RESPIRATORY MECHANICS DURING ANESTHESIA IN HUMANS

by

Panagiotis K. Behrakis

Department of Medicine

Division of Experimental Medicine

McGill University

Montreal

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

June 1986

TO MY FAMILY

TO DR. J. MILIC-EMILI

A C K N O W L E D G E M E N T S

I am greatly indebted to Dr. J. Milic-Emili my supervisor, for accepting me as a graduate student, keeping me headed in the right direction and teaching me a great deal of experimental design, analysis of results and how to conduct research in general. Dr. Milic-Emili was for me not only the supervisor of my thesis, but also a great teacher to whom I owe virtually all that I know about research.

My wife, Katerina, and my children have put up with the long hours of work and the many inherent crises and frustrations. Their moral support was invaluable. Katerina has also provided invaluable help in preparing the graphs included in this thesis.

I am grateful to my friends and colleagues, Drs. W. Zin and A. Baydur, for their experimental assistance, and to Professors B. Higgs and D. Bevan for covering the special problems related to the management of anesthetized patients, and their useful criticisms. I have also to acknowledge the highly intellectual and constructive contributions of Dr. Marc Jaeger in the early stages of my work. His influence in my way of thinking has been important and will never be forgotten.

Since the whole thesis was accomplished during my fellowship in Montreal, I would also like to express my thanks to Dr. S. Magriotis, the Head of the Respiratory Center of Sotiria

Hospital of Athens and to Dr. N. Tsoutis, Physician-in-Chief of the same hospital for supporting this fellowship.

I wish to extend my deep thanks to my friend and compatriot, Professor Charalambos Roussos, who recommended that I pursue my postgraduate studies in Montreal and offered me the warmest hospitality and moral support throughout my stay in Canada.

Finally, I would like to thank Dr. H. Ghezzo for invaluable assistance in the statistical analysis of the results, and Mrs. Joan Longo for typing the thesis.

ABSTRACT

This thesis provides the first systematic measurements of respiratory mechanics in humans anesthetized with halothane. Measurements were made both in anesthetized and anesthetized-paralyzed states. Both active and passive elastance and flow resistance values of the total respiratory system are presented. Next, the passive mechanics data are partitioned into lung and chest wall components. As this partitioning is based on measurements of esophageal pressure, a simple method for validating the esophageal balloon-catheter technique for indirect measurement of pleural surface pressure has also been developed, and applied to anesthetized subjects. In addition, lung mechanics has been studied in awake normal subjects in different body postures (sitting, supine, right and left lateral decubitus). The present approach can be readily extended to investigate the effects of other anesthetics and drugs used in conjunction with anesthesia on respiratory mechanics.

RÉSUMÉ

Cette thèse rapporte pour la première fois une analyse systématique des propriétés mécaniques respiratoires chez l'homme anesthésié à l'halotane. Les mesures ont été effectuées sous anesthésie seule aussi que sous anesthésie-paralysie. Les valeurs d'élastance active et passive, et de résistance du système respiratoire total sont présentées. Les données mécaniques passives sont ensuite réparties selon leurs composantes pulmonaires et thoraciques. Cette répartition étant basée sur la mesure de pression oesophagienne selon la technique du ballonnet-catheter. Une méthode simple permettant de valider cette technique comme méthode de mesure de la pression pleurale de surface a été developpé, et son application vérifiée sur les sujets anesthésiés. De plus les propriétés mécaniques pulmonaires ont été etudiées chez des sujets normaux à l'état vigile en différente positions corporelles (position assis, de supination, et de décubitus latéral gauche et droit). L'approche utilisée pour déterminer les propriétés mécaniques respiratoires peut dès lors être étendue à l'étude des effets d'autres anesthésiques ou agents pharmacologiques utilisés en anesthésie générale.

P R E F A C E

This thesis describes a series of experiments which were designed to study the effects of anesthesia on respiratory mechanics in humans. The research was performed under the supervision of Dr. J. Milic-Emili. The thesis is presented taking advantage of the option provided by Section of the guidelines concerning thesis preparation. Chapter II has appeared in the Journal of Applied Physiology, Vol.55, pp.1085-1092, 1983. Chapter III has been published in the Journal of Applied Physiology, Vol. 54, pp.1477-1481, 1983. Chapter IV has appeared in the American Review of Respiratory Disease, Vol. 126, pp.788-791, 1982. Chapter V has been published in Chest, Vol. 83, pp.643-646, 1983. Chapter VI has appeared in Anesthesiology, Vol. 59, pp.340-343, 1983, while Chapter VII was printed in the Journal of Applied Physiology, Vol. 58, pp.285-289, 1985.

The original ideas developed in this thesis stem from unique collaboration between the writer, as fellow, and Dr. J. Milic-Emili as professor-supervisor.

The writer has been in charge of the planning and execution of all experiments described. He has also analyzed all experimental results and has prepared all manuscripts, except for Chapter IV whose data were analyzed in part by Dr. A. Baydur. The latter has also provided technical assistance in the experiments described in Chapters II, III, IV and V. Technical assistance in chapters II, III and IV was also provided by Dr. W. A. Zin.

Dr. B. D. Higgs, Assistant Professor of Anesthesia, was responsible for the clinical management of the subjects during anesthesia (Chapters II, III, VI and VII) and also provided technical assistance in the experiments of chapter VI. Dr. D. Bevan, Professor of Anesthesia, provided the patients of his Department and also useful advice for chapters VI and VII. Dr. M. Jaeger, Visiting Professor at McGill University, provided useful guidance and technical advice to chapters IV and V.

Each of the above investigators was a co-author of some of the six published papers encompassing this thesis which describes only a part of the writer's work during his stay at McGill University (Two additional papers are in press in the Journal of Applied Physiology).

In the present thesis, units are expressed in conventional respiratory physiology terms. The only unit used which differs from SI (international system of metric units) is that for pressure, where cmH_2O is used instead of kilo-Pascal, kP (1 cmH_2O = 0.0981 kP).

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

A. INTRODUCTION

General anesthesia is "a drug induced absence of perception of all sensations" (Marshall and Wollman, 1980) usually applied for the purpose of analgesia during surgical procedures. Although the primary target organ of anesthetic drugs is the central nervous system, these agents have a multitude of additional effects on other organs too.

The respiratory system is known to be affected by general anesthesia since the early report of Snow (1858) who assessed the depth of anesthesia on the basis of alterations in the pattern of thoracoabdominal motion. Since then, the effects of general anesthesia on pulmonary gas exchange, control of breathing, distribution of ventilation within the lungs, pulmonary circulation and respiratory defence mechanisms have been extensively studied (for general reviews see Severinghaus and Larson, 1969; Rehder et al., 1975; Kafer, 1977; Hickey and Severinghaus, 1981).

This Thesis focuses on the effects of general anesthesia on respiratory mechanics. This topic has been the object of previous extensive reviews (Rehder et al., 1975; Kafer, 1977.) This chapter provides an updated general account of the present knowledge of the effects of general anesthesia on the <u>passive</u> mechanical properties of the respiratory system, the functional residual capacity and the <u>active</u> mechanical properties of the respiratory system. A more specific account is provided in each individual chapter. Finally, a brief review on the pharmacological effects of halothane and nitrous oxide (N_2O) is provided here because these agents were used in the experiments described in this Thesis.

For the purposes of this Thesis, general anesthesia with spontaneous breathing will be denoted "anesthesia" while anesthesia with drug-induced muscle paralysis and mechanical ventilation will be denoted "anesthesia-paralysis", in line with Howell and Peckett (1957).

B. EFFECTS OF ANESTHESIA ON RESPIRATORY MECHANICS

1. PASSIVE MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM DURING ANESTHESIA

Total respiratory system elastance, Ers

The static pressure-volume relationship of the total respiratory system in humans has been studied during anesthesia and anesthesia-paralysis using various anesthetic agents. The elastic recoil pressure of the respiratory system increases after induction of anesthesia in humans (Westbrook et al., 1973; Rehder et al., 1974), i.e. at comparable lung volumes, a greater inflating pressure is required during anesthesia than awake.

Available evidence indicates that anesthesia and anesthesia-paralysis result in increased elastance of the total respiratory system, as first reported by Nims et al. (1955). During anesthesia-paralysis with thiopental, N_2O, cyclopropane and succinylcholine, they found that Ers measured in four females increased from 5.6 cm $H_2O.l^{-1}$ before anesthesia-paralysis to 9.0 cm $H_2O.l^{-1}$ during anesthesia-paralysis. The results of Nims et al. (1955) were confirmed by most subsequent investigations (Brownlee et al., 1956; Van Lith et al., 1967; Westbrook et al., 1973; Margaria et al., 1973; Rehder et al., 1974). As shown in Table I.1 there is a variable increase in Ers during both anesthesia and anesthesia-paralysis, except for the study of Van Lith et al. (1967) in which Ers decreased

TABLE I.1

Passive elastance of the total respiratory system (Ers) during anesthesia and anesthesia-paralysis, compared to the awake state in supine humans

Reference	No. of Subjects	Anesthetic agents	$Ers(cmH_2O.l^{-1})$ Awake	Anesthesia	Anesthesia-Paralysis
Nims et al. (1955)	4*	Thiopental, N_2O, Cyclolpropane, Succinylcholine	5.6	-	9.0
Brownlee et al. (1956)	11*	Thiopental, Cyclopropane Diethylether, Succinylcholine, Curare	6.8	-	22.4
Van Lith et al. (1967)	26	Thiopental, Succinylcholine	11.8	-	9.4
Westbrook et al. (1973)	5	Thiopental, Meperidine, (Succinylcholine)**	8.4	11.1	10.7
Margaria et al. (1973)	3	Thiopental	11.9	18.5	-
Rehder et al. (1974)	4	Isoflurane Succinylcholine	9.1	-	12.1

* Various combinations of these anesthetic agents were used
**Drug used only during anesthesia-paralysis

following anesthesia-paralysis. In this connection it should be noted, however, that it is very difficult to measure Ers in awake subjects (Agostoni and Mead, 1964) because complete relaxation of the respiratory muscles is difficult to ascertain. The study of Westbrook et al. (1973) is of particular interest because it showed that Ers is similar during both anesthesia and anesthesia-paralysis. The increase in Ers is not progressive with time and cannot be prevented by repeated large inflations of the lungs (Westbrook et al., 1973). Increasing the depth of anesthesia does not result in further increase of Ers (Rehder et al., 1974)

Pulmonary Elastance, El

Induction of anesthesia in supine subjects (Westbrook et al., 1973; Rehder et al., 1974) results in a rigthward shift of the static pressure-volume relationship of the lung, indicating an increase in pulmonary elastic recoil pressure. Elastic recoil pressure of the lungs after induction is not altered by addition of muscle paralysis but appears to be related to the magnitude of the reduction in functional residual capacity (FRC) (Westbrook et al., 1973).

Most evidence suggests that El increases by a variable extent during anesthesia as compared to the awake state (Table I.2). However, some authors found no change (Foster et al., 1957; Van Lith et al., 1967). The increase in El is not pro-

TABLE I.2

Passive elastances ($cm\ H_2O.l^{-1}$) of the lungs (El) and the chest wall (Ew) during anesthesia, anesthesia-paralysis and awake state

Reference	No. of Subj.	Anesthetic Agent*	Awake		Anesthesia		Anesthesia Paralysis	
			El	Ew	El	Ew	El	Ew
Wu et al. (1956)	10	C.D.	8.0	-	14.9	-	-	-
Butler and Smith (1957)	33	T.Cal.	-	-	-	-	6.5	3.7
Foster et al. (1957)	10	T.S.	6.9	-	-	-	6.3	-
Howell and Peckett (1957)	15	T.	-	-	-	-	12.9	6.8
	4	T.S.Tub.Cal.	15.0	-	-	-	6.5	-
Van Lith et al. (1967)	26	T.S.	5.7	5.9	-	-	5.6	3.7
Westbrook et al. (1973)	5	T.M.S.	4.9	4.1	7.4	3.8	7.8	2.9
Rehder et al. (1974)	5	I.S.	4.7	4.2	-	-	6.4	5.7
Grimby et al. (1975)	6	T.Dr.F.	-	-	13.5	8.8	-	-
Hedenstierna et al. (1975)	9	T.P.Ha	5.7	-	-	-	11.1	-
Dohi and Gold (1979)	11	T.M.H	9.4	-	-	-	14.0	-

* T = thiopental; S = succinylcholine; M = morphine; I = isoflurane; C = cyclophropane; D = diethylether; Tub = tubocurarine; Cal = callamine triethiodine; Dr = droperidrol; Ha = halothane; P = pancuronium; H = hydroxyzide.

gressive with time (Westbrook et al., 1973), is not affected by depth of anesthesia (Rehder et al., 1974) and cannot be prevented by large inflations of the lungs (Westbrook et al., 1973).

The static pressure-volume relationship of the lungs may be altered by several mechanisms. Lung elastic recoil pressure may be increased by a deformation of the thoracic cavity which distorts the lung (Scheidt et al., 1981). If the lung is distorted from its natural shape, a larger transpulmonary pressure is needed to distend the lung to a given volume. Lung elastance can be increased by the effect of anesthetic agents on airway smooth muscle, of interstitial pulmonary edema, pulmonary vascular congestion, airway closure, atelectasis and changes in surfactant function.

Anesthetic agents, muscle relaxants, and other drugs administered during anesthesia could reduce lung compliance by causing contraction of smooth muscle in alveolar ducts and respiratory bronchioles, possibly through release of histamine. Some drugs which are used in association with anesthesia, e.g. morphine and d-tubocurarine, release histamine; in dogs, d-tubocurarine reduces lung compliance, an effect that can be partly blocked by antihistaminics (Safar and Bachman, 1956). This effect is not present when relaxants other than d-tubocurarine are used. Increase in lung elastance is not seen in dogs subjected to gallamine triethiodide, succinylcholine chloride, and decamethonium bromide (Safar and Bachman, 1956). Furthermore, this mechanism is unlikely to be active in anesthetized humans because subjects anesthetized in the sitting position do not experience an increase in lung elastance (Rehder et al., 1972), whereas supine subjects do (Westbrook et al., 1973). The effects of smooth muscle contraction should be present and equal in both sitting and supine subjects, if this mechanism were important.

Accumulation of pulmonary extravascular water or vascular congestion can increase El (Frank, 1959), but comparative measurements of pulmonary extravascular water in conscious and anesthetized states have not been made. No evidence exists for pulmonary congestion during anesthesia.

Lung elastance may increase as a result of a drecrease in the number of lung units with open airways (gas trapping) or atelectasis. Simultaneous measurements of FRC by body plethysmography and N_2 clearance give similar results (Westbrook et al., 1973). This provides evidence against a significant amount of gas trapping during anesthesia. As inflation of the lungs to high airway pressures does not reverse the increase in lung elastance, atelectasis seems also unlikely as a major factor in the increase of El (Westbrook et al., 1973). This notion is also supported by the very small increase in right-to-left shunt (Rehder et al., 1979) which occurs during anesthesia in supine normal humans. Additional evidence against atelectasis as an important mechanism for increased El is provided by the lack of correspondence between the decrease in FRC and the ircrease in El (Mead and Collier, 1959; Collier and Mead, 1964).

One of the most likely factors which may cause alterations in El is a change in the surface tension exerted by the film lining the alveoli. Anesthetic agents affect the surface lining layer in excised, unperfused, ventilated dog lungs (Woo et al., 1969). In intact animals, however, this effect appears to be small (Woo et al., 1970). Surfactant function also can be altered by breathing at low lung volumes. Since anesthesia in supine humans reduces the FRC, this mechanism is likely to operate. A similar hypothesis has been advanced to explain the increase in El seen when breathing at a low lung volume as a result of chest strapping (Stubbs et al., 1972; Scheidt et al., 1981; Klineberg et al., 1981).

In conclusion, the most important mechanism causing the reduction in El during anesthesia is an alteration in surfactant function. Other factors, however, cannot be ruled out.

Elastance of the chest wall, Ew

Few measurements of Ew during anesthesia have been reported (Table I.2). In these studies neither Ew nor elastic recoil of the chest wall changes significantly (Westbrook et al., 1973; Rehder et al., 1974) but at low lung volume there was a tendency for a reduction in the outward recoil of the chest wall after induction of anesthesia. This may be one of the causes of reduction of FRC during anesthesia (Westbrook et al., 1973).

In all studies of Table I.2, pleural pressure was estimated indirectly, from esophageal pressure. Esophageal pressure may not give an accurate estimate of pleural pressure with subjects lying supine (Knowles et al., 1959; Mead and Gaensler, 1959), and this may explain in part the variable results of Ew and El found in the literature.

Pressure-flow relationships

Pulmonary (Rl) and total respiratory (Rrs) resistances have been examined during anesthesia and anesthesia-paralysis using various anesthetic agents, although no estimates have been made of the effect of anesthesia on the tissue resistance of chest wall (Rw).

Few comparative measurements of pulmonary resistance before and during anesthesia have been reported (Table I.3). From these studies, it appears that pulmonary resistance is increased after induction of anesthesia and placement of an endotracheal tube. This conclusion is supported by the finding of abnormally high total respiratory system resistances in anesthetized subjects (Don and Robson, 1965; Crago et al., 1972; Bergman and Waltemath, 1974). Some authors (Gold et al., 1966), however, found a decrease in pulmonary resistance with induction of anesthesia, but in these studies the control values for the awake state, which were obtained from premedicated patients, were abnormally high. In considering the data in Table I.3, it should be noted that in only two of the studies was Rl corrected for the resistance offered by the endotracheal tube. Furthermore, Rl was in most instances measured at only one flow rate (varying between 0.5 and 1 $l.s^{-1}$). The same is also valid in terms of the measurements of Rrs. Accordingly, it appears that up to the present time there have not been any comprehensive measurements of Rrs and Rl during anesthesia. In this connection it should also be noted that in the studies of Table I.3, pleural pressure was estimated from esophageal pressure. Therefore, the reservations mentioned above regarding the estimation of pleural from esophageal pressure, also apply to the estimation of pulmonary resistance.

Two major sets of mechanisms can contribute to alterations in pulmonary resistance after induction of anesthesia. These mechanisms are changes in the physical properties of the inspired gas mixture and changes in the diameters of the airways. Even in the absence of changes in airway geometry, changes in density or viscosity will alter resistance to gas flow. Densities and viscosities of common anesthetic gases and vapors vary greatly from those of air and oxygen (Radford, 1964).

TABLE I.3

Lung resistance (Rl) during anesthesia and anesthesia-paralysis, compared to the awake state in supine humans

Reference	No. of Subj.	Anesthetic Agent	Rl ($cmH_2O.l^{-1}.s$) Awake	Anesthesia	Anesthesia-Paralysis
Wu et al. (1956)	10	Cyclopropane Diethylether	3.7	5.6**	--
Gold and Helrich (1965)	13	Thiopental Halothane	7.7*	6.3	--
Gold et al. (1968)	9	Thiopental N_2O Halothane	9.0*	4.4	7.7
Rehder et al. (1974)	5	Isoflurane Succinylcholine	2.8	---	3.9**
Hedenstierna and McCarthy (1975)	9	Thiopental Halothane	2.5	---	5.3**
Dobi and Gold (1979)	19	Morphine Thiopental Hydroxyzide Tubocurarine Succinylcholine	3.8	---	5.5

* Measurements done during inspiring high oxygen concentration through a mask.
** Resistance of the endotracheal tube was subtracted.

Nitrous oxide is used in high concentrations which alter the density and viscosity of the mixture; potent volatile anesthetic agents are used in low concentrations and hence have neglibible effects on density and viscosity of gas mixtures (Table I.4). The overall change in resistance resulting from inhalation of mixtures of N_2O and O_2, however, cannot be predicted without knowledge of the relative extents of turbulent, transitional, and laminar flow.

The diameters of airways are affected by alterations in transmural airway pressure or in bronchomotor tone caused by anesthesia. The transmural pressure is the difference between the external and intraluminal pressure. The external pressure is related to pleural pressure, which changes with lung volume. Even in the absence of alterations in bronchomotor tone, airway resistance would be predicted to be larger in supine anesthetized man than in erect awake man because of the reduction in FRC associated with change from the erect to the supine postion and the further reduction in FRC associated with induction of anesthesia.

Inhalational anesthetic agents are generally considered to be bronchodilators (Hickey et al., 1969; Aviado, 1975). Bronchomotor tone can be altered by direct action of the anesthetic agent on airway smooth muscle or by reflex modulation (De Jong et al., 1967). Bronchomotor tone may be increased by agents such as d-tubocurarine, which release histamine,

TABLE I.4

Physical characteristics of commonly used carrier gases during anesthesia (values refer to 37°C)

Gas	Density (g/l)	Viscosity (micropoises)	Kinematic Viscosity (relative to air)
Air	1.13	193	1.00
Oxygen	1.26	217	1.01
Nitrogen	1.10	188	1.01
N_2O	1.73	152	0.52

even though the effect of histamine on the airway smooth muscle is reduced during anesthesia (Hickey et al., 1969). The presence of an endotracheal tube also may contribute to altered bronchomotor tone (Gal, 1980). As discussed above, the changes in elastance and resistance associated with anesthesia may be linked in part to the concomitant changes in FRC. Accordingly, the effects of anesthesia on FRC need to be considered.

Functional residual capacity

FRC is reduced in supine humans after induction of anesthesia (Howell and Peckett, 1957; Bergman et al., 1963; Don et al., 1970; Rehder et al., 1971, Don et al., 1972; Dobbinson et al., 1973; Hickey et al., 1973; Westbrook et al., 1973; Hewlett et al., 1974a; Hewlett et al., 1974b; Rehder et al., 1974; Rehder et al., 1977; Juno et al., 1978; Rehder et al., 1978).

The reduction in FRC occurs soon after induction of anesthesia, is not progressive with time (Westbrook et al., 1973; Hewlett et al., 1974a) and is not affected by muscle paralysis (Howell and Peckett, 1957; Westbrook et al., 1973). FRC is reduced by many anesthetic agents such as thiopental-meperidine (Howell and Peckett, 1957; Westbrook et al., 1973; Rehder et al., 1977), methoxyflurane and isoflurane (Rehder et al., 1974), halothane (Don et al., 1970; Don et al., 1972; Hickey et al., 1973; Hewlett et al., 1974a; Hewlett et al., 1974b) and occurs both with low and high inspired O_2 concentrations (Don et al., 1972).

The mechanisms causing the reduction of FRC are not clear. Increased thoracic blood volume, increased intra-abdominal pressure with consequent cephalad displacement of the diaphragm, atelectasis, increased recoil of the lung, decreased recoil of the chest wall, or any combination of these factors could contribute to the reduced FRC.

Conditions favoring atelectasis frequently exist during anesthesia, because the inspired gas mixture may contain high O_2 concentrations and very soluble anesthetic gases or vapors. Atelectasis as a major factor for reduction of FRC is favored by some authors (Dery, et al., 1965) but not others (Don et al., 1970; Hewlett et al., 1974a). Gas trapping distal to closed airways does not appear to be a major cause for the reduction of FRC, because concomitant measurements of FRC using N_2 clearance and body plethysmography show comparable results (Westbrook et al., 1973).

No systematic studies of the effect of anesthesia on thoracic blood volume have been published. This mechanism, therefore, remains unproven.

Abdominal volume increases after induction of anesthesia (Jones et al., 1979) possibly as a result of blood shifting from the lower extremities. This additional abdominal blood volume should increase intra-abdominal pressure, causing a cephalad shift of the diaphragm which then reduces the FRC. Abdominal blood volume may also increase during anesthesia because the smooth muscle of blood vessel walls or the autonomic regulation of blood flow distribution (or both) may be affected by anesthetics.

At FRC, the elastic recoil of the lung is balanced by the outward recoil of the chest. Hence, the increase in recoil of the lung and the decrease in outward recoil of the chest wall, both of which are induced by anesthesia (Westbrook et al., 1973; Rehder et al., 1974), could reduce FRC. Whether these effects occur concurrently during anesthesia or one is the result of the other is not clear. Whatever the cause of the reduction in FRC during anesthesia, a direct pharmacologic effect of anesthetic agents can be excluded by the failure to demonstrate a reduction in FRC in sitting subjects following induction of anesthesia (Rehder et al., 1972). This observation supports the notion that reduction in FRC in supine humans results from a shift of blood from the lower extremities into the abdomen.

2. ACTIVE MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

When the respiratory muscles are relaxed the impedance of the respiratory system is simply due to the volume-elastic and flow-resistive impedances offered by the passive mechanical properties of the airways, lung and chest wall. Inertance is normally negligible. When the respiratory muscles contract agonistically, their active force-length and force-velocity properties add to the internal impedance: the force-length properties to the volume-elastic impedance (elastance) and the force-velocity properties to the flow-resistive impedance (flow resistance). In addition to pressure losses within the respiratory muscles themselves, active breathing may also involve pressure losses due to distortion of the respiratory system from its relaxed (passive) configuration (Goldman et al., 1978). As a result, during active breathing the respiratory system behaves as if its impedance is greater than its passive value.

Assessment of the active impedance of the respiratory system is difficult. It has been first attempted by Marshall (1962) in anesthetized cats and dogs subjected to electrophrenic respiration. This techique has subsequently been applied by Pengelly et al. (1971) to both anesthetized cats and awake humans. Such data, however, cannot be readily applied to spontaneous breathing. Recently, the active and passive inspiratory impedance of the respiratory system has been determined in cats anesthetized with pentobarbital by Siafakas et al. (1981) and Zin et al. (1982). In these studies, the overall impedance of the respiratory system during active breathing could be approximated by a constant resistance (R'rs) and elastance (E'rs), which henceforth will be referred to as "active" values. R'rs includes both the passive flow-resistance of the total respiratory system (Rrs) and the flow-related pressure losses resulting from force-velocity properties, while E'rs includes the passive elastance (Ers) and the volume-related pressure losses resulting from force-length properties and geometrical arrangement of the inspiratory muscles, as well as those resulting from distortion of the respiratory system. In both studies E'rs was markedly greater than Ers while R'rs exceeded Rrs only slightly. The results of Zin et al., (1982) are given in Table I.5.

So far, no measurements of E'rs and R'rs have been reported for anesthetized humans or for animal species other than cats.

TABLE I.5

Values of passive and active elastance, flow resistance and time constant of the total respiratory system in 6 cats anesthetized with pentobarbital sodium (35 mg/kg).* (Zin et al., 1982b)

Passive			Active		
Ers ($cmH_2O.ml^{-1}$)	Rrs ($cmH_2O.ml^{-1}.s$)	τrs (s)	E'rs ($cmH_2O.ml^{-1}$)	R'rs ($cmH_2O.ml^{-1}.s$)	τ'rs (s)
0.20	0.05	0.25	0.32	0.06	0.18

* Flow resistance of equipment amounted to 0.025 $cmH_2O.ml^{-1}.s$.

C. PHARMACOLOGICAL CONSIDERATIONS OF HALOTHANE AND NITROUS OXIDE ANESTHESIA

1. HALOTHANE (2-Bromo-2-chloro-1,1,1-trifluorethane).

Halothane is a potent volatile anesthetic agent widely used for inhalation anesthesia. The minimum alveolar concentration (MAC) is 0.75%, the vapor pressure amounts to 243 mm Hg. [MAC is the minimum alveolar concentration of anesthetic at 1 atmosphere that produces immobility in 50% of patients exposed to a noxious stimulus (Eger et al., 1965.)].

Side effects

The main side effects of halothane are related to circulatory disturbances. Deutsch et al. (1962) reported a dose-dependent reduction in arterial blood pressure during halothane anesthesia, accompanied by a reduction in cardiac output and stroke volume. During halothane anaesthesia at concentrations of 1 MAC, cardiac output falls by 20-50% (Marshall et al., 1969). The halothane-induced reduction of cardiac output has been attributed to depression of myocardial contractility (Price, 1960; Sungai et al., 1968; Sonntag et al., 1978) and to inhibition of the baroreceptor control system (Price et al, 1960; Biscoe and Millar, 1964). Cerebral blood flow and cerebrospinal fluid pressure, however, increase during halothane anesthesia (Wollman et al., 1964; Lassen and Christensen, 1976).

