAR DEAD SPACE

6.2.3 Parameter Sensitivity Analysis: In order to investigate the effect of variations in model parameters on the model outputs, all the parameters were varied one at a time (variable 1 with reference to fig 6.1) and a new set of solutions thus obtained.

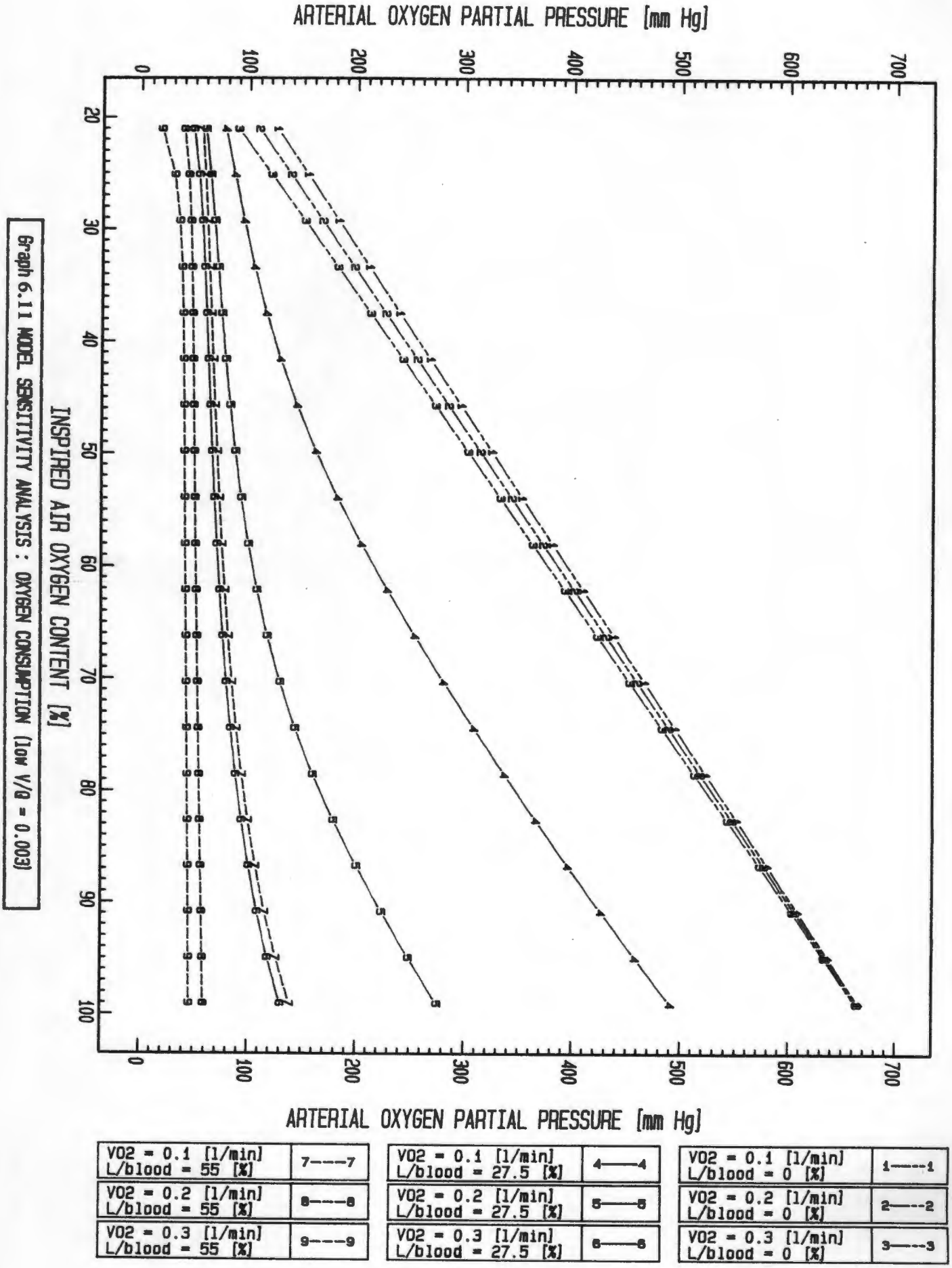
The above-mentioned exercise was repeated twice; in the one instance the range of variations in the physiological variables was selected to represent the most extreme conditions compatible with life. This series is represented by graphs 6.10 to 6.25.

In the second instance a 10% deviation around what are considered to be the mean values was induced. The results are summarised in Appendix C.

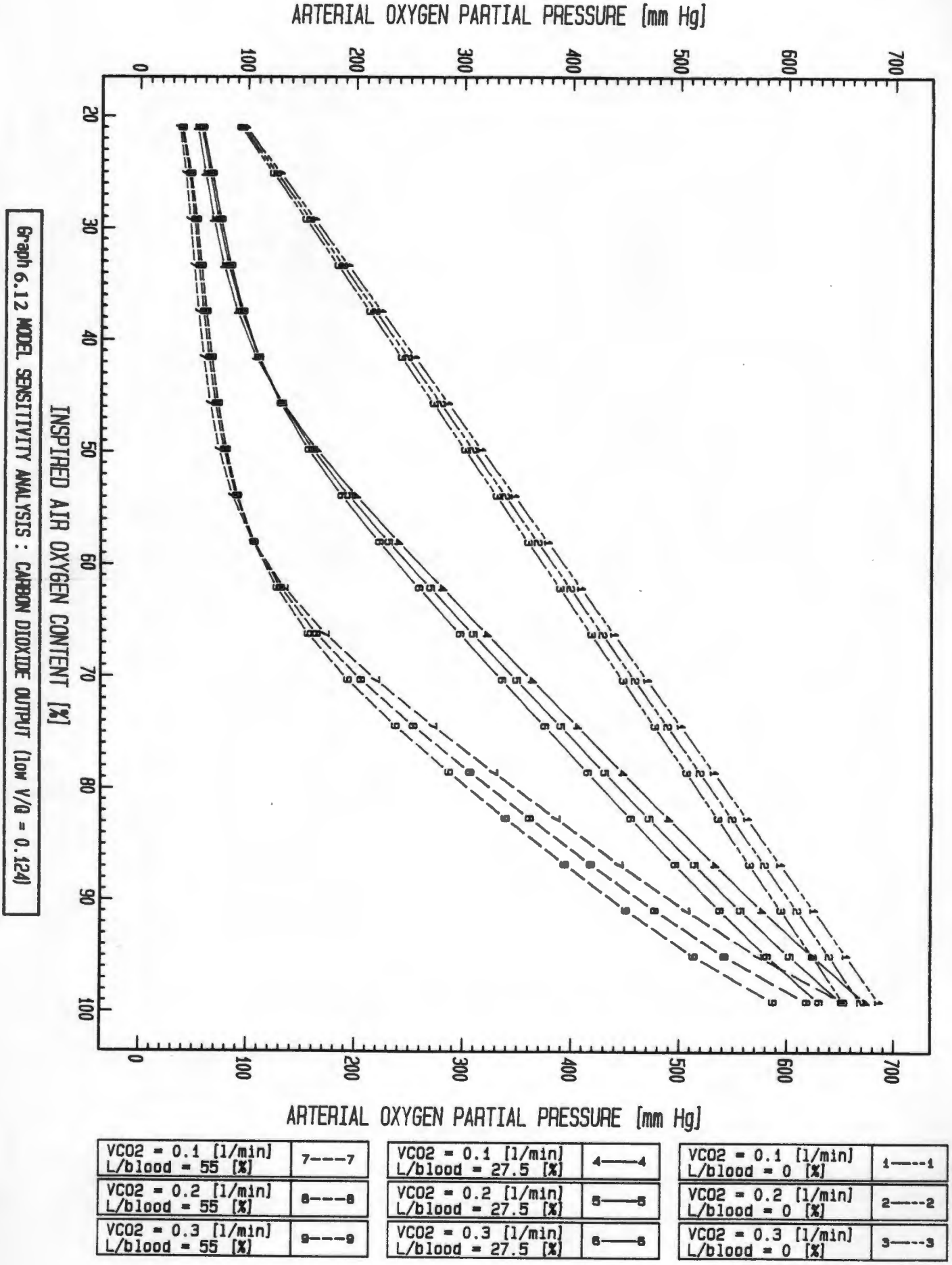
It is noteworthy that due to the nonlinear nature of the model, it is not possible to assume that the effect of a change in more than one of these parameters at a time will result in the sum total of the effect of the individual changes. Due to the limitation on computer processing speed (the average computer runtime is 2 hours and 12 minutes for a single simulation), it is not practical to investigate different combinations at this stage.



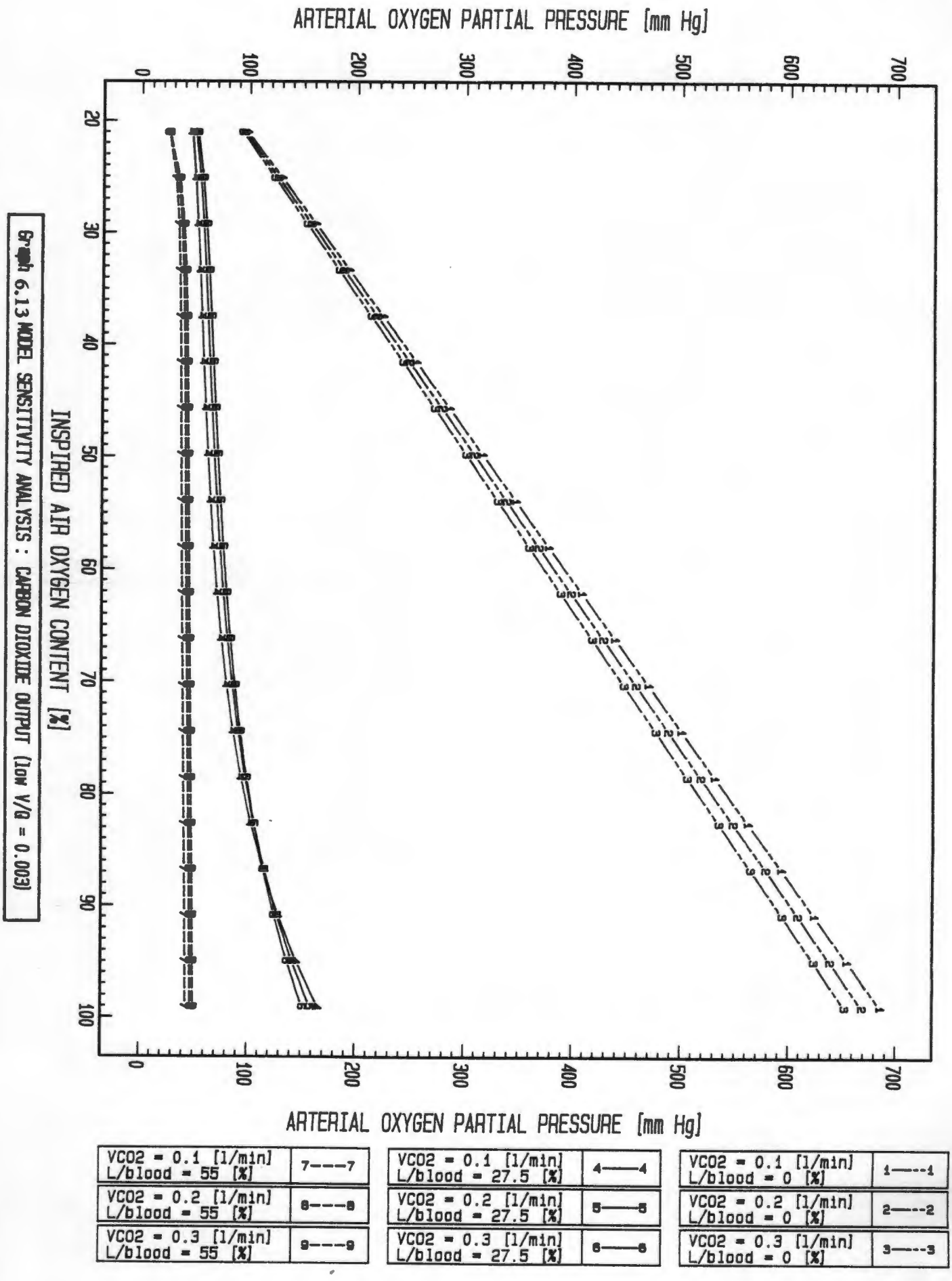
Graph 6.10 MODEL SENSITIVITY ANALYSIS : OXYGEN CONSUMPTION (low V/Q = 0.124)



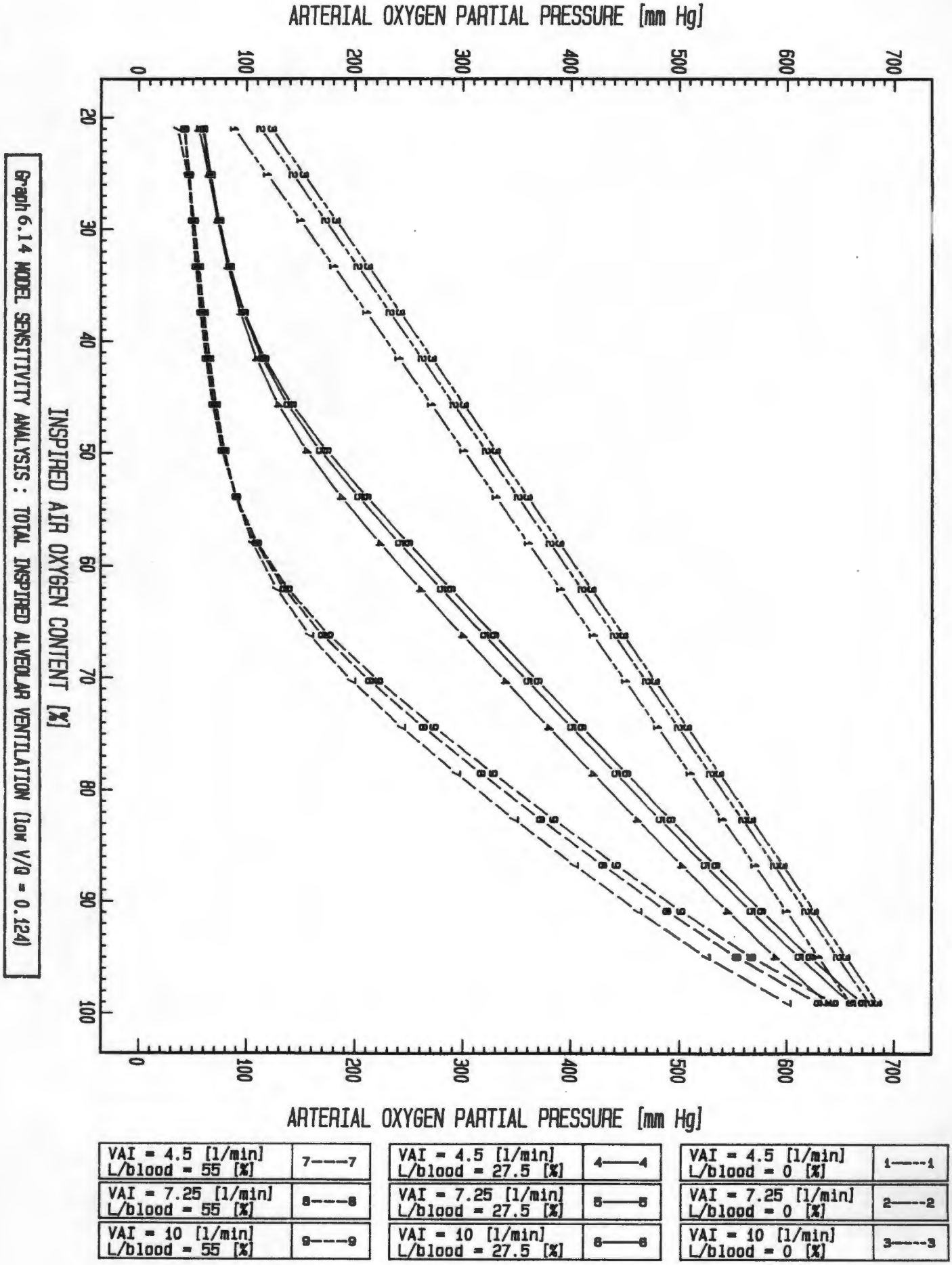
Graph 6.11 MODEL SENSITIVITY ANALYSIS : OXYGEN CONSUMPTION (low V/Q = 0.003)