Renal blood flow and glomerular filtration rate falls by 50% with halothane anesthesia at concentration of 1 MAC (Mazze et al., 1963) but blood flow distribution within the renal cortex and medulla does not change (Leighton and Bruce, 1975).

Hepatic blood flow is also reduced, but there is no evidence of halothane induced ischemic liver dysfunction.

Halothane and respiratory function

Spontaneous breathing during halothane anesthesia is associated with increased arterial partial pressure of CO_2 ($PaCO_2$), indicating alveolar hypoventilation. Characteristically, tidal volume decreases, frequency of breathing increases and the ventilatory response to CO_2 decreases as a result of central nervous system depression during halothane anesthesia (Burnap et al., 1958: Devine et al., 1958; Fink et al., 1962; Ngai et al., 1965; Brandstater et. al., 1965; Severinghaus and Larson, 1965; Munson et al., 1966). At high levels of halothane anesthesia alveolar ventilation is little changed from awake normal values (Devine et al., 1958; Deutsch et al., 1962; Hornbein et al., 1969). The response to inhaled CO_2 is near linear at concentrations that provide minimal surgical anesthesia. As halothane concentration is increased, the response to inhaled CO_2 is not only decreased, but the tension at which CO_2 ceases to stimulate ventilation is reduced (Brandstater et al., 1965). Changes in the relative movements of rib cage and diaphragm have been shown by Tusiewich et al. (1977).

These authors have also shown that a major component of the ventilatory depression associated with halothane anesthesia is due to preferential suppression of intercostal muscle function with relative sparing of diaphragmatic activity.

Nunn et al. (1964) studied the effects of halothane anesthesia on the arterial oxygen partial pressure (PaO_2) and found that alveolare-arterial PO_2 gradient was increased, probably as a result of uneven ventilation-perfusion ratios. These results were confirmed by Bjertnaes et al. (1976) who showed the inhibitory effects of halothane on hypoxic pulmonary vascular constriction, and Landmark et al. (1977) who reported increased right-to-left shunt and ventilation prefusion mismatching during halothane anesthesia.

Finally, halothane has been proved to be a bronchodilator agent (Coon and Kampine, 1975) and to depress mucociliary activity (Forbes, 1976).

2. NITROUS OXIDE (dinitrogen monoxide, N_2O

Nitrous oxide is a colorless gas without appreciable odor or taste. It is heavier than the air (density 1.73 g/l, Table I.4) and is not flammable. N_2O is characterized by very low solubility in blood (blood/gas partition coefficient of 0.47% at 37°C) and very high minimal alveolar concentration (1MAC=105%), (Winter et al., 1972), thus it cannot be used alone as an anesthetic except under hyperbaric conditions. Hence N_2O is used in anesthesia as an adjuvant. In the presence of 70% N_2O in O_2, the concentration of potent inhalational anesthetic agents can be markedly reduced. The MAC of halothane, for example, falls from 0.75% to 0.29%, resulting in less circulatory or respiratory side-effects (Marshall and Wollman, 1980). N_2O is rapidly and predominantly eliminated via the expired gas.

Side effects

The role of N_2O in anesthesia is to reduce the side effects of potent inhalational agents. When added to halothane in combined concentrations, arterial blood pressure, total peripheral vascular resistance and cardiac output rise (Horbein et al., 1969; Smith et al., 1970). N_2O does not have any effect on cerebral blood flow. The liver, kidneys, and gastrointestinal organs show no marked effects of N_2O and there is no evidence of toxicity (Larson et al., 1984). Nausea and vomiting, however, are not uncommon in the recovery period (Marshall and Wollman, 1980). Lassen et al. (1956) have provided evidence of interference with production of white and red blood cells but only after prolonged administration of N_2O.

N_2O and respiratory function

The effects of N_2O on ventilatory drive are small. Slight or no depression of the ventilatory response to CO_2 has been reported with 50% N_2O; however, when N_2O is added to other anesthetic agents further depression is uniqivocal (Hornbein et al., 1969). The response to hypoxia is reduced when 50% N_2O is given along (Yacumb et al., 1975).

The main effects of N_2O on respiratory function are related to its physical properties and to its high alveolar concentration. During anesthesia with 70% N_2O, approximately 10 l of the gas are absorbed by the body of a normal adult, and this large uptake has two main effects (Smith et al., 1980):

a) The second gas effect: As N_2O is removed from the alveoli, some additional fresh gas must flow in from the airways, this augments the ventilatory volume and increases the delivery of all the gases to the alveoli.

b) The concentration effect: At the same time, the flow of N_2O into the blood stream reduces the total gas volume, so that the remaining gases are concentrated.

D. CONCLUSIONS AND RESEARCH PLAN

The above review of the literature indicates that (a) while there are several reports on Ers during anesthesia, no systematic measurements of the pressure-flow relationship of the total respiratory system during anesthesia have been reported; (b) no measurements of E'rs and R'rs for anesthetized humans are as yet available; (c) there is uncertainty as to the reliability of the use of esophageal pressure as an index of pleural pressure in supine position in both awake and anesthetized subjects; and (d) there is no systematic study in the literature in which the passive mechanical properties of the total respiratory system (both elastance and flow resistance) have been partitioned into lung and chest wall components.

Chapter II of this thesis provides the first detailed analysis of the passive pressure-flow relationship of the total respiratory system together with the values of Ers in anesthetized humans. Chapter III gives the first information concerning active impedance in anesthetized humans. Chapter IV describes a simple method ("occlusion test") for validating the esophageal pressure measurements in awake humans in differemt body positions, while chapter V provides results of pulmonary mechanics obtained in awake humans in different positions using the "validated" esophogeal balloon technique. In Chapter VI the "occlusion test" is applied to supine anesthetized humans, showing that with appropriate precautions the esophageal pressure measured with the balloon-catheter technique can provide a valid measure of changes in pleural pressure in supine anesthetized humans. Finally, Chapter VII provides the first data of partitioning of respiratory mechanics between lung and chest wall in anesthetized humans, based on "validated" esophangeal pressure measurements.

REFERENCES

1. Agostoni, E., and J. Mead. Statics of the respiratory system. In: Handbook of Physiology. Respiration. Washington, D.C. Am Physiol. Soc., Sect. 3, Vol. I, Chapt. 13, p. 387-409, 1964.

2. Aukburg, B.E., P.J. Cohen, C.H. Klingenmaier, and S. Aukburg. Pulmonary venous admixture before, during and after halothane anesthesia in man. J. Appl. Physiol. 27:653-657, 1969.

3. Aviado, D.M. Regulation of bronchomotor tone during anesthesia. Anesthesiology 42:68-80, 1975.

4. Bergman, N.A. Distribution of inspired gas during anesthesia and artificial ventilation. J. Appl. Physiol. 18:1085-1089, 1963.

5. Bergman, N.A., and C.L. Walltemath. A comparison of some methods for measuring total respiratory resistance. J. Appl. Physiol. 36:131-134, 1974.

6. Biscoe, T.J., and R.A. Millar. Effects of inhalation anaesthetics on carotic body chemoreceptor activity. Br. J. Anaesth. 40:2-12, 1968.

7. Bjertnaes, L.J., A. Hauge, K.F. Nakken, and J.E. Bredeson. Hypoxic pulmonary vasoconstriction:inhibition due to anesthesia. Acta Physiol.Scand. 96:283-289, 1976.

8. Brandstater, B., E.I. Eger, and G. Edelist. Constant-depth halothane anesthesia in respiratory studies. J. Appl. Physiol. 20:171-174, 1965.

9. Brownlee, W.E., and F.F. Allbritten, Jr. The significance of the lung-thorax compliance in ventilation during thoracic surgery. J. Thoracic Surg. 32:454-463, 1956.

10. Burnap, T.K., J. Galla, and T.D. Vandam. Anesthetic, circulatory and respiratory effects of fluothane. Anesthesiology 19:307-320, 1958.

11. Collier, C.R., and J. Mead. Pulmonary exchange as related to altered pulmonary mechanics is anesthetized dogs. J. Appl. Physiol. 19:659-664, 1964.

12. Coon, R.L., and J.P. Kampine. Hypocapnic bronchoconstriction and inhalation anesthetics. Anesthesiology 43:635-641, 1975.

13. Crago, R.R., A.C. Bryan, A.K. Laws, and A.E. Winestock. Respiratory flow resistance after curare and pancuronium, measured by forced oscillations. Can. Anaesth. Soc. J. 19:607-614, 1972.

14. Cullen, D., and L.B. Kadis. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 32:410-421, 1970.

15. De Jong, R.H., W.N. Hershey, and I.H.Wagman. Measurement of a spinal reflex response (H-reflex) during general anesthesia in man. Association between reflex depression and muscular relaxation. Anesthesiology 28:382-389, 1967.

16. Dery, R., J. Pelletier, A. Jacques, M. Clavet, and J. Houde. Alveolar collapse induced by denitrogenation. Can. Anaesth. Soc. J. 12:531-544, 1965.

17. Deutsch, S., H.W. Linde, R.D. Dripps, and H.L. Price. Circulatory and respiratory actions of halothane in normal man. Anesthesiology 23:631-638, 1962.

18. Devine, J.C., W.K. Hamilton, and C.B. Pittinger. Respiratory studies in man during fluothane anethesia. Anesthesiology 19:11-18, 1958.

19. Dobbinson, R.L., H.I.A. Nisbet, D.A. Pelton, and H. Levinson. Functional residual capacity (FRC) and compliance in anesthetized paralysed children. Part II. Clinical results. Can.Anaesth. Soc. J. 20:322-333, 1973.

20. Don, H.F., and J.G. Robson. The mechanics of the respiratory system during anesthesia. The effects of atropine and carbon dioxide. Anesthesiology 26:168-178, 1965.

21. Don, H.F., M. Wahba, L. Cuadrado, and K. Kelkar. The effects of anesthesia and 100 per cent oxygen on the functional residual capacity of the lungs. Anesthesiology 32:521-529, 1970.

22. Don, H.F., W.M. Wahba, and D.B. Craig. Airway closure, gas trapping, and the functional residual capacity during anesthesia. Anesthesiology 36:533-539, 1972.

23. Eckenhoff, J.E., and M. Helrich. The effect of narcotics, thiopental and nitrous oxide upon respiration and respiratory response to hypercapnia. Anesthesiology 19:240-253, 1958.

24. Eger, E.I., II, L.J. Saidman, and B. Brandstater. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 26:756-763, 1965.

25. Frank, N.R. Influence of pulmonary vascular congestion on recoiling force of excised cat lung. J. Appl. Physiol. 14:905-908, 1959.

26. Frank, N.R., J. Mead, and B.J. Ferris. The mechanical behavior of the lungs in healthy elderly persons. J. Clin. Invest. 36:1680-1687.

27. Forbes, A.R. Halothane depresses mucociliary flow in the trachea. Anesthesiology 45:590-63, 1976.

28. Foster, C.A., P.J.D. Heaf, and S.J.G. Semple. Compliance of the lung in anesthetized paralyzed subjects. J. Appl. Physiol. 11:383-384, 1957.

29. Gal, T.J. Pulmonary mechanics in normal subjects following endotracheal intubation. Anesthesiology 52:27 - 35, 1980.

30. Gold, M.I., Y.H. Han, and M. Helrich. Pulmonary mechanics during anesthesia: III. Infuence of intermittent positive pressure and relation to blood gases. Anesth. Analg. 45:631-640, 1966.

31. Goldman, M.D., A. Grassino, J. Mead, and T.A. Sears. Mechanics of the human diaphragm during voluntary contraction: dynamics. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 44:840-848, 1978.

32. Hewlett, A.M., G.H. Hulands, J.F. Nunn, and J.F. Heath. Functional residual capacity during anaesthesia. II: Spontaneous respiration. Br. J. Anaesth. 46:486-494, 1974a.

33. Hewlett, A.M., G.H. Hulands, J.F. Nunn, and J.S. Milledge. Functional residual capacity during anaesthesia. III: Artificial ventilation. Br. J. Anaesth. 46:495-503, 1974 b.

34. Hickey, R.F., P.D. Graf, J.A. Nadel, and C.P. Larson, Jr. The effects of halothane and cyclopropane on total pulmonary resistance in the dog. Anesthesiology 31:334-343, 1969.

35. Hickey, R.F., and J.W. Severinghaus. Regulation of breathing: Drug effects. In: Regulation of Breathing. New York: Marcel Dekker Inc., Part II, chapt. 21, p. 1251-1312, 1981.

36. Hickey, R.F., W.D. Visick, H.B. Fairley, and H.E. Fourcade. Effects of halothane anesthesia on functional residual capacity and alveolar-arterial oxygen tension difference. Anesthesiology 38:20-24, 1973.

37. Hornbein, T.F., W.E. Martin, J.J. Bonica, F.G. Freund and P. Parmentier. Nitrous oxide effects on the circulatory and ventilatory responses to halothane. Anesthesiology 31:50-260, 1969.

38. Hornbein, T.F., W.E. Martin, J.J. Bonica, et al. Nitrous oxide effects on the circulatory and ventilatory responses to halothane. Anesthesiology 31:250-260, 1969.

39. Howell, J.B.L., and B.W. Peckett. Studies of the elastic properties of the thorax of supine anaesthetized paralyzed human subjects. J. Physiol. (London) 136:1-19, 1957.

40. Jones, J.G., D. Faithfull, C. Jordan, and B. Minty. Rib cage movement during halothane anaesthesia in man. Br. J. Anaesth. 51:399-406, 1979.

41. Juno, P., H.M. Marsh, T.J. Knopp, and K. Rehder. Closing capacity in awake and anesthetized-paralyzed man. J. Appl. Physiol. 44:238-244, 1978.

42. Kafer, E.R. Anesthesia and respiratory function. Boston. International Anesthesiology Clinics, 1977.

43. Klinesberg, P.L., K. Rehder, and R.E. Hyatt. Pulmonary mechanics and gas exchange in seated normal men with chest restriction. J. Appl. Physiol:Respirat. Environ. Exercise Physiol. 51:26-32, 1981.

44. Knowles, J.H., S.K. Hong, and H. Rahn. Possible errors using esophageal baloon in determination of pressure-volume characteristics of the lung and thoracic cage. J. Appl. Physiol. 14:525-530, 1959.

45. Landmark, S.J., T.J. Knopp, K. Rehder, and A.D. Sessler. Regional pulmonary perfusion and $\dot{V}/\dot{Q}$ in awake and anesthetized-paralyzed man. J. Appl. Physiol. 43:993-1000, 1977.

46. Lassen, H.C.A., E. Henriksen, F. Neukirch, and H.S. Kristensen. Treatment of tetanus: severe bone-marrow depression after prolonged nitrous-oxide anesthesia. Lancet 1:527-530, 1956.

47. Leighton, K., and C. Bruce. Distribution of kidney blood flow:a comparison of methoxyflurane and halothane effects as measured by heated thermocouple. Can. Anesth. Soc.J. 22:125-137, 1975.

48. Margaria, C.E., S. Iscoe, L.D. Pengelly, J. Couture, H. Don, and J. Milic-Emili. Immediate ventilatory response to elastic loads and positive pressure in man. Respir. Physiol. 18:347-369, 1973.

49. Marshall, R. Relationships between stimulus and work of breathing at different lung volumes. J. Appl. Physiol. 17:917-927, 1962.

50. Marshall, B.E., and H. Wollman. General Anesthetics. In: Goodman and Gilman's the Pharmacological Basis of Therapeutics. New York: McMillan Publishing Co. Inc., 1980, Chapt. 14, p. 276-299.

51. Mazze, R.I., F.D. Schwartz, H.C. Slocum, and K.G. Barry. Renal function during anesthesia and surgery. I. The effects of halothane anesthesia. Anesthesiology 24:279-284, 1963.

52. Mead, J., and C. Collier. Relation of volume history of lungs to respiratory mechanics in anesthetized dogs. J. Appl. Physiol. 14:669-678, 1959.

53. Nims, R.G., E.H. Conner, and J.H. Comroe, Jr. The compliance of the human thorax in anesthetized patients. J. Clin. Invest. 34:744-750, 1955.

54. Mead, J., and E.A. Gaensler. Esophageal and pleural pressure in man, upright and supine. J. Appl. Physiol. 14:81-83, 1959.

55. Munson, E.S., C.P. Larson, Jr., A.A. Babad, M.J. Regan, D.R. Buechel, and E.I. Eger, II. The effects of halothane, fluroxene, and cyclopropane on ventilation:a comparative study in man. Anesthesiology 27:716-728, 1966.

56. Ngai, S.H., R.L. Katz, and S.E. Farhie. Respiratory effects of trichloroethylene, halothane, and methoxyflurane in the cat. J. Pharmacol. Exp. Ther. 148:123-130., 1965.

57. Nunn, J.F. and R.L. Mattews. Gaseous exchange during halothane anesthesia: the steady respiratory state. Br. J. Anaesth. 1:330-340, 1959.

58. Pengelly, L.D., A.M. Alderson, and J. Milic-Emili. Mechanics of the diaphragm. J. Appl. Physiol. 30:797-805, 1971.

59. Radford, E.P., Jr. The physics of gases. In: Handbook of Physiology. Respiration. Washington, D.C. Am. Physiol. Soc., Sect. 3, Vol. I, Chapt. 3, p. 125-152, 1964.

60. Rehder, K., D.J. Hatch, A.D. Sessler, and W.S. Fowler. Effects of general anesthesia, muscle paralysis and mechanical ventilation on pulmonary nitrogen clearance. Anesthesiology 35:591-601, 1971.

61. Rehder, K., T.J. Knopp, A.D. Sessler, and E.P. Dider. Ventilation-perfusion relationship in young healthy awake and anesthetized-paralyzed man. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 47:745-753, 1959.

62. Rehder, K., T.J. Knopp, and A.D. Sessler. Regional intra-pulmonary gas distribution in awake and anesthetized-paralyzed prone man. J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 45:528-535, 1978.

63. Rehder, K., J.E. Mallow, E.E. Fibuch, D.R. Krabill, and A.D. Sessler. Effects of isoflurane anaesthesia and muscle paralysis on respiratory mechanics in normal man. Anesthesiology 41:477-485, 1974.

64. Rehder, K., A.D. Sessler, and H.M. Marsh. General Anesthesia and the Lung. Am. Rev. Respirat. Dis. 112:541-563, 1975.

65. Rehder, K., A.D. Sessler, and J.R. Rodarte. Regional intrapulmonary gas distribution in awake anesthetized-paralyzed man. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 42:391-402, 1977.

66. Rehder, K., R. Sittipong, and A.D. Sessler. The effects of thiopental-meperidine anesthesia with succinylcholine paralysis on funtional residual capacity and dynamic lung compliance in normal sitting man. Anesthesiology 37:395 - 398, 1972.

67. Safar, P., and L. Bachman. Compliance of the lungs and thorax in dogs under the influence of muscle relaxants. Anesthesiology 17:334-346, 1956.

68. Scheidt, M., R.E. Hyatt, and K. Rehder. Effects of rib cage or abdominal restriction on lung mechanics. J. Appl. Physiol:Respirat. Environ. Exercise Physiol., 51: 1115-1121, 1981.

69. Severinghaus, J.W., and C.P. Larson, Jr. Respiration in Anesthesia. In: Handbook of Physiology. Respiration. Washington, D.C.: Am. Physiol. Soc. 1964, Sect.3, Vol. II, Chapt. 49, 1219-1264.

70. Siafakas, N.M., R. Peslin, M. Bonora, H. Gautier, B. Duron, and J. Milic-Emili. Phrenic activity, respiratory pressures, and volume changes in cats. J. Appl.Physiol.: Respirat, Environ. Exercise Physiol. 51:109-121, 1981.

71. Smith, C.S., L.H. Cooperman, and H. Wollman. History and principles of anesthesiology. In: Goodman and Gilman , the Pharmacological Basis of Therapeutics. New York: McMillan Publishing Co. Inc., Chapt. 13, p. 258-275.,1980.

72. Snow, J. On chloroform and other anaesthetics: Their action and administration. London: Churchill, 1858.

73. Sonntag, H., U. Donath, W. Hillebrand, R.G. Merin, and J. Radke. Left ventricular function in conscious man and during halothane anesthesia. Anesthesiology 48:320-324, 1978.

74. Stubbs, S.E., and R.E. Hyatt. Effect of increased lung recoil pressure on maximal expiratory flow in normal subjects. J. Appl. Physiol. 32:325-331, 1972.

75. Sugai, N., S. Shimosato, and B.E. Etsten. Effect of halothane on force-velocity relations and dynamic stiffness of isolated heart muscle. Anesthesiology 29:267-274, 1968.

76. Summary of the National Halothane Study. J.A.M.A. 197:775-788, 1966.

77. Tusiewicz, K., A.C. Bryan, and A.B. Froese. Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anesthesia. Anethesiology 47:327-337, 1977.

78. Van Lith, P., F.N. Johnson, and J.T. Sharp. Respiratory elastances in relaxed and paralyzed states in normal and abnormal men. J. Appl. Physiol. 23:475-486, 1967.

79. Westbrook, P.R., S.E. Stubbs, A.D. Sessler, K. Rehder, and R.E. Hyatt. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J. Appl. Physiol. 34:81-86, 1973.

80. Winter, P.M., T.F. Hornbein, G. Smith, et al. Hyperbaric nitrous oxide anesthesia in man.: determination of anesthetic potency (MAC) and cardiorespiratory effects. Abstracts of Scientific Papers, ASA Annual Meeting 103, 1972.

81. Wollman, H., S.C. Alexander, P.J. Cohen, P.E. Chase E. Melman, and M.G. Behar. Celebral circulation of man during halothane anesthesia: effects of hypocarbia and d-tubocurarine. Anesthesiology 25:180-184, 1964.

82. Woo, S.W., D. Berlin, and J. Hedley-Whyte. Surfactant function and anesthetic agents. J. Appl. Physiol. 26:571-577, 1969.

83. Woo, S.W., D. Berlin, U. Buch, and J. Hedley-Whyte. Altered perfusion, ventilation, anesthesia and lung surface forces in dogs. Anesthesiology 33:411-418,1970.

84. Yacoub, O., Doell, D., Dryger,M.H., and N.R. Anthonisen. Depression of hypoxic ventilatory response by nitrous oxide. Anesthesiology 45:385-389, 1976.

85. Zin, W.A., L.D. Pengelly, and J. Milic-Emili. Active impedance of respiratory system in anesthetized cats. J. Appl. Physiol.:Respirat. Environ. Exercise Physiol. 53:149-157, 1982.

CHAPTER II

RESPIRATORY MECHANICS DURING HALOTHANE ANESTHESIA AND ANESTHESIA PARALYSIS IN HUMANS

ABSTRACT

In six spontaneously breathing anesthetized subjects (halothane ~ 1 minimum anesthetic concentration, MAC, 70% N_2O-30% O_2), flow ($\dot{V}$), volume (V), and tracheal pressure (Ptr) were measured. With airway occluded at end-inspiration, Ptr was measured when the subjects relaxed their respiratory muscles. Dividing relaxed Ptr by tidal volume (V_T), total respiratory system elastance (Ers) was obtained. While the subjects were still relaxed, the occlusion was released to obtain the $\dot{V}$-V relationship during the ensuing relaxed expiration. Under these conditions, the expiratory driving pressure is V x Ers, and thus the pressure-flow relationship of the system can be obtained. By subtracting the flow resistance of equipment, the intrinsic respiratory flow resistance (Rrs) is obtained. Similar measurements were repeated during anesthesia-paralysis (succinylcholine). Ers averaged 23.9 ± 4 (±SD) during anesthesia and 21 ± 1.8 cm $H_2O.l^{-1}$ during anesthesia-paralysis. The corresponding values of intrinsic Rrs were 1.6 ± 0.7 and 1.9 ± 0.8 cm $H_2O.l^{-1}.s$, respectively. These results indicate that Ers increases substantially during anesthesia, whereas Rrs remains within the normal limits. Muscle paralysis has no significant effect on Ers and Rrs. The first measurements of inspiratory muscle activity and related negative work during spontaneous expiration in anesthetized humans is also

provided. These show that 36-74% of the elastic energy stored during inspiration is wasted in terms of negative inspiratory muscle work.

A. INTRODUCTION

There is ample evidence indicating that anesthesia results in increased elastance of the total respiratory system (Ers) (Nims et al., 1955; Brownlee and Allbritten, 1956; Opie et al., 1959; Don and Robson, 1965; Bergman, 1966; Bergman, 1969; Westbrook et al., 1973; Bergman and Waltemath, 1974; Rehder et al., 1974). An increase of total flow resistance (Rrs) has also been reported, but the number of papers on this topic is relatively small. Bergman (1966) and Bergman (1969) has measured Rrs in anesthetized-paralyzed subjects by analysis of volume-flow curves obtained during relaxed expirations, a method first described by McIlroy et al. (1963) who used it on conscious humans. This approach has recently been applied to spontaneously breathing anesthetized cats by Zin et al. (1982). In this study a new method for determining the pressure exerted by the inspiratory muscles during spontaneous expiration ($Pmus_I$) is proposed.

In the present investigation, a modification of the method of McIlroy et al. (1963) to determine the elastic and flow-resistive properties of the total respiratory system in six subjects during both anesthesia and anesthesia-paralysis was utilized. In addition, using the approach of Zin et al. (1982) the first measurements of the time course of $Pmus_I$ during spontaneous expirations in anesthetized nonparalyzed humans were provided. Knowledge of this may sometimes be important, since $Pmus_I$ modulates the time course of expiratory flow during spontaneous breathing (Agostoni, 1979).

B. MATERIALS AND METHODS

Six patients (two males and four females, aged 21-49 yrs.), undergoing standard general anesthesia as practiced in our institution for minor plastic or orthopedic surgery, were studied prior to the operation. None had a history or clinical evidence of cardiopulmonary disease. The research was approved by the institutional ethics committee and informed consent was obtained from all subjects.

Flow ($\dot{V}$) was recorded with a Fleisch no. 2 pneumotachograph connected to the breathing circuit via a cone and a Validyne MP45 differential pressure transducer. Volume (V) was obtained by integration of the flow signal (Hewlett-Packard 8815A integrator). Tracheal pressure (Ptr) was measured through a side port on the connector between the anesthesia circuit and the endotracheal tube using a Validyne MP45-2 differential pressure transducer. The equipment dead space was 70 ml (endotracheal tubes not included).

End-tidal CO_2 and halothane concentrations were monitored by a Beckman LB-2 infrared gas analyzer. A three-way tap was used to occlude the airway opening or to connect the tracheal tube either to the anesthesia circuit or to the room.

All signals were amplified (Hewlett-Packard 8805A amplifier) and recorded on a Gould Brush 2600 six-channel recorder, as well as on tape (Hewlett-Packard 3968A tape recorder). Flow-volume curves were obtained on an X-Y plotter (Hewlett-Packard 7046A) by playing back at slow speed the signals stored on magnetic tape.

Flow Resistance of Equipment

The flow resistance of the equipment included two components: 1) the pneumotachograph with the tap, which was linear and amounted to 0.4 cm $H_2O.l^{-1}.s$ for flows up to $3.l.s^{-1}$; and 2) the endotracheal tube with its connector, which was curvilinear and depended on the size of the tube used (Figure II.1). Flow resistance constants of Rohrer's equation ($P = K_1\dot{V} + K_2\dot{V}^2$) of three endotracheal tubes commonly used during anesthesia are given in Table II.1. Both components described immediately above were determined for the same gas mixture used during anesthesia (70% N_2O-30% O_2). These measurements were made with flow of the gas mixture directed in the experimental expiratory direction. To obtain K_1 and K_2, we divided both sides of Rohrer's equation by $\dot{V}$ to obtain a linear function, $P/\dot{V} = K_1 + K_2\dot{V}$, and used regression analysis on our experimental values of $P/\dot{V}$ vs. $\dot{V}$.