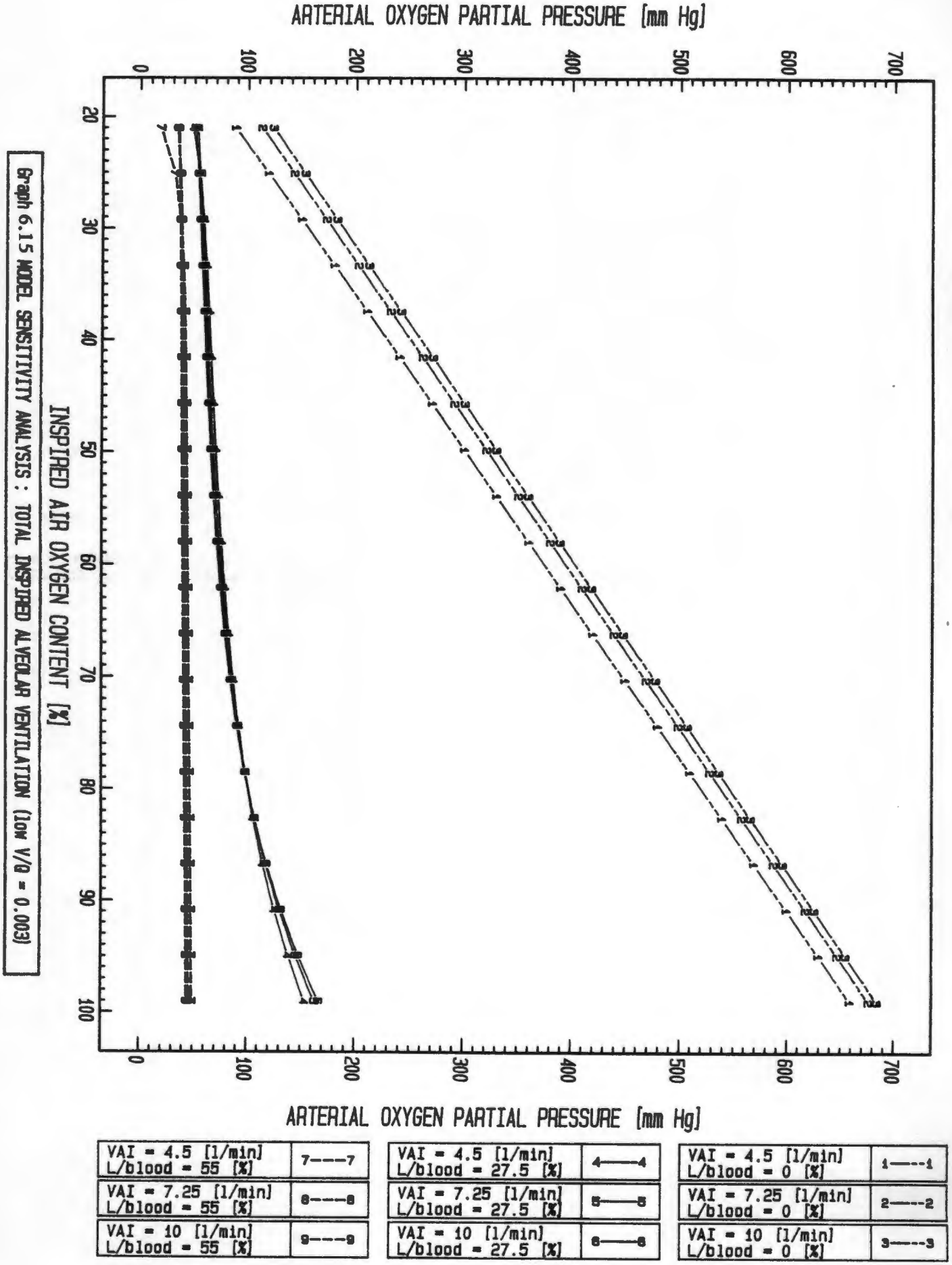
Graph 6.12 MODEL SENSITIVITY ANALYSIS : CARBON DIOXIDE OUTPUT (low V/Q = 0.124)



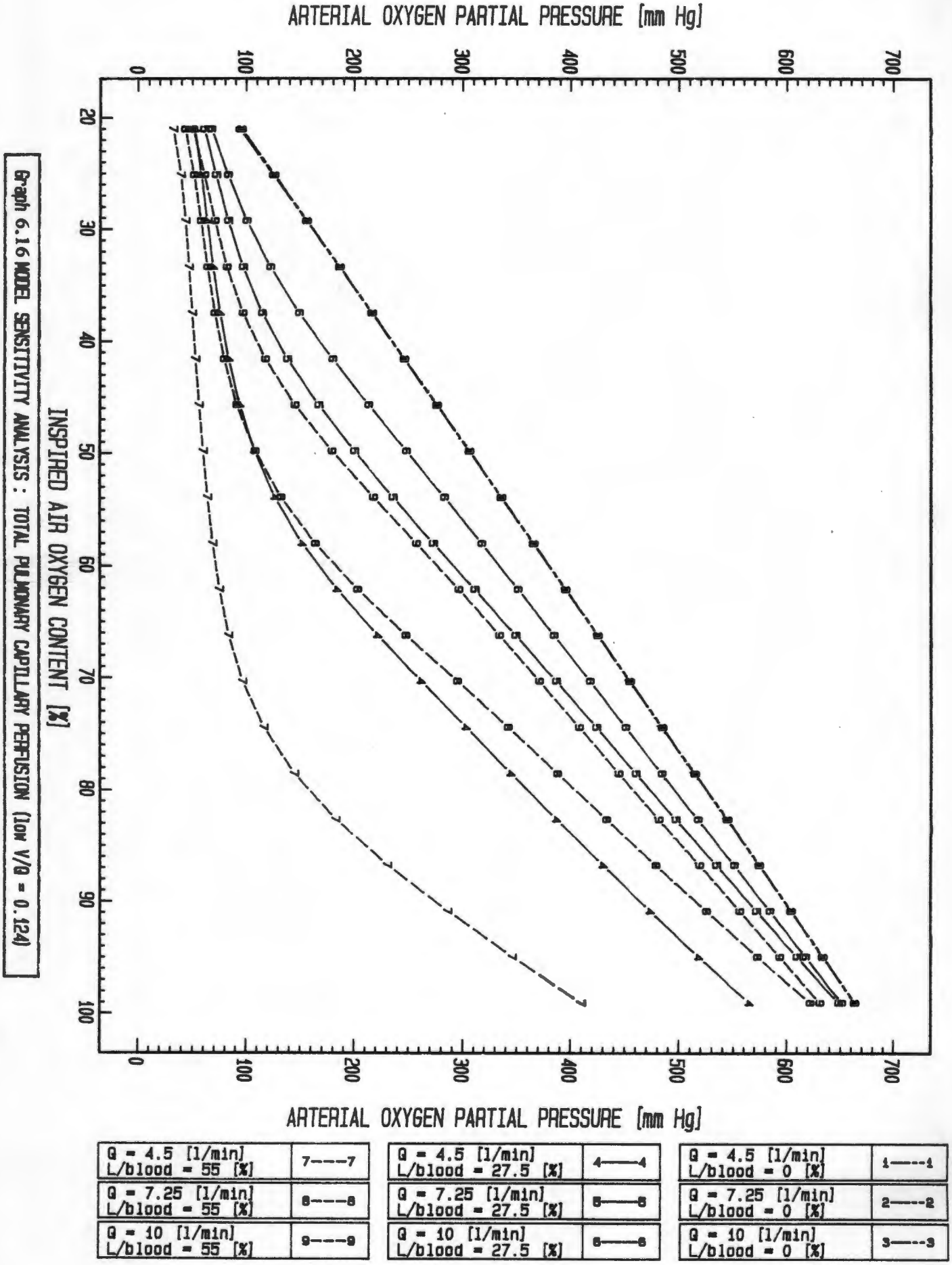
Graph 6.13 MODEL SENSITIVITY ANALYSIS : CARBON DIOXIDE OUTPUT (low V/Q = 0.003)



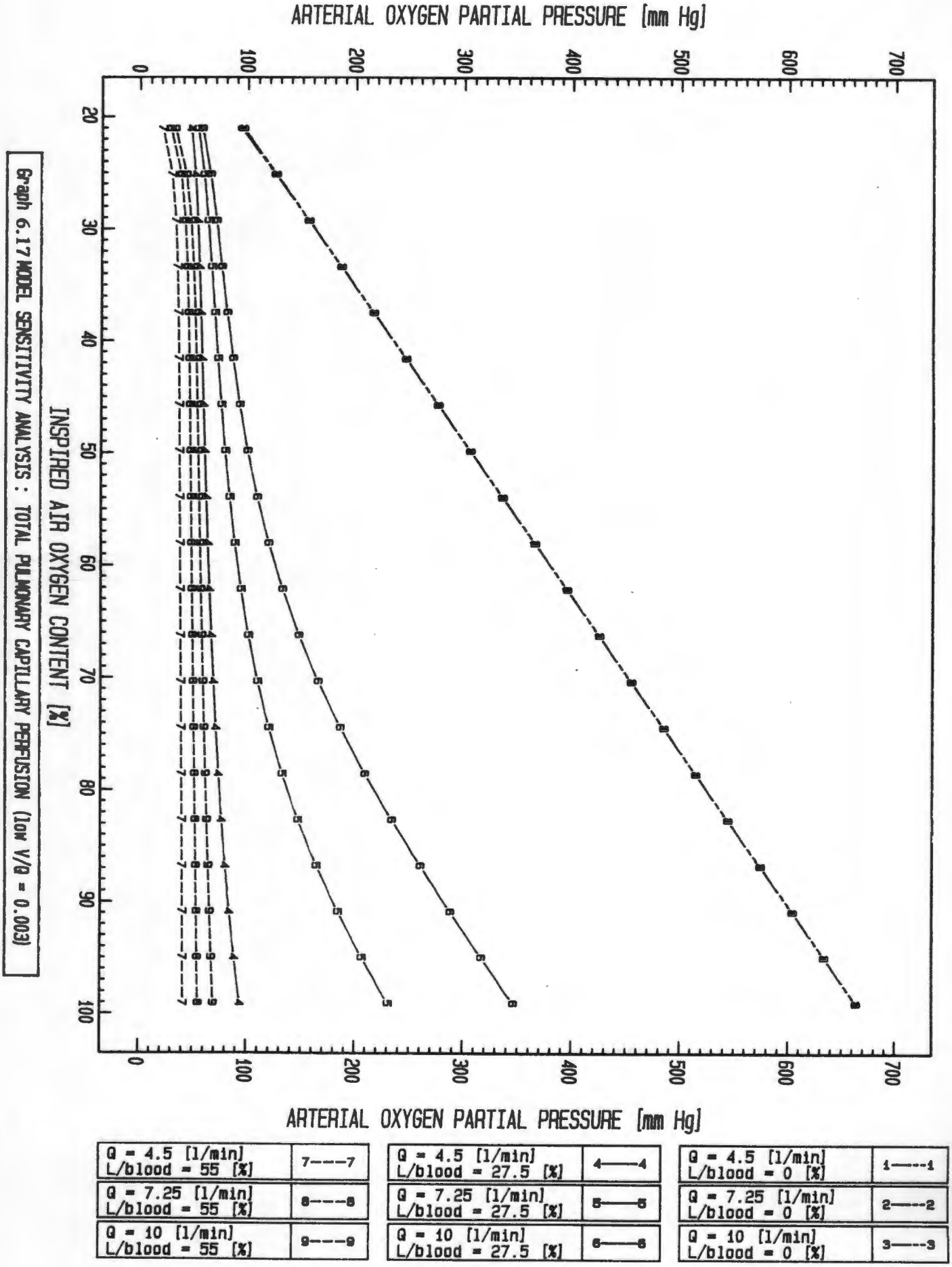
Graph 6.14 MODEL SENSITIVITY ANALYSIS : TOTAL INSPIRED ALVEOLAR VENTILATION (low V/Q = 0.124)



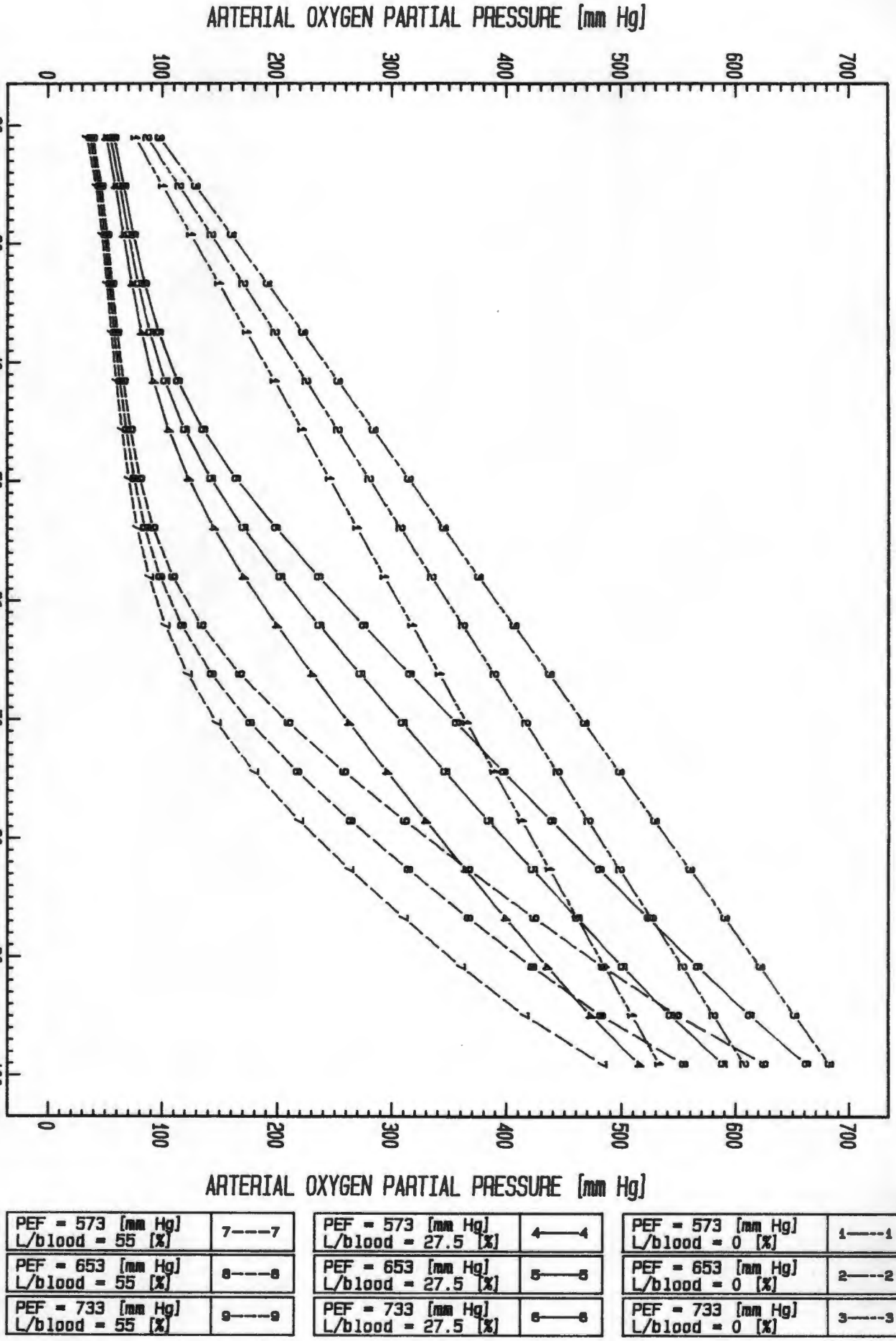
Graph 6.15 MODEL SENSITIVITY ANALYSIS : TOTAL INSPIRED ALVEOLAR VENTILATION (low V/Q = 0.003)



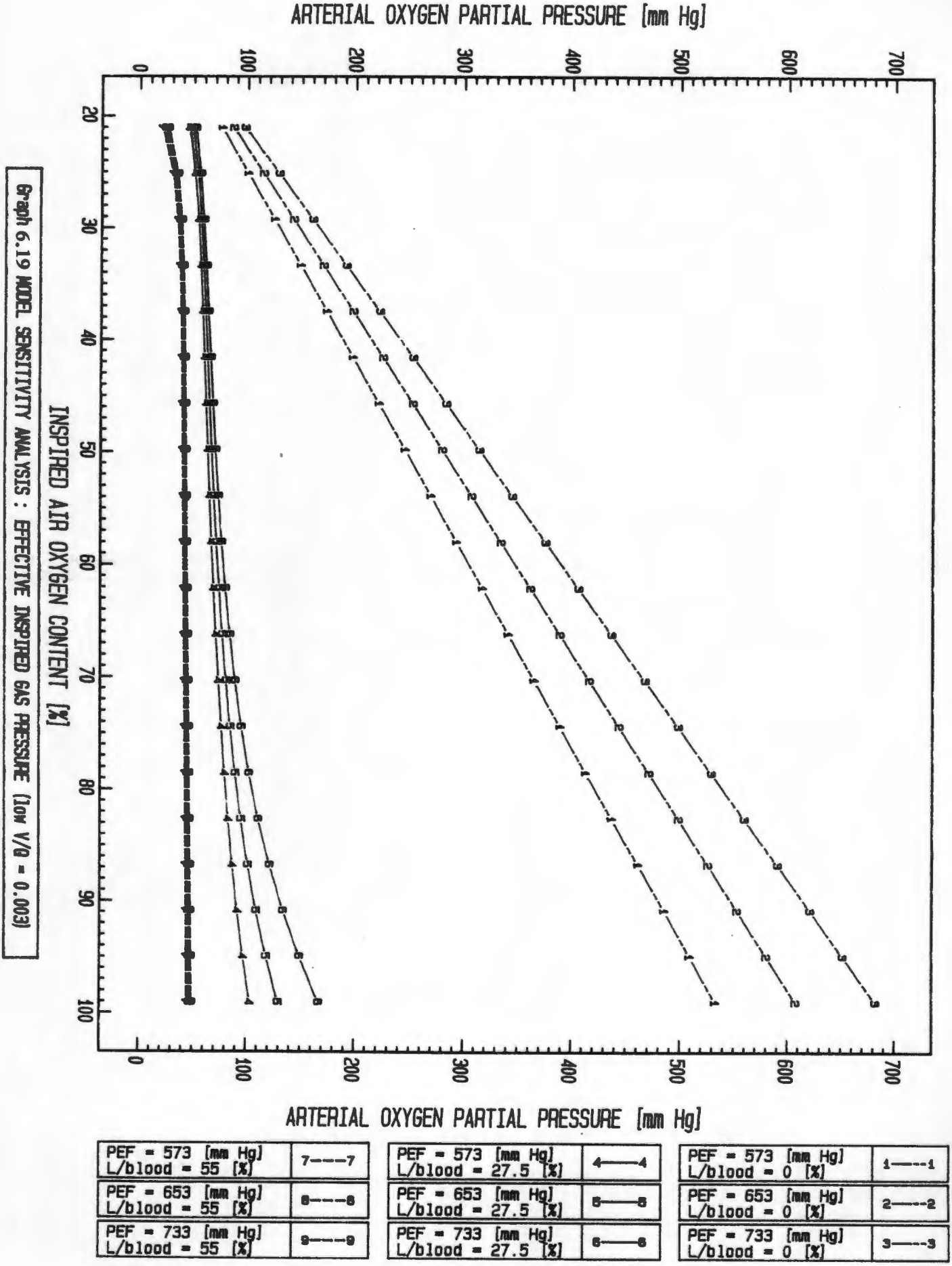
Graph 6.16 MODEL SENSITIVITY ANALYSIS : TOTAL PULMONARY CAPILLARY PERFUSION (low V/Q = 0.124)



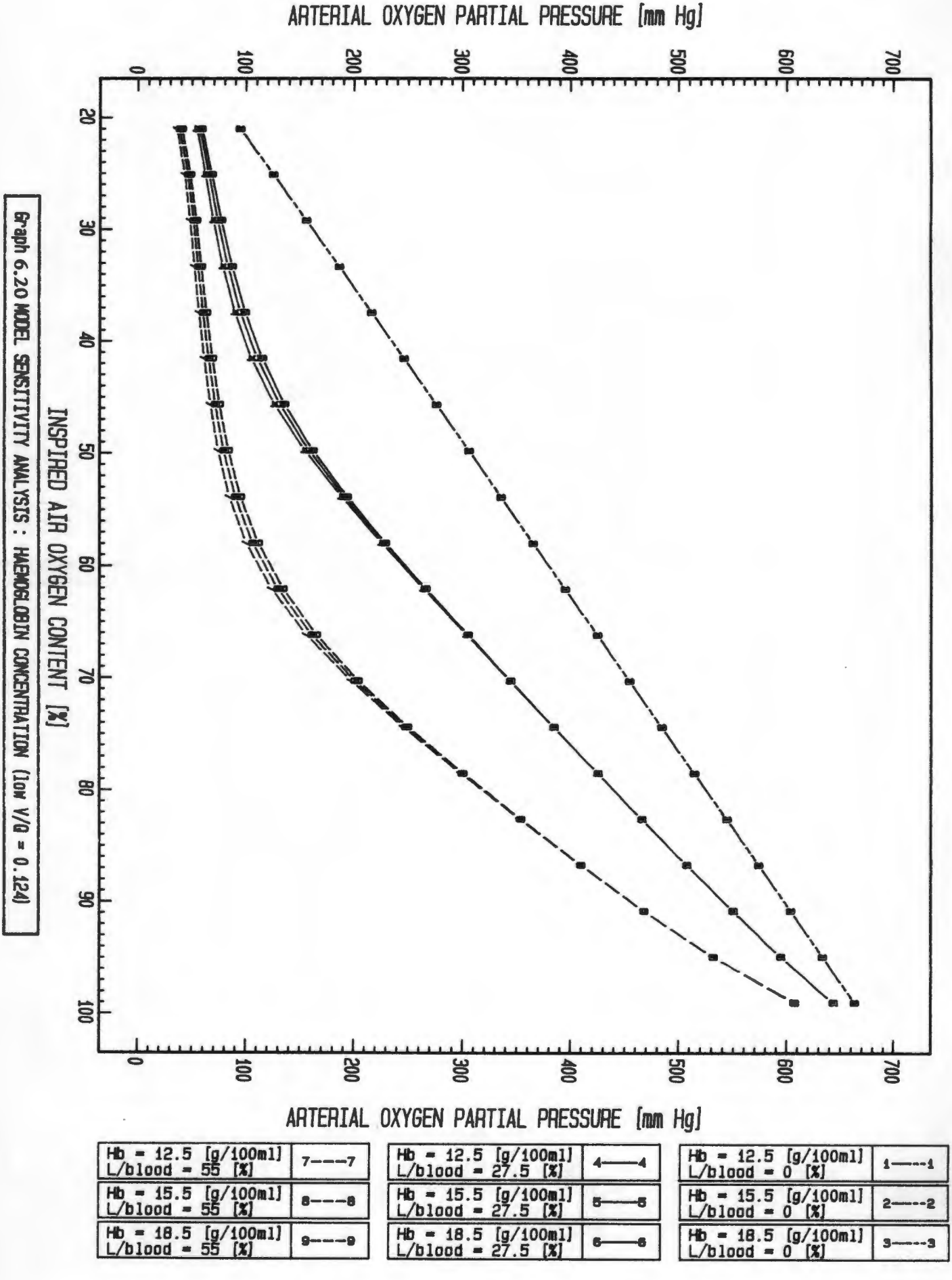
Graph 6.17 MODEL SENSITIVITY ANALYSIS : TOTAL PULMONARY CAPILLARY PERFUSION (low V/Q = 0.003)



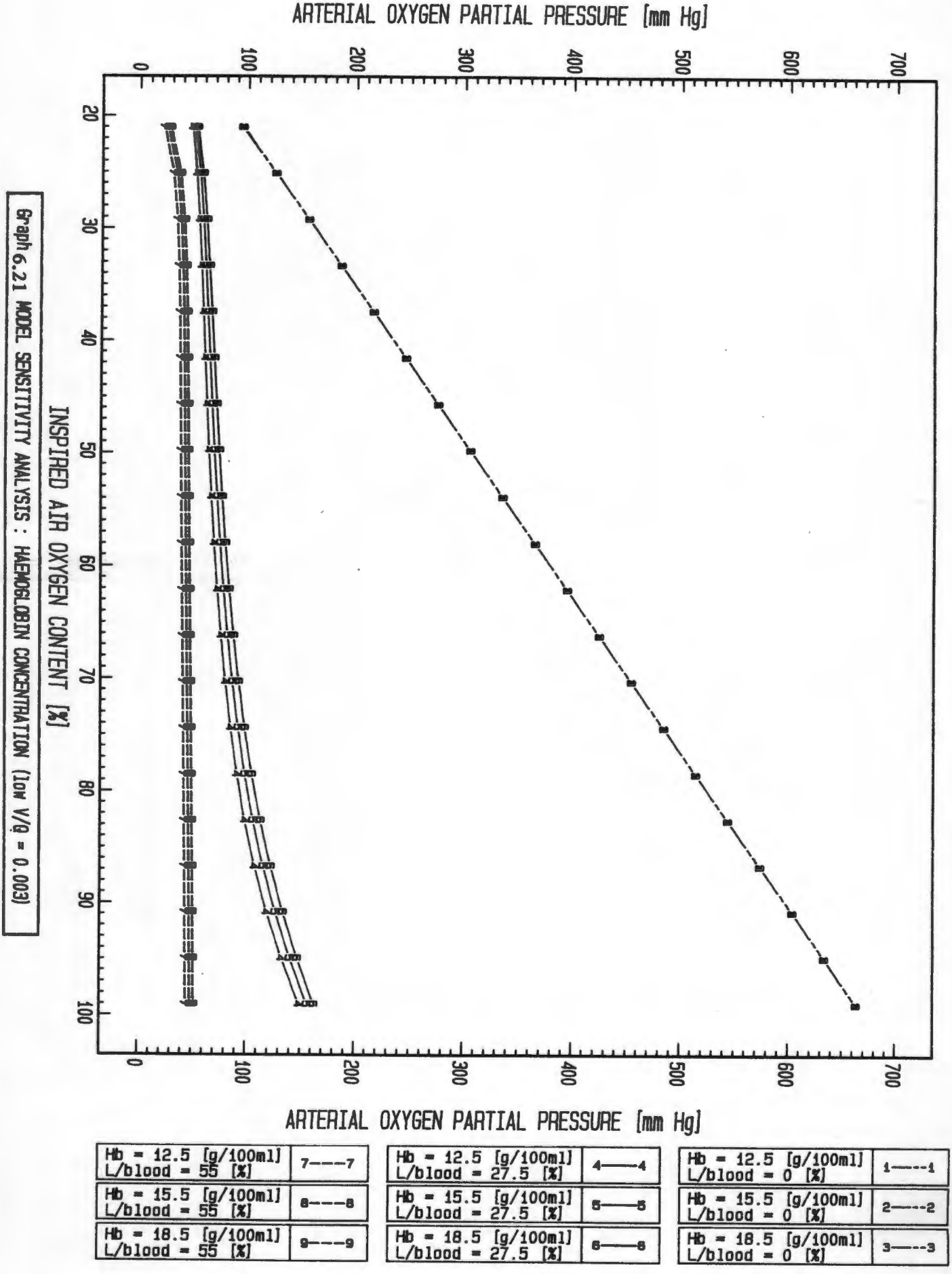
Graph 6.18 MODEL SENSITIVITY ANALYSIS : EFFECTIVE INSPIRED GAS PRESSURE (low V/Q = 0.124)

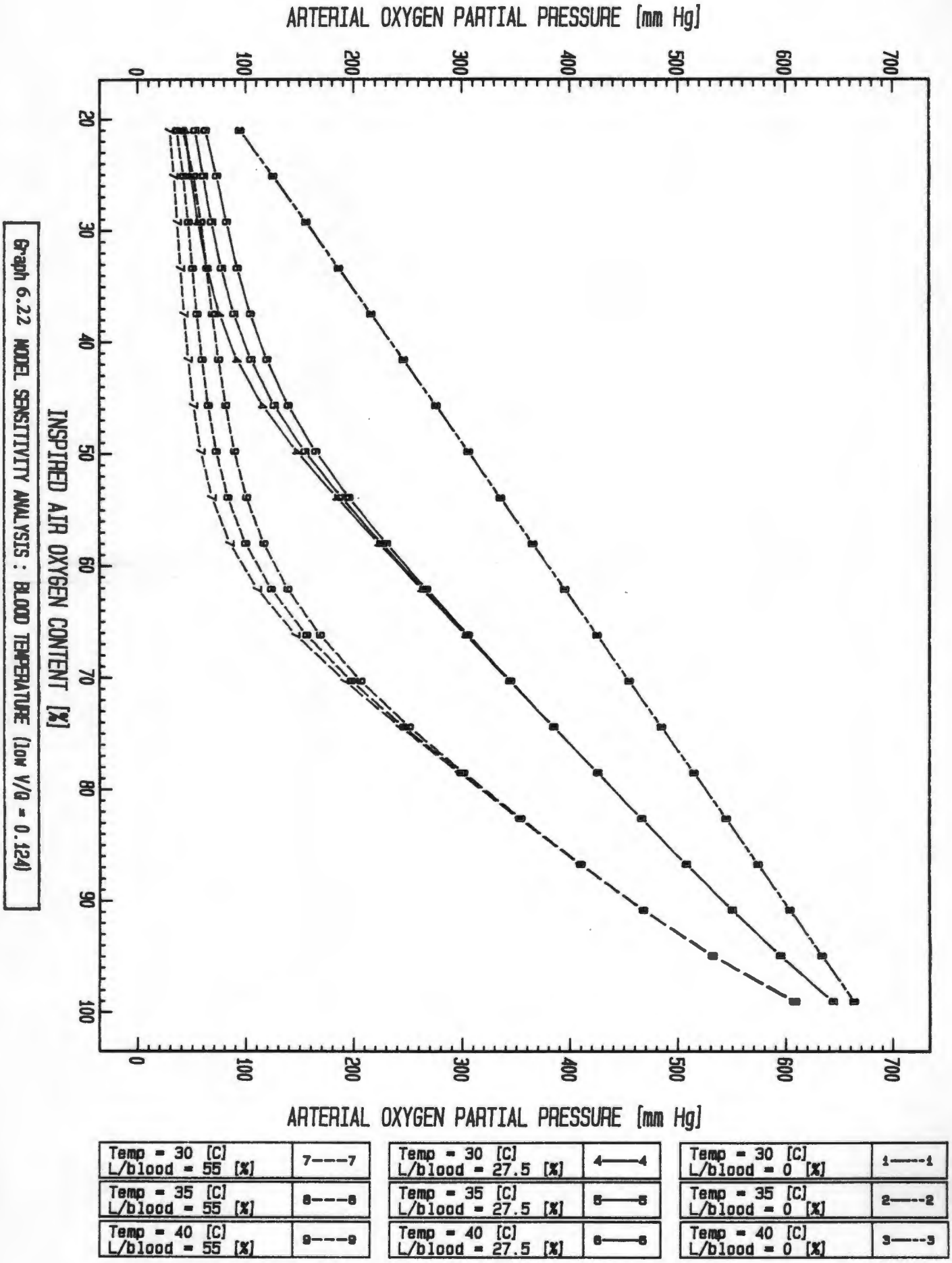


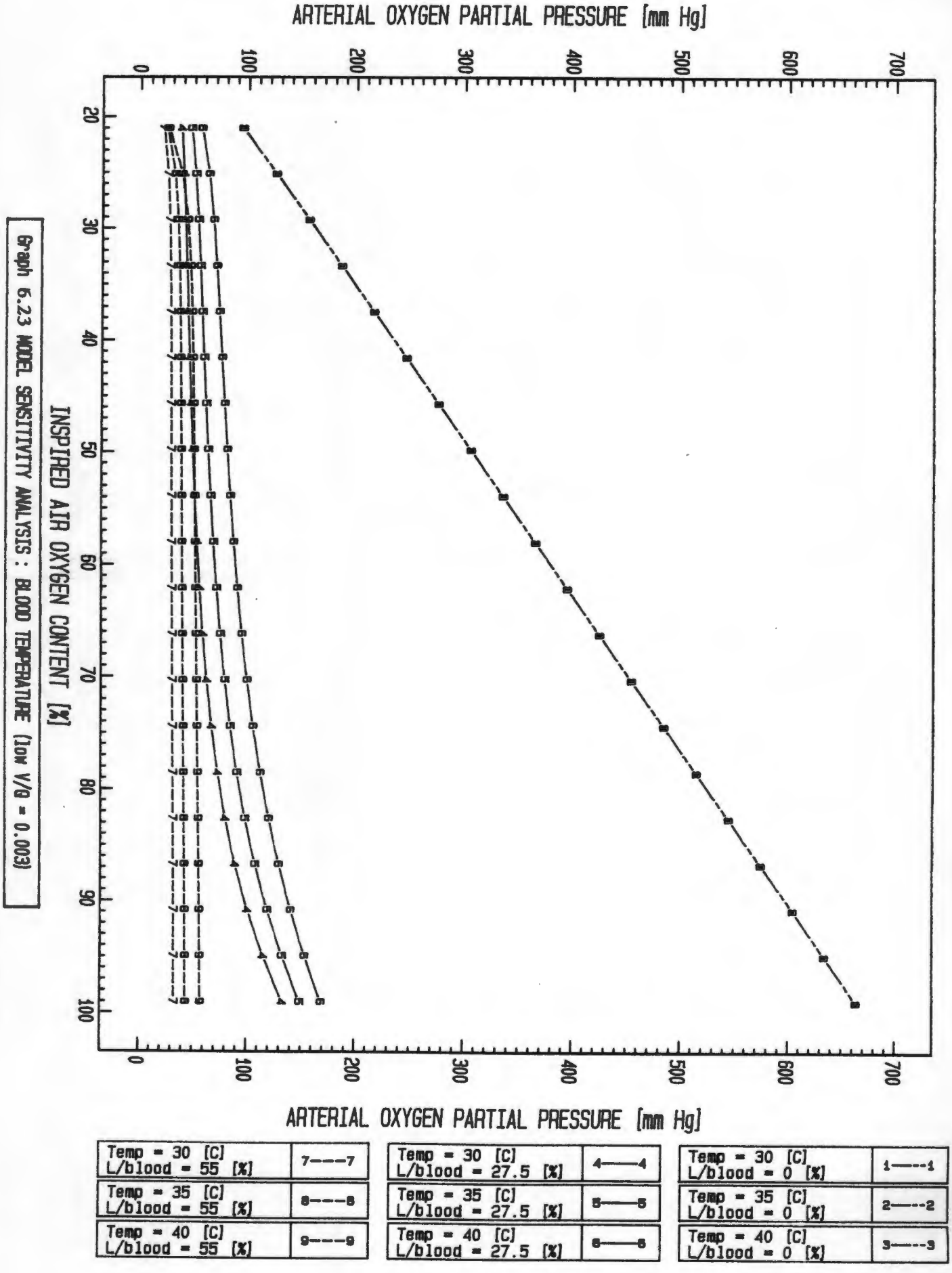
Graph 6.19 MODEL SENSITIVITY ANALYSIS : EFFECTIVE INSPIRED GAS PRESSURE (low V/Q = 0.003)