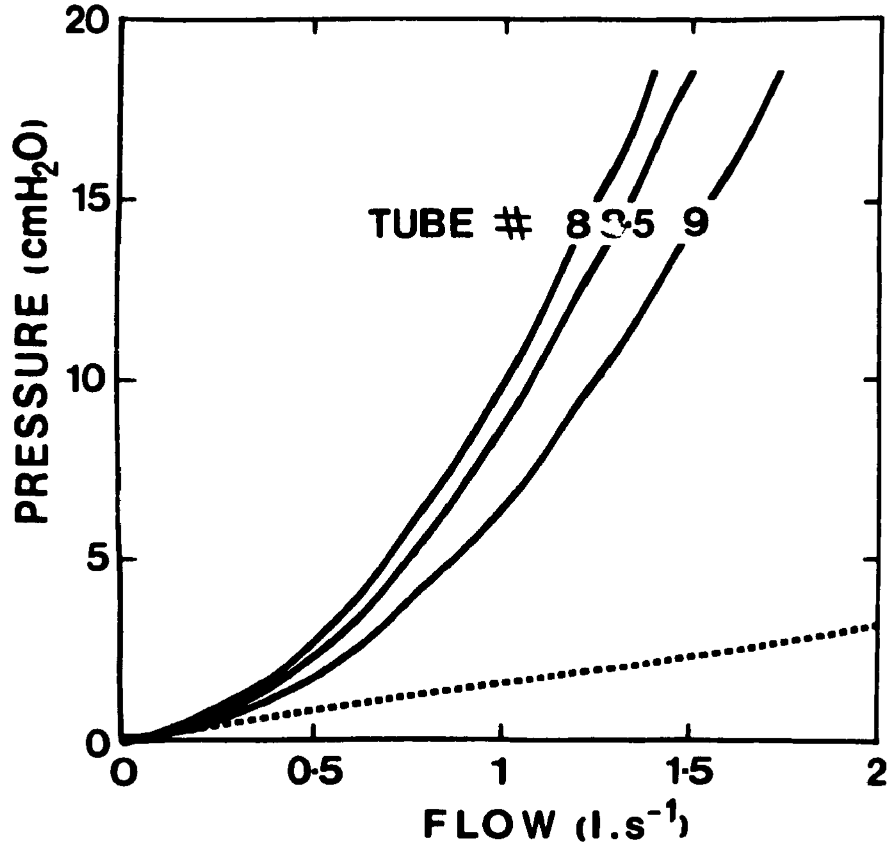

Figure II.1: Pressure-flow curves of 3 commonly used endotracheal tubes. Measurements pertain to gas mixture of 70% N_2O-30% O_2. Broken line represents average intrinsic total flow resistance of 6 anesthetized nonparalyzed subjects (upper airways excluded).

TABLE II.1

Values of K_1 and K_2 of three endotracheal tubes (including connectors)

Tube No.	K_1, $cmH_2O.l^{-1}.s$	K_2, $cmH_2O.l^{-2}.s^2$
8.0	1.2	8.6
8.5	1.0	7.8
9.0	0.6	5.9

Values pertain to 70% N_2O-30% O_2. **K_1 and K_2,** flow- resistance constants. **Tube no.** indicates internal diameter in millimeters. Length of all tubes was 35 cm.

Procedure

Patients were premedicated with atropine (0.3-0.6 mg) and meperidine (1 mg/kg) 45 min prior to anesthesia. Anesthesia was induced with thiopental sodium (4-6 mg/kg); succinylcholine (1.5 mg/kg) was given to facilitate intubation with cuffed endotracheal tubes. Anesthesia was maintained with halothane [1 minimum anesthetic concentration (MAC)] in 70% N_2O-30% O_2. While the subjects were paralyzed they were passively ventilated with tidal volumes of approximately 0.4 liter, starting from lung volume at zero applied pressure (relaxed functional residual capacity). The artificial breathing pattern was chosen to mimic spontaneous breathing. Paralysis was assessed with a peripheral nerve stimulator applied both to facial and ulnar nerves; no muscle response was observed in any of the subjects. Since during this paralytic period there was absence of respiratory movements without assisted ventilation, it is likely that the respiratory muscles were also paralyzed.

A few minutes after the start of the passive ventilation and while the subject was still paralyzed, the airway was occluded at the end of a tidal inspiration (tidal volume = 0.4 liter). Immediately after a stable Ptr was achieved the occlusion was suddenly released to obtain a relaxed expiration. In this case the three-way tap was turned so that the subject exhaled into the room (and not into the anesthesia circuit). This maneuver was performed several times under paralyzed conditions, and repeated no earlier than 15-20 min after the subjects had established a steady spontaneous breathing pattern to allow for recovery from the effects of succinylcholine (Katz and Ryan, 1969). Airway occlusions during spontaneous breathing were performed at the end of tidal inspirations and held until the subjects relaxed their respiratory muscles, as evidenced by a plateau on the tracheal pressure tracing (Figure II.2A). The occlusion was then rapidly released, and the subjects were allowed to exhale passively to functional residual capacity (FRC). To avoid active inspiration before the passive expiration was completed, the airway occlusions at end expiration were held as short as possible (usually about 1.5 s). The latter sufficed to obtain a plateau in Ptr. No sighs were present for at least 10 breaths before each maneuver.

During spontaneous breathing, each subject exhibited an expiratory pause (i.e., a period of zero flow toward the end of expiration, as shown by the example in Figure II.2A), indicating that the end-expiratory volume was probably the elastic equilibrium point of the respiratory system (Zin et al., 1982). Tnis was further supported by the fact that when in the same subjects the airways were occluded at end expiration, Ptr during the occluded expiration returned to zero (atmospheric) pressure (Zin et al., 1982). The measurements during spontaneous breathing were made over a period of less than 20 min.

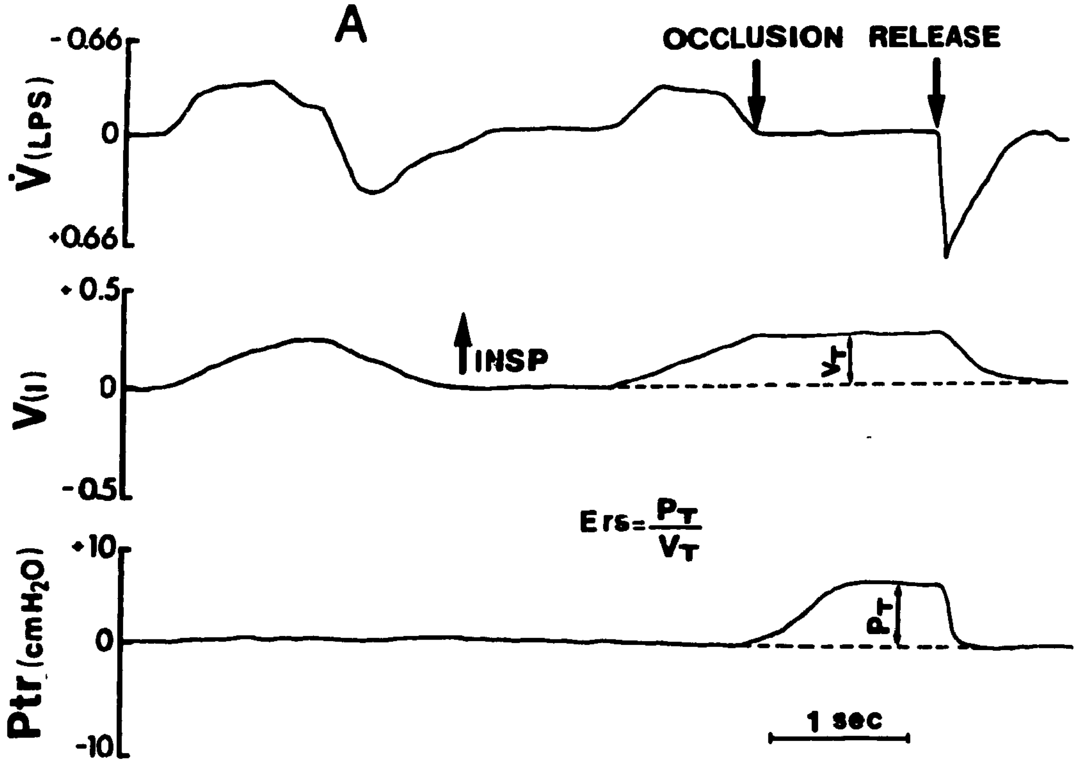

Figure II.2A: Tracing of flow ($\dot{V}$), volume (V), and tracheal pressure (Ptr) in a spontaneously breathing anesthetized subject. Airway occlusion at end inspiration was performed at point indicated by first arrow. After relaxation of respiratory muscles indicated by plateau in Ptr tracing, occlusion was released (second arrow) and subject exhaled freely.

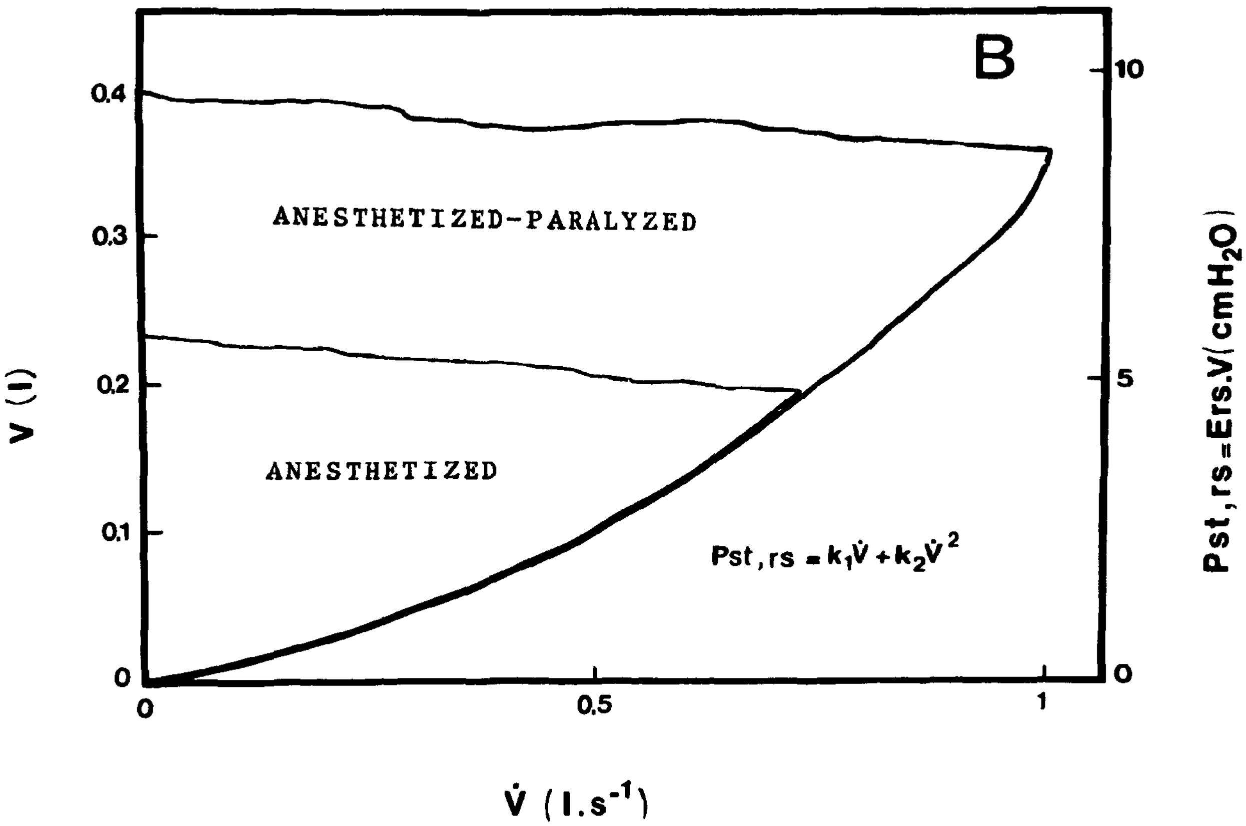

Figure II.2B: Volume-flow and pressure-flow relationships corresponding to passive expirations of same subject under anesthetized and anesthetized-paralyzed conditions.

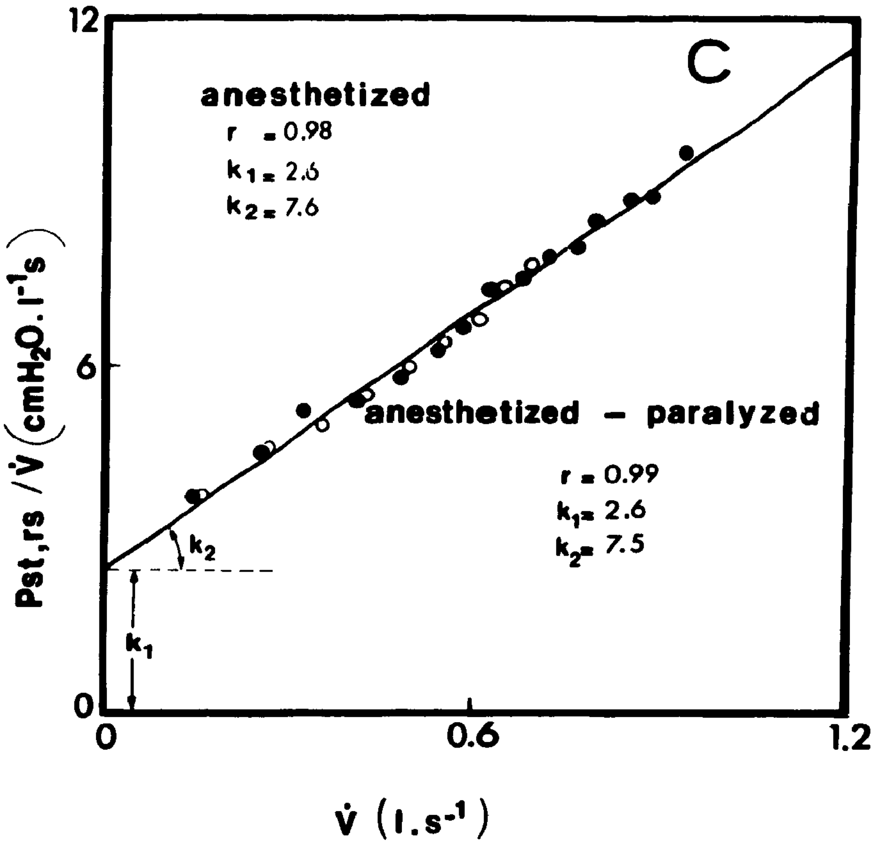

Figure II.2C: Graphical computation of K_1 and K_2 by plotting Pst,rs/$\dot{V}$ vs. $\dot{V}$. Filled circles, paralyzed. Open circles, nonparalyzed.

Data Analysis

Elastance. The passive elastance of the total respiratory system (Ers) was determined as previously described (Zin et al., 1982) by dividing values of relaxed Ptr, representing the elastic recoil pressure of the total respiratory system (Pst,rs) by the corresponding volume above FRC (Figure II.2A). Ten occlusions at end inspiration were analyzed in each subject under both paralyzed and nonparalyzed conditions. The average coefficient of variation of Ers in the six subjects amounted to less than 5% under both anesthetized and anesthetized-paralyzed conditions. The constancy of Ers over the experimental range of lung volumes was confirmed by occluding the airway at intermediate volumes between FRC and FRC + 0.4 liter.

Flow resistance. The method used was based on the technique first described by McIlroy et al. (1963) on conscious humans and subsequently applied by Bergman (1966) and Bergman (1969) to anesthetized-paralyzed subjects. Volume-flow (V-$\dot{V}$) curves obtained during relaxed expirations were analyzed for measurement of the flow-resistive properties of the total respiratory system (Figure II.2B). For such analysis, volume was translated into elastic recoil pressure according to the equation

$$\mathbf{Pst,rs = Ers.V} \qquad (1)$$

Thus the Pst,rs vs. $\dot{V}$ relationships obtained during relaxed expirations under anesthesia and anesthesia-paralysis (Figure II.2B) provide the pressure-flow characteristics of the lower respiratory system plus that of the tracheal tube and breathing equipment. This relationship was curvilinear in all subjects and closely fitted Rohrer's equation

$$Pst,rs = K_1\dot{V} + K_2\dot{V}^2 \qquad (2)$$

The constants K_1 and K_2 were obtained by regression analysis of a modification of equation 2 namely

$$Pst,rs/\dot{V} = K_1 + K_2\dot{V} \qquad (3)$$

Equation 3 is a linear function of the general type y = a + bx, with intercept equal to K_1 and slope equal to K_2 (Figure II.2C). The correlation coefficients (r) of these linear functions ranged between 0.960 and 0.999.

Analysis according to equations 1-3 is based on the assumption that the static elastic recoil of the respiratory system represents the driving pressure during dynamic relaxed expiration. This has been validated in anesthetized cats by Zin et al. (1982). They computed Ers by adding a series of linear resistances (ΔR) during relaxed expirations and found that in spite of the reduction of expiratory flows caused by the R's, Ers was constant.

Under both anesthetized and anesthetized - paralyzed conditions, the repeated relaxed expiratory volume-flow curves were superimposed in each of the six subjects, suggesting that the flow-resistive properties of the respiratory system were constant over the measurement period.

Inspiratory muscle activity during spontaneous expiration. In the absence of expiratory muscle activity, the pressure exerted by the inspiratory muscles during spontaneous expiration, ($Pmus_I$) is given by:

$$Pmus_I(t) = Ers\ V(t) - K_1\dot{V}(t) - K_2\dot{V}^2(t) \qquad (4)$$

where V is volume and $\dot{V}$ is flow at any instant t. Since Ers, K_1, and K_2 are known (see above), the decay of $Pmus_I$ during spontaneous expiration can be computed from instantaneous measurements of V and $\dot{V}$ (Zin et al., 1982). For such measurements the spontaneous expirations were made with the three-way tap connected to the room.

The negative work done by the inspiratory muscles during spontaneous expiration was computed according to Rahn's diagram as the difference between the expiratory flow-resistive work (Wres) and the total elastic work (Wel) available in the system for expiration (Figure II.3). In this analysis, the flow-resistive pressure drop at any instant t during the spontaneous expiration, Pres,rs(t) was obtained according to

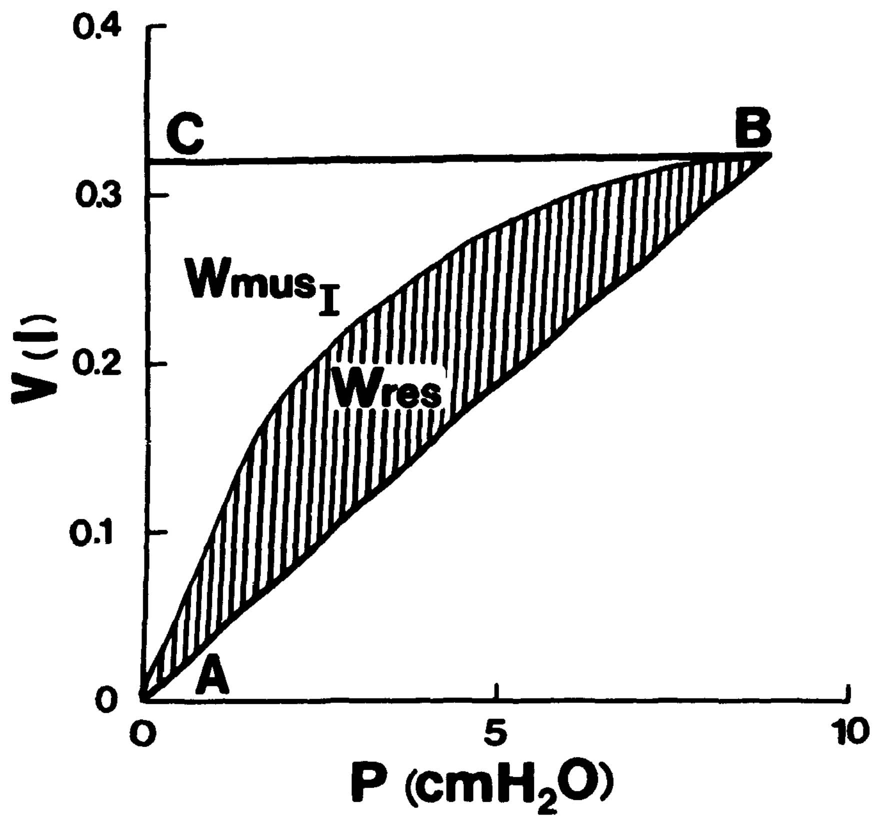

Figure II.3: Volume-pressure relationship (Rahn's diagram) showing flow-resistive work (Wres) during a spontaneous expiration (hatched area). Area A B C represents total elastic work available for expiration (Wel). Difference between Wel and Wres represents negative work done by inspiratory muscles during expiration (Wmus$_I$).

$$Pres,rs(t) = K_1\dot{V}(t) + K_2\dot{V}^2(t) \qquad (5)$$

The values of Pres,rs were determined at intervals of 0.1s after the onset of spontaneous expiration and plotted against the corresponding volumes; the enclosed area represents Wres (Figure II.3).

Statistical analysis of the data was made by the paired t test.

C. RESULTS

In the anesthetized nonparalyzed state, the average tidal volume (V_T) was 0.34 ± 0.04 (±SD) liter. As indicated in the methods, measurements of Ers in this state were made over the range of lung volume between FRC and the above values of V_T. During anesthesia-paralysis, Ers was studied over a similar volume range (FRC + about 0.4 liter). The mean values of Ers amounted to 21 ± 1.8 (±SD) cm $H_2O.1^{-1}$ in the paralyzed and 23.9 ± 4 cm $H_2O.1^{-1}$ in the nonparalyzed state (Table II.2). There was a tendency for Ers to be slightly greater under nonparalyzed conditions, but the difference was not statistically significant.

Total flow-resistance constants of Rohrer's equation (K_1 and K_2) obtained under paralyzed and nonparalyzed conditions are given in Table II.3. By subtraction of K_1 of the equipment

TABLE II.2

Physical characteristics and values of passive elastance in six subjects anesthetized and anesthetized-paralyzed

Subj. No.	Sex	Age,yr	VC,liters	Elastance, $cmH_2O.l^{-1}$	
				Anesthetized	Anesthetized-paralyzed
1	F	24	3.9	19.0±1.9	21.3±1.2
2	M	21	5.2	27.0±2.5	23.4±2.1
3	M	22	4.9	24.8±2.6	18.1±2.4
4	F	25	4.1	26.7±2.1	20.2±1.9
5	F	49	3.8	18.6±2.0	21.6±1.7
6	F	38	4.0	27.1±1.9	21.5±1.4
Mean ±SD		29.8 ±11.2	4.3 ±0.6	23.9 ±4.0	21.0 ±1.8

Values are for 10 measurements. VC, vital capacity.

(including the endotracheal tube) from the total values of K_1, the K_1 values of the lower respiratory system (lower airways, pulmonary, and chest wall tissues) were obtained. These averaged 1.9 ± 0.9 (±SD) and 1.6 ± 0.7 cm $H_2O.l^{-1}.s$ in paralyzed and nonparalyzed states, respectively. The difference between the two conditions was not significant. In both anesthetized and anesthetized-paralyzed conditions, the experimental values of K_2 were not significantly different from the K_2 values of the endotracheal tubes (Table II.3). Indeed, this difference was very small; expressed as a percentage fraction of the K_2 of the tubes, it averaged -1.8 ± 3.3% (±SD) during anesthesia and -2.1 ± 4.6% during anesthesia-paralysis. This suggests that the flow resistance of the lower respiratory system was essentially linear and could be quantified in terms of difference between total and equipment K_1.[1] For further validation of the method for deriving intrinsic flow resistance see APPENDIX.

Results of $Pmus_I$ decay, measured at intervals of 0.1 s during spontaneous expiration, are depicted in Figure II.4. On the average, $Pmus_I$ lasted about 1.5 s, but after 0.7 s it amounted to less than 1 cm H_2O. Total expiratory duration (T_E) of the spontaneous breaths averaged 2.1 ± 0.5 s, and accordingly $Pmus_I$ persisted on the average for about 70% of T_E (range 54 to 81%).

Flow-resistive work and negative work done by the inspira-

[1] Because the base line values of K_2 for the endotracheal tubes were so high (Table II.1) and the limitations inherent in curve fitting of experimental data to Rohrer's equation ($P = K_1\dot{V} + K_2\dot{V}^2$), curvilinearities in the intrinsic pressure-flow relationship of the respiratory system with upper airway excluded may have been missed.

TABLE II.3

Values of K_1 ($cmH_2O.l^{-1}.s$) and K_2 ($cmH_2O.l^{-2}.s^2$) on six anesthetized and anesthetized-paralyzed subjects with corresponding values of equipment used.

Subj. No.	Anesthesia		Anesthesia-Paralysis		Equipment	
	K_1	K_2	K_1	K_2	K_1	K_2
1	2.8	5.9	4.1	5.9	1.0	5.9
2	2.6	7.3	2.6	7.5	1.4	7.8
3	2.0	5.9	2.0	5.8	1.0	5.9
4	3.9	6.2	3.5	6.1	1.0	5.9
5	2.8	7.3	2.4	7.3	1.4	7.8
6	2.6	7.4	4.0	7.6	1.4	7.8

K_1 and K_2 flow-resistance constants.

Equipment used included endotracheal tube.

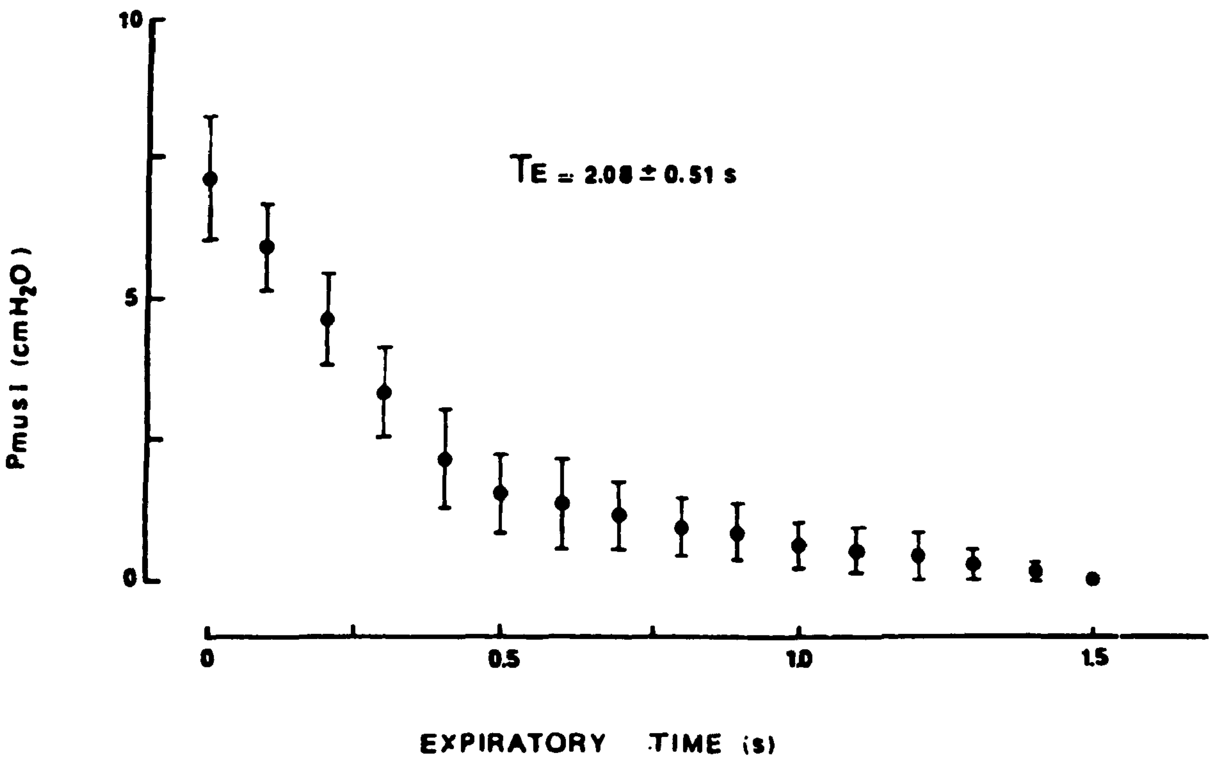

Figure II.4: Average time course (±SD) of pressure developed by inspiratory muscles ($Pmus_I$) during spontaneous expiration in 6 anesthetized subjects. Average (±SD) total duration of expiration (T_E) is also indicated.

tory muscles ($Wmus_I$) during spontaneous expiration is given in Table 4. Average values for Wres were 0.072 ± 0.020 (±SD) J and for $Wmus_I$ 0.078 ± 0.032 J, the latter corresponding to 52% of the total available expiratory work (Wel = 0.149 0.039 J).