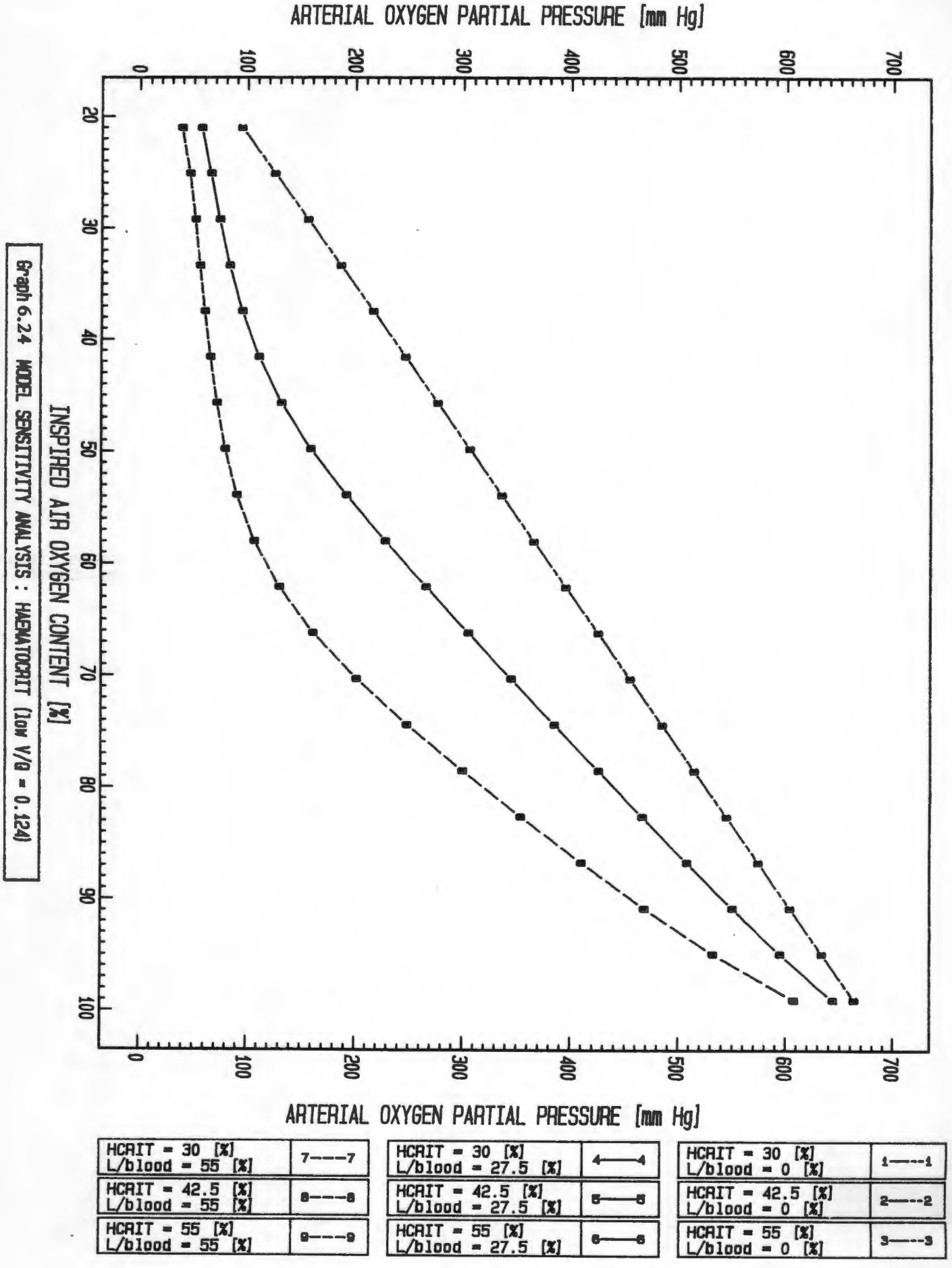


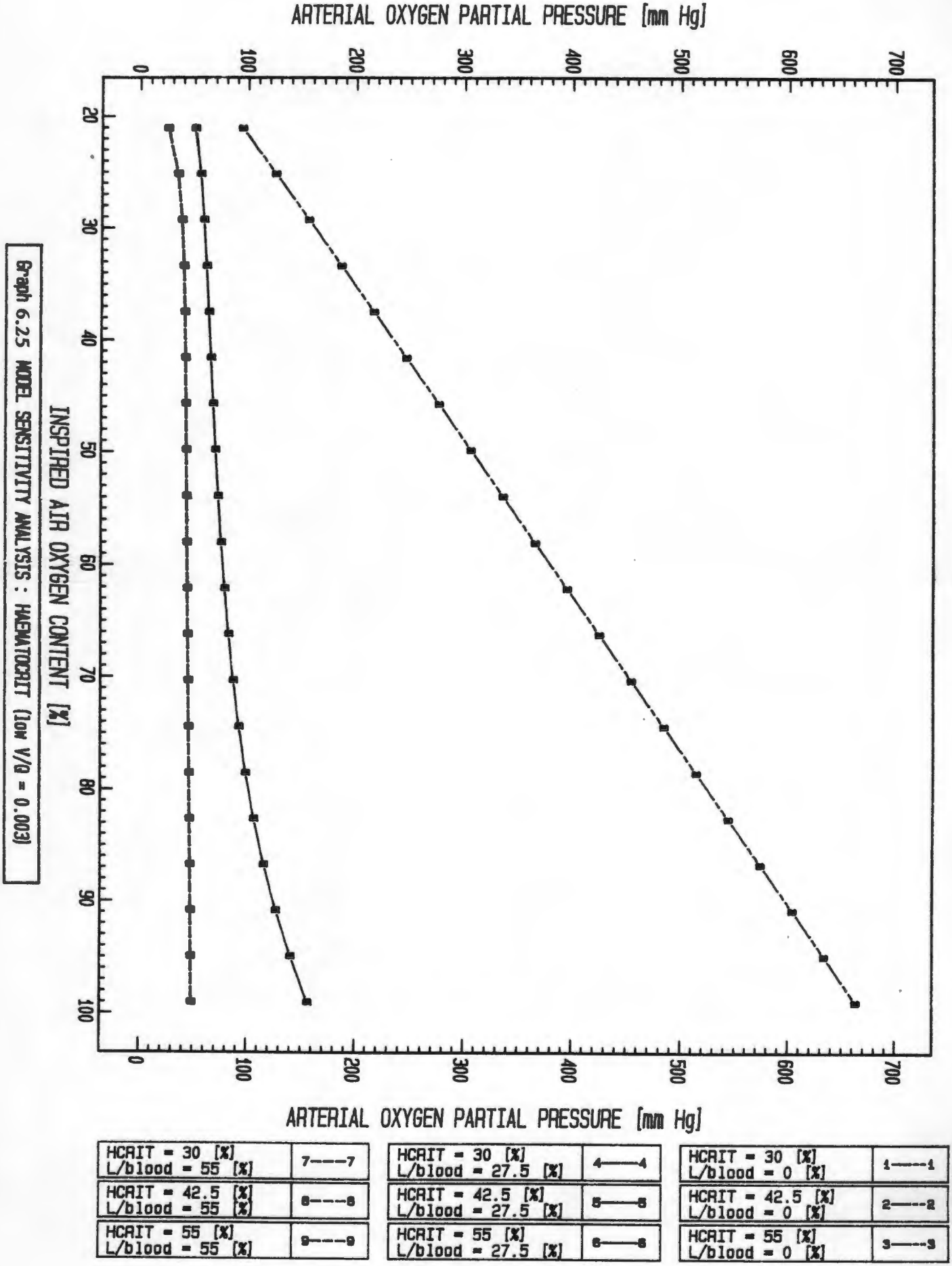
Graph 6.20 MODEL SENSITIVITY ANALYSIS : HAEMOGLOBIN CONCENTRATION (low V/Q = 0.124)


ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
0
100
200
300
400
500
600
700
20
30
40
50
60
70
80
90
100
INSPIRED AIR OXYGEN CONTENT [%]
Graph 6.21 MODEL SENSITIVITY ANALYSIS : HAEMOGLOBIN CONCENTRATION (low V/Q = 0.003)
ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
Hb = 12.5 [g/100ml] L/blood = 55 [%] 7---7
Hb = 15.5 [g/100ml] L/blood = 55 [%] 8---8
Hb = 18.5 [g/100ml] L/blood = 55 [%] 9---9
Hb = 12.5 [g/100ml] L/blood = 27.5 [%] 4---4
Hb = 15.5 [g/100ml] L/blood = 27.5 [%] 5---5
Hb = 18.5 [g/100ml] L/blood = 27.5 [%] 6---6
Hb = 12.5 [g/100ml] L/blood = 0 [%] 1---1
Hb = 15.5 [g/100ml] L/blood = 0 [%] 2---2
Hb = 18.5 [g/100ml] L/blood = 0 [%] 3---3


ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
0
100
200
300
400
500
600
700
INSPIRED AIR OXYGEN CONTENT [%]
20
30
40
50
60
70
80
90
100
Graph 6.22 MODEL SENSITIVITY ANALYSIS : BLOOD TEMPERATURE (low V/Q = 0.124)
ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
Temp = 30 [C] L/blood = 55 [%] 7---7
Temp = 35 [C] L/blood = 55 [%] 8---8
Temp = 40 [C] L/blood = 55 [%] 9---9
Temp = 30 [C] L/blood = 27.5 [%] 4---4
Temp = 35 [C] L/blood = 27.5 [%] 5---5
Temp = 40 [C] L/blood = 27.5 [%] 6---6
Temp = 30 [C] L/blood = 0 [%] 1---1
Temp = 35 [C] L/blood = 0 [%] 2---2
Temp = 40 [C] L/blood = 0 [%] 3---3


ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
0
100
200
300
400
500
600
700
20
30
40
50
60
70
80
90
100
INSPIRED AIR OXYGEN CONTENT [%]
Graph 6.23 MODEL SENSITIVITY ANALYSIS : BLOOD TEMPERATURE (low V/Q = 0.003)
ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
Temp = 30 [C] L/blood = 55 [%] 7---7
Temp = 35 [C] L/blood = 55 [%] 8---8
Temp = 40 [C] L/blood = 55 [%] 9---9
Temp = 30 [C] L/blood = 27.5 [%] 4---4
Temp = 35 [C] L/blood = 27.5 [%] 5---5
Temp = 40 [C] L/blood = 27.5 [%] 6---6
Temp = 30 [C] L/blood = 0 [%] 1---1
Temp = 35 [C] L/blood = 0 [%] 2---2
Temp = 40 [C] L/blood = 0 [%] 3---3


ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
0
100
200
300
400
500
600
700
20
30
40
50
60
70
80
90
100
INSPIRED AIR OXYGEN CONTENT [%]
Graph 6.24 MODEL SENSITIVITY ANALYSIS : HAEMATOCRIT (low V/Q = 0.124)
ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
HCRIT = 30 [%] L/blood = 55 [%] 7---7
HCRIT = 42.5 [%] L/blood = 55 [%] 8---8
HCRIT = 55 [%] L/blood = 55 [%] 9---9
HCRIT = 30 [%] L/blood = 27.5 [%] 4---4
HCRIT = 42.5 [%] L/blood = 27.5 [%] 5---5
HCRIT = 55 [%] L/blood = 27.5 [%] 6---6
HCRIT = 30 [%] L/blood = 0 [%] 1---1
HCRIT = 42.5 [%] L/blood = 0 [%] 2---2
HCRIT = 55 [%] L/blood = 0 [%] 3---3


ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
0
100
200
300
400
500
600
700
20
30
40
50
60
70
80
90
100
INSPIRED AIR OXYGEN CONTENT [%]
ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]
Graph 6.25 MODEL SENSITIVITY ANALYSIS : HAEMATOCRIT (low V/Q = 0.003)
HCRIT = 30 [%] L/blood = 55 [%] 7----7
HCRIT = 42.5 [%] L/blood = 55 [%] 8----8
HCRIT = 55 [%] L/blood = 55 [%] 9----9
HCRIT = 30 [%] L/blood = 27.5 [%] 4----4
HCRIT = 42.5 [%] L/blood = 27.5 [%] 5----5
HCRIT = 55 [%] L/blood = 27.5 [%] 6----6
HCRIT = 30 [%] L/blood = 0 [%] 1----1
HCRIT = 42.5 [%] L/blood = 0 [%] 2----2
HCRIT = 55 [%] L/blood = 0 [%] 3----3

CHAPTER 7
CLINICAL APPLICATION OF THE MODEL

7.1 INTRODUCTION

A great deal has been said in the preceding chapters about related physiology, mathematical modelling and the actual simulation results; it would have been a rather luxurious exercise if no further useful information was derived from the model under discussion.

One of the applications of modelling, which sometimes unfortunately passes unnoticed, is the educational value it contains for those with a thorough understanding of the underlying mathematics contained within it. Interrelationships between the various physiological parameters, causality principles (i.e. relationship between cause and effect) and the aspect of supply and demand of the entities under investigation are elucidated; additional insight is gained into the problem and occasionally it may even lead to new discoveries.

It is not, however, always possible to invest the required time to study a model in detail, or the user may even lack the necessary specialised training to attempt it. It is therefore of great benefit if an easy-to-use algorithm which bears some clinical relevance can be extracted from the model; to be applied by the user without substantial knowledge concerning the underlying theory.

Such a method was developed by the author and is discussed in the following section; if feasible at all, the model (as discussed in Chapter 5) should be studied in conjunction with the simplified algorithm.

7.2 INTERRELATEDNESS OF PARAMETERS AND THE CLINICAL RELEVANCE OF THIS RELATIONSHIP

A few interesting points from the simulation results in Chapter 6 deserve mentioning.

With reference to graphs 6.20 to 6.25 it is clear that maximal changes in

haemoglobin concentration, blood temperature and haematocrit will affect the arterial oxygen pressure to a negligible extent (less than 10% change in P_aO_2 for a maximum change in these parameters respectively). The same can be said for the carbon dioxide output (graphs 6.12 and 6.13).

Another interesting fact is that an increase of 100% in the total alveolar ventilation, results in a maximum increase of 10% for the PaO_2. In the case of a low $\dot{V}_A/\dot{Q}$ value of 0,003 the effect is even less. This is of major clinical significance, since it implies that an increase in minute ventilation for the ARDS patient will contribute only marginally towards the improvement of the PaO_2 level (graphs 6.14, 6.15 and Appendix C8).

The parameters with a substantial effect on the PaO_2 level are the effective inspired pressure (P_{EF}), oxygen consumption ($\dot{V}O_2$) and the total pulmonary perfusion ($\dot{Q}$); graphs 6.18, 6.19, 6.10, 6.11, 6.16 and 6.17 illustrate this point.

At a F_IO_2 of 1,0 an increase in P_{EF} can be as high as an equal increase in the PaO_2; the proportionality constant decreases with a worsening in the $\dot{V}_A/\dot{Q}$ distribution. This is a well known fact and is one of the major therapeutic measures for the ARDS patient. A direct effect of PEEP is to increase the P_{EF}; it does also improve the $\dot{V}_A/\dot{Q}$ distribution, which has an indirect and probably more marked effect on the PaO_2 level.

The effects of $\dot{V}O_2$ and $\dot{Q}$ are directly interrelated, which is partially illustrated by equations 5.6 and 5.9, as repeated below:

$$\sum_{i=1}^{N} \dot{Q}i \; [CaO_2 - C_{\bar{v}}O_2] = \dot{V}O_2 \qquad (5.6)$$

$$\sum_{i=1}^{N} \dot{Q}i = \dot{Q} \qquad (5.9)$$

The $(CaO_2 - C_{\bar{v}}O_2)$ difference relates the respective $\dot{Q}i$ components and the total oxygen consumption. Due to the unequal distribution of blood in

the lung, depicted by the $\dot{V}_A/\dot{Q}$ distribution and summation component in 5.6 and 5.9, the relationship is non-linear. It is tempting to argue that if $\dot{V}O_2$ is held constant and $\dot{Q}$ is increased; the $(CaO_{2_i} - C_{\bar{v}}O_2)$ difference must decrease and will therefore result in a decrease of CaO_2.

The opposite is however true, although the $(CaO_2 - C_{\bar{v}}O_2)$ difference decreases, the sum total of CaO_{2_i} will increase, matched by an increase of the $P_{\bar{v}}O_2$ level.

It follows from graphs 6.16 and 6.17 that for $\dot{V}O_2$ held constant, an increase in $\dot{Q}$ will result in an increase in PaO_2 (the magnitude of which increases with a worsening of the $\dot{V}_A/\dot{Q}$ distribution). In the case of a severe $\dot{V}_A/\dot{Q}$ mismatch, i.e. a low $\dot{V}_A/\dot{Q}$ of 0,003 and 55% of the total perfusion to the low region, the effect of an increase in $\dot{Q}$ is less marked (graph 6.17). The same can be said for a constant $\dot{Q}$ and a decrease in O_2 (graphs 6.10 and 6.11). In practice an increased cardiac output, caused by a factor which will also substantially influence the $\dot{V}_A/\dot{Q}$ distribution, may fail to elicit the desired increase in PaO_2.

The oxygen consumption normally increases for ARDS patients due to an increased metabolic rate; the fact that it sometimes shows a decrease can be ascribed to a decrease in the supply and not the demand (Danek et al, 1980). A decrease in the oxygen supply may be due to a decrease in the cardiac output (and therefore $\dot{Q}$). The concept of cause and effect are thus clearly illustrated through this example.

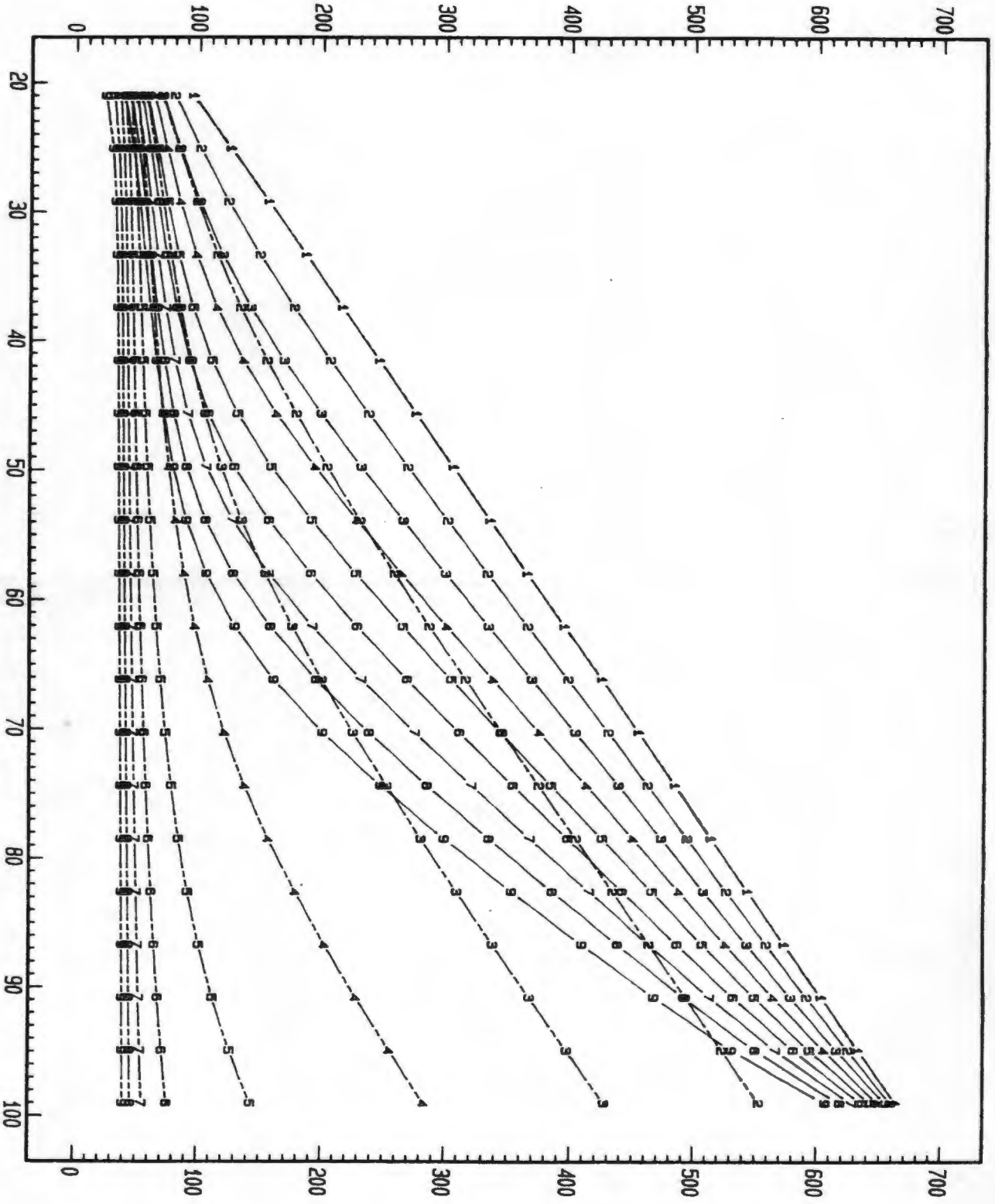
It is noteworthy that apart from the inspired oxygen concentration and the effective inspired pressure, the cardiac output is the only physiological parameter that can be manipulated with a significant effect on the arterial oxygen content and therefore the oxygen supply.

low V/Q = 0.003 L/blood = 41.2 [%]	7——7
low V/Q = 0.003 L/blood = 48.1 [%]	8——8
low V/Q = 0.003 L/blood = 55 [%]	9——9

low V/Q = 0.003 L/blood = 20.6 [%]	4——4
low V/Q = 0.003 L/blood = 27.5 [%]	5——5
low V/Q = 0.003 L/blood = 34.4 [%]	6——6

low V/Q = 0.003 L/blood = 0 [%]	1——1
low V/Q = 0.003 L/blood = 6.9 [%]	2——2
low V/Q = 0.003 L/blood = 13.7 [%]	3——3

ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]



Graph 7.1 RELATIVE BLOOD REDISTRIBUTION : BIMODAL VENT/PERF DISTRIBUTIONS

ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]

low V/Q = 0.124 L/blood = 41.2 [%]	7——7
low V/Q = 0.124 L/blood = 48.1 [%]	8——8
low V/Q = 0.124 L/blood = 55 [%]	9——9

low V/Q = 0.124 L/blood = 20.6 [%]	4——4
low V/Q = 0.124 L/blood = 27.5 [%]	5——5
low V/Q = 0.124 L/blood = 34.4 [%]	6——6

low V/Q = 0.124 L/blood = 0 [%]	1——1
low V/Q = 0.124 L/blood = 6.9 [%]	2——2
low V/Q = 0.124 L/blood = 13.7 [%]	3——3

7.3 $\dot{V}_A/\dot{Q}$ DISTRIBUTION

The reasons for selecting, and the clinical relevancy of the two different types of $\dot{V}_A/\dot{Q}$ distributions used in the simulations are discussed in this section.

The results in graph 7.1 are a superposition of both of the bimodal distribution types used (i.e. graphs 6.6 and 6.7 combined) and represent the two extreme cases of $\dot{V}_A/\dot{Q}$ distributions for the ARDS syndrome.

A maximum percentage of pulmonary perfusion to the low $\dot{V}_A/\dot{Q}$ area of 55% were chosen in both instances. The reason for this is because a physiological shunt of 50% seems to be the maximum observed in ARDS patients (Covelli et al, 1983; Ralph and Robertson, 1981).

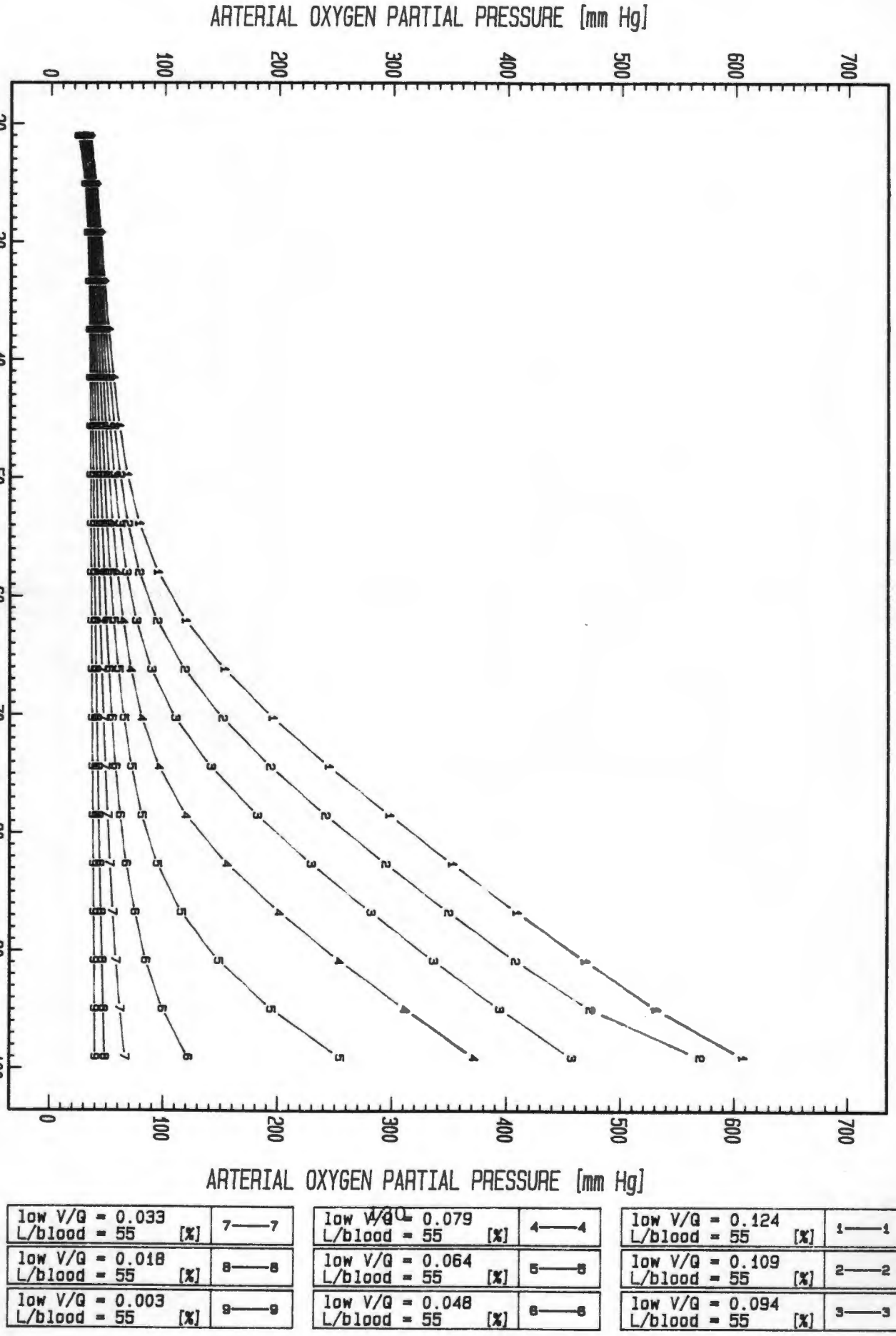
The series of F_IO_2, PaO_2 curves (graph 7.1), representing the low $\dot{V}_A/\dot{Q}$ value of 0,124 is analogous to the situation of alveoli partially filled with fluid; at a high F_IO_2 of 1,0 , maximum oxygen-transfer can still be obtained. This is a result of the sigmoidal shape of the oxygen-haemoglobin dissociation curve.

On the other hand the series of F_IO_2, PaO_2 curves (graph 7.1) representing the low $\dot{V}_A/\dot{Q}$ value of 0,003 is analogous to a situation of alveoli filled with fluid to such an extent that maximum oxygen transfer cannot be achieved any more, even at the high F_IO_2 value of 1,0.

The following assumptions were made regarding the two series of $\dot{V}_A/\dot{Q}$ distributions:

(a) The $\dot{V}_A/\dot{Q}$ distribution in any ARDS patient or patient susceptible to the ARDS syndrome can be represented by a combination of the two series as discussed.

(b) The sequence of changes in the $\dot{V}_A/\dot{Q}$ distribution for a healthy patient to a susceptible patient and finally to confirmed ARDS, will be from a unimodal distribution to a bimodal distribution with a low $\dot{V}_A/\dot{Q}$ value 0,124 to a bimodal distribution with a low $\dot{V}_A/\dot{Q}$ value of 0,003. The transformation is not discrete, but will at any moment



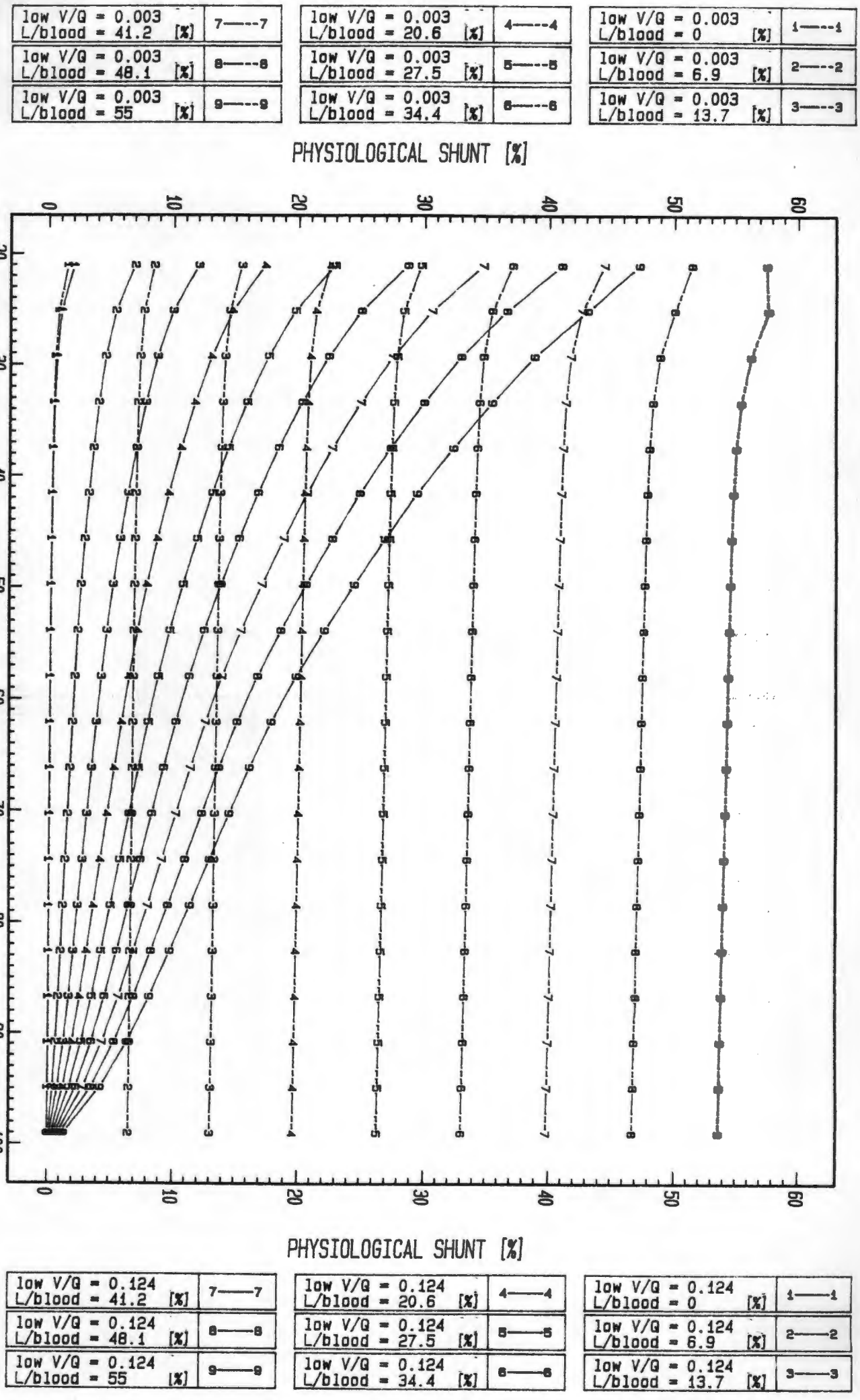
Graph 7.2 BIMODAL VENT/PERF DISTRIBUTION : CHANGES IN THE LOW V/Q REGION (L/BLOOD = 55 %)

in time result in a distribution which can be represented by a combination of the two conditions as illustrated in graph 7.1.