D. DISCUSSION

In normal nonanesthetized sitting subjects, in the resting tidal volume range, Ers amounts to about 0.45 cm H_2O per percent change of vital capacity (VC) (Agostoni and Mead, 1964), and it does not change appreciably when shifting to the supine position (Berger and Burki, 1982). Present values of Ers obtained during halothane anesthesia (1.03 cm H_2O/%VC) and anesthesia-paralysis (0.91 cm H_2O/%VC) were considerably higher. This is in agreement with previous studies on paralyzed subjects (succinylcholine) anestheized with either thiopental (Nims et al., 1955; Brownlee and Allbritten, 1956; Westbrook et al., 1973) or isoflurane (Rehder et al., 1974). Also in agreement with Westbrook et al. (1973) Ers was found to be similar in anesthetized and anesthetized-paralyzed states, and this provides direct evidence that the subjects in this study were relaxed when Ers and flow resistance were measured in the nonparalyzed state. The increase of Ers during anesthesia has been attributed to alterations in static pressure-volume characteristics of the chest wall associated with an increase

TABLE II.4

Resistive work and negative inspiratory muscle work during spontaneous expirations in 6 anesthetized subjects with elastic work available for expiration.

Subj. No.	Wel, J	Wres, J	$Wmus_I$, Negative, J
1	0.127	0.071	0.056
2	0.120	0.071	0.049
3	0.132	0.034	0.098
4	0.220	0.095	0.125
5	0.167	0.076	0.091
6	0.128	0.082	0.046
Mean ±SD	0.149 ±0.039	0.072 ±0.020	0.078 ±0.032

Wel, total elastic work; **Wres**, expiratory flow-resistive work; **$Wmus_I$**, negative work done by inspiratory muscles.

in elastic recoil of the lung (Westbrook et al., 1973). Although the nature of these changes is not fully understood, altered lung surfactant function during anesthesia has been postulated as a major contributory factor. In this connection it should be noted that lung compliance is known to decrease substantially in halothane-anesthetized supine subjects (Gold and Helrich, 1965; Hedenstierna and McCarthy, 1975).

The present results show that in both anesthetized and anesthetized-paralyzed subject, Rrs (excluding the equipment and endotracheal tube resistance) was within the normal limits of awake state. Indeed, the viscous resistance of the chest wall in humans ranges between 0.5 and 1 cm $H_2O.l^{-1}.s$ (Opie et al., 1959), and the lower pulmonary flow resistance in young awake supine subjects following atropine amounts to 0.6-1.0 cm $H_2O,l^{-1}.s$ (Vincent et al., 1970). Thus, excluding the upper airways, flow resistance should range between 1.1 and 2.0 cm $H_2O.l^{-1}.s$. Corresponding values of Rrs averaged 1.6 cm $H_2O.l^{-1}.s$ in anesthetized state and 1.9 cm $H_2O.l^{-1}.s$ during anesthesia-paralysis.

There are few previous reports concerning total flow resistance of the respiratory system during anesthesia (Don and Robson, 1965; Bergman, 1966; Bergman, 1969;; Crago et al., 1972; Bergman and Waltemath, 1974; Lehane et al., 1980). These indicate higher resistance values than in the present study, but in some cases no correction was made for the resistance of the endotracheal tube (Bergman and Waltermath, 1974; Crago et al., 1974). Using the method of constant flow rate inflation, Don and Robson (1965) measured the inspiratory flow resistance of the lower total respiratory system in subjects anesthetized with N_2O and paralayzed with succinylcholine both before and after administration of atropine (0.012 mg/kg). Before atropine, Rrs averaged 6.2 + 2.5 cm $H_2O.l^{-1}.s$ and decreased by 40% following atropine. Their values on atropinized subjects are twice as large as those found in the present study. This may reflect the fact that their subjects were older [mean age 47.6 ± 12.7 (±SD) yr] than those in the present study (Tables 1, 2). Indeed, older individual have a marked tendency to develop small airway closure in the dependent lung zones in supine posture, particularly during anesthesia (Juno et al., 1978). This should result in increased pulmonary flow resistance and hence also in Rrs. Bergman (1966) and Bergman (1969) used a similar approach to the present one, but his analysis of the data was not valid (see below). More recently, Lehane et al. (1980) have studied the influence of halothane on respiratory airflow resistance in anesthetized-paralyzed man using the forced airflow oscillation technique. Their values of intrinsic resistance are on the average higher than the present ones (3.7 vs. 1.9 cm $H_2O.l^{-1}.s$). Their subjects, however, were older than the present ones (42.9 vs. 29.8 yr), and furthermore they were not premedicated with atropine. This, apart from a different methodology, may explain the discrepancy between the present results and those of Lehane et al. (1980). In this connection it should also be noted that in younger individuals the changes in FRC during anesthesia are apparently much smaller than in older subjects (Juno et al., 1979).

While in the present study the intrinsic Rrs was deduced to be linear or nearly so, the pressure-flow relationships of the endotracheal tubes were highly curvilinear. It should be noted that the K_2 constants of the three tubes shown in Table II.1 were markedly greater than the values of K_2 for total respiratory system found in nonanesthetized normal subjects during both mouth (0.26 cm $H_2O.l^{-2}.s^2$) or nose breathing (0.79 cm $H_2O.l^{-2}.s^2$) (Ferris et al., 1964). The high K_2 values of the tubes have important implications. First, because the overall pressure-flow relationship (including tubes) is curvilinear, the volume-flow curves during passive expirations are by necessity also curvilinear (Figure II.2B), and hence the respiratory system with the endotracheal tubes cannot be characterized in terms of a single time constant as was the case in anesthetized cats (Zin et al., 1982). In this connection it should be noted that Bergman (1966) derived the time constant of the respiratory system by fitting straight lines to expiratory volume-flow curves obtained in paralyzed subjects anesthetized with N_2O and halothane. His own data (Figure 4, in Reference 4), however, show that the volume-flow curves were curvilinear as in the present study (Figure II.2B). Thus his derived time constants are questionable. Bergman, (1969) further noted (and the present data confirm) that during relaxed expiration in anesthetized-paralyzed subjects, the time course of volume cannot be described by a single exponential function as would be the case in a system consisting of constant Rrs and Ers (McIlroy et al., 1963). In the latter case, the time constant is given by Rrs/Ers. However, when the Pst,rs vs. $\dot{V}$ relationship is curvilinear, no single time constant value applies. Second, the higher K_2 values of the endotracheal tubes impose increased work of breathing, as shown in Figure II.5 where the mechanical work rate done by the inspiratory muscles in overcoming flow resistance ($\dot{W}_I$,res) is plotted against minute ventilation ($\dot{V}_I$). This was computed according to the following equation

$$\dot{W}_{I,res} = b\dot{V}_I^2 + c\dot{V}_I^3 \qquad (6)$$

where b and c are constants, and correspond to $0.25\pi^2 . K_1$ and $0.67\pi^2 K_2$, respectively (Otis et al., 1950; Milic-Emili et al. 1969). Equation 6 has been deduced by Otis et al. (1956) on the assumption that the velocity pattern of air flow during respiration is a sinusoidal function of time. Although this assumption is not entirely valid, (Read et al., 1974),the relationships in Figure II.5 provide a useful approximation of

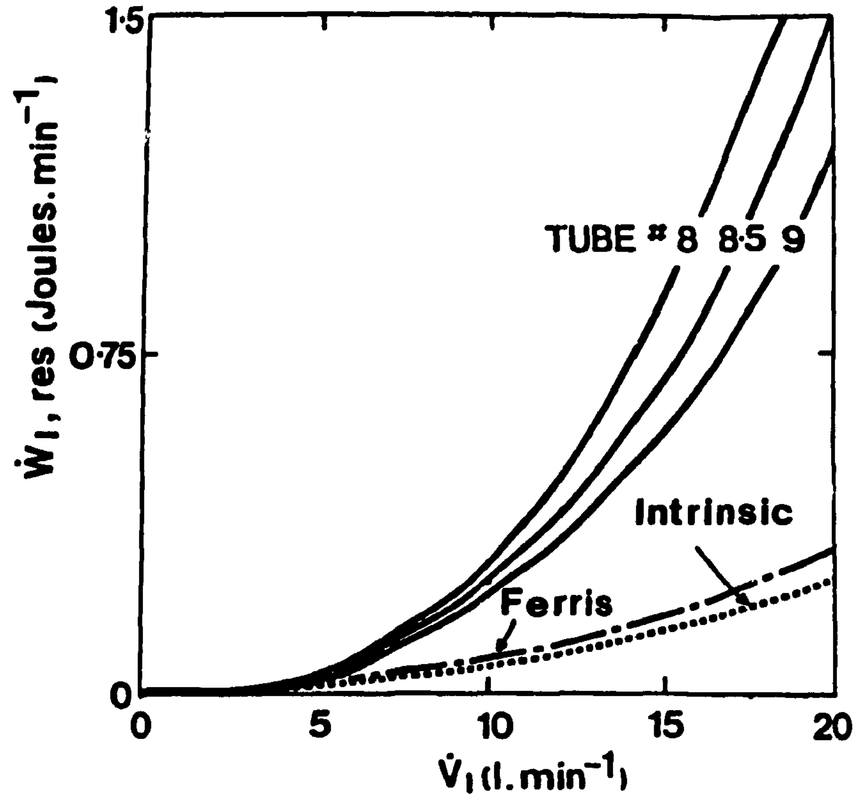

Figure II.5: Inspiratory resistive work rate ($\dot{W}_I$,res) plotted as a function of minute ventilation ($\dot{V}_I$). Solid curves indicate total $\dot{W}_I$,res in anesthetized nonparalyzed subjects intubated with 3 different tubes. Dotted curve indicates $\dot{W}_I$,res required to overcome their intrinsic `ow resistance. Also shown by broken line is relationship for conscious normal seated men during mouth breathing computed according to Ferris et al. (1964). For further explanation see text.

the inspiratory flow-resistive work rate required in nonparalyzed anesthetized subjects to overcome the intrinsic Rrs (dotted curve) as well as the overall flow resistance, i.e., including that offered by the endotracheal tubes (solid curves). The dotted curve was computed using average value of intrinsic Rrs obtained in the nonparalyzed state (1.6 cm $H_2O.l^{-1}.s$), whereas in the case of the solid curves the K_1 and K_2 values of the endotracheal tubes (Table II.1) were added. Figure II.5 shows that at any given value of $\dot{V}_I$, total $\dot{W}_I$,res is considerably greater than the $\dot{W}_I$,res required to overcome the intrinsic flow resistance, the difference being particularly striking with increase $\dot{V}_I$. Clearly the endotracheal tubes impose a considerable burden on the inspiratory muscles. In this connection it should be noted that narrower tubes than those in Table II.1 are often used in transnasal patient intubation. These should provide even greater added loads to the respiratory system. In this context it should also be noted that the increased Ers during anesthesia causes a further increase of inspiratory work. Also shown in Figure II.5 is the relationship between $\dot{W}_I$,res and $\dot{V}_I$ for normal conscious seated men during mouth breathing (broken line). These were computed according to Ferris et al. (1964). Since in this case the upper airway resistance is relatively small, these values are close to those pertaining to the intrinsic resistance of our anesthetized subjects. Third, the high flow rrsistance due to endotracheal tubes considerably retards expiration. This, however, is in part compensated by the stiffer respiratory system during anesthesia, which provides increased recoil pressures during expiration. When the elastic recoil of the respiratory system is reduced and/or the intrinsic flow resistance is increased (e.g. pulmonary emphysema or old age), expiration will be further impeded so that the equilibrium volume of the respiratory system may not be achieved at end expiration. A shorter duration of expiration, which is found with some anesthetics (e.g., thiopental and alphadione) (Gautier and Gaudy, 1978) should have the same effect. However, the subjects of present work were normal and relatively young, so that the end-expiratory volume during spontaneous breathing was in all instances at or very near to the elastic equilibrium point. This was in spite of the substantial inspiratory muscle activity observed during spontaneous expiration (Figure II.4).

The data of inspiratory muscle activity during expiration (Figure II.4) show a prolongation of $Pmus_I$ in comparison with previous results obtained in anesthetized cats (Zin et al., 1982) and conscious humans (Agostoni and Citterio, 1979). In the cats, however, a different anesthetic agent was administered (pentobarbital sodium), whereas in the human experiments of Agostoni and Citterio (1979), a different method for measurement of $Pmus_I$ was used. The latter authors reported that in conscious seated humans, the decay of $Pmus_I$ to 25% of its initial value is relative fast (≈0.5 s), and this is in agreement with the current data (Figure II.4). Agostoni and Citterio (1979) however, did not observe the late slow decay of $Pmus_I$ which has been found in the anesthetized subjects in this study. The nature of this phenomenon is not clear, although altered inspiratory muscle activity has been observed during halothane anesthesia (Tusiewicz et al., 1977; Jones et al., 1979).

The inspiratory muscle activity during expiration involved negative work and energy expenditure of the inspiratory muscles. The mechanical efficiency of pliometric work (work done while the muscles are lengthened) is, however, considerably greater than during miometric work (work done with muscle shortening) (Margaria, 1979). Accordingly, in terms of energy expenditure, the negative inspiratory work during expiration should involve relatively little extra energy expenditure.

E. APPENDIX

Chang and Mortola (1981) have recently suggested that the resistance of the tracheal tube in isolation may exceed the resistance of the respiratory system and tube in situ because of the sudden reduction of cross-sectional area at the transition from the trachea to the tube. Since this phenomenon could invalidate the method in this study for deriving the intrinsic resistance of the respiratory system (see the results), the following in vitro experiments were performed. The flow-resistive properties of the equipment (including the endotracheal tube) were measured separately, using airflow instead of the anesthetic gas mixture. In addition, similar measurements were made on a tube (internal diameter 1.85 cm, length 12 cm) connected in series to a linear resistor consisting of a multiple-wire sheet screen. The total resistance of the tube and resistor amounted to 1.7 cm $H_2O.l^{-1}s$, and was mainly due to the resistor (85%). The dimensions of the tube were chosen to simulate the trachea, and the resistor was selected to represent the resistance of the total respiratory system (excluding upper airways and trachea). Next, the endotracheal tube was inserted into the larger tube representing the trachea, the cuff was inflated, and the flow-resistive properties of the total system were determined. Measurements were made at airflows of 0.25, 0.5, 0.75, and 1 $l.s^{-1}$, the flow being directed to simulate in vivo expiration. In all instances the flow resistive properties of the combined system were almost identical to the sum of the flow-resistive properties of the two compartments measured separately. For example, the K_1 and K_2 for equipment with tube 8 amounted to 2.0 cm $H_2O.l^{-1}.s$ and 4.7 cm $H_2O.l^{-2}.s^2$, respectively. For the combined system, K_1 and K_2 amounted to 3.6 cm $H_2O.l^{-2}.s$ and 4.6 cm $H_2O.ml^{-2}.s^2$, respectively. The difference in K_1 between the total system and separate equipment (including tube 8) closely reflected the resistance of the resistor and tube simulating the trachea (1.6 vs. 1.7 cm $H_2O.l^{-1}.s$). As in the in vivo experiments, the K_2 of the combined system was virtually the same as the K_2 of the equipment (including tube 8) measured separately. Thus it appears that the subtraction method for deriving the intrinsic resistance of the respiratory system is valid. This is also supported by the fact that when the direction of flow was inverted (simulating inspiration), the flow-resistance properties of the combined system were not appreciably different to those found with flow directed to simulate expiration. Indeed, according the Chang and Mortola (1981),a different behavior should be observed if the sudden reduction of cross-sectional area between the endotracheal tube and the "trachea" played an important role. This does not imply that the study of Chang and Mortola (1981) was not valid. Present model analysis simply shows that if the resistances of two compartments are relatively high, the local phenomena elicited by an abrupt change in cross-sectional area become unimportant. Stated otherwise, if two long tubes of different diameter are joined together, the sum of the separate resistances will be much closer to the combined resistance than if the tubes are short (and hence offer little resistance).

G. REFERENCES

1. Agostoni, E., and G. Citterio. Relative decay rate of inspiratory muscle pressure and breath timing in man. Respir. Physiol. 38:335-346, 1979.

2. Agostoni, E., and J. Mead. Statics of the respiratory system. In: Handbook of Physiology. Respiration. Washington, D.C.: Am. Physiol. Soc., 1964, sect. 3, vol. I, chapt. 13, p. 387-409.

3. Berger, R., and N.K. Burki. The effects of posture on total respiratory compliance. Am. Rev. Respir. Dis. 125:262-263, 1982.

4. Bergman, N.A. Measurement of respiratory resistance in anesthetized subjects. J. Appl. Physiol. 21:1913-1917, 1966.

5. Bergman, N.A. Properties of passive exhalations in anesthetized subjects. Anesthesiology 30:378-387, 1969.

6. Bergman, N.A., and C.L. Waltemath. A comparison of some methods for measuring total respiratory system resistance. J. Appl. Physiol. 36:131-134, 1974.

7. Brownlee, W.E., and F.F. Allbritten, Jr. The significance of the lung-thorax compliance in ventilation during thoracic surgery. J. Thoracic Surg. 32:454-463, 1956.

8. Chang, H.K., and J.P. Mortola. Fluid dynamic factors in tracheal pressure measurements. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51:218-225, 1981.

9. Crago, R.R., A.C. Bryan, A.K. Laws, and A.E. Winestock. Respiratory flow resistance after curare and pancuronium, measured by forced oscillation. Can. Anesth. Soc. J. 19:607-614, 1972.

10. Don, H.F., and J.G. Robson. The mechanics of the respiratory system during anesthesia. The effects of atropine and carbon dioxide. Anesthesiology 26:168-178, 1965.

11. Ferris, B.C., Jr., J. Mead, and L.H. Opie. Partitioning of respiratory flow resistance in man. J. Appl. Physiol. 19:653-658, 1964.

12. Gautier, H., and J.H. Gaudy. Changes in ventilatory pattern induced by intravenous anesthetic agents in human subjects. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 45:171-176, 1978.

13. Gold, M.I., and M. Helrich. Pulmonary compliance during anesthesia. Anesthesiology 26:281-288, 1965.

14. Hedenstierna, G., and G. McCarthy. Mechanics of breathing, gas distribution, and functional residual capacity at different frequencies of respiration during spontaneous and artificial ventilation. Br. J. Anaesth. 47:706-711, 1975.

15. Jones, J.G., D. Faithfull, C. Jordan, and B. Minty. Rib cage movement during halothane anesthesia in man. Br. J. Anaesth. 51:399-407, 1979.

16. Juno, P., M. March. T.J. Knopp, and K. Rehder. Closing capacity in awake and anesthetized-paralyzed man. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 44:238-244, 1978.

17. Katz, R.L., and J.F. Ryan. The neuromuscular effects of suxamethonium in man. Br. J. Anaesth. 41:381-390, 1969.

18. Lehane, J.R., C. Jordan, and J.G. Jones. Influence of halothane and enflurane on respiratory airflow resistance and specific conductance in anesthetized man. Br. J. Anaesth. 52:773-781, 1980.

19. Margaria, R. Biomechanics and Energetics of Muscle Exercise. London: Oxford Univ. Press, p. 70, 1979.

20. McIlroy, M.B., D.F. Tierney, and J.A. Nadel. A new method for measurement of compliance and resistance of lungs and thorax. J. Appl. Physiol. 18:424-427, 1963.

21. Milic-Emili, J., J.M. Petit, and R. Deroanne. Mechanical work of breathing during exercise in trained and untrained subjects. J. Appl. Physiol. 17:43-46, 1962.

22. Nims, R.G., E.G. Conner, and J.H. Comroe, Jr. The compliance of the human thorax in anesthetized patients. J. Clin. Invest. 34:744-750, 1955.

23. Opie, L.H., J.M.K. Spalding, and F.D. Scott. Mechanical properties of chest during intermittent positive-pressure respiration. Lancet 1:545-551, 1959.

24. Otis, A.B., W.O. Fenn, and H. Rahn. Mechanics of breathing in man. J. Appl. Physiol. 2:592-607, 1950.

25. Read, D.J.C., S. Freedman., and E.R. Kafer. Pressures developed by loaded inspiratory muscles in conscious and anesthetized man. J. Appl. Physiol. 37:207-218, 1974.

26. Rehder, K., J.E. Mallow, E.E. Fibuch, D.P. Krabill, and A.D. Sessler. Effects of isoflurane anesthesia and muscle paralysis on respiratory mechanics in normal man. Anesthesiology 41:477-485, 1974.

27. Tusiewicz, K., A.C. Bryan, and A.B. Froese. Contributions of changing rib cage diaphragm interactions to the ventilatory depression of halothane anesthesia. Anesthesiology 47:327-337, 1977.

28. Vincent, N.J., R. Knudson, D.E. Leith, P.T. Macklem, and J. Mead. Factors influencing pulmonary resistance. J. Appl. Physiol. 29:236-243, 1970.

29. Westbrook, P.R., S.E. Stubbs, A.D. Sessler, K. Rehder, and R.E. Hyatt. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J. Appl. Physiol. 34:81-86, 1973.

30. Zin, W.A., L.D. Pengelly, and J. Milic-Emili. Single-breath method for measurement of respiratory mechanics in anesthetized animals. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 52:1266-1271, 1982.

CHAPTER III

ACTIVE INSPIRATORY IMPEDANCE IN HALOTHANE ANESTHETIZED HUMANS

ABSTRACT

The method of Siafakas et al. (1981b) for determining active elastance (E'rs) and flow resistance (R'rs) of the respiratory system was applied in eight spontaneously breathing humans anesthetized with halothane. From measurements of (a) flow ($\dot{V}$) and volume (V) during unoccluded inspirations, and (b) of tracheal pressure ($P^{o}tr$) during subsequent inspirations with the airways occluded at end-expiration. E'rs and R'rs were computed as slopes and intercepts of the following function: $-P^{o}tr/\dot{V} = R'rs + E'rs\ V/\dot{V}$. These measurements were repeated during inspirations loaded with a series of linear flow resistances (ΔR). Neither E'rs nor R'rs were significantly affected by ΔR. On the average E'rs and R'rs were, respectively, 34.4% and 16.7% higher than the corresponding passive elastance and flow resistance of the respiratory system, indicating that during active breathing the internal impedance of the respiratory system increases. This provides an internal mechanism by which passive loads are compensated.

A. INTRODUCTION

With relaxed respiratory muscles, the impedance of the respiratory system is represented by the volume-elastic and flow-resistive impedances offered by the passive mechanical properties of the airways, lungs and chest wall. Inertance is normally negligible. When the respiratory muscles contract, their active force-length and force-velocity properties add to the internal impedance: the force-length properties to the volume-elastic impedance (elastance) and the force-velocity properties to the flow-resistive impedance (flow-resistance) (Marshall, 1962; Pengelly et al., 1971). Consequently, during active breathing the impedance of the respiratory system is higher than its passive value.

Recently, Siafakas et al. (1981b) have determined the active respiratory elastance (E'rs) and resistance (R'rs) in spontaneously breathing anesthetized cats. Their analysis was based on the following equation of motion:

$$- P^{o}tr = R'rs.\dot{V} + E'rs.V \qquad (1)$$

where $P^{o}tr$ is tracheal pressure during an inspiratory effort with the airways occluded at functional residual capacity (representing the inspiratory driving pressure) and $\dot{V}$ and V are, respectively, the instantaneous flow and volume changes during a control breath, immediately preceding the occluded effort.

The analysis according to Equation 1 involves several assumptions (e.g., that the inspiratory neural drive is the same during the occluded and corresponding unoccluded inspiration; that $P^{o}tr$ represents the driving pressure potentially available for producing changes in lung volume; and that R'rs and E'rs are constant), and Siafakas et al. (1981b) recognized that justification of their approach required further investigation. Accordingly, Zin et al. (1982a) tested the validity of the above approach by adding linear resistive loads during inspiration in anesthetized cats, and comparing the observed inspirograms with those predicted according to the analysis of Siafakas et al. (1981b). The good agreement between observed and predicted inspirograms provided support for the validity of this analysis, at least in anesthetized cats.

In the present study the analysis of Siafakas et al. (1981b) was applied in human subjects anesthetized with halothane and breathing a mixture of 70% N_2O-30% O_2. Measurements of active impedance were done both with and without linear resistances added to inspiration.

B. MATERIALS AND METHODS

Eight subjects (three males and five females, aged 21-49 years) undergoing general anesthesia for minor plastic or orthopedic surgery were studied prior to operation. None had a history or clinical evidence of cardiopulmonary disease. The research was approved by the institutional Ethics Committee, and informed consent was obtained from all patients.

Flow ($\dot{V}$) was recorded with a Fleisch No. 2 pneumotachograph connected to a Validyne MP 45 differential pressure transducer. Volume (V) was obtained by integration of the flow signal (HP 8815 A integrator). Tracheal occlusion pressure ($P^{o}tr$) was measured through a side port of the connector between the anesthesia circuit and the endotracheal tube using a Validyne MP-45-2 differential pressure transducer. End-tidal CO_2 and halothane concentrations were monitored by a Beckman LB2 infrared analyzer. All signals were amplified (HP 8805 A amplifier) and recorded on a Gould Brush 2600 six channel recorder as described in Chapter II.

A three-way tap was used to occlude the airway opening or to have the subjects breathe through three different external flow resistances (ΔR), amounting to 4.8, 8.8 and 16.4 cm $H_2O.l^{-1}.s$, respectively. These were connected to the inspiratory line via a cone, and consisted of multiple wire sheet screens. All were linear with flows up to 3 $l.s^{-1}$. The resistance of the pneumotachograph assembly amounted to 0.4cm $H_2O.l^{-1}.s$ and was linear within the experimental range of flows. The pressure-flow characteristics of the three endotracheal tubes (internal diameter: 8.0, 8.5 and 9.0 mm) were curvilinear, fitting Rohrer's equation ($P= K_1\dot{V} + K_2\dot{V}^2$). The

K_1 and K_2 constants of the tubes have been previously described (Table 1, Chapter II). All resistance values pertain to a gas mixture of 70% N_2O-30% O_2.

Procedure

Patients were premedicated with atropine (0.3-0.6 mg, i.m.) and meperidine (Demerol, 1 mg/kg) 45 minutes prior to anesthesia. Anesthesia was induced with thiopentone (4-6 mg/kg) and succinylcholine (1.5 mg/kg) was given to facilitate intubation. Anesthesia was maintained with halothane (~1 MAC) in 70% N_2O-30% O_2. All measurements were made at least 20 minutes after the subjects had established a steady spontaneous breathing pattern, to allow for recovery from the effects of succinylcholine (Stanski and Sheiner, 1979). Depending on the size of the subjects, endotracheal tubes of size 8.0, 8.5 and 9.0 were used.

The flow resistances were added randomly at end-expiration and maintained for one breath. Following each load, the subjects were allowed to breathe freely for about 10 breaths, and then the airway opening was occluded at end-expiratory lung volume to obtain tracheal occlusion pressure ($P^o tr$). Records illustrating the procedure are shown in Figure III.1.

Data Analysis

From records such as shown in Figure III.1 E'rs and R'rs were computed by a modification of the approach used by Zin et

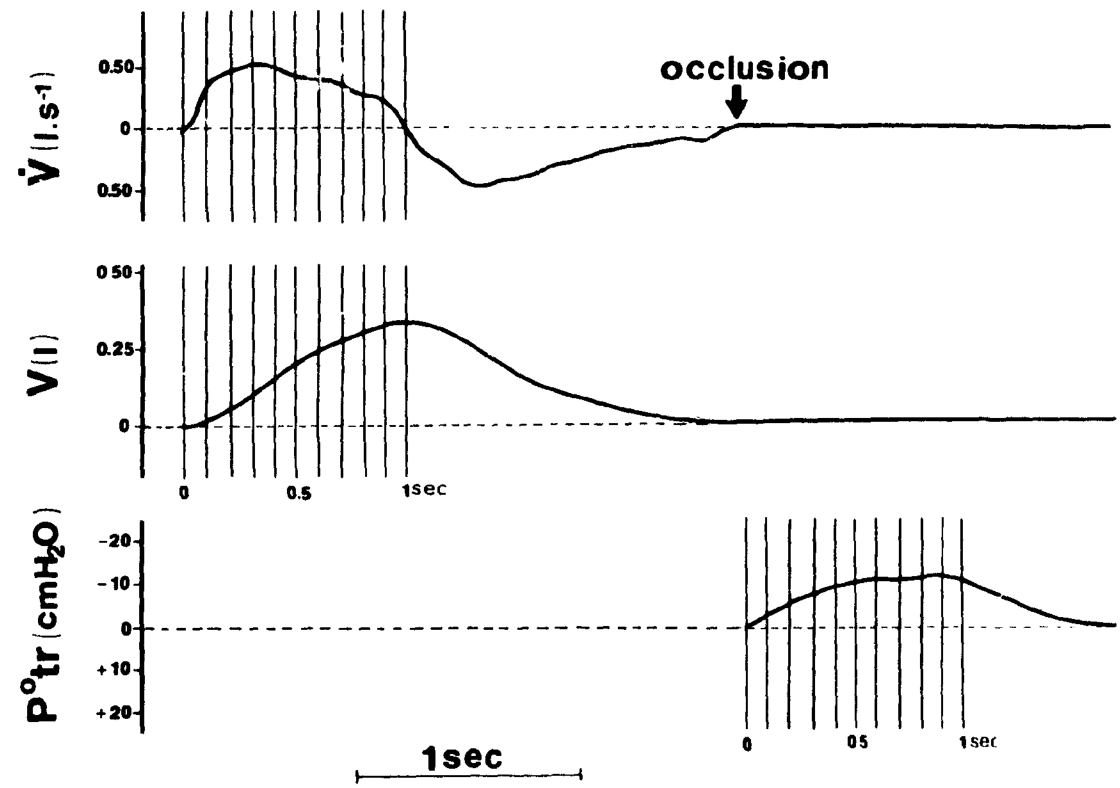

Figure III.1: Tracing of flow ($\dot{V}$), volume (V) and tracheal occlusion pressure ($P^o tr$) in a spontaneously breathing anestnetized subject. Occlusion of external airways was performed at end-expiration, as indicated by arrow and maintained during a whole respiratory cycle. During this period the patient performed an inspiratory effort as indicated by negative tracheal occlusion pressure which was measured at intervals of 0.1.s after the onset of occluded inspiration. V and $\dot{V}$ of the preceding breath were also measured in the same way, and the data plotted according to Equation 2.

al. (1982a). This consisted in subtracting from $-P^{o}tr$ in Equation 1 the resistive pressure drop (Peq) due to the equipment (including the endotracheal tube) and dividing both sides of the equation by $\dot{V}$:

$$(-P^{o}tr - K_1\dot{V} - K_2\dot{V}^2)/\dot{V} = R'rs + E'rsV/\dot{V} \qquad (2)$$

where the constant K_1 is the sum of the K_1 of the pertinent endotracheal tube (Table 1, Chapter II) and of the linear resistance offered by the pneumotachograph assembly (0.4 cm $H_2O.l^{-1}.s$); and the constant K_2 again pertains to the appropriate endotracheal tube.

Equation 2 is a linear function of the general type $y = a + bx$, where E'rs is the slope and R'rs is the intercept on the y-axis.

$P^{o}tr$, V and $\dot{V}$ were measured at 0.1s intervals after the onset of inspiration, the former during the occluded inspiratory effort, and V and $\dot{V}$ from the immediately preceding spontaneous unloaded inspiration (Figure III.1). Onset of inspiration was assessed in terms of beginning of inspiratory flow and/or of a negative deflection of $P^{o}tr$. For better resolution, $P^{o}tr$ was also recorded on a separate channel at high gain.

When breathing against the added flow resistance (ΔR) Equation 2 becomes:

$$(-P^{o}tr - Peq)/\dot{V} = R'rs + R + E'rs\ V/\dot{V} \qquad (3)$$

where Peq corresponds to $K_1\dot{V} + K_2\dot{V}^2$ in Equation 2, and the sum of R'rs and ΔR is the intercept of the line on the y-axis.

The intercepts during loaded breaths will be defined by the symbol $\Delta R^{L}rs$ ($R'rs + \Delta R$).

Three control and three loaded breaths (one for each added resistance) were analyzed per subject.

In all individuals the passive elastance (Ers) and passive resistance (Rrs) of the respiratory system, was also determined using the method described in Chapter II. Briefly, this consisted of occluding the airway at end-inspiration (V_T) and measuring the tracheal pressure, Ptr when the subjects relaxed their respiratory muscles. Ers was obtained by dividing relaxed Ptr by V_T. While the subjects were still relaxed the airways were reopened, and analysis of the ensuing relaxed expiratory volume-flow relationship allowed computation of the flow resistance (for details see Chapter II, Methods).

C. RESULTS

Figure III.2 shows a plot of $(-P^{o}tr-Peq)/\dot{V}$ versus $V/\dot{V}$ obtained in a subject during an unloaded (filled circles) and a loaded inspiration (open circles).[1] Linear relationships are obtained in both instances, the correlation coefficients (r) being greater than 0.99. While the lines are virtually parallel, the intercept on the y-axis is higher with the added external load, by an amount close to ΔR. Similar straight lines, with correlation coefficients ranging between 0.960 and 0.999, were obtained in all subjects both with and without

[1] The duration of loaded inspirations was in general slightly longer than that of control breaths, in line with previous results, (Whitelaw et al., 1976). This explains 10 data points for the loaded breath and only 9 for the unloaded inspiration in Figure III.2.

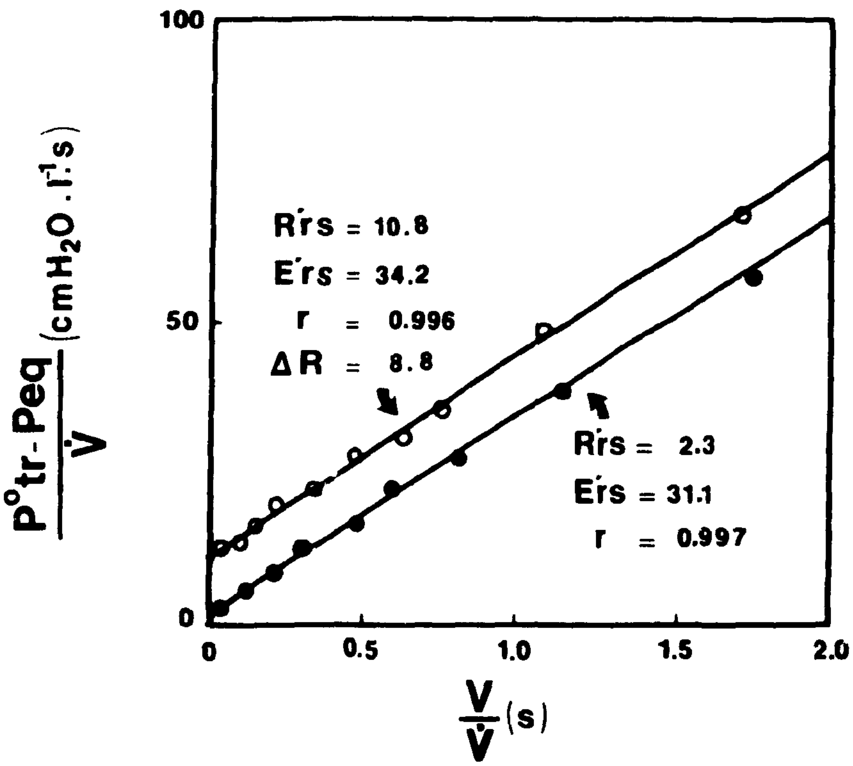

Figure III.2: Examples of graphical solutions of Equations 2 and 3 for a loaded (ΔR = 8.8 cm $H_2O.l^{-1}.s$; open circles) and an unloaded (ΔR = 0; filled circles) breath. The two lines are almost parallel, indicating that ΔR has no effect on E'rs. The intercepts of the lines with and without ΔR are, respectively, 10.8 and 2.3 cm $H_2O.ml^{-1}.s$, the difference (8.5 cm $H_2O.l^{-1}.s$) corresponding closely to the added resistance. Correlation coefficients (r) are shown.

ΔR. Active values of elastance and resistance of the eight subjects obtained under unloaded conditions are presented in Table III.1, together with the corresponding passive values.

Figure III.3 illustrates the relationship between E'rs and ΔR in the 8 subjects. Although there was a slight tendency for E'rs to increase with increased loads, the difference between E'rs measured under unloaded and loaded conditions was not statistically significant (paired t-test). As shown in Fig. III 4, R^Lrs increased linearly with added resistances ($r = 0.994$; $p < 0.001$). This increase (ΔR^Lrs) was equal to ΔR, the mean value obtained from all eight subjects lying on the identity line of the graph ΔR^Lrs vs. ΔR (right ordinate in Figure III.4).

D. DISCUSSION

In the present study, E'rs and R'rs was determined in anesthetized humans, using the approach of Siafakas et al. (1981b) and Zin et al. (1982a). The linearity in the graphic solution of Equation 2, found in all instances, suggests that this approach is applicable in anesthetized humans, and implies that R'rs and E'rs were constant within the experimental range of volumes (up to 0.43 l above FRC) and flows (up to 0.7 $l.s^{-1}$). In addition, the validity of this approach is supported by the fact that after addition of linear resistances (ΔR), the intercepts of the relationships defined by

TABLE III.1

Physical Characteristics and Respiratory Mechanics of Subjects

Subject	Sex	Age (Yrs)	Height (m)	Weight (Kg)	VC (l)	ERs, $cmH_2O.l^{-1}$		Rrs, $cmH_2O.l^{-1}.s$	
						Passive	Active	Passive	Active
1	F	24	1.64	66	3.9	19.0	35.2	1.8	2.3
2	M	21	1.73	60	5.2	27.0	33.7	1.2	1.3
3	M	22	1.75	73	4.9	24.8	31.2	1.0	1.5
4	F	25	1.66	63	4.1	26.7	38.6	2.9	3.0
5	F	49	1.62	70	3.8	18.6	22.4	1.4	1.3
6	F	38	1.70	72	4.0	27.1	31.7	1.2	2.3
7	F	37	1.60	50	3.9	22.2	31.1	2.8	2.8
8	M	48	1.77	82	5.1	19.9	25.5	2.0	2.2
Mean ±	**SD**	**33±11.5**	**1.68±0.06**	**67±9.6**	**4.4±0.6**	**23.2±3.7**	**31.2±5.2**	**1.8±0.7**	**2.1±0.7**

VC, vital capacity; Ers, respiratory system elastance; Rrs, respiratory system resistance.

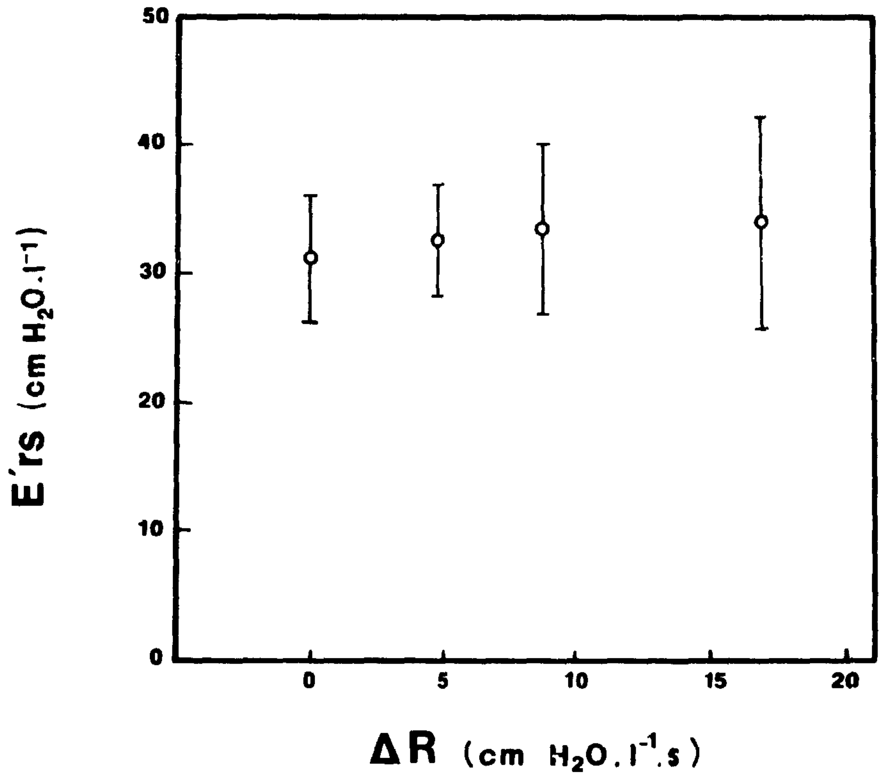

Figure III.3: Mean values (± SD) of E'rs in 8 subjects with different added resistances (ΔR). No significant changes were observed.

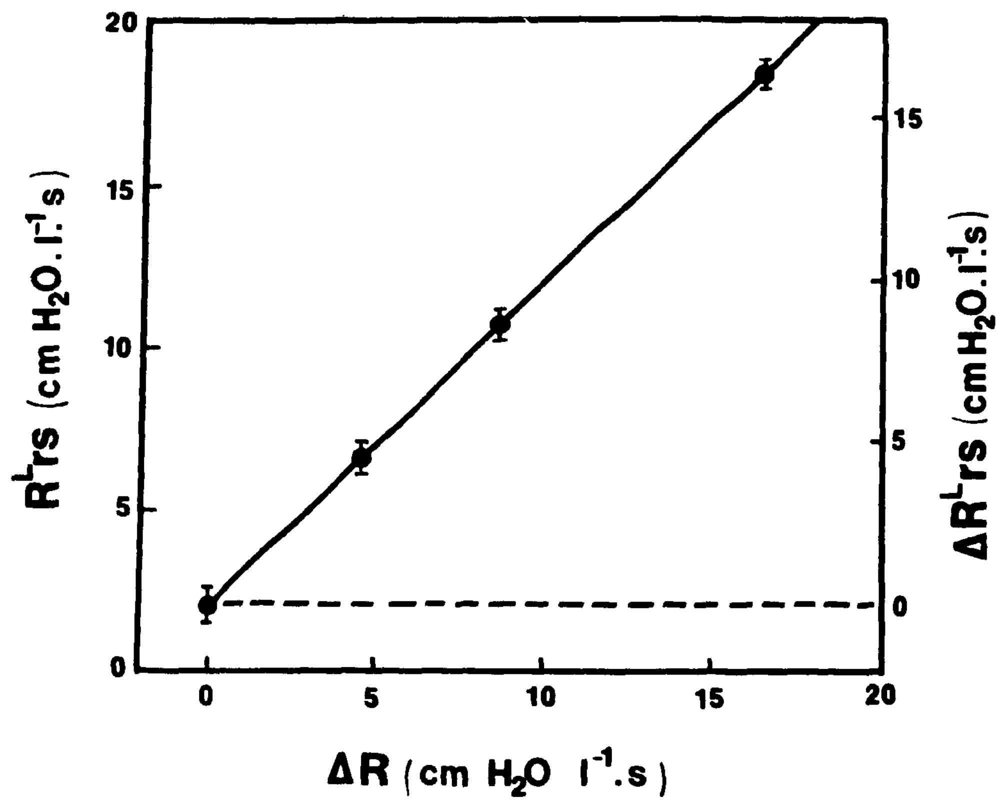

Figure III.4: Mean values (±SD) of R^Lrs in 8 subjects with different added resistances (ΔR). R^Lrs increases linearly with ΔR, the changes (R^Lrs) being equal to the added resistances, as indicated by the fact that the data fall on a line with slope = 1.

Equation 3 increased by virtually the same amount as ΔR (Figure III.4), while the slope (E'rs) did not change significantly (Figure III.3).

In the present analysis the non-linear equipment flow resistance (including the endotracheal tube) was subtracted, so that values of R'rs do not include the upper airway resistance. The values of R'rs were 16.7% higher ($p<0.05$, paired t-test) than the corresponding passive values (Table III.2). Similarly, E'rs was higher than Ers, the percentage difference averaging 34.4% and being statistically significant ($p<0.001$). These data are qualitatively in agreement with the results obtained by Siafakas et al. (1981b) and Zin et al. (1982a) in anesthetized cats. Quantitatively, however, the average increase in elastance found by these authors between passive and active conditions was greater, amounting to 90% and 52% respectively.[2] Similarly, according to the data of Zin et al. (1982a) the average increase of intrinsic resistance (Req subtracted) during active breathing over its passive value was greater in the cats (36%) than in the human subjects of the present study (16.7%). These discrepancies could reflect differences in species or anesthetic used. In this connection it should be noted that, whereas in humans the passive elastance is substantially greater during anesthesia than in the awake state (Nims et al., 1955; Westbrook et al., 1973), this does not appear to be the case in experimental animals (Rich et al., 1979). Thus, the smaller relative

[2] It is important to note that the active elastance (E'rs), as measured in this paper, differs from the "effective" elastance previously described in studies dealing with tidal volume defense against elastic loads, (Lynne-Davies et al., 1971). The latter is measured as ratio of peak airway occlusion pressure to tidal volume, and hence depends on the strength of the Breuer-Hering inflation reflex, while E'rs is independent of such a reflex.

increase of elastic impedance observed during active breathing in anesthetized humans may simply reflect the fact that their passive elastance is already high. Indeed, during unilateral electrophrenic stimulation in seated awake subjects, Pengelly et al. (1971) reported a 70% increase in elastance between passive and active states, the absolute difference amounting to 5.4 $cmH_2O.l^{-1}$. This difference, however, is still somewhat smaller than that found in the anesthetized subjects of the present work (8 $cm\ H_2O.l^{-1}$). Similarly, contrary to the present results, Pengelly et al. (1971) found that R'rs was not constant but varied with lung volume. Data obtained with unilateral electrophrenic stimulation however, are not readily comparable to those observed during spontaneous breathing, as previously pointed out by Younes and his group (Riddle and Younes, 1981; Younes and Riddle 1981; Younes et al., 1981). In a series of elegant reports these authors also attempted to determine the active properties of the respiratory system in anesthetized subjects. They did not, however, take into account the non-linear equipment flow resistance, and hence their results cannot readily be compared to the present ones.

The nature of the increased impedance during active breathing has been extensively discussed by previous authors (Marshall, 1962; Pengelly, et al., 1971; Siafakas et al., 1981b; Riddle and Younes, 1981; Younes and Riddle, 1981; Younes et al., 1981; Zin et al., 1982a). It is generally accepted that the force-length and force-velocity properties of the contracting respiratory muscles add, respectively, an elastic-like and a resistive-like component to the internal impedance of the respiratory system. In addition, active breathing may also involve pressure losses due to distortion of the respiratory system from its relaxed (passive) configuration (Zin et al., 1982a). It should be noted, however, that the values of E'rs and R'rs obtained according to Equation 2 neglect the pressure losses that may occur during the occluded inspiratory effort. Although there is some evidence suggesting that during the occluded inspirations the contraction of the diaphragm may be nearly isometric (Siafakas et al., 1981a), the occluded efforts may *per se* involve some pressure losses due to force-length and force-velocity properties of the inspiratory muscles. Thus, strictly speaking, the present results and those of Siafakas et al (1981b) and Zin et al. (1982a) may simply indicate that during unoccluded inspirations, relative to the occluded ones, additional flow-related pressure losses are minimal, whereas additional volume-related pressure losses are substantial.

By adding to the internal impedance, the intrinsic properties of the contracting muscles render the respiratory system more stable in the face of increased mechanical loading. In this connection, it should be noted that in the anesthetized subjects of the present work, Ers averaged 23.2

cm $H_2O.l^{-1}$, a value substantially higher than that obtained in awake individuals (about 10 cm $H_2O.l^{-1}$) (Agostoni et al., 1964). This increase of Ers during anesthesia, which has been extensively documented in humans (Nims et al., 1955; Westbrook et al., 1973; Rich et al., 1979), results in increased internal impedance of the respiratory system, and hence is load compensatory. Similarly, although in the anesthetized subjects of this study, the intrinsic Rrs was within normal limits (Ferris et al., 1964), the overall resistance increased as a result of the high added resistance provided by the endotracheal tubes (Table 1, Chapter II). This further increased the overall respiratory impedance. This high passive impedance, though costly in terms of energy expenditure for unloaded breathing, may also be regarded as a mechanism by which external loads are compensated.

Finally, it should be noted that as a result of a proportionally greater increase of elastance (34.4%) than intrinsic resistance (16.7%) during active breathing, the active intrinsic time constant was, on average, somewhat shorter (0.067 $\pm$ 0.018 s) than the corresponding passive values (0.079 $\pm$ 0.033 s). These values were computed, respectively, as ratios of R'rs and E'rs and Rrs and Ers from Table III.1. However, because of the highly curvilinear flow resistance offered by the endotracheal tubes, the overall (tubes included) behaviour of either passive or active respiratory system cannot be characterized by single time constants (see Chapter II), as was the case in the cats studied by Siafakas et al. (1981b). and Zin et al. (1982a) and Zin et al. (1982b), in which the equipment resistance was linear within the experimental range of flows.

In conclusion, the present results indicate that the approach for determining active elastance and flow resistance introduced by Siafakas et al. (1981b) is valid, at least as a useful first approximation, in anesthetized humans.

F. REFERENCES

1. Agostoni, E., and J. Mead. Statics of the respiratory system. In: Handbook of Physiology, Respiration. Washington, D.C.: Am. Physiol. Soc., 1964, Section 3, Vol. 1, chap. 13, p. 387-409.

2. Ferris, B.C. Jr., J. Mead, and L.O. Opie. Partitioning of respiratory flow resistance in man. J. Appl. Physiol. 19:653-658, 1964.

3. Lynne-Davies, P., J. Couture, L.D. Pengelly, D. West, P.R. Bromage, and J. Milic-Emili. Partitioning of immediate ventilatory stability to added elastic loads in cats. J. Appl. Physiol. 30:814-819, 1971.

4. Marshall, R. Relationships between stimulus and work of breathing at different lung volumes. J. Appl. Physiol. 17:917-927, 1962.

5. Nims, R.G., E.H. Conner, and J.H. Comroe, Jr. The compliance of the human thorax in anesthetized patients. J. Clin. Invest. 34: 744-750, 1955.

6. Pengelly, L.D., A.M. Alderson, and J. Milic-Emili. Mechanics of the diaphragm. J. Appl. Physiol. 30:797-805 1971.

7. Rich, C.R., K. Rehder, T.J. Knopp, and R.E. Hyatt. Halothane and enflurane anesthesia and respiratory mechanics in prone dogs. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 46:646-653, 1979.

8. Riddle, W., and M. Younes. A model for the relation between respiratory neural and mechanical outputs. II Methods. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51:979-989, 1981.

9. Siafakas, N.M., H.K. Chang, M. Bonora, H. Gautier, J. Milic-Emili, and B. Duron. Time course of phrenic activity and respiratory pressures during airway occlusion in cats. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51:99-108, (a)1981.

10. Siafakas, N.M., R. Peslin, M. Bonora, H. Gautier, B. Duron, and J. Milic-Emili. Phrenic activity, respiratory pressures, and volume changes in cats. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51:109-121, (b)1981.

11. Stanski, D.R., and L.B. Sheiner. Parmacokinetics and dynamics of muscle relaxants. Anesthesiology 51:103-105, 1979.

12. Westbrook, P.R., S.E. Stubbs, A.D. Sessler, W. Rehder, and R.E. Hyatt. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J. Appl. Physiol. 34:81-86, 1973.

13. Whitelaw, W.A., J-P. Derenne, J. Couture, and J. Milic-Emili. Adaptation of anesthetized men to breathing through an inspiratory resistor. J. Appl. Physiol. 41:285-291, 1976.

14. Younes, M., and W. Riddle. A model for the relation between respiratory neural and mechanical outputs. I. Theory. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51:963-978, 1981.

15. Younes, M., W. Riddle, and J. Polachek. A model for the relation between respiratory neural and mechanical outputs. III. Validation. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51:990-1001, 1981.

16. Zin, W.A., L.D. Pengelly, and J. Milic-Emili. Single-breath method for measurement of respiratory mechanics in anesthetized animals. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 52:1266-1271, (a)1982.

17. Zin, W.A., L.D. Pengelly, and J. Milic-Emili. Active impedance of respiratory system in anesthetized cats. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 53:149-157, (b) 1982.

CHAPTER IV

A SIMPLE METHOD FOR ASSESSING THE VALIDITY OF THE ESOPHAGEAL BALLOON TECHNIQUE

ABSTRACT

The validity of the conventional esohageal balloon technique as a measure of pleural pressure (Milic-Emili et al., 1964) was tested in ten subjects in sitting, supine and lateral positions by occluding the airways at end-expiration and measuring the ratio of changes in esophageal (ΔPes) and mouth pressure (ΔPm) during the ensuing spontaneous occluded inspiratory efforts. Similar measurements were also made during static Mueller maneuvers. In both tests ΔPes/ΔPm values were close to unity in sitting and lateral positions, whereas in supine position, substantial deviations from unity were found in some instances. However, by repositioning the balloon to different levels in the esophagus, even in these instances a locus could be found where the ΔPes/ΔPm ratio was close to unity. No appreciable phase difference between ΔPes and ΔPm was found. It is concluded that by positioning the balloon according to the "occlusion test" procedure, valid measurements of pleural pressure can be obtained in all the tested body positions.

A. INTRODUCTION

The conventional approach used to validate the esophageal balloon technique as a measure of pleural surface pressure consists of having subjects perform static voluntary efforts (glottis open) against a closed airway, and comparing the changes in esophageal pressure (Δ Pes) with the corresponding changes in mouth pressure (Δ Pm) (Milic-Emili et al., 1964). A concordance between Pes and Pm is taken to indicate that the esophageal pressure provides a valid measure of changes in pleural surface pressure. This maneuver, however, can not be readily performed by many untrained subjects because of glottal closure, poor coordination, etc. Furthermore,it can not be used in children, during anesthesia or in very sick patients. A possible alternative is to compare ΔPes and ΔPm during spontaneous respiratory efforts made against a closed airway. This "occlusion test" has been used by Milner et al. (1978) and Beardsmore et al. (1980) in neonates.Asher et al. (1982) have recently used it in order to verify the validity of the esophageal water-filled catheter technique in neonates.

In the present investigation the "occlusion test" was used for testing the esophageal balloon technique in 10 normal adults, in sitting, supine and lateral positions.