(c) The relative clinical significance of the two series is related as follows:

The severity of a situation of 55% of total pulmonary perfusion to a low $\dot{V}_A/\dot{Q}$ region of 0,124 is equal to the severity of a 21% of total pulmonary perfusion to a low $\dot{V}_A/\dot{Q}$ region of 0,003 (lines 9 and 4 in graph 7.1). Although the arterial oxygen content at an F_IO_2 of 1,0 is relatively high in the first instance compared to the second, it must be noted that a much higher percentage of blood is distributed to the low $\dot{V}_A/\dot{Q}$ region in the first instance (it is analogous to a situation of relatively mild but widely dispersed oedema compared to relatively localised but severe oedema).

The justification for the respective low $\dot{V}_A/\dot{Q}$ values of 0,124 and 0,003 is explained by the results of graph 7.2. In this particular case the percentage perfusion to the low $\dot{V}_A/\dot{Q}$ region was kept constant at 53% and the low $\dot{V}_A/\dot{Q}$ value was varied (which is representative of a shift in the mean of the low $\dot{V}_A/\dot{Q}$ mode). It can be observed from this graph that a low $\dot{V}_A/\dot{Q}$ value of 0,124 represents the cut-off point where the PaO_2 at a F_IO_2 of 1,0 starts to decrease from the maximum value observed at this point in normal unimodal $\dot{V}_A/\dot{Q}$ distributions (a decrease of 10% from the maximum value). Furthermore the low $\dot{V}_A/\dot{Q}$ value of 0,003 represents the distribution where there is no notable increase in PaO_2 from a F_IO_2 of 0,21 up to 1,0.



Graph 7.3 RELATIVE BLOOD REDISTRIBUTION : BIMODAL VENT/PERF DISTRIBUTIONS : PHYSIOLOGICAL SHUNT

7.4 THE PHYSIOLOGICAL SHUNT AS A DIAGNOSTIC INDICATOR

The physiological shunt is widely used as a diagnostic indicator in patients suffering from $\dot{V}_A/\dot{Q}$ mismatch in the lung and therefore also in the case of ARDS patients. Although it is a useful concept, it does have certain limitations and may in some instances result in a serious misconception of the problem.

This point is illustrated in graph 7.3. It is clear that the physiological shunt for the series with a low $\dot{V}_A/\dot{Q}$ value of 0,124 is a function of F_IO_2. For example line 9 (low $\dot{V}_A/\dot{Q}$ = 0,124) varies from a 48% to a 1,5% physiological shunt, depending on F_IO_2. It was previously explained that this case, insofar as the condition of the $\dot{V}_A/\dot{Q}$ distribution is concerned, is equivalent to line 4 (low $\dot{V}_A/\dot{Q}$ = 0,003) which has a nearly constant physiological shunt of 20% over the entire F_IO_2 range.

For a patient with a distribution of a low $\dot{V}_A/\dot{Q}$ value = 0,124, the shunt measured will therefore either give a too high or too low indication of the state of the $\dot{V}_A/\dot{Q}$ mismatch; depending at which F_IO_2 it is measured. Physiological shunt measurements are normally done at a F_IO_2 level of 1,0, which will create a false impression of safety for the low $\dot{V}_A/\dot{Q}$ = 0,124 series.

It is true that once the low $\dot{V}_A/\dot{Q}$ = 0,003 phase has been reached, i.e. an established ARDS syndrome, the physiological shunt will serve as an accurate indicator; during the preceding phases this will not be the case. This may even explain the reason for the apparent **"sudden onset"** of the ARDS syndrome; since the method employed to calculate the physiological shunt is not sensitive enough to detect the underlying ventilation/perfusion inequalities already in progress in the early stages of the syndrome, only once the low $\dot{V}_A/\dot{Q}$ = 0.003 phase has been reached does it succeed in detecting the abnormalities.

At this stage it should be clear to the reader that there is only one reliable indicator of the condition of the lung during all stages of the clinical course and that is the actual shape of the $\dot{V}_A/\dot{Q}$ distribution itself.

7.5 PARAMETER IDENTIFICATION TECHNIQUE

Mathematical modelling of complex systems is closely related to the technique referred to in engineering terms as parameter identification.

From an engineering point of view any system can be subdivided into a set of input variables, a set of system parameters and a set of output variables. The system parameters are normally contained within the transfer function, which relates the output variables to the input variables.

In this particular model, the transfer is represented by all the equations as discussed in Chapter 5 and the parameters are those values as discussed in 6.2.2. and Appendix A.

A technique is often used in engineering whereby the input variables are varied (normally in the form of a step response) and the related changes in the output variables are then observed. Either the dynamic or stabilised changes in the output variables are observed; these are referred to as the transient and steady state characteristics respectively. Through observation of these changes, unknown parameters contained within the transfer function can be identified. Figure 7.1 illustrates the point for the specific model as discussed. In this case there is a single variable input (i.e. F_IO_2) which can be changed in discrete steps between 0,21 to 1,0 (step input) and a single variable output (i.e. PaO_2). The unknown parameters represent the shape of the $\dot{V}_A/\dot{Q}$ distribution.

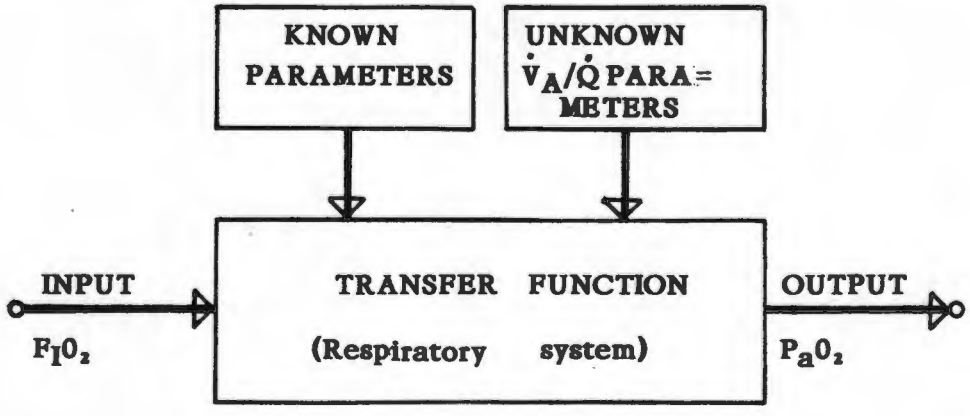


Figure 7.1 Respiratory Input/Output system.

The information that can be obtained about the system by using these techniques is superior to any conventional clinical measuring techniques where very little sophisticated processing techniques are applied (for example the physiological shunt measurement).

The model developed is not time-dependent and therefore only simulates steady-state conditions (i.e. the exact nature of the increase in PaO_2 inbetween the time periods related to an increase in F_IO_2 is not addressed).

A simplified flow chart of a method to identify the $\dot{V}_A/\dot{Q}$ distribution parameters and therefore the shape of the distribution, is presented in Fig. 7.2. The ideal would be to increase the F_IO_2 for the patient in steps of 0,2 and in each instance to measure the PaO_2 as well as all those physiological parameters as required by the model. The model is then simulated through a series of iterations until such time that the output matches the data as measured in the patient; the likely shape of the $\dot{V}_A/\dot{Q}$ distribution within the patient will then be intimated.

Due to a limitation on the processing time of computers, it may not be feasible to go through this complete sequence at this stage, unless dedicated access to an ultra fast computer is available. Another disadvantage is the number and frequency of measurements required. Bearing in mind that automatic measuring equipment may not be available and the nature of the ICU environment, it is unlikely to be feasible to attempt these consecutive measurements every time the shape of the $\dot{V}_A/\dot{Q}$ distribution needs to be determined.

Alternatively a few assumptions can be made that greatly simplify matters:

(a) Only one set of parameters need be measured at the beginning of the PaO_2 measurements and it is then assumed that they remain relatively constant during the preceding changes in F_IO_2. Alternatively, the parameters may not be measured at all and the standard set of values (as discussed in 6.2.2) can be used.

(b) Only three PaO_2 measurements need be made, at F_IO_2 equal to 0,5; 0,8 and 1,0.

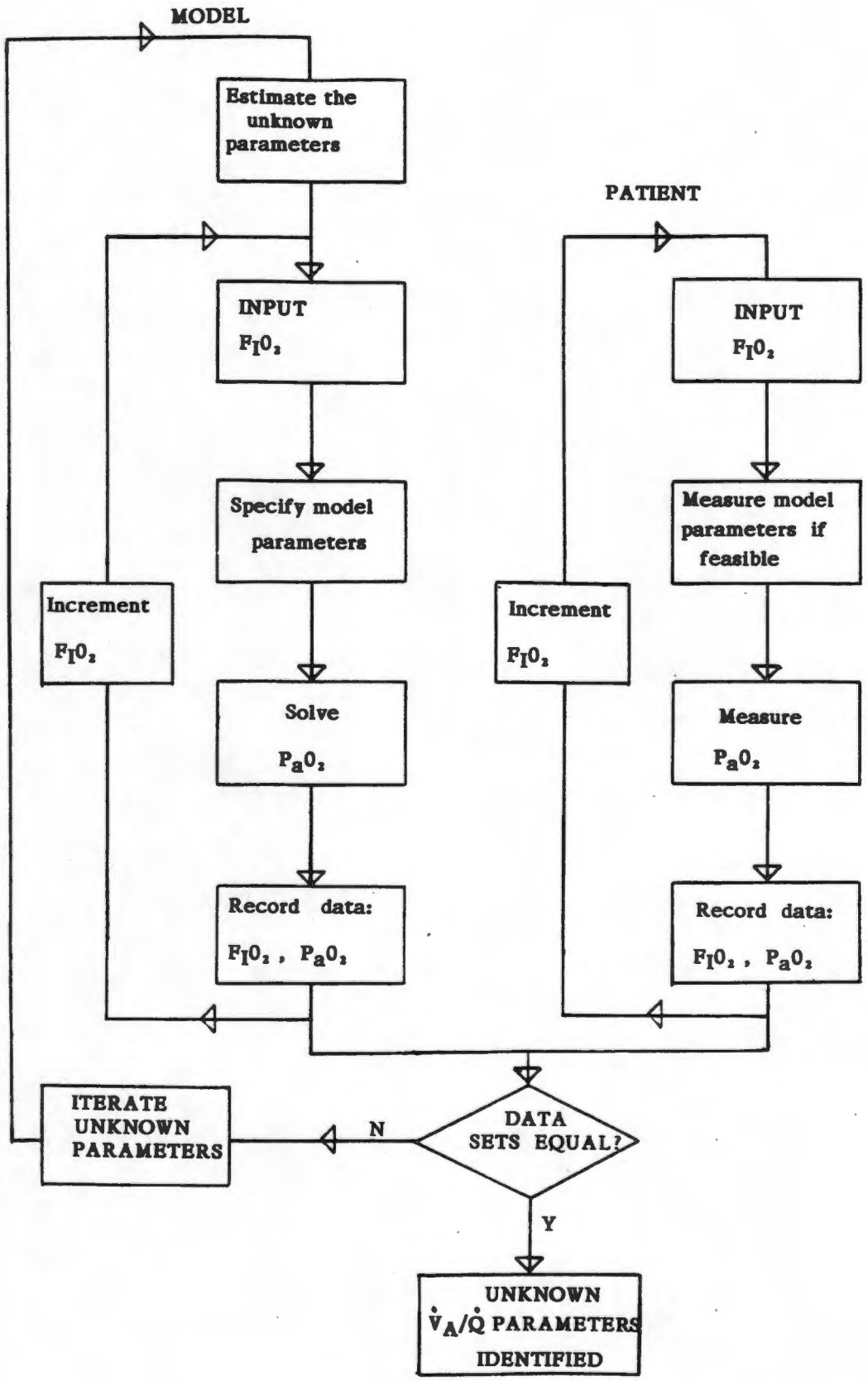


Figure 7.2 Flow chart of a parameter identification technique.

(The implications of these assumptions are discussed in a subsequent section.)

If only three PaO_2 measurements are made on a patient at a F_IO_2 of 0,5; 0,8 and 1,0, the points can be plotted onto Graph 7.1 and, depending on its position, an indication can be obtained of the shape of the $\dot{V}_A/\dot{Q}$ distribution in the patient. (The standard set of parameters is assumed.) Alternatively, one set of parameter measurements can precede the PaO_2 measurements and a graph similar to the one in Graph 7.1 can be generated for this specific patient; this will naturally render more accurate results.

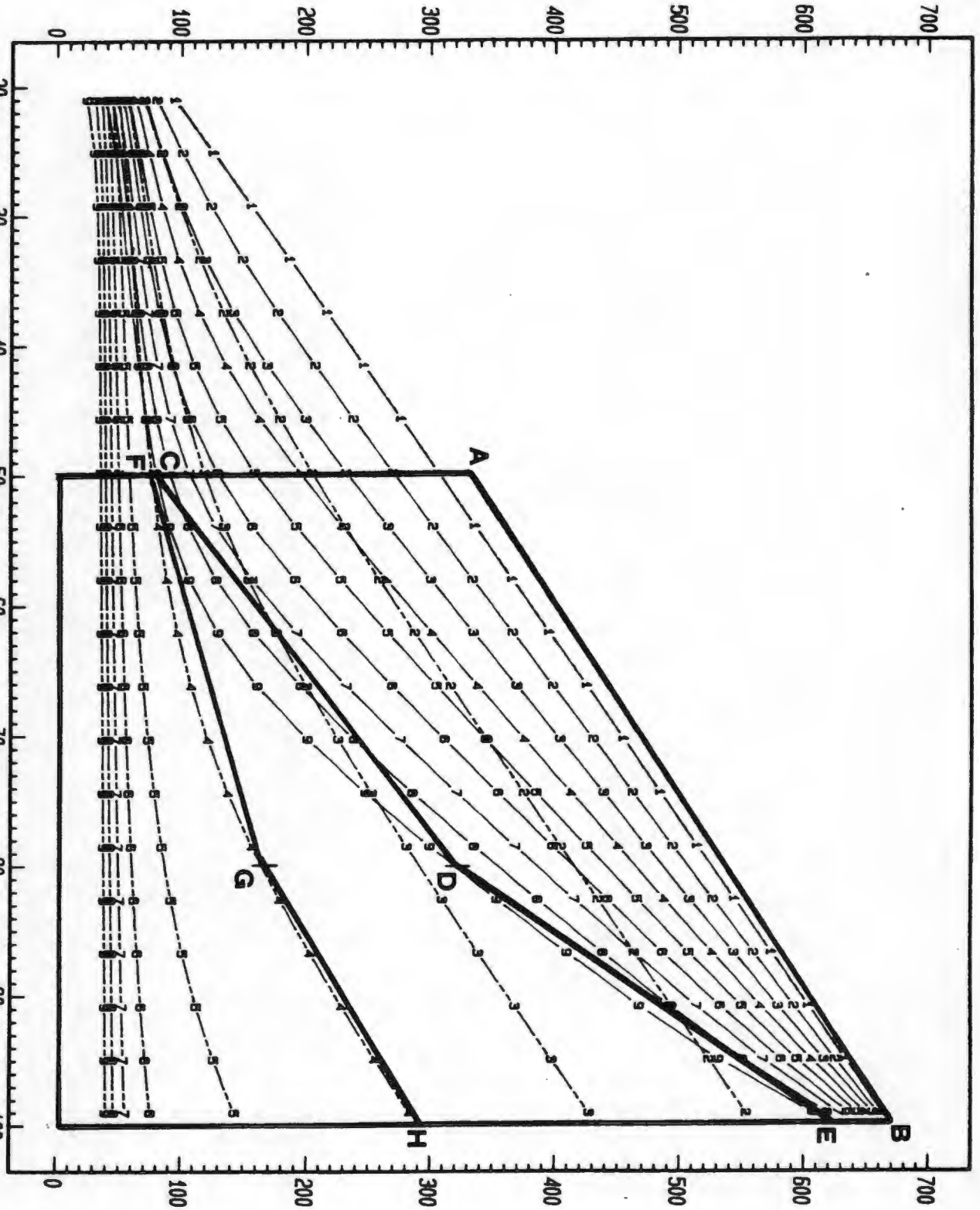
7.6 DERIVATION OF A NEW CLINICAL INDICATOR

The more precise procedure as described in the previous section will render reliable results if the software and computer facilities are available. If the standard curves in Graph 7.1 are used, it is difficult to relate the measured PaO_2 values with a specific percentage of low blood distribution and either one, or a combination of the two low $\dot{V}_A/\dot{Q}$ values. As explained previously the measured PaO_2 values will in most cases represent a combination of these two series of distributions.