B. MATERIALS AND METHODS

Studies were performed in 10 young healthy male volunteers with a mean age (± SD) of 31.4 ± 3.5 yrs, mean (± SD) vital capacity of 5.34 ± 0.38 l (105 ± 9.5 % of predicted) and mean (± SD) forced expiratory volume in one second (FEV_1) 4.28 ± 0.41 l (106 ± 11.4 % of predicted) (Goldman and Becklake, 1959). All subjects were experienced in respiratory studies. Esophageal pressure was measured with a 5 cm long balloon whose circumference was 3.2 cm, sealed over one end of a polyethylene catheter (internal diameter: 1.4 mm; length: 94 cm). The other end of the catheter was connected to a Sanborn 267 differential pressure transducer (Sanborn Co., Waltham MA). The volume-pressure curve of the balloon was flat within a range of volumes between 0.2 and 5 ml. Mouth pressure was measured with a similar catheter connected to another Sanborn 267 transducer. The Pes and Pm systems were tested with a sine-wave pressure generator and found to have a flat frequency response up to 10 Hz. Volume changes were measured by integration of the flow signal obtained with a Fleisch No. 2 pneumotachograph. A tap attached to the pneumotachograph was used to occlude the airway opening. All signals were amplified (No. 8805 amplifier, Hewlett-Packard, Waltham MA) and recorded on a six-channel chart recorder (Hewlett-Packard No. 7700). Transpulmonary pressure (Ptp) was obtained by electrical subtraction of Pes from Pm, and was recorded on a separate channel. The signals were also stored on tape (Hewlett-Packard No. 3968A) and were later played back on an X-Y recorder (Hewlett-Packard No. 7046A) in order to obtain the changes of Pes versus Pm during the "occlusion tests". Phase difference between Δ Pes and Δ Pm was computed from these loops by dividing the vertical width of each loop at mid-point of horizontal (Δ Pm) deflection by the total swing in Pes (Jaeger and Bouhuys, 1969). This analysis makes no allowance for the influence of cardiogenic changes on esophageal pressure, the cardiac artifact contributing to the measured phase differences.

Procedure

After topical anesthesia of the nasal mucosa and pharynx with lidocaine, the balloon was passed transnasally into the stomach and then gradually withdrawn until a negative deflection was present during inspiration. The balloon was then withdrawn another 10 cm and secured at that level (a distance varying between 37 and 40 cm from the nose to the tip of the balloon, depending on the subject). The balloon volume during measurements was 0.5 ml. Each subject, with his glottis open, was instructed to develop a constant negative pressure (-10 to -20 cm H_2O) against the closed airway (static Mueller maneuver) (Milic-Emili et al., 1964).This maneuver was repeated several times. The subject next breathed quietly through the pneumotachograph and a series of two to three "occlusion tests" were performed. These consisted of occluding the airway opening at end-expiration and allowing the subject to perform a series of three to five spontaneous (dynamic) occluded inspiratory efforts. The tests were performed in all 10 subjects in sitting, right and left lateral, and supine positions with the balloon top placed 10 cm above the cardia in sitting position. In four of the ten subjects the balloon was repositioned at 5 and 15 cm from balloon top to the cardia, and the same procedure was repeated in all postures. The volume of air in the balloon was checked after each change in balloon level or body position.

C. RESULTS

Measurements with balloon top 10 cm from cardia.

Figure IV.1A illustrates the changes in Pes, Pm and Ptp during an "occlusion test" in a seated subject. Apart from small oscillations reflecting cardiac artifacts, Ptp was constant throughout the three occluded inspiratory efforts. Figure IV.1B shows a representative plot of occluded Pes versus Pm in the same subject in sitting posture. The slope of the relationship (Δ Pes/Δ Pm) is close to the identity line and there is minimal loop formation. Table IV.1 shows the

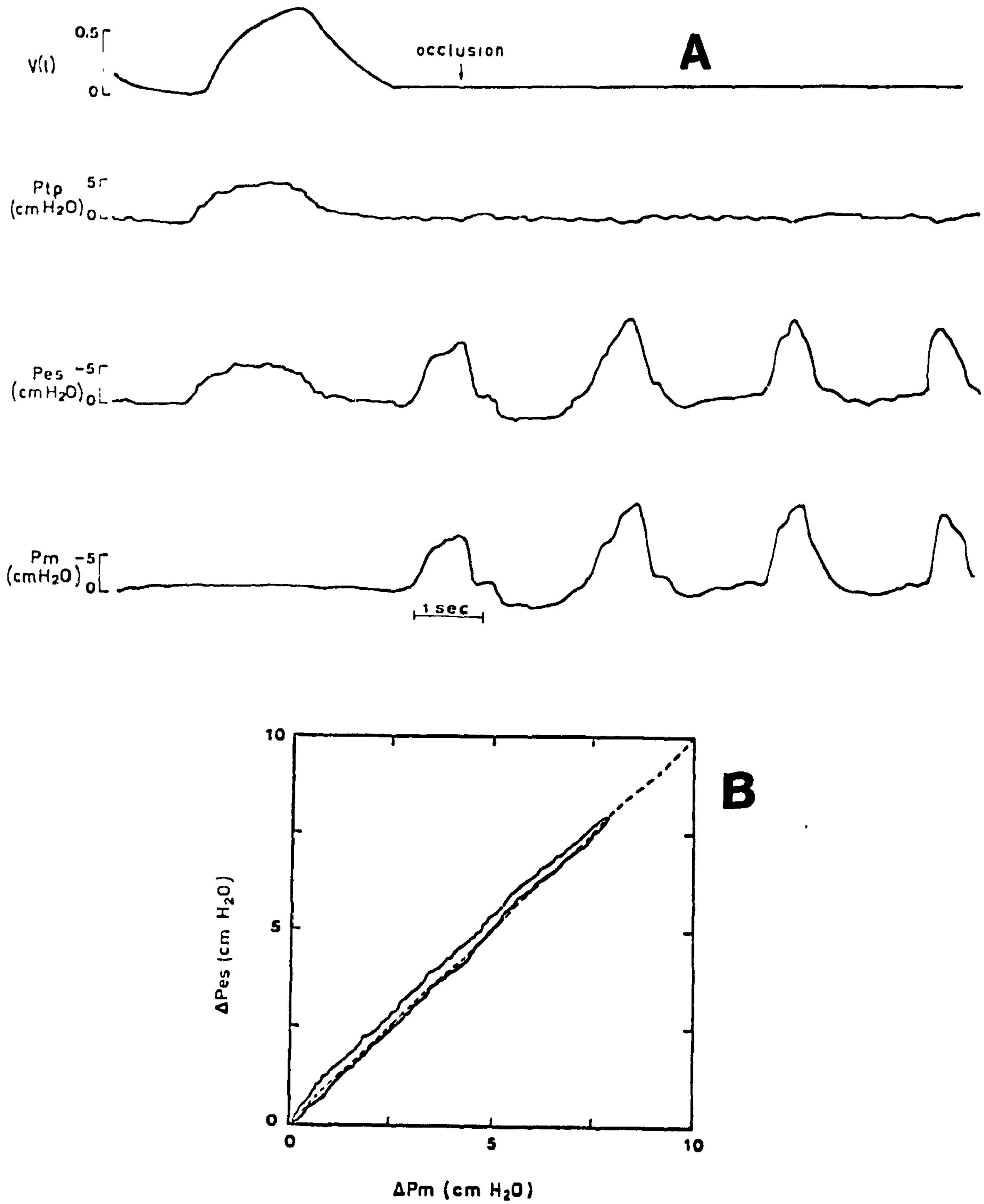

Figure IV.1: A: Tracing of volume (V), transpulmonary pressure (Ptp), esophageal pressure (Pes) and mouth pressure (Pm) during an "occlusion test" in a seated subject. Balloon top placed 10 cm from cardia.
B: Plot of Δ Pes versus Δ Pm for the first occluded inspiratory effort in A.

TABLE IV.1

ΔPes/ΔPm ratio measured during "occlusion test" in ten subjects, four body positions with esophageal balloon top 10 cm from cardia. Each Number is the mean of ten measurements.

SUBJECT	SITTING	R. LATERAL	L. LATERAL	SUPINE
1	1.08	1.00	1.04	0.77 (0.87)*
2	0.99	1.00	0.91	0.61 (1.09)
3	1.01	1.03	1.08	1.04
4	1.08	0.99	1.03	0.89
5	1.08	1.03	1.00	1.00
6	1.00	0.94	0.86	0.87
7	1.00	1.04	0.99	1.10
8	1.05	1.00	0.99	0.88
9	1.10	1.10	1.07	0.86
10	1.05	1.06	0.86	0.97
Mean ± SD	**1.04 ± 0.04**	**1.02 ± 0.04**	**0.98 ± 0.08**	**0.90 ± 0.14 (0.96 ± 0.095)**

* Values in parenthesis indicate "best values" obtained by changing balloon position to 15 cm from cardia in subject 1 and 5 cm from cardia in subject 2.

ratios between the swings in esophageal and mouth pressure (Δ Pes/ Δ Pm) during the "occlusion test" for each body position for ten subjects. Each individual value is the mean of 10 measurements. In sitting and lateral positions the group average ΔPes/Δ Pm was close to unity, the individual ratios not deviating from unity by more than 14% in any subject. On the other hand, in supine position the ΔPes/ΔPm was less than unity in seven out of ten subjects, with two values amounting to 0.77 and 0.61 (subjects 1 and 2, respectively). The phase difference between Δ Pes and Δ Pm during the "occlusion tests" was close to zero, exceeding + 3 degrees in only six instances (in subject 5 in all body positions, and subjects 2 and 9 in right lateral posture). In all body positions studied there was no significant difference between results obtained with the "occlusion test" and the Mueller maneuvers. The average values ($\pm$ SD) of ΔPes/ΔPm during the static Mueller maneuvers amounted to 1.06 $\pm$ 0.05 in sitting, 1.00 $\pm$ 0.06 in right lateral posture, 0.98 $\pm$ 0.09 in left lateral position, and 0.95 $\pm$ 0.09 in supine posture.

Changes of esophageal pressure due to cardiac artifact averaged (mean $\pm$ SD) 1.3 $\pm$ 0.8 cm H_2O in sitting, 2.0 $\pm$ 1.1 cm H_2O in right lateral, 1.8 $\pm$ 0.9 cm H_2O in left lateral and 3.5 $\pm$ 1.8 cm H_2O in supine position. The difference between the supine position with all other postures was statistically significant ($p < 0.01$). The phase difference between Pes and

Pm and the magnitude of the cardiac artifact were significantly correlated ($r = 0.96$).

Measurements with balloon top 5, 10 and 15 cm from cardia.

Figure IV.2 shows the ΔPes/ Δ Pm ratios during the "occlusion tests" in four subjects studied in four body positions, with the esophageal balloon placed at three different levels. In sitting and lateral positions there is only one point deviating appreciably from unity. In supine position, the points are more scattered, with four values out of the + 15% range, the Δ Pes/ Δ Pm ratio tending to be higher with the esophageal balloon placed in the lower esophagus. Figure IV.2 also shows that even in supine position there is at least one esophageal balloon level at which the ΔPes/ΔPm ratio during the "occlusion test" was close to unity.

Phase differences between ΔPes and ΔPm of these four subjects are close to zero in all instances (ranging between +5 and -5 degrees), and there are no systematic changes with balloon position.

Figure IV.3 shows the relationship between the mean values ($\pm$ SE) of Δ Pes/ΔPm obtained with static (Meuller maneuvers) and the corresponding values obtained with the "occlusion test". In all instances there is a close agreement between the two tests. As were the values obtained with the "occlusion test", the Δ Pes/ Δ Pm values obtained with the

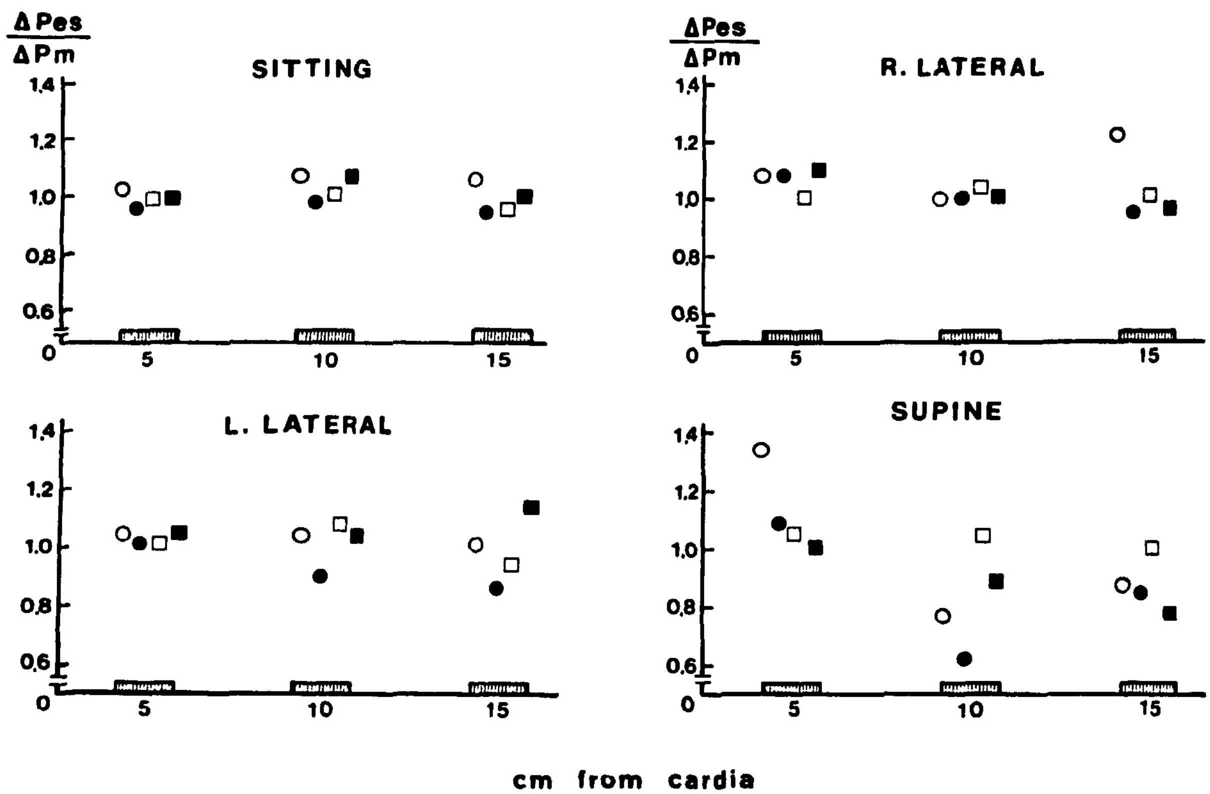

Figure IV.2: The $\Delta Pes/\Delta Pm$ ratio measured during "occlusion test" in four subjects, in different body positions with the esophageal balloon top 5, 10 and 15 cm above cardia. Each symbol represents the mean value of 10 measurements in each subject.

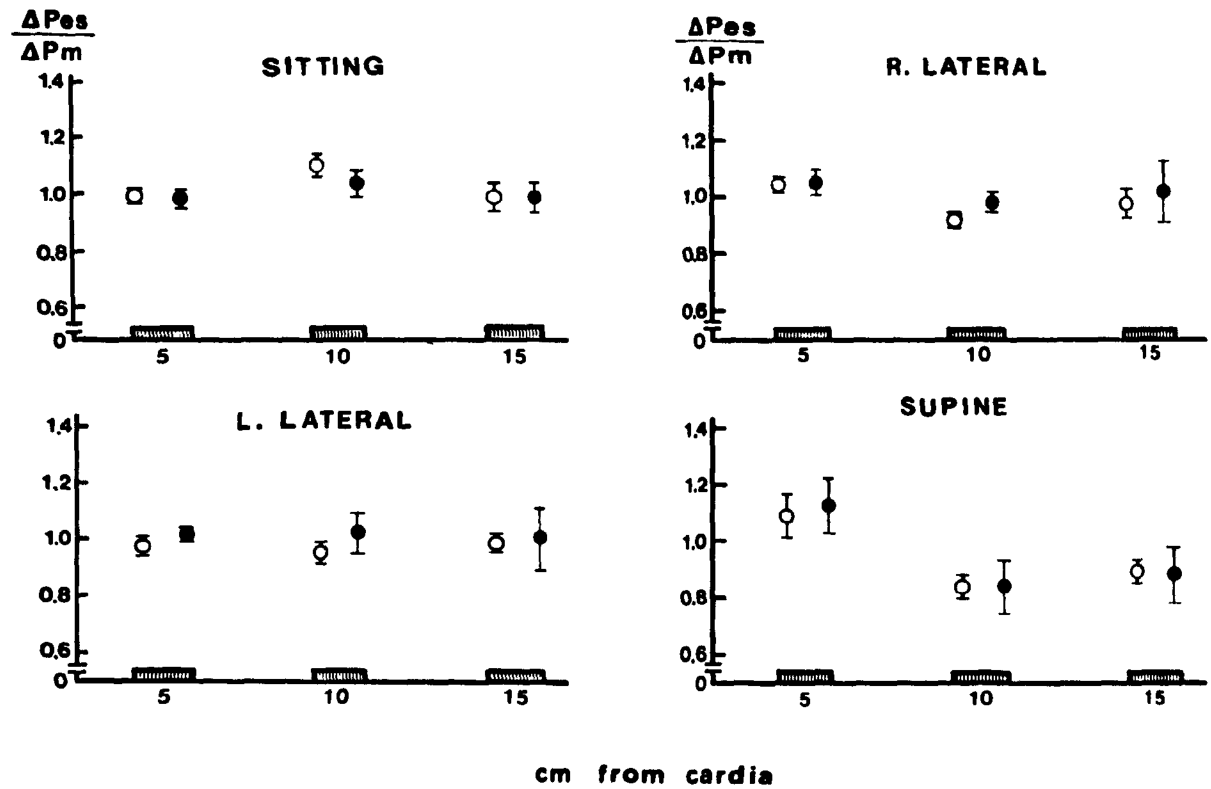

Figure IV.3: Mean values ($\pm$ SE) of Δ Pes/ ΔPm ratio measured during "occlusion tests" (o) and Mueller maneuvers (•) in four subjects, four body positions, with the esophageal balloon top 5, 10 and 15 cm above cardia.

Mueller maneuvers in supine position also tended to be higher with the balloon placed in the lower esophagus.

The size of the cardiac artifact on the average did not vary substantially with balloon position in any of the body postures, but its magnitude was greatest in the supine position. In any given subject, however, the magnitude of the cardiac artifact varied substantially with different balloon positions.

D. DISCUSSION

In the present study the validity of the esophageal balloon technique as a measure of pleural surface pressure was assessed in young adults in different body positions. Results of $\Delta Pes/\Delta Pm$ ratios obtained with the Mueller maneuvers support the validity of the technique, at least in sitting and lateral positions, and are in agreement with previous results reported by Milic-Emili et al (1964). They used Mueller and Valsalva maneuvers but only in sitting position. Such static maneuvers, however, cannot readily be performed by patients who are not experienced in respiratory experiments, as many among them find it difficult to keep the glottis open during the test or are unable to hold a steady airway pressure. Accordingly, in the present study the "occlusion test" was used, which requires no active cooperation from the subjects and in all instances did not involve any problems due to closure of the glottis.

Individual values of $\Delta Pes/\Delta Pm$ obtained with the "occlusion test" in sitting and lateral postures with the esophageal balloon in the conventional position (balloon top 10 cm above cardia) were close to unity (Table IV.1)[1]. On the other hand, in supine position $\Delta Pes/\Delta Pm$ tended to be less than one in most subjects. In this connection, it should be noted that in supine position, the $\Delta Pes/\Delta Pm$ values obtained during the Mueller maneuvers corresponded closely with those obtained with the "occlusion test". Hence, the low $\Delta Pes/\Delta Pm$ values obtained in supine position can not be attributed to problems in transmission of alveolar pressure to the mouth. Indeed, in normal individuals this transmission is very quick, the relevant time constant amounting to only a few milliseconds (Milic-Emili et al., 1981). Consistent with this, no appreciable phase lag between Pes and Pm was observed during the "occlusion tests". The small loop formation which was found in some instances can probably be attributed to cardiac artifacts. Indeed, the tendency of both the phase differences and the magnitude of the cardiac artifacts to increase in supine position supports the notion that cardiac artifacts were responsible for the observed loop formation. The correlation coefficient between the magnitude of cardiogenic oscillations and phase difference between ΔPes and ΔPm in different body positions was 0.96 ($p < 0.05$).

Results of $\Delta Pes/\Delta Pm$ obtained with the balloon positioned at three different levels in the esophagus showed no system-

[1] On theoretical grounds (Pimmel et al., 1979; Asher et al., 1982), because of decompression of alveolar gas during the "occlusion test", the $\Delta Pes/\Delta Pm$ ratio should be slightly greater than one (about 1.02).

atic changes (Figure IV.2), except in supine position where the $\Delta Pes/\Delta Pm$ ratio tended to increase as the balloon was moved towards the cardia. This suggests that in supine position there is a horizontal gradient in changes of pleural surface pressure, with the greater values towards the lung base. This is in agreement with Sybrecht et al. (1976) who, on the basis of indirect evidence obtained using ^{133}Xe, postulated that in supine subjects there may be an apex-to-base gradient of changes in pleural surface pressure, with the greater pressure swings at the lung base. The present results suggest that in left and right lateral positions such apex-to-base gradient is not present (Figure IV.2). This is in agreement with Kaneko et al. (1966) who found no difference in ventilation distribution along the horizontal axis of the lung in subjects studied in lateral positions.

The present results indicate that in some supine subjects the esophageal pressure measured with the balloon positioned conventionally does not reflect the presumed overall change in pleural surface pressure, as reflectead by Pm. With repositioning of the balloon at a different level, however, a locus can be found where $\Delta Pes/\Delta Pm$ ratio is close to unity, and hence measurements of lung mechanics based on esophageal pressure changes from this locus are presumably valid. In the other positions, the conventional balloon technique appears valid, at least in normal subjects. In this connection it should be noted that in some patients with severe airways obstruction this transmission of dynamic changes in alveolar pressure to the mouth may be impaired because of increased relevant time constant, i.e., the product of airways flow-resistance and upper airway compliance (Marazzini et al., 1978; Musciano et al., 1982). Accordingly, in such patients the Pes/ Pm ratio during the dynamic "occlusion test" should be greater than unity, while during the Mueller and Valsalva maneuvers there should be a better concordance between static values of Pes and ΔPm. Thus, in patients with obstructive lung disease such combined static and dynamic measurements should povide useful information concerning transmission of alveolar pressure to the mouth.

F. REFERENCES

1. Asher, M.I., A.L. Coates, J.M. Collinge, and J. Milic-Emili. Measurements of pleural pressure in neonates. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 52:491-494, 1982.

2. Beardsmore, C.S., P. Helms, J. Stocks, D.J. Hatch, and M. Silverman. Improved esophageal balloon technique for use in infants. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 49:735-742, 1980.

3. Goldman, H.L., and M.R. Becklake. Respiratory function tests: Normal values of mean altitudes and the prediction of normal results. Am. Rev. Tuberc. 79:457-467, 1959.

4. Jaeger, M.J., and Bouhuys, A. Loop formation in pressure vs flow diagrams obtained by body plethysmographic techniques. Progr. Resp. Res. 4:116-130, 1969.

5. Kaneko, K., J. Milic-Emili, M.B. Dolovich, A. Dawson, and D.V. Bates. Ventilation and perfusion as a function of body position. J. Appl. Physiol. 21:767-777, 1966.

6. Marazzini, L., R. Canestri, D. Gori, L. Gatti, and E. Longhini. Difference between mouth and esophageal occlusion pressure during CO_2 rebreathing in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 118:1027-1033, 1978.

7. Milic-Emili, J., J. Mead, and J.M. Turner. Topography of esophageal pressure as a function of posture in man. J. Appl. Physiol., 19:212-216, 1964.

8. Milic-Emili, J., W.A. Whitelaw, and A. Grassino. Regulation of breathing. In: Lung Biology in Health and Disease. T. Hornbein, ed. Part II. New York, Marcel Dekker, Inc., p. 675-743, 1981.

9. Milner, A.D., R.A. Saunders, and J.E. Hopkin. Relationship of intra-esophageal pressure to mouth pressure during the measurement of thoracic gas volume in the newborn. Biol. Neonate 33:314-319, 1978.

10. Murciano, D., M. Aubier, S. Bussi, J.P. Derenne, R. Pariente, and J. Milic-Emili. Comparison of esophageal, tracheal, and mouth occlusion pressure in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am. Rev. Respir. Dis. 126:837-841, 1982.

11. Pimmel, R.L., and E.L. Eldridge. Difference between occluded airway pressure and generated muscle pressure. Ann. Biomed. Eng. 7:67-72, 1979.

11. Sybrecht, G., L. Landau, B.G. Murphy, L.A. Engel, R.R. Martin, and P.T. Macklem. Influence of posture on flow dependence of distribution of inhaled ^{133}Xe boli. J. Appl. Physiol. 41:489-496, 1976.

CHAPTER V

LUNG MECHANICS IN SITTING AND HORIZONTAL BODY POSITIONS

ABSTRACT

Lung compliance, pulmonary flow-resistance, and expiratory reserve volume (ERV) were measured in ten healthy young adults in sitting, supine, and lateral positions. Average lung compliance was 0.21 in sitting, 0.19 in lateral and 0.16 $l.cm\ H_2O^{-1}$ in supine positions. The change was significant ($p<0.01$) between sitting and supine position. Flow-resistance increased from 1.78 in sitting to 2.5 $cm\ H_2O.l^{-1}.s$ ($p<0.001$) in lateral positions, and did not increase further in the supine posture in spite of a 35 percent decrease in ERV ($p<0.001$). Since it is known that lower airways resistance increases with decreasing lung volume, the lack of change in flow-resistance when shifting from lateral to supine posture suggests that upper airways flow-resistance (larynx and oropharynx) is greater in the lateral decubitus than in the supine positions. The decrease of lung compliance in horizontal postures probably reflects increased pulmonary blood volume and small airways closure.

A. INTRODUCTION

Several studies (Attinger et al., 1956; Cherniack et al., 1957; Lim and Luft, 1959; [illegible]anathy et al., 1959; Linderholm, 1963; Sasaki et al., 1977) have shown that when shifting from the sitting to supine position, dynamic lung compliance (Cdyn,l) decreases while pulmonary flow-resistance (Rl) increases. This has been attributed mainly to the reduction in functional residual capacity (FRC) in the supine posture, although the lung mechanics data obtained in this position have been questioned on the grounds that in supine subjects the esophageal balloon technique may not be valid (Mead and Gaensler, 1959). However, as it was shown in Chapter IV by using the "occlusion test", reliable measurements of changes in pleural pressure can be obtained with the esophageal balloon technique not only in the upright but also in the horizontal postures (supine and lateral). The occlusion test consists in comparing the changes in esophageal (ΔPes) and mouth (ΔPm) pressure during spontaneous inspiratory effects made against a closed airway. A concordance between ΔPes and ΔPm indicates that the esophageal pressure is a valid measure of changes in pleural pressure.

In the present investigation we have measured the static and dynamic lung compliance, Cdyn,l togetner with pulmonary flow-resistance in ten normal subjects in the sitting, right and left lateral, and supine positions. In all instances the measurements of esophageal pressure were validated using the occlusion test.

B. MATERIALS AND METHODS

The study was performed on ten healthy male volunteers with a mean age (±SD) of 31.4±3.5 years, mean vital capacity of 5.34±0.38 l (105±9.5 percent predicted), and mean FEV_1 of 4.28±0.41 l (106±11.4 percent predicted) (Goldman and Becklake, 1959). Measurements were made in the sitting, supine and right and left lateral positions, in a random sequence. A pillow was used when subjects were tested in lateral postures to keep the head horizontal.

Esophageal pressure (Pes) was measured with the esophageal balloon technique previously described (Milic-Emili et al., 1964). The balloon was 5 cm long and 3.5 cm across. It was made of 0.06 mm thick Latex (Young Rubber Corp.) and was sealed over one end of a 240 PE polyethylene catheter. The catheter was 94 cm long with an inner diameter of 1.4 mm. The balloon-catheter system had a pressure-volume curve flat over a volume range between 0.2 and 5 ml. It was connected to a port of a Sanborn 267 differential pressure transducer. The other port was connected to the mouthpiece via a similar catheter. The frequency response of the system was flat up to 10 Hz.

Flow ($\dot{V}$) was measured with a No. 2 Fleisch pneumotachograph and a Validyne MP 45 pressure transducer. The signal of the transducer was integrated to obtain volume. The pneumotachograph-mouthpiece assembly had a resistance of 0.64 $cmH_2O.l^{-1}.s$ for flows up to 1 $l.s^{-1}$. All signals were amplified and recorded on a Hewlett-Packard 7700 6-channel recorder.

Procedure

The balloon was introduced via the nose into the stomach, withdrawn a further 10 cm, and inflated with 0.5 ml of air. The validity of the technique as a measure of pleural pressure was tested in all positions with the "occlusion test" previously described (see Chapter IV). In sitting and lateral positions, the ratio of Pes to Pm during this test was in all instances close to unity. The average value of $\Delta Pes/\Delta Pm$ (±SE) for the ten subjects amounted to 1.04±0.01 in sitting position, 1.02±0.01 right lateral, and 0.98±0.02 left lateral. In the supine position, the $\Delta Pes/\Delta Pm$ ratio was close to unity in eight subjects, but in the other two it amounted to only 0.61 and 0.77, respectively. In these two individuals the balloon was repositioned in the esophagus so that acceptable $\Delta Pes/\Delta Pm$ ratios were obtained (0.87 and 1.09, respectively). With repositioning of the esophageal balloon in these two individuals, the average (±SE) $\Delta Pes/\Delta Pm$ ratio in the ten subjects amounted to 0.96±0.03.

For measurement of static lung compliance (Cst,l) the subject was asked to inspire approximately 1 l of air from FRC and hold his breath with glottis open for about five seconds. $C_{st,l}$ was computed as a mean of three measurements in each position. Afterward, five minutes of quiet breathing was recorded for measurement of dynamic lung compliance and pulmonary flow-resistance. $C_{dyn,l}$ was computed by dividing the volume changes between points of zero flow by the corresponding changes of transpulmonary pressure. The average pulmonary flow resistance i.e., the ratio of pressure difference to the sum of inspiratory and expiratory flow rates of isovolume points (mid-tidal volume) was calculated after the method of Frank et al. (1957). Values of $C_{dyn,l}$ and R_l were derived from at least ten breaths in each position. The time constant of lungs, l, was computed as the product of R_l and $C_{dyn,l}$. Three vital capacities (VC) and expiratory reserve volumes (ERV) were measured in each position.

Significance was determined by analysis of variance.

C. RESULTS

Average values (±SE) of VC and ERV in the ten subjects in four body positions are presented in Table V.1. VC decreased by about 5 percent from sitting to lateral positions, the difference being statistically significant ($p<0.05$). There was no significant difference between right and left lateral or between the sitting and supine positions.

The ERV decreased by about 22 percent when moving from sitting to lateral positions and by 50 percent from sitting to supine. These differences were statistically significant ($p<0.001$). Equally significant ($p<0.001$) were the observed differences of ERV between lateral and supine position amounting to about 35 percent, whereas values obtained in right and left lateral positions were very close.

Lung Compliance, Flow Resistance, and Time Constant

Average values ($\pm$SE) of $C_{st,l}$, $C_{dyn,l}$, and R_l are summarized in Table V.1. $C_{st,l}$ and $C_{dyn,l}$ were essentially the same in each position studied. Both decreased from sitting to supine position by 24 percent ($p<0.01$). Equally significant ($p<0.01$) were the differences between values of compliances obtained in the supine and both lateral positions. There was no significant difference between sitting and lateral or between the two lateral positions, although there was a tendency for compliance to decrease when shifting from sitting to the right or left lateral posture.

R_l increased by 40 percent when moving from sitting to either the lateral or supine position. These differences were statistically significant ($p<0.001$). There were no differences between the two lateral or between the supine and both lateral positions.

Figure V.1 depicts changes of $C_{dyn,l}$ and R_l as a function of ERV in four body positions. There was an approximately

TABLE V.1

Average values (±SE) of lung volumes and lung mechanics of ten subjects in four body positions

Measurement	Sitting	R Lateral	L Lateral	Supine
VC (l)	5.24 ±0.12	4.96 ±0.14	4.97 ±0.11	5.14 ±0.13
ERV (l)	1.84 ±0.11	1.45 ±0.12	1.41 ±0.12	0.92 ±0.10
Cst,l ($l.cmH_2O^{-1}$)	0.21 ±0.02	0.19 ±0.02	0.21 ±0.02	0.16 ±0.01
Cdyn,l ($l.cmH_2O^{-1}$)	0.21 ±0.02	0.19 ±0.02	0.19 ±0.02	0.16 ±0.01
Rl ($cmH_2O.l^{-1}.s$)	1.78 ±0.13	2.52 ±0.25	2.48 ±0.20	2.50 ±0.20
τl (s)	0.39 0.04	0.49 0.08	0.47 0.06	0.40 0.04

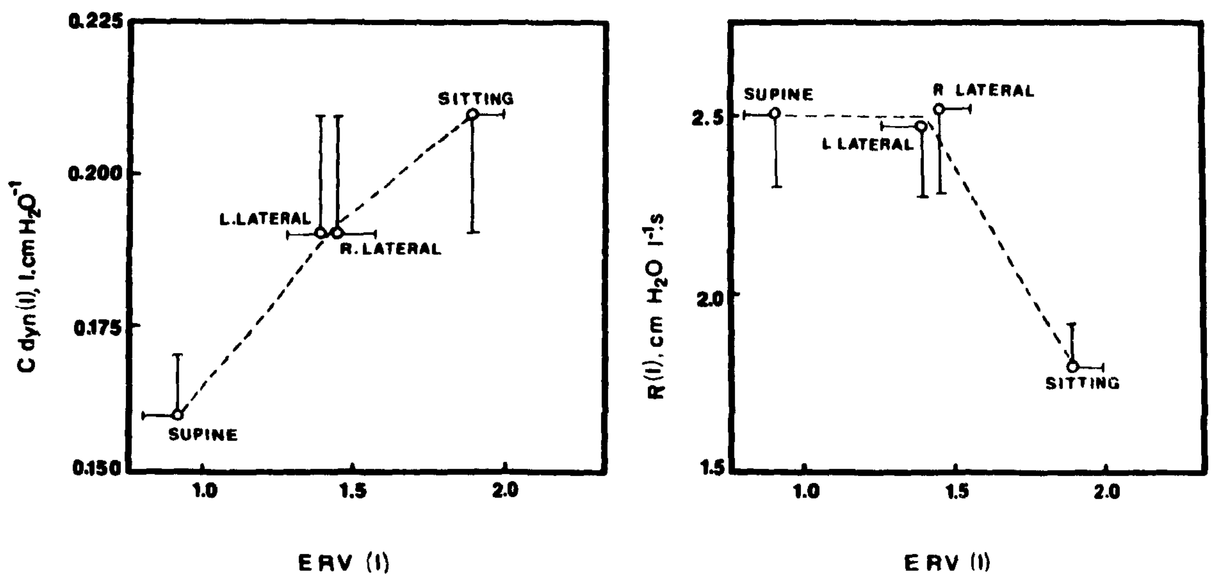

Figure V.1: Mean values (±SE) of Cdyn,l and Rl as a function of ERV in ten subjects in four body positions.

linear relationship between Cdyn,l, and ERV, whereas Rl was essentially the same in supine and lateral positions, although ERV differed significantly.

The pulmonary time constant was approximately the same in the sitting and supine positions, reflecting nearly proportionate decrease in Cdyn,l, and increase in Rl. On the other hand, was significantly higher in the lateral position relative to both the sitting and supine posture ($p<0.01$).

D. DISCUSSION

In agreement with previous (Moreno and Lyons 1961; Milic-Emili et al, 1964; Milic-Emili et al, 1964) we found a small reduction of VC in the horizontal postures, which can probably be attributed to increased thoracic blood volume (Sasaki et al, 1977).

Also in agreement with previous reports, (Moreno and Lyons, 1961; Milic-Emili et al, 1964; Milic-Emili et al, 1964; Sasaki et al, 1977), the ERV decreased progressively when shifting to lateral and then to supine position. This reflects mainly gravitational effects, which cause a cephalad displacement of the horizontal postures, although changes in thoracic blood volume also contribute to this reduction in ERV (Sasaki et al, 1977).

Both static and dynamic lung compliance decreased in the supine position, in line with previous reports (Attinger et al., 1956; Cherniack et al., 1957; Lim and Luft, 1959; Granath et al., 1959; Linderholm, 1963; Sasaki et al., 1977) (Table V.2), while in the lateral positions intermediate values were obtained. The latter is in agreement with Linderhölm (1963). The reduction in lung compliance in the horizontal postures can probably be attributed to: (1) increased pulmonary blood volume, which decreases the recoil of the lung at low volumes (Agostoni and Mead, 1964), and (2) to small airways closure (Sutherland et al., 1968). Consistent with our ERV data, the FRC is smaller in the supine than in the lateral positions (Agostoni and Mead, 1964), a greater reduction of lung compliance would be expected in the former position due to both mechanisms (1) and (2).

While the mean values of static and dynamic lung compliance in the four body positions studied were related approximately linearly with the corresponding ERV, this was not the case of Rl (Figure V.1). Indeed, pulmonary flow-resistance increased about 40 percent when shifting from sitting to the lateral positions, and no further change was found when shifting from the lateral positions to the supine posture. This is contrary to the results of Linderhölm (1963), who in four subjects found that Rl averaged 1.64 sitting, 2.21 right lateral, and 3.07 $cmH_2O.l^{-1}.s$ supine. These results, however, were obtained during panting. Furthermore, he used a 15 cm long esophageal balloon whose upper end may have extended into

TABLE V.2

Summary of literature on Cdyn,l and Rl measurements, sitting and supine

Reference	No. of Subjects	Cdyn,l ($l.cmH_2O^{-1}$)		Rl($l.cmH_2O^{-1}$).s)	
		Sitting	Supine	Sitting	Supine
Attinger et al (1956)	8	0.195	0.137	2.40	3.44
Cherniack et al* (1956)	5	0.185	0.118	1.90	2.95
Granath et al (1959)	6	0.190	0.120	1.40	2.00
Linderholm (1963)	6	0.230	0.200	1.44	2.17
Lim and Luft (1959)	6	0.190	0.138	--	--
Sasaki et al**	6	0.155	0.122	--	--
Present results	10	0.210	0.160	1.78	2.50

*Data of pulmonary flow resistance obtained by averaging the inspiratory and expiratory values, which are given separately.
**Values obtained from a graph, since no table is provided in the publication.

the upper part of the esophagus, where the esophageal pressure is not reliable (Milic-Emili et al., 1964).

Since lower pulmonary flow-resistance is known to increase progressively with decreasing lung volume (Vincent et al., 1970), present finding of the same value of Rl in supine and lateral positions in spite of substantial differences in ERV suggests that other factors must be involved in determining the postural changes of Rl. Thus, it is likely that posture is associated with changes in upper airways flow-resistance. Whatever the nature of the postural changes in Rl (eg. changes in geometry of the upper airways and/or aperture of the glottis) and in Cst,l the present results probably provide the first reliable measurements of these variables in the horizontal positions. Furthermore, we also show that the pulmonary time constant does not change between the sitting and supine positions, and increases only slightly in lateral postures. It is also of interest that although the small airways closure in dependent lung zones was probably present in at least some of our subjects when supine (Leblanc et al., 1970), Cst,l and Cdyn,l did not differ in this position. This indicates absence of frequency-dependence of lung compliance, at least up to eupneic respiratory frequencies. The same was true in all the other positions studied.

E. REFERENCES

1. Agostoni, E., and J. Mead. Statics of the respiratory system. In: Respiration. Handbook of Physiology. Washington, D.C.: Am. Physiol. Soc., Sect. 3, Vol. I, Chapt. 13, p. 387-409, 1964.

2. Attinger, E.O., R.D. Monroe, and M.C. Segal. The mechanics of breathing in different body positions: I. In normal subjects. J. Clin. Invest. 35:904-911, 1956.

3. Beardsmore, C.S., P. Helms, J. Stocks, D.J. Hatch, and M. Silverman. Improved esophageal balloon technique for use in infants. J. Appl. Physiol. 49:735-742. 1980.

4. Blair, E., and J.B. Hickam. The effect of change in body position on lung volume and intrapulmonary gas mixing in normal subjects. J. Clin. Invest. 34:383-389, 1955.

5. Cherniack, R.M., T.E. Cuddy, and J.B. Armstrong. Significance of pulmonary elastic and viscous resistance in orthopnea. Circulation 15:858-864, 1957.

6. Frank, N.R., J. Mead, and B.J. Ferris. The mechanical behavior of the lungs in healthy elderly persons. J. Clin. Invest. 36:1680-1687, 1957.

7. Goldman, H.L., and M.R. Becklake. Respiratory function tests: Normal values of mean altitudes and the prediction of normal results. Am. Rev. Tuber. 79:457-467, 1959.

8. Granath, A., E. Horie, and H. Linderhölm. Compliance and resistance of the lungs in the sitting and supine positions at rest and during work. Scand. J. Clin. Lab. Invest. 11L226-234, 1959.

9. Leblanc, P., F. Ruff, and J. Milic-Emili. Effects of age and body position on "airway closure" in man. J. Appl. Physiol. 28:448-451, 1970.

10. Lim, T.P.K., and U.C. Luft. Alterations in lung compliance and functional residual capacity with posture. J. Appl. Physiol. 14:164-166, 1959.

11. Linderhölm, H. Lung mechanics in sitting and horizontal postures studied by body plethysmographic methods. Am. J. Physiol. 204:85-91, 1963.

12. Mead, J., and E.A. Gaensler. Esophageal and pleural pressures in man, upright and supine. J. Appl. Physiol. 14:81-83, 1959.

13. Milic-Emili, J., J. Mead, and J.M. Turner. Topography of esophageal pressure as a function of posture in man. J. Appl. Physiol. 19;212-216, 1964.

14. Milic-Emili, J., J. Mead, J.M. Turner, and E.M. Glauser. Improved technique for estimating pleural pressure from esophageal balloons. J. Appl. Physiol. 19:207-211, 1964.

15. Moreno, F., and H.A. Lyons. Effect of body posture on lung volumes. J. Appl. Physiol. 16:27-29, 1961.

16. Sasaki, H., W. Hida, and T. Takishima. Influence of body position on dynamic compliance in young subjects. J. Appl. Physiol. 42:706-710, 1977.

17. Svanberg, L. Influence of posture on the lung volumes, ventilation and circulation of normals. Scand. J. Clin. Lab. Invest. 25:1-195, 1957.

18. Sutherland, P.W., T. Katsura, and J. Milic-Emili. Previous volume history of the lung and regional distribution of gas. J. Appl. Physiol. 25:566-574, 1968.

19. Vincent, M.J., R. Knudson, D.E. Leith, P.T. Macklem, and J. Mead. Factors influencing pulmonary resistance. J. Appl. Physiol. 29:236-243, 1970.

CHAPTER VI

MEASUREMENT OF PLEURAL PRESSURE WITH ESOPHAGEAL BALLOON IN ANESTHETIZED HUMANS

ABSTRACT

Simultaneous measurement of tracheal and esophageal pressures during occluded inspiratory efforts (occlusion test) was used to assess the validity of the esophageal balloon technique in anesthetized supine subjects. Ten ASA 1 patients[1] undergoing general anesthesia (halothane ~1 MAC, 70% N_2O-30% for minor surgery were studied. Esophageal pressure (Pes) was measured using a 5 cm long balloon and was plotted against tracheal pressure (Ptr). Occlusion tests were performed at end expiration with the balloon top positioned 5, 10, 15, and 20 cm above the cardia. The results show that with the balloon positioned at the classical level of 10 cm above the cardia, the difference between Pes and Ptr did not exceed 8% in seven of ten subjects. In the remaining three, however, the difference between Pes and Ptr ranged between +20% and -40%. By repositioning the balloon to 5 or 15 cm above the cardia, a locus was found in all subjects where the difference is less than 10%. We conclude that the esophageal balloon technique can be used in anesthetized supine subjects to give reliable measurements of changes in pleural pressure, provided that it is validated with the occlusion test.

A. INTRODUCTION

The esophageal balloon technique is used widely in the measurement of lung mechanics (Milic-Emili et al., 1964). In the supine position, however, the validity of the pressure measurements from the balloon has been questioned (Knowles et al., 1959; Mead and Gaensler, 1959). Static inspiratory and expiratory efforts with an open glottis and a closed external airway (Mueller and Valsava maneuvers) have been proposed to validate the technique (Milic-Emili et al., 1964; Macklem et al., 1974). Equal changes in esophageal (Pes) and in tracheal (Ptr) pressures during these maneuvers indicate that changes in esophageal pressures provide a valid estimate of changes in pleural surface pressure. This approach requires cooperation from the subject and cannot be applied in anesthetized subjects. An alternative is to compare Pes and Ptr during spontaneous respiratory efforts made against a closed external airway. This "occlusion test" has been used by Milner et al. (1978) and Beardsmore et al. (1980) in neonates. Asher et al. (1982) have used it to verify the accuracy of the esophageal water-filled catheter technique in neonates. The "occlusion test" in awake adults in different body positions (sitting, lateral, and supine) has been discussed previously in Chapter IV. It was found that in some supine subjects, repositioning of the esophageal balloon was necessary to obtain satisfactory Pes/ Ptr ratios during occluded inspiratory efforts.

During anesthesia, the esophageal balloon technique has been used by many authors (Howell and Peckett, 1957; Gold et al., 1966; Van Lith et al., 1967; Westbrook et al., 1973; Rehder et al., 1974), who have followed the conventional method of positioning the balloon (balloon top 10 cm above the cardia), but the validity of the technique in anesthetized supine subjects has not been assessed previously, except for Westbrook et al. (1973) and Rehder et al. (1974). In anesthetized, paralyzed subjects, they manually compressed the chest for detection of recording artifacts. They stated that Pes and Ptr were "rather similar", but did not provide quantitative data.

The purpose of this study was to test the accuracy of the conventional balloon technique in estimating pleural pressure in subjects anesthetized while in the supine position, using the occlusion test.

B. MATERIALS AND METHODS

Ten subjects undergoing general anesthesia for a variety of surgical procedures were studied. Their average age (±SD) was 33.7±12.7 yr and body surface area 1.7±0.15 m^2. All subjects were ASA 1. The study was approved by the hospital Ethics Committee, and informed consent was obtained from all individuals.

Esophageal pressure (Pes) was recorded using a 5 cm long balloon with a circumference of 3.2 cm. The balloon was sealed over one end of a polyethylene catheter (internal diameter 1.4 mm; length 94 cm) with several side holes within the balloon. The other end of the catheter was connected to a Validyne MP 45 differential pressure transducer. The volume-pressure curve of the balloon was flat within a range of volume between 0.2 and 5 ml. Using a similar catheter (but without balloon) and another Validyne MP 45 transducer, tracheal pressure (Ptr) was measured at the proximal end of the endotracheal tube. The Pes and Ptr systems were tested with a sinewave pressure generator and found to have a flat frequency response up to 10 Hz. Transpulmonary pressure (Ptp) was obtained by electronic subtraction of Pes from the Pt signal. Flow ($\dot{V}$) was measured with a Fleisch No. 2 pneumotachograph, connected to a Validyne MP 45 (± 2 cm H_2O) differential pressure transducer, and volume (V) was obtained by integrating the flow signal (HP 8815A integrator). All signals were amplified (Hp 8805A amplifiers) and recorded on a Gould Brush 2600 6-channel recorder and on tape (HP 3968A tape recorder). Tracheal versus esophageal pressure was displayed on a Tektronix storage-oscilloscope (Tektronix LC-5) and photographs were taken using a Tektronix polaroid camera.

Procedure

Anesthesia was induced in all subjects with halothane in a mixture of 70% N_2O-30% O_2, and tracheal intubation was performed without the use of a muscle relaxant. Anesthesia was maintained with halothane ($\sim$1 MAC) and nitrous oxide and oxygen. The subjects breathed spontaneously throughout the experiment. The esophageal balloon was emptied of air and introduced transorally under direct vision into the esophagus. The balloon was filled with 0.5 ml air and passed into the stomach. The balloon then was withdrawn until a negative pressure deflection was recorded during inspiration. Subsequently, the balloon was withdrawn into the esophagus and positioned with the top 5 cm from the cardia. The balloon gas volume was checked at frequent intervals.

The "occlusion test" was performed by occluding the external airway at end expiration (functional residual capacity-FRC) and simultaneously recording the esophageal and tracheal pressure changes during the following two or three occluded inspiratory efforts. The records of Pes versus Ptr also were displayed on the storage oscilloscope and photographed, allowing on line measurement of the slope. The balloon then was withdrawn to 10, 15, and 20 cm from the cardia, and the occlusion tests were repeated.

Movements of the heart cause changes in Pes. The magnitude of this cardiac artifact was measured at each balloon position, and analysis of variance was applied to these data.

C. RESULTS

Figure VI.1 shows a tracing of an occlusion test. It can be seen that during the occluded inspiratory effort, apart from the cardiac artifact, Ptp remained nearly constant, indicating that the changes in esophageal pressure were close to the corresponding changes in Ptr, i.e. in this case the ΔPes/ΔPtr ratio was near to unity. A similar result also is shown in Figure VI.2, which is a tracing of ΔPes versus ΔPtr obtained on the oscilloscope during an occlusion test. It can be seen that the relationship is linear with the slope close to unity, the deviations from the line of identity representing cardiac artifacts. In each subject and at all balloon levels, the ΔPes versus ΔPtr relationship virtually was superimposed on a breath-by-breath basis. However, the ΔPes/ΔPtr ratio was not always close to unity, as indicated in Table VI.1, which summarized the results obtained in all ten subjects, at the four balloon positions studied.

Five subjects had their optimum ΔPes/ΔPtr ratio (0.98, 0.99, 0.96, 1.0, 1.0) when the balloon top was 5 cm from the cardia.

With the balloon 10 cm from the cardia, four individuals had their optimum ΔPes/ΔPtr ratios (0.96, 1.0, 1.0, 0.96), and three had acceptable ratios of 0.92, 1.07, and 0.95, respectively. The remaining three subjects had ΔPes/ΔPtr ratios far from the ideal (1.2, 0.6, 0.75).

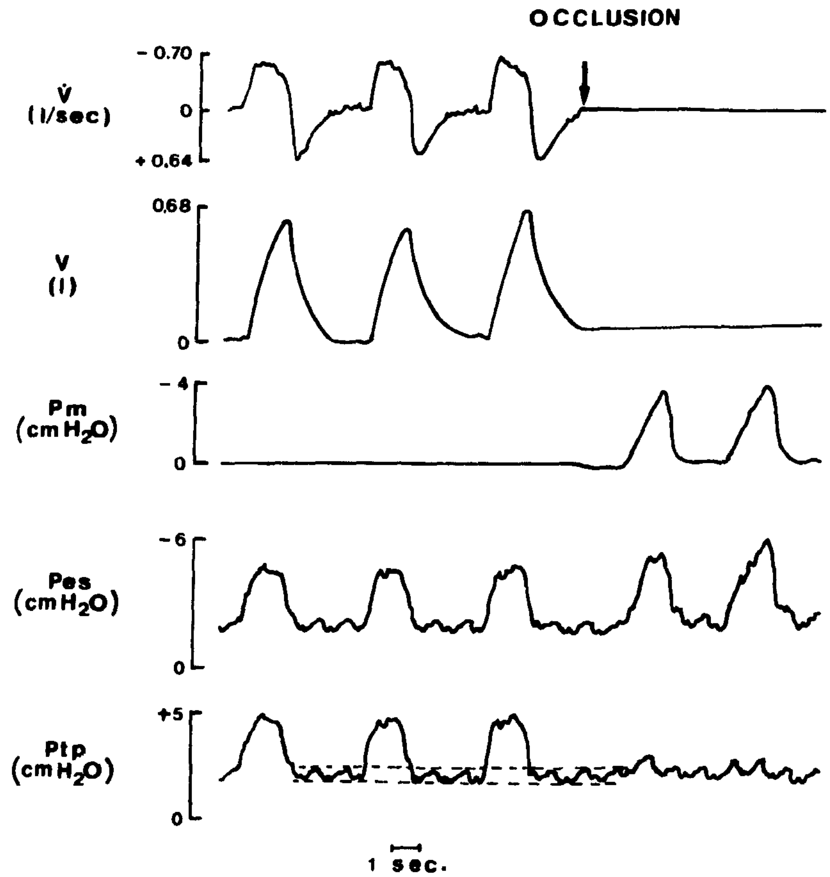

Figure VI.1: Represenative tracing of flow ($\dot{V}$), volume (V), tracheal (Ptr), esophageal (Pes), and transpulmonary (Ptp) pressures during an occlusion test. Dotted lines indicate variations of Ptp resulting from the cardiac artifact. Balloon level: 10 cm above cardia; Subject 2.

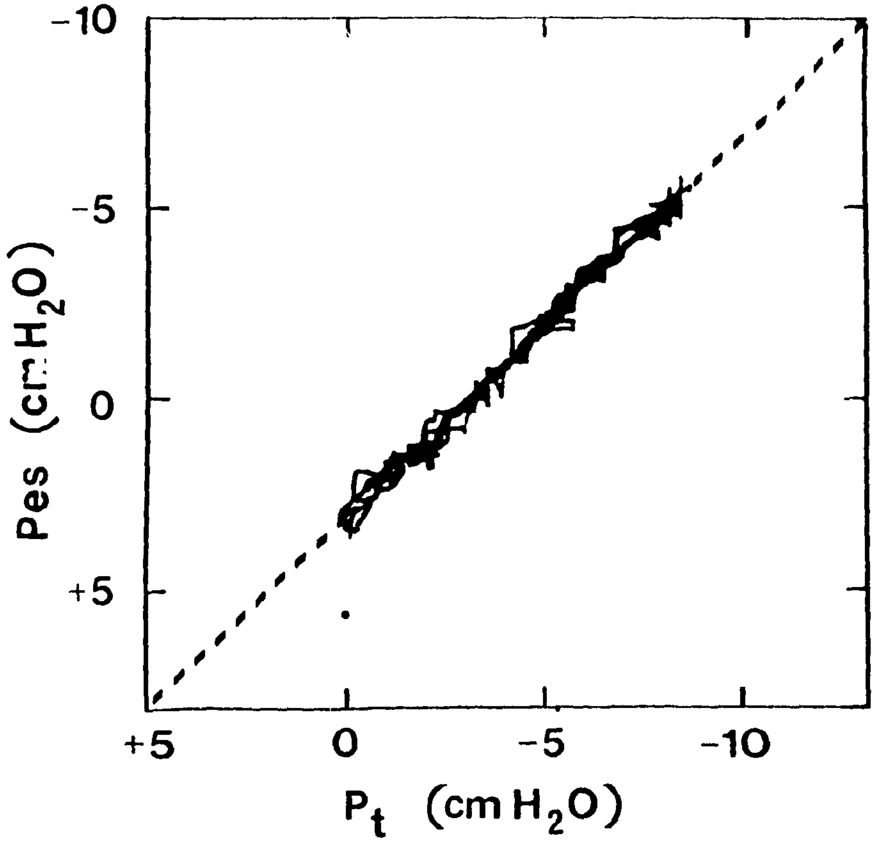

Figure VI.2: Tracing of esophageal (ΔPes) versus tracheal pressure (ΔPtr) during an occlusion test. Pes of the same magnitude as Pt and in phase with it. Deviations from the line of identity (broken line) result from cardiac artifacts. Balloon level: 10 cm above cardia; Subject 6.