A $\dot{V}_A/\dot{Q}$ index ($^I\dot{V}_A/\dot{Q}$) was defined instead, which requires the minimum of measurements and involves an easy algebraic calculation.

low V/Q = 0.003 L/blood = 41.2 [%]	7——7	low V/Q = 0.003 L/blood = 20.6 [%]	4——4	low V/Q = 0.003 L/blood = 0 [%]	1——1
low V/Q = 0.003 L/blood = 48.1 [%]	8——8	low V/Q = 0.003 L/blood = 27.5 [%]	5——5	low V/Q = 0.003 L/blood = 6.9 [%]	2——2
low V/Q = 0.003 L/blood = 55 [%]	9——9	low V/Q = 0.003 L/blood = 34.4 [%]	6——6	low V/Q = 0.003 L/blood = 13.7 [%]	3——3

ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]



INSPIRED AIR OXYGEN CONTENT [%]

GRAPH 7.4 ILLUSTRATION OF THE V_A/Q-INDEX

ARTERIAL OXYGEN PARTIAL PRESSURE [mm Hg]

low V/Q = 0.124 L/blood = 41.2 [%]	7——7	low V/Q = 0.124 L/blood = 20.6 [%]	4——4	low V/Q = 0.124 L/blood = 0 [%]	1——1
low V/Q = 0.124 L/blood = 48.1 [%]	8——8	low V/Q = 0.124 L/blood = 27.5 [%]	5——5	low V/Q = 0.124 L/blood = 6.9 [%]	2——2
low V/Q = 0.124 L/blood = 55 [%]	9——9	low V/Q = 0.124 L/blood = 34.4 [%]	6——6	low V/Q = 0.124 L/blood = 13.7 [%]	3——3

7.6.1 Definition of the $\dot{V}_A/\dot{Q}$ Index: The index is based on three consecutive measurements of PaO_2 at a F_IO_2 of 0,5; 0,8 and 1,0 respectively. These measurements should be preceded by measurements of the other model parameters if possible, otherwise standard values may be used instead.

The definition of the index is illustrated in Graph 7.4. Line A-B represents the ideal case of two uniform compartments for the ventilation and perfusion respectively; this is the maximum possible PaO_2 for the standard set of parameters. Two additional lines are illustrated C-D-E and F-G-H, which respectively represent line 9 (low $\dot{V}_A/\dot{Q}$ = 0,124) and line 4 (low $\dot{V}_A/\dot{Q}$ = 0,003) for the three F_IO_2 values as discussed.

The index is defined as that fraction of the area under the ideal line A-B that is represented by the line formed by the three PaO_2 points as measured.

$$I\dot{V}_A/\dot{Q} = \frac{\text{Area under the three measured points}}{\text{Area under ideal line A-B}} \qquad (7.1)$$

A decrease in the index (maximum = 1) is therefore analogous to a more severe mismatch in the $\dot{V}_A/\dot{Q}$ distribution. It was previously stated that lines C-D-E and F-G-H are representative of the same degree of clinical severity. According to equation (7.1) this is however not the case; a compensating factor was therefore incorporated in the index. The compensation is based on the fact that the gradient of all lines interconnecting the points at F_IO_2 = 0,8 and 0,1 in the low $\dot{V}_A/\dot{Q}$ = 0,124 series exceed that of the ideal gradient A-B; the opposite is true for those gradients in the low $\dot{V}_A/\dot{Q}$ = 0,003 series. A compensating factor for the low $\dot{V}_A/\dot{Q}$ = 0,124 series was introduced, based on the gradient as discussed and which equates the index value for line C-D-E with that of line F-G-H. Depending on the position of the measured points, the compensating factor is decreased proportionally to the gradient until it equals the A-B gradient, in which case it is zero. Gradients less than that of A-B represent the low $\dot{V}_A/\dot{Q}$ = 0,003 series and in these cases the factor reduces to zero. The compensation concept is illustrated in Fig. 7.3.

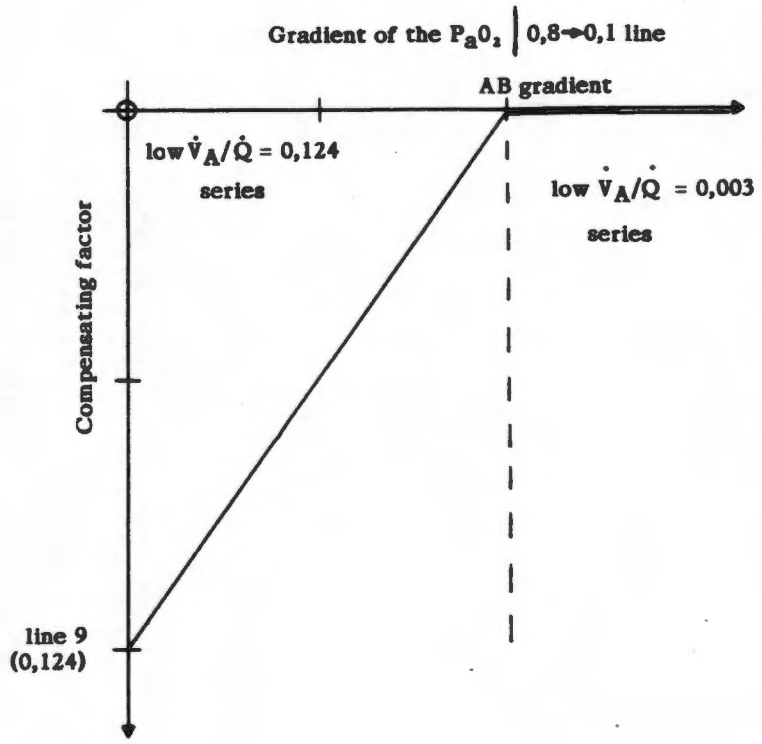


Figure 7.3 $\dot{V}_A/\dot{Q}$ - Index compensating factor.

The $\dot{V}_A/\dot{Q}$ is therefore redefined as follows:

$$I\dot{V}_A/\dot{Q} = \frac{A4}{A1} + f(x) \qquad (7.2)$$

$$f(x) = \frac{(G4 - G1) \,.\, (A3 - A2)}{(G2 - G1) \,.\, A1} \quad \text{for} \quad f < 0$$

$$\text{and} \quad f(x) = 0 \quad \text{for} \quad f > 0$$

with reference to Graph 7.4:

A_1 : the area under the ideal line A-B.

A_2 : the area under the line connecting the three PaO_2 points on line 9 ($\dot{V}_A/\dot{Q}$ = 0,124).

A_3 : the area under the line connecting the three PaO_2 points on line 4 ($\dot{V}_A/\dot{Q}$ = 0,003)

A_4 : the area under the line connecting the three PaO_2 points as measured at F_IO_2 = 0,5; 0,8 and 1,0.

Analogously G_1, G_2 and G_4 are the respective gradients between the two PaO_2 points at F_IO_2 = 0,8 and 1,0.

Ideally the model parameters should be measured and the points A, B, C, D, E, F, G and H as on Graph 7.4 should be generated for a specific patient; the parameters A_1, A_2, A_3, G_1, G_4 are then determined for a specific case. In the typical clinical situation the total pulmonary perfusion ($\dot{Q}$), the oxygen consumption ($\dot{V}O_2$) and the carbon dioxide output ($\dot{V}CO_2$) are not always known (a Swan-Ganz catheter may for instance not be installed); in those cases the standard set of parameters should be assumed, in which case equation 7.2 simplifies to:

$$I\ \dot{V}_A/\dot{Q} = \frac{0,15.Pa(50) + 0,25.Pa(80) + 0,1.Pa(100)}{246,263} - 0,00182.f(x) \quad (7.3)$$

$f(x) = Pa(100) - Pa(80) - 144,0$ for $f < o$

$f(x) = o$ for $f > o$

Pa(50, Pa(80), Pa(100) are the arterial oxygen partial pressure measurements at F_IO_2 = 0,5; 0,8 and 1,0 respectively.

The price paid for the lack of information is a reduced diagnostic sensitivity; the results nevertheless contain more information than any of the other diagnostic indicators in the same category, (e.g. the physiological shunt).

7.6.2 Clinical significance of the $\dot{V}_A/\dot{Q}$ Index: The $\dot{V}_A/\dot{Q}$ index (as defined in equation 7.2) serves as an indicator of the shape of the $\dot{V}_A/\dot{Q}$ distribution and decreases with an increase in a $\dot{V}_A/\dot{Q}$ mismatch. The relationship is non-linear and is eluciated with reference to the respective distributions in graph 7.1; the clinical significance of the index value is obtained through correlation of the distributions in graph 7.1 with the respective index values. The results of this exercise are displayed in Table 7.1 (the index values were calculated for the respective distributions represented in graph 7.1 and the standard parameters assumed as in equation 7.3).

% perfusion to the low $\dot{V}_A/\dot{Q}$ region	$\dot{V}_A/\dot{Q}$ Index	
	low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0 (unimodal)	0,992	0,992
6.9	0,921	0,773
13,7	0,845	0,546
20,6	0,766	0,332
27,5	0,682	0,123
34,4	0,598	0,123
41,2	0,513	0,100
48,1	0,423	0,087
55	0,332	0,077

TABLE 7.1: $\dot{V}_A/\dot{Q}$ Index for various $\dot{V}_A/\dot{Q}$ distributions.

It should be noted that the index values for the two extreme series of low $\dot{V}_A/\dot{Q}$ values differ for equal perfusion of these regions; this illustrates the fact that these conditions are representative of different degrees of clinical severity in the patient (as explained in paragraph 7.3). Furthermore a specific patient will in all probability display a combination of these two extremes, in which case the combined effect of the distributions in the patient will be reflected in the index value.

With the preceding discussion in mind, it is possible to attach clinical judgements to the complete spectrum of the index value (0 to 1); this has been done based on the discussion in paragraph 7.3 and the correlations obtained through Table 7.1. Four major clinical judgements related to the nature of the $\dot{V}_A/\dot{Q}$ distribution in the patient, based on the index value, have been defined : i.e. a normal $\dot{V}_A/\dot{Q}$ distribution, a relatively safe region, a region where the patient is prone to develop severe $\dot{V}_A/\dot{Q}$ abnormalities and finally a severe $\dot{V}_A/\dot{Q}$ mismatch as in the case of established ARDS.

Figure 7.4 illustrates the clinical judgements that can be made about the value of the index.

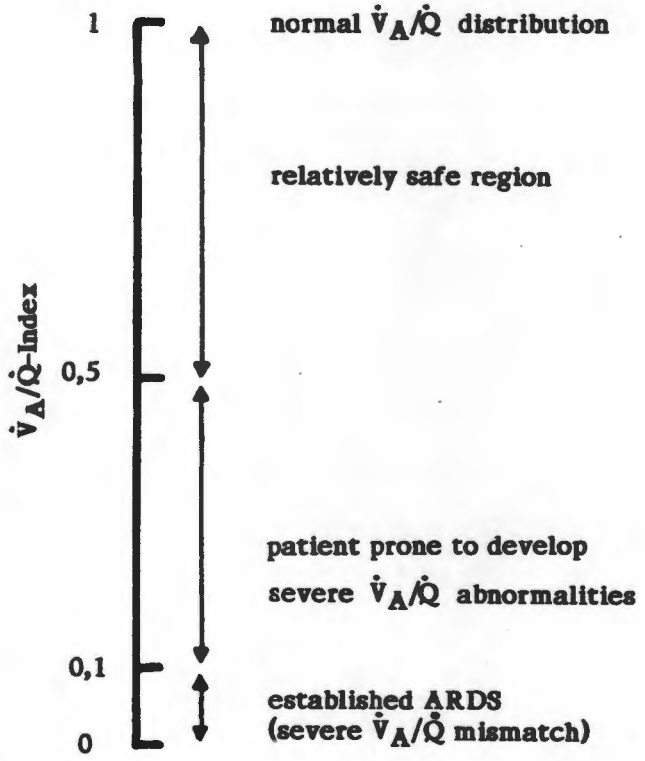


Figure 7.4 Clinical significance of the $\dot{V}_A/\dot{Q}$ - Index

A very important aspect is the changes that may occur over a period of time in the index value. It is obvious that a downward trend of the index value is an indication of a deteriorating clinical picture. The index can also be used to detect early changes in the $\dot{V}_A/\dot{Q}$ distribution and can therefore be used in a predictive capacity. The complete clinical course should however be taken into consideration when the index is judged. An improvement of the index following fluid administration may only be due to increased perfusion, without any real improvement of the adverse $\dot{V}_A/\dot{Q}$ distribution. The sensitivity of the index is indicative of the extent to which misjudgements of this nature will be excluded, the details of which are addressed in the following section.

7.6.3 Sensitivity and Specificity of the $\dot{V}_A/\dot{Q}$ Index: The following is understood under the concepts of sensitivity and specificity pertaining to the $\dot{V}_A/\dot{Q}$ index:

The diagnostic sensitivity and specificity of the index pertaining to the ARDS syndrome can only be defined once the exact correlation between the syndrome and the $\dot{V}_A/\dot{Q}$ distribution has been established (hypothesis I in this thesis).

Specificity: the probability that if the index is calculated for a specific $\dot{V}_A/\dot{Q}$ distribution and set of theoretical parameters in the model, it will be equal to a similar $\dot{V}_A/\dot{Q}$ distribution and set of physiological parameters in the patient.

The validity of the model was not addressed in this thesis, i.e. the physiological correctness of the equations used in the model have not been proved, it can nevertheless be assumed they are a reliable reflection of the actual state (refer to the citations in Chapter 5). Furthermore, the effect of nitrogen gas in the air and blood phase has been taken into consideration, which further contributes to its accuracy. It follows from this discussion that the index complies with a high specificity level.

Sensitivity: the probability that if a specific $\dot{V}_A/\dot{Q}$ distribution does exist in the lung; the index as determined with the measurements will be a reflection of a similar theoretical $\dot{V}_A/\dot{Q}$ distribution in the model.

It should be clear that the sensitivity of the index depends on the amount of information available pertaining to the true values of parameters within the patient. If all the parameters as required by the model are measured in the patient and the simulation completed for this specific case (equation 7.2 is applied to evaluate the index), it can be assumed that the index will exhibit a high sensitivity level as well.

The oxygen consumption, carbon dioxide output, cardiac output and minute ventilation are not always readily available in the typical clinical situation. In the deriviation of equation 7.3 for the index it was therefore assumed that the standard set of parameters is valid for all

patients; this is not always true and will effect the index sensitivity. The effect on the model output due to deviations that might occur in the model parameters, was addressed in the model sensitivity analysis. The resulting changes in the $\dot{V}_A/\dot{Q}$ index were calculated for the maximum physiological deviations that may occur in the standard values and the results are presented in Appendix D.

It is clear from these results that the only two parameters that could cause a severe misinterpretation of the index as illustrated in Fig. 7.4 and calculated according to equation 7.3 are the total pulmonary capillary perfusion ($\dot{Q}$) and the oxygen consumption ($\dot{V}O_2$). An increase in $\dot{V}O_2$ will however not lead to misinterpretation and as explained in a preceding section, a decrease in $\dot{V}O_2$ is a consequence of other factors (primarily a drop in $\dot{Q}$); the actual oxygen demand in a patient is unlikely to decrease and will in most cases, in fact, increase.

That leaves $\dot{Q}$ as the only parameter which may lead to misinterpretation of the index due to deviations around the standard assumed value. The most marked effect results from an increase in the standard value, which will cause an erroneously high index value, when the $\dot{V}_A/\dot{Q}$ distribution is in fact severely affected. In this respect the clinical course and therapy must play an important role in the interpretation of the index. It should be emphasised that if all the parameters are measured (or at least $\dot{Q}$) and equation 7.2 is applied, the sensitivity problem can be minimised.

To conclude, it should be clear that the $\dot{V}_A/\dot{Q}$ index, as introduced in the previous sections, exhibits a high sensitivity level if all the parameters as defined in paragraph 6.2.2 are known, if in the absence of enough clinical data these values are assumed to be equal to the standard values, the sensitivity of the index and therefore its ability to detect $\dot{V}_A/\dot{Q}$ inequalities, is still superior to other methods in use (e.g. the physiological shunt).

7.6.4 Method of physiological measurements: If the model parameters are to be measured in the patient (and the standard values are not assumed) this should be done at the onset of the series of PaO_2 measurements and should be measured at the present F_IO_2 level set for the patient; since this is a true reflection of the combined clinical and therapeutic status.

The series of three PaO_2 measurements must be performed consecutively with approximately two minutes allowed for stabilisation of the PaO_2 level (Nunn, 1969) after the F_IO_2 has been set to 0,5; 0,8 and 1,0 respectively.

The patient should not be kept on these high levels of inspired oxygen for longer than the two minutes each, since it can affect the nature of the $\dot{V}_A/\dot{Q}$ distribution as well as other physiological variables. It is assumed that over a short period these parameters remain relatively constant and small changes will not affect the calculated index value.

Since the respiratory system exhibits hysteresis (the PaO_2 equilibrium time in the reverse direction is in excess of fifteen minutes compared to the two minutes in the forward direction) it is not advisable to compare the PaO_2 measurements in a sequence of decreasing F_IO_2; the results may be different since the actual shape of the distribution may be affected by the longer periods of high F_IO_2 levels.

It was, for the purpose of this discussion, assumed that the patient is not presently on a F_IO_2 level exceeding 0,5 (since the index is meant to be used primarily in a predictive capacity); the test can however be adapted to accommodate higher levels of F_IO_2.

CHAPTER 8

CONCLUSIONS AND RECOMMENDATIONS

8.1 CONCLUSIONS

(a) The art of modelling complex biological systems and clinical application of results requires insight into as well as a thorough understanding of concepts related both to the biological and engineering sciences.

(b) A mathematical model of a complex biological system can contribute towards the understanding of the interrelatedness of the various physiological parameters and processes, as well as clarification of causality principles.

(c) Modelling and parameter identification techniques can be applied with success in the clinical environment in order to facilitate the management of patients.

(d) The advent of ultra fast computers will greatly facilitate and enhance the simulation of biological systems.

(e) The development of a computer program that guarantees the successful operation of a program over the complete range of all the physiological variables is a time consuming process and may present various problems related to numerical mathematics.

(f) It is virtually impossible to grasp the inherent complexities of the respiratory system without the application of computer simulation techniques.

(g) The $\dot{V}_A/\dot{Q}$ index as defined by the author can be applied in the clinical environment for the early identification of patients susceptible to ARDS as well as the management of any patient suffering from a mismatch in the $\dot{V}_A/\dot{Q}$ distribution.

8.2 RECOMMENDATIONS

The following aspects justify further study:

(a) Measurement of the $\dot{V}_A/\dot{Q}$ index in the clinical environment should be correlated with actual patient prognosis and other diagnostic indicators; with specific reference to patients susceptible to the ARDS syndrome.

(b) The correlation between the onset of the ARDS syndrome and the nature of the $\dot{V}_A/\dot{Q}$ distribution should be studied in more detail.

APPENDIX A

MODEL PARAMETERS AND VARIABLES

A1. INPUT VARIABLE

F_IO_2	fraction of inspired oxygen concentration	fraction

A2. PARAMETERS TO BE SPECIFIED

1.	DP_{50}	amount by which the P_{50} (at 37°C; pH = 7,4; PCO_2 = 40 mmHg) of the subject's blood exceeds the standard of 26,8 mmHg.	mmHg
2.	Temp	blood temperature	°C
3.	HBv	venous haemoglobin concentration	g/100 ml blood
4.	HBa	arterial haemoglobin concentration	g/100 ml blood
5.	SOL_{N_2}	solubility of nitrogen in blood	ml N_2/100 ml blood
6.	K	BTPS to STPD conversion factor	-
7.	F_ICO_2	fraction of inspired carbon dioxide concentration	fraction
8.	F_IN_2	fraction of inspired nitrogen concentration	fraction
9.	SOL_{O_2}	solubility of oxygen in blood	ml O_2/100 ml blood
10.	$HCRIT_v$	venous haematocrit	%
11.	HCRITa	arterial haematocrit	%
12.	P_{EF}	effective inspired gas pressure	mmHg
13.	$\dot{V}O_2$	oxygen consumption	l/min
14.	$\dot{V}CO_2$	carbon dioxide output	l/min
15.	$\dot{V}N_2$	nitrogen exchange in the lungs	l/min
16.	$\dot{V}_{AI}$	total inspired alveolar ventilation	l/min
17.	$\dot{Q}$	total pulmonary capillary perfusion	l/min
18.	N	number of compartments in the lung	integer

A3. PARAMETERS RELATED TO THE $\dot{V}_A/\dot{Q}$ DISTRIBUTION (to be identified)

Ventilation distribution

1.	NV	number of modes in the ventilation distribution (maximum 2)
2.	MV1	mean value of mode 1
3.	SDV1	standard deviation of mode 1
4.	RLV1	skewing factor for mode 1 (left)
5.	RRV1	skewing factor for mode 1 (right)
6.	MV2	mean value of mode 2
7.	SDV2	standard deviation of mode 2
8.	RLV2	skewing factor for mode 2 (left)
9.	RRV2	skewing factor for mode 2 (right)
10.	RATL	the mean ratio of the relative distribution of air between the modes.

Perfusion distribution

11.	NQ	number of modes in the perfusion distribution (maximum 2)
12.	MQ1	mean value of mode 1
13.	SDQ1	standard deviation of mode 1
14.	RLQ1	skewing factor for mode 1 (left)
15.	RRQ1	skewing factor for mode 1 (right)
16.	MQ2	mean value of mode 2
17.	SDQ2	standard deviation of mode 2
18.	RLQ2	skewing factor for mode 2 (left)
19.	RRQ2	skewing factor for mode 2 (right)
20.	PERSQ1	the percentage of the total perfusion to mode 1

A4. OUTPUT VARIABLES

1.	PaO_2	arterial oxygen partial pressure	mmHg
2.	$PaCO_2$	arterial carbon dioxide partial pressure	mmHg
3.	PaN_2	arterial nitrogen partial pressure	mmHg
4.	CaO_2	arterial oxygen content	ml O_2/100 ml blood
5.	$CaCO_2$	arterial carbon dioxide content	ml CO_2/100 ml blood
6.	CaN_2	arterial nitrogen content	ml N_2/100 ml blood

7.	$P_{\bar{v}}O_2$	mixed venous oxygen partial pressure	mmHg
8.	$P_{\bar{v}}CO_2$	mixed venous carbon dioxide partial pressure	mmHg
9.	$P_{\bar{v}}N_2$	mixed venous nitrogen partial pressure	mmHg
10.	$C_{\bar{v}}O_2$	oxygen concentration in mixed venous blood	ml O_2/100 ml blood
11.	$C_{\bar{v}}CO_2$	carbon dioxide concentration in mixed venous blood	ml CO_2/100 ml blood
12.	$C_{\bar{v}}N_2$	nitrogen concentration in mixed venous blood	ml N_2/100 ml blood
13.	P_AO_2	alveolar oxygen partial pressure	mmHg
14.	P_ACO_2	alveolar carbon dioxide partial pressure	mmHg
15.	P_AN_2	alveolar nitrogen partial pressure	mmHg
16.	pHa	arterial pH	-
17.	pHv	venous pH	-
18.	$\dot{V}_A$	resulting total alveolar ventilation	l/min
19.	$\dot{V}_{DA}/\dot{V}_A$	alveolar dead space	%
20.	$\dot{Q}sp/\dot{Q}t$	physiological shunt	%

APPENDIX B
Newton Raphson Algorithm

Newton Raphson algorithm for solving the roots of a set of non-linear simultaneous equations.

Assume the roots of the following set of n-simultaneous non-linear equations need to be solved:

$$y = F(x)$$

y : n x 1 vector
x : n x 1 vector

In order to solve the roots for the above set of equations, the following algorithm is iterated until such time that y approximates the zero vector close enough.

1. $y = F(x)$
2. $x = x - J^{-1} * y$
3. Repeat 1 and 2

J^{-1} : the inverse n x n Jacobiaan matrix for the set of equations in 1

(In those cases where it is not possible to derive exact equations for the respective partial derivatives, numerical differentiation techniques are applied.)

APPENDIX C

MODEL SENSITIVITY ANALYSIS

C1. INTRODUCTION

A parameter sensitivity index (SI) is defined as follows:

$$SI = \frac{\Delta\ P_aO_2}{\Delta\ \text{parameter}} \ /\ \text{other parameters constant}$$

The parameters are varied around the mean values as specified in 6.2.2 with a plus and minus 10% deflection.

C2. BLOOD TEMPERATURE SENSITIVITY

Temp = 7,4°C

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	-0,007	-0,007
	0.80	-0,003	-0,003
	0,99	-0,004	-0,004
27,5	0,50	1,951	3,491
	0,80	0,010	4,235
	0,99	-0,017	3,932
55	0,50	3,359	2,342
	0,80	0,422	2,566
	0,99	-0,163	2,702

C3. HB SENSITIVITY

$\Delta HB = 3,1$ g/100 ml blood

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	-0,003	-0,003
	0,80	0,000	0,000
	0,99	0,000	0,000
27,5	0,50	1,255	1,567
	0,80	0,012	2,306
	0,99	0,000	2,298
55	0,50	1,565	1,174
	0,80	0,291	1,188
	0,99	0,001	1,202

C4. HCRIT SENSITIVITY

Δ HCRIT = 9,4 %

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	-0,106	-0,106
	0,80	-0,185	-0,185
	0,99	-0,234	-0,234
27,5	0,50	-0,085	0,117
	0,80	-0,445	0,149
	0,99	-0,819	0,032
55	0,50	0,138	0,043
	0,80	-0,860	0,068
	0,99	-1,915	0,096

C5. P_{EF} SENSITIVITY

ΔP_{EF} = 142,6 mmHg

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	0,430	0,430
	0,80	0,739	0,739
	0,99	0,933	0,933
27,5	0,50	0,282	0,046
	0,80	0,702	0,190
	0,99	0,916	0,512
55	0,50	0,064	0,015
	0,80	0,619	0,020
	0,99	0,889	0,024

C6. $\dot{V}O_2$ SENSITIVITY

$\Delta\dot{V}O_2$ = 0,055 l/min

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	-115,9	-115,9
	0,80	- 52,1	- 52,1
	0,99	- 12,2	- 12,2
27,5	0,50	-828,1	-159,1
	0,80	-859,2	-522,6
	0,99	-226,5	-1176,6
55	0,50	-392,8	- 80,0
	0,80	-1974,1	- 92,6
	0,99	-852,6	-104,6

C7. $\dot{V}CO_2$ SENSITIVITY

$\Delta \dot{V}CO_2 = 0,046$ l/min

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	- 75,7	- 75,7
	0,80	-130,0	-130,0
	0,99	-164,2	-164,2
27,5	0,50	- 40,2	35,0
	0,80	-164,3	10,6
	0,99	-217,3	- 73,1
55	0,50	22,9	25,5
	0,80	-209,4	26,4
	0,99	-319,5	26,4

C8. $\dot{V}_A$ SENSITIVITY

$\Delta \dot{V}_A = 1$ l/min

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	9,950	9,950
	0,80	8,953	8,953
	0,99	8,336	8,336
27,5	0,50	5,888	-1,004
	0,80	10,123	0,481
	0,99	10,363	4,341
55	0,50	-0,244	-1,028
	0,80	10,849	-1,222
	0,99	13,419	-1,285

C9. $\dot{Q}$ SENSITIVITY

$\Delta \dot{Q}$ = 1.18 l/min

Percentage of perfusion to the low $\dot{V}_A/\dot{Q}$ region (L/blood)	F_IO_2	Sensitivity Index (SI)	
		low $\dot{V}_A/\dot{Q}$ = 0,124	low $\dot{V}_A/\dot{Q}$ = 0,003
0	0,50	0,061	0,061
	0,80	0,074	0,074
	0,99	0,086	0,086
27,5	0,50	35,371	6,809
	0,80	38,997	23,053
	0,99	11,691	53,403
55	0,50	17,159	3,597
	0,80	92,760	4,295
	0,99	44,259	4,898

APPENDIX D

SENSITIVITY ANALYSIS OF THE $\dot{V}_A/\dot{Q}$ INDEX ($I_{\dot{V}_A/\dot{Q}}$)

D1. Parameter : Temp [°C]

Standard value : 37
minimum value : 30
maximum value : 40

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	0	0,992	0,993	0,1	0,992	0
0,124	27,5	0,682	0,676	- 0,9	0,687	0,7
	55,0	0,332	0,312	- 6,0	0,343	3,3
0,003	27,5	0,184	0,163	-11,4	0,237	28,8
	55,0	0,077	0,064	-16,9	0,111	44,2

D2. Parameter : HB [g/100 ml blood]

standard value : 15,5
minimum value : 12,5
maximum value : 18,5

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	o	0,992	0,992	0	0,992	0
0,124	27,5	0,682	0,680	- 0,3	0,685	0,4
	55,0	0,332	0,327	- 1,5	0,338	1,8
0,003	27,5	0,184	0,198	7,6	0,224	21,7
	55,0	0,077	0,086	11,7	0,101	31,2

D3. Parameter : HCRIT [%]

standard value : 47,0
minimum value : 30,0
maximum value : 55,0

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	0	0,992	0,993	0,1	0,992	0
0,124	27,5	0,682	0,683	0,1	0,683	0,1
	55,0	0,332	0,332	0	0,332	0
0,003	27,5	0,184	0,212	15,2	0,212	15,2
	55,0	0,077	0,094	22,1	0,094	22,1

D4. Parameter : P_{EF} [mmHg]

Standard value : 713
minimum value : 573
maximum value : 733

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	0	0,992	0,800	-19,4	0,926	- 6,7
0,124	27,5	0,682	0,566	-17,0	0,700	2,6
	55,0	0,332	0,266	-19,9	0,343	3,3
0,003	27,5	0,184	0,165	-10,3	0,221	20,1
	55,0	0,097	0,088	14,3	0,095	23,4

D5. Parameter : $\dot{V}O_2$ [l/min]

Standard value : 0,275
minimum value : 0,100
maximum value : 0,300

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	0	0,992	1,016	2,4	0,987	- 0,5
0,124	27,5	0,682	0,969	42,1	0,612	-10,3
	55,0	0,332	0,897	170,2	0,217	-34,6
0,003	27,5	0,184	0,645	2,2	0,188	2,2
	55,0	0,077	0,200	159,7	0,090	16,9

D6. Parameters : $\dot{V}CO_2$ [l/min]

Standard value : 0,234
minimum value : 0,100
maximum value : 0,300

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	0	0,992	1,017	2,5	0,979	- 1,3
0,124	27,5	0,682	0,708	3,8	0,671	- 1,6
	55,0	0,332	0,349	5,1	0,324	- 2,4
0,003	27,5	0,184	0,208	13,6	0,211	14,7
	55,0	0,077	0,083	7,8	0,097	26,4

D7. Parameters : $\dot{V}_A$ [1/min]

Standard value : 5,0
minimum value : 4,5
maximum value : 10,0

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	0	0,992	0,982	- 1,0	1,041	4,9
0,124	27,5	0,682	0,673	- 1,3	0,667	- 2,2
	55,0	0,332	0,326	- 1,8	0,361	8,7
0,003	27,5	0,184	0,211	14,7	0,214	16,3
	55,0	0,077	0,095	23,4	0,086	11,7

D8. Parameter : $\dot{Q}$ [1/min]

Standard value : 5,9
minimum value : 4,5
maximum value : 10,0

low $\dot{V}_A/\dot{Q}$ value	% of total perfusion to low $\dot{V}_A/\dot{Q}$ region	Standard $I_{\dot{V}_A/\dot{Q}}$	Minimum $I_{\dot{V}_A/\dot{Q}}$	% change	Maximum $I_{\dot{V}_A/\dot{Q}}$	% change
unimodal	0	0,992	0,992	0	0,993	0,1
0,124	27,5	0,682	0,535	-21,6	0,890	30,5
	55,0	0,332	0,148	-55,4	0,768	131,3
0,003	27,5	0,184	0,148	-19,6	0,427	132,1
	55,0	0,077	0,081	5,2	0,126	63,6

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