TABLE VI.1

ΔPes/ΔPtr ratios for 10 supine anesthetized subjects at four balloon levels

Subject No.	Balloon Level (cm from the cardia)			
	5	10	15	20
1	0.73	0.92	1.00*	0.74
2	0.98*	1.07	0.94	0.55
3	0.99*	0.95	0.77	0.74
4	0.96*	0.96*	0.64	0.72
5	0.84	1.00*	0.84	0.36
6	0.70	1.00*	0.99	0.80
7	0.70	0.96*	0.60	0.50
8	1.00*	1.20	0.60	0.80
9	0.80	0.60	0.90*	0.80
10	1.00*	0.75	0.75	0.62
Mean ±SD	0.87 ±0.13	0.94 ±0.16	0.80 ±0.15	0.66 ±0.15

The mean and standard deviation (SD) of the ratio at each level is shown. The optimum for each subject is marked with an asterisk (*).

Only two subjects had their optimim $\Delta Pes/\Delta Ptr$ ratios at 15 cm from the cardia. One of these (Subject 1) also had an acceptable ratio at 10 cm from the cardia (0.92), while the other one (Subject 9) had an acceptable $\Delta Pes/\Delta Ptr$ ratio only at this balloon position.

No subject had an acceptable $\Delta Pes/\Delta Ptr$ ratio with the balloon 20 cm from the cardia.

Table VI.2 lists the magnitude of the cardiac artifact in all subjects at each balloon level. Statistical analysis showed that the cardiac artifact did not change significantly with balloon position, although individually there were substantial changes with balloon level.

D. DISCUSSION

Esophageal pressure generally is used as a measure of pleural pressure. The balloon top conventionally is positioned 10 cm from the cardia.

The measurement of $\Delta Pes/\Delta Ptr$ ratio during an occluded inspiratory effort allows the reliability of the esophageal balloon technique to be tested. During such a maneuver, the changes in pleural pressure should be identical to changes in tracheal pressure, apart from a negligible difference resulting from thoracic gas rarefication (Mead and Milic-Emili, 1964). If the esophageal pressure changes are close to those in tracheal pressure, then esophageal balloon measurements are a

TABLE VI.2

Changes in esophageal pressure (cmH_2O) due to cardiac artifact in 10 subjects at four balloon levels

Subject No.	Balloon Level (cm from the cardia)			
	5	10	15	20
1	2.0	1.0	1.0	2.0
2	4.0	1.0	4.0	3.0
3	3.5	7.0	5.0	1.7
4	1.0	3.0	3.0	5.0
5	2.2	1.0	2.5	2.0
6	3.0	1.0	2.0	2.0
7	2.0	3.0	3.5	2.0
8	3.0	4.0	3.0	2.0
9	4.7	3.5	3.5	3.0
10	3.0	5.5	3.0	1.0
Mean ±SD	2.8 ±1.1	3.0 ±2.1	3.1 ±1.1	2.2 ±0.7

valid measure of the changes in pleural surface pressure.

It has been found that in awake subjects reliable estimate of pleural pressure were obtained with an esophageal balloon (10 cm from the cardia) in the sitting and lateral positions, but in the supine position, two out of ten subjects had unacceptable $\Delta Pes/\Delta Ptr$ ratios. In these two subjects, however, they were able to obtain acceptable $\Delta Pes/\Delta Ptr$ ratios were obtained by repositioning the balloon in the esophagus.

The $\Delta Pes/\Delta Ptr$ ratio was measured in anesthetized supine subjects using the occlusion test with the balloon positioned 5, 10, 15, 20 cm from the cardia. Present results show that with the balloon conventionally positioned (10 cm from cardia), the difference between ΔPes and ΔPtr was less than 10% in most (seven out of ten) of the subjects. In the remaining three individuals, the $\Delta Pes/\Delta Ptr$ ratios were unacceptable. However, by repositioning the balloon, acceptable ratios were obtained also in these three subjects (i.e. the difference between ΔPes and ΔPtr was within 10%).

With the balloon optimally positioned in each subject, the average $\Delta Pes/\Delta Ptr$ ratio (±SD) amounted to 0.98(±0.03).

Measurement of the mechanical properties of the lungs may become problematic in the presence of large cardiac artifacts. In the subjects of the present study, the optimum balloon positions did not always correspond to the locus of minimum cardiac artifact. The same was true for the conventional balloon position (10 cm from the cardia). Indeed, in the latter position, the cardiac artifact ranged between 4 and 7 cm H_2O in three individuals. In all of these subjects, however, by repositioning the balloon, a smaller cardiac artifact could be obtained while maintaining an acceptable $\Delta Pes/\Delta Ptr$ ratio.

E. REFERENCES

1. Asher, M.J., L.A. Coates, J.M. Collinge , and J. Milic-Emili. Measurement of pleural pressure in neonate. J. Appl. Physiol. 52:491-494, 1982.

2. Beardsmore, C.S., P. Helms, J. Stocks, D.J. Hatch, and M. Silverman. Improved esophageal ballon technique for use in infants. J. Appl Physiol. 149:735-742, 1980.

3. Gold, M.I., Y.H. Han, and M. Helrich. Pulmonary mechanics during anesthesia: III. Influence of intermittent positive pressure and relation to blood gases. Anesth. Analg. 45:631-640, 1966.

4. Howell, J.B.L., and B.W. Peckett. Studies of the elastic properties of the thorax of supine anesthetized paralyzed human subjects. J. Appl. Physiol. 136:1-19, 1957.

5. Knowles, J.H., S.K. Hong, and H. Rahn. Possible errors using esophageal balloon in determination of pressure-volume characteristics of the lung and thoracic cage. J. Appl. Physiol. 14:525-530, 1959.

6. Mead, J., and E.A. Gaensler. Esophageal and pleural pressures in man, upright and supine. J. Appl. Physiol. 14:81-83, 1959.

7. Mead, J., and J. Milic-Emili. Theory and methodology in respiratory mechanics with glossary of symbols. In: Handbook of Physiology, Respiration Am. Physiol. Soc. Sect. 3, Vol. I, Chapt 1. pp. 363-376, 1964.

8. Macklem, P.T., D.E. Leith, and J. Mead. Procedures for Standardization Measurements of Lung Mechanics and Principles of Body Plethsmography. New York, National Heart Institute, Division of Lung Disease, 1974.

9. Milic-Emili, J., J. Mead, and J.M. Turner. Improved technique for estimating pressure from esophageal balloons. J. Appl. Physiol. 19:207-211, 1964.

10. Milner, A.D., R.A. Saunders, and J.E. Hopkin. Relationship of intra-esophageal pressure to mouth pressure during measurements of thoracic gas volume in the newborn. Biol. Neonate 33:314-319, 1978.

11. Rehder, K., J.E. Mallow, E.E. Fibuch, D.R. Krabill, and A.D. Sessler. Effects of isoflurane anesthesia and muscle paralysis on respiratory mechanics in normal man. Anesthesiology 41:477-485, 1974.

12. Van Lith, P., F.M. Johnson, and J.T. Sharp. Respiratory elastances in relaxed and paralyzed states in normal and abnormal men. J. Appl. Physiol. 23:475-486, 1967.

13. Westbrook, P.R., S.E. Stubbs, A.D. Sessler, K. Rehder, and R.E. Hyatt. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J. Appl. Physiol. 34:81-86, 1973.

CHAPTER VII

PARTITIONING OF RESPIRATIORY MECHANICS IN HALOTHANE ANESTHETIZED HUMANS

ABSTRACT

In five spontaneously breathing anesthetized subjects (halothane ~1MAC; N_2O:70%; O_2:30%), the elastance (Ers) and flow-resistance (Rrs) of the total respiratory system were partitioned into the lung and chest wall components. Ers averaged (±SD) 23.0±4.9 cm $H_2O.l^{-1}$, while the corresponding values of pulmonary (El) and chest wall (Ew) elastance were 14.3±3.2 and 8.7±3.0 cm $H_2O.l^{-1}$, respectively. Intrinsic Rrs (upper airways excluded) averaged 2.3±0.2 cm $H_2O.l^{-1}.s$, the corresponding values for pulmonary (Rl) and chest wall (Rw) flow-resistance amounting to 0.8±0.4 and 1.5±0.5 cm $H_2O.l^{-1}.s$, respectively. Ers was increased relative to normal values in awake state, mainly reflecting increased El. Rw was slightly higher than previous estimates on awake subjects (0.5-1.0 cm $H_2O.l^{-1}.s$). Rl was relatively low, reflecting the fact that the subjects had received atropine (0.3-0.6 mg) and were breathing N_2O. This is the first study in which both respiratory elastic and flow-resistive properties have been partitioned in anesthetized humans.

A. INTRODUCTION

There is ample evidence indicating that anesthesia in general results in increased elastance of the total respiratory system. Apart from a few studies (Van Lith et al., 1967; Westbrook et al., 1973; Rehder et al., 1974; Grimby et al., 1975), however, total respiratory elastance has not been partitioned into lung and chest wall components, whereas partitioning of the flow-resistive properties of the respiratory system has not yet been performed in anesthetized humans. Furthermore, the feasibility of such partitioning has been questioned in the past on the grounds that in supine position the esophageal balloon technique may not be valid. As it was shown in supine subjects, both awake (Chapter IV) and anesthetized (Chapter VI), the esophageal balloon technique can be validated using the "occlusion test".

In the present study the esophageal balloon technique was used to determine the elastic and flow-resistive properties of the total respiratory system, lung and chest wall in subjects anesthetized with halothane. In addition, the mechanical work of breathing was measured in anesthetized humans.

B. MATERIALS AND METHODS

Five subjects undergoing general anesthesia for minor plastic or orthopedic surgery were studied. None had a history or clinical evidence of cardiopulmonary disease. Their anthropometric data are given in Table VII.1. The research was approved by our institutional Ethics Committee and informed constent was obtained from all subjects.

Flow ($\dot{V}$) was recorded with a Fleisch No. 2 pneumotachograph connected to a Validyne MP 45 differential pressure transducer. The flow calibration was made with the gas mixture used during anesthesia. Volume (V) was obtained by integration of the flow signal (HP 8815 A Integrator). Esophageal pressure (Pes) was recorded using a 5 cm long balloon with circumferences of 3.2 cm. The balloon was made of latex (0.06 thick) sealed over the end of a polyethylene catheter (i.d.: 1.4 mm; length: 94 cm) with several holes within the balloon. The other end of the catheter was connected to a Validyne MP 45-2 differential pressure transducer. The volume-pressure curve of the balloon was flat within a range of volume between 0.2 and 5 ml. All measurements of Pes were made with balloon volume of 0.5 ml. Using a similar catheter and another Validyne MP 45-2 differential pressure transducer, the airway opening (tracheal) pressure (Ptr) was measured at the proximal end of the endotracheal tube. The Pes and Ptr systems were tested with a sinewave generator and found to be flat up to at least 10 Hz. Transpulmonary pressure (Ptp) was obtained by electronic subtraction of Pes from the Ptr signal. End tidal CO_2 and halothane concentrations were monitored by a Beckman LB2 infrared analyzer. All signals were amplified (HP 8805 A amplifier)

TABLE VII.1

Physical characteristics, balloon position and $\Delta Pes/\Delta Ptr$ ratio obtained during "occlusion tests" in five anesthetized subjects.

Subjects	Sex	Age (yrs)	Height (cm)	Weight (kg)	Balloon Level (cm above cardial)	$\Delta Pes/\Delta Ptr$
1	F	49	157	58.1	10	0.99
2	F	22	170	63.5	5	0.99
3	F	42	155	59.9	10	1.08
4	M	50	173	67.9	10	1.00
5	F	42	169	83.1	10	0.98
Mean		40.8	164.6	67.3		1.00
±SD		±11.1	±8.1	±11.7		±0.05

and recorded on a Gould Brush 2600 six channel recorder and on tape (HP 3968 A tape recorder). Ptr vs. Pes pressure was displayed on a storage-oscilloscope (Tektronix LC-5) and photographs were taken using a Tektronix polaroid camera. A three way tap was used to occlude the airway opening. Volume-flow (V-$\dot{V}$) and volume-transpulmonary pressure curves were obtained on an X-Y plotter (HP 7046 A) by playing back at slow speed the signals stored on magnetic tape. The equipment dead space was 70 ml (endotracheal tube not included); the flow resistance of the tap and the pneumotachograph amounted to 0.4 cm $H_2O.l^{-1}.s$ and was linear for flow rates up to 3 $l.s.^{-1}$.

All patients were intubated with a Portex 8.5 cuffed endotracheal tube. The pressure-flow curve of the tube was curvilinear, fitting Rohrer's equation: $P = K_1\dot{V} + K_2\dot{V}^2$, with K_1 = 1.0 cm $H_2O.l^{-1}.s$ and K_2 = 7.8 cm $H_2O.l^{-2}.s^2$ for the gas mixture used during anesthesia (70% N_2O-30% O_2) as discribed in Chapter II.

Procedure and data analysis.

All measurements were performed prior to surgery. Patients were premedicated with atropine (0.3 - 0.6 mg i.m.) and meperidine (Demerol 1 mg/kg) 45 minutes prior to anesthesia. Anesthesia was induced with thiopentone (4-6 mg/kg), and succinylcholine (1.5 mg/kg) was given to facilitate intubation. Anesthesia was maintained with halothane (1 MAC) in nitrous oxide (70%) and oxygen (30%).

The esophageal balloon was introduced transorally under direct vision into the esophagus. "Occlusion tests" were performed with the balloon top positioned 5, 10 and 15 cm above the cardia. The "occlusion test" as described in Chapters IV and VI, consists of occluding the external airway at end-expiration and recording on the oscilloscope the simultaneous changes of Pes and Ptr during the ensuing spontaneous inspiratory efforts. The ratio of ΔPes/ΔPtr, is an index of the accuracy of pleural pressure measurements. The balloon was positioned at a point where ΔPes/ΔPtr ratio was closest to unity (Table VII.1). In the five subjects, the ratio ranged between 0.95 and 1.08, indicating that the measurement of Pes was a satisfactory index of the changes in pleural surface pressure, according to Chapters IV and VI.

All measurements of respiratory mechanics were made at least 20 minutes after the subjects had established a steady spontaneous breathing pattern, to allow for recovery from the effects of succinylcholine (Katz and Ryan, 1969).

The procedure for obtaining the passive mechanical properties of the total respiratory system has been described in detail in Chapter II. Briefly, the airway opening was occluded at end inspiration. After a plateau in Ptr was achieved, the occlusion was released to obtain a relaxed expiration. The passive elastance of the total respiratory system (Ers) was computed by dividing the Ptr obtained after relaxation of the respiratory muscles during occlusion at end expiration (i.e., the plateau Ptr pressure) by the corresponding tidal volume (V_T). The lung (El) and chest wall (Ew) static elastances were computed by dividing, respectively, ΔPtp and ΔPes (measured under the same relaxation conditions described above) by V_T.

The flow-resistive properties of the total respiratory system (including equipment and endotracheal tube) were determined by analysis of the $\dot{V}$-V curves obtained during relaxed inspiration, as previously described in detail (Chapter II). By subtracting the flow-resistance of the equipment and endotracheal tube, the <u>intrinsic</u> flow-resistances (Rrs) of the respiratory system (upper airways not included) was obtained. The above measurements of elastance and flow-resistance were repeated several times.

The pulmonary flow-resistance, including endotracheal tube, was obtained from measurements of Ptp, $\dot{V}$ and V during spontaneous breaths using the iso-volume method of Frank et al. (1957). By subtracting the flow-resistive pressure due to the endotracheal tube, the intrinsic pulmonary flow-resistance (Rl) was obtained.[1] During the unoccluded inspirations we also determined the dynamic lung elastance (Edyn,l). This was obtained by dividing changes in Ptp at points of zero flow by the corresponding changes in volume. Twenty breaths were averaged per subject in order to minimize errors in measurement of Ptp due to cardiac artifact.

[1] In such computations, the total resistive pressure drop due to the endotracheal tube was obtained by determining separately its inspiratory and expiratory components. The inspiratory component was calculated from the pressure-flow relationship of the tube ($P = 1.0\dot{V} \quad 7.8\dot{V}^2$) using the pertinent inspiratory flow while the expiratory pressure component was similarly derived using the pertinent expiratory flow.

Inspiratory resistive work per breath (Wres) was obtained from plots of volume vs. transpulmonary pressure as described previously (Milic-Emili and Tyler, 1963). This included work done in overcoming the pulmonary flow-resistance and that of the endotracheal tube. The inspiratory elastic work per breath (Wel) was computed according to the following equation: $Wel = 0.5\ (Edyn,l + Ew) \times V_T^2$. By adding Wres and Wel, total work per breath (Wtot) was obtained. Inspiratory work per minute ($\dot{W}tot$) was obtained by multiplying work per breath by respiratory frequency. For measurement of work of breathing five breaths were analyzed per subject. The measurements of resistive and total mechanical work of breathing did not include the resistive work done on the chest wall. Minute ventilation ($\dot{V}_E$) and breathing pattern were also determined as average values of the same five breaths used for measurements of work. In this connection it should be noted that there was little breath-by-breath variability in all of the subjects.

C. RESULTS

The values of static elastances of the total respiratory system, lung and chest wall of the five anesthetized subjects are given in Table VII.2. Static El averaged about 62% of Ers. Dynamic lung elastance averaged 15.5 cm $H_2O.l^{-1} \pm 3.7$ (SD), and was slightly higher than static El ($p < 0.05$). All elastance values were highest in subject 5 who was moderately overweight.

TABLE VII.2

Values of static elastances and flow-resistances of total respiratory system, lung and chest wall of five anesthetized subjects.

Subject	Ers $(cm_2\ HO.l^{-1})$	El $(cmH_2O.l^{-1})$	Ew $(cmH_2O.l^{-1})$	Rrs $(cmH_2O.l^{-1}.s)$	Rl $(cmH_2O.l^{-1}.s)$	Rw $(cmH_2O.l.^{-1}s)$
1	20.6	10.9	9.7	2.1	1.4	0.7
2	19.0	14.0	5.0	2.6	1.0	1.6
3	23.9	17.0	6.9	2.5	0.5	2.0
4	20.4	11.6	8.8	2.1	0.5	1.6
5	31.2	18.2	13.0	2.2	0.7	1.5
Mean	23.0	14.3	8.7	2.3	0.8	1.5
±SD	±4.9	±3.2	±3.0	±0.2	±0.4	±0.5

Ers, El and Ew; static elastance of total respiratory system, lung and chest wall, respectively; **Rrs, Rl and Rw:** flow-resistances of total respiratory system, lung and chest wall, respectively.
Resistance offered by endotracheal tube and equipment was subtracted in all instances.

The values of intrinsic flow-resistances of the total respiratory system, lung and chest wall are provided in Table VII.2. On the average, Rl and Rw amounted to 35% and 65% of Rrs, respectively.

The ventilatory variables and the data of mechanical work of breathing are given in Table VII.3.

D. DISCUSSION

Partitioning of respiratory elastances

In normal awake sitting subjects, in the resting tidal volume range, Ers amounts to about 0.45 cm H_2O per 1 per cent of vital capacity, VC (Agostoni and Mead, 1964) and its does not change appreciably when shifting to the supine position (Berger and Burki, 1982). Values of Ers in the present study were considerably higher (mean +SD: 0.81 ± 0.18 cm H_2O/%VC), in line with reports on subjects anesthetized with halothane-N_2O (Chapters II and III). For such normalization, vital capacity of the subjects was predicted from anthropometric data according to Goldman and Becklake (1959).

Most of the increase in Ers was due to increased static lung elastance which averaged 0.51 ± 0.12 cm H_2O/%VC. On the other hand, static chest wall elastance (0.30 ± 0.10 cm H_2O/%VC) was closer to the values which are obtained in awake subjects (about one-half of awake Ers).

Table VII.4 provides the values of Ers and El for anesthe-

TABLE VII.3

Ventilatory variables and inspiratory work data of five anesthetized subjects.

Subject	$\dot{V}_E$ ($l.min^{-1}$)	V_T (l)	f (min^{-1})	Wel (Joules)	Wres* (Joules)	Wtot* (Joules)	$\dot{W}$tot* ($Joules.min^{-1}$)
1	8.21	0.31	26.6	0.100	0.023	0.123	3.27
2	6.80	0.28	24.7	0.080	0.045	0.125	3.09
3	7.72	0.26	30.3	0.083	0.031	0.114	3.45
4	9.13	0.32	28.4	0.103	0.032	0.135	3.83
5	7.77	0.32	23.8	0.164	0.040	0.204	4.86
Mean	7.93	0.30	26.8	0.106	0.034	0.140	3.70
±SD	±0.85	±0.03	±2.7	±0.034	±0.009	±0.036	±0.70

$\dot{V}_E$: minute ventilation; **V_T:** tidal volume; **f:** respiratory frequency; **Wel:** inspiratory elastic work per breath; **Wres:** inspiratory resistive work per breath; **Wtot:** inspiratory work per breath; **$\dot{W}$tot:** total inspiratory work per min.

* These data include work done in overcoming flow resistance of the lung and endotracheal tube.

TABLE VII.4

Elastance of total respiratory system (Ers) and lung (El) in anesthetized subjects.

Reference	No. of Subjects	Age (Yrs)	VC (l)	Anesthetic Agents	Ers ($cmH_2O.l^{-1}$)	El ($cmH_2O.l^{-1}$)	El/Ers (%)
11	6	47	3.99*	Thiopental, droperidol fentanyl	22.3	13.5	67
22	5	26	5.33	Isoflurane (%), succinylcholine	11.6	6.2	54
25	26	47	4.98	Thiopental, succinyl-choline	9.4	5.6	60
27	5	26	4.98	Thiopental, meperidine	11.2	7.4	67
Present Study	5	41	3.52*	Thiopental, meperidine halothane, N_2O	23.0	14.3	62

*VC (vital capacity) predicted according to Goldman and Becklake (1959).

tized humans reported in the literature. Apart from Grimby et al. (1975), the values of both Ers and El of the present study was about twice as large as those found by the other authors. This may reflect the fact that in the previous studies the subjects breathed air while in the present investigation a mixture of 70% N_2O-30%O_2 was inhaled. The latter should promote atelectasis, and hence result in increased El. On the other hand, the subjects of Grimby et al. (1975) inhaled air, and yet they exhibited values of Ers and El comparable to those of the present study. Differences in body size could not explain the discrepancies in Table VII.4 because most of the differences persisted after the values of Ers and El were normalized for different VC's.

The percentage ratio of El to Ers in the different studies shown in Table VII.4 ranged between 54 to 72%. In awake supine individuals this ratio tends to be lower than 50%, indicating that in anesthetized subjects El tends to increase proportionately more than Ew (Westbrook et al., 1973; Rehder et al., 1974). By contrast, Van Lith et al. (1967) found that Ew decreased during anesthesia while El did not change at all. Their study is the only one in which Ers was found to decrease during anesthesia. This can not be attributed to respiratory muscle paralysis, since Westbrook et al. (1973) have shown that Ers, El and Ew do not differ appreciably between anesthesia and anesthesia-paralysis. In halothane-N_2O anesthetized subjects

Ers also does not differ appreciably between the anesthetized and anesthetized-paralyzed states, as it was shown in Chapter II.

The increase of El during anesthesia has been attributed to increased elastic recoil of the lung due either to altered lung surfactant function, anesthesia-induced alveolar duct and terminal airway constriction, atelectasis associated with the fall in functional residual capacity, and increased thoracic blood volume (Van Lith et al., 1967; Westbrook et al., 1973; Rehder et al., 1974; Grimby et al., 1975). Present data do not provide further insight into the nature of the increased El during anesthesia, except that with halothane-N_2O anesthesia rather high values of El are obtained.

Partitioning of respiratory flow-resistances

As previously pointed out in Chapters II and III, the endotracheal tubes offer a high non-linear flow-resistance, and hence it is axiomatic that overall flow-resistance increases during anesthesia. In this connection it should also be noted that the flow-resistance offered by the endotracheal tubes should be greater for 70% N_2O and 30% O_2 mixture than for air because of the different physical properties (Radford, 1964).

The intrinsic flow-resistance of the total respiratory system (upper airway excluded) in the subjects of present study averaged 2.3 cm $H_2O.l^{-1}.s$. This is slightly greater than previous results on halothane anesthetized subjects (1.6 cm $H_2O.l^{-1}.s$) (Chapter II). The slightly greater intrinsic Rrs of the present subjects probably reflects the fact that they were older than the subjects of previous investigation (40.8 vs. 29.8 yrs) (Frank et al., 1957).

Intrinsic Rl averaged 0.8 cm $H_2O.l^{-1}.s$, a value that is only slightly higher than the lower pulmonary flow-resistance (upper airway excluded) found in normal awake subjects breathing air following administration of atropine, namely 0.6 cm $H_2O.l^{-1}.s$ (Vincent et al., 1970). In this connection it should be noted that since the viscosity of a $N_2O:O_2$ mixture is less than that of air (Radford, 1964), the resistance where laminar flow is occurring should decrease during nitrous oxide breathing. Since previous studies (Chapters II and III) indicate that the intrinsic flow-resistance is constant or nearly so (reflecting laminar flow), it is probable that the relatively low values of Rl were due in part to the physical properties of the gas mixture breathed.

Measurements of Rl during anesthesia have been previously reported (Wu et al., 1956; Gold and Helrich, 1965; Rehder et al., 1974; Hedenstierna and McCarthy, 1975; Dobi and Gold, 1969). In paralyzed subjects anesthetized with isoflurane (1%), Rehder et al. (1974) found an average Rl value of 2.8 cm $H_2O.l^{-1}.s$. This value is higher than the present one, the discrepancy probably reflecting at least in part the fact that atropine was not administered to the subjects studied by Rehder et al. In subjects anesthetized with halothane and paralyzed with pancuronium, breathing a mixture of O_2 in air, Hedenstierna and McCarthy (1975) found an average value of Rl of about 5 cm $H_2O.l^{-1}.s$. Their nine subjects, however, included four individuals whose age ranged between 57 and 69 years, and Rl is known to increase with age (Frank et al., 1957). Furthermore, these subjects had not received atropine.

Dynamic lung elastance was slightly higher than static El, in line with a previous report indicating frequency-dependence of pulmonary compliance during anesthesia (Hedenstierna and McCarthy 1975).

Present results indicate that Rw amounted, on the average, to 1.5 cm $H_2O.l^{-1}.s$. These values are slightly higher than previous estimates of Rw on awake subjects, namely 0.5-1.0 cm $H_2O.l^{-1}.s$ (Opie et al., 1959; Mead and Agostoni, 1964; Grmby et al, 1968). Rw has not been previously measured in anesthetized humans.

In both halothane and enflurane anesthetized dogs breathing spontaneously, Rich et al. (1979) found that the dynamic Ptp vs. V loops were in general reversed, i.e. Ptp was greater during expiration than inspiration. We did not find this phenomenon in any of our subjects. Normal Ptp vs. V looping has also been reported by Grimby et al. (1979) in subjects anesthetized with thiopentone. This may reflect differences between species (more deformable chest wall in dogs) or in techniques. In this connection it should be noted that Rich et al. (1979) measured Ptp in the anesthetized dogs with a catheter inserted into the trachea. This should result in pressure artefacts due to convective acceleration of gas at the transition between the trachea and the endotracheal tube (Mead, 1961).

Breathing pattern and work of breathing

In line with previous results with halothane (Munson et al., 1966), the pattern of breathing in the subjects of present study was consistently rapid and shallow (Table VII.3). Minute ventilation was within the normal limits for awake subjects at rest. The elastic work per breath (Wel) is given by 0.5 (Edyn,l + Ew) x V_T^2. Since Edyn,l was high, this should lead to increased Wel. On the other hand, all subjects exhibited a low tidal volume, a factor leading to a substantial decrease of Wel, since the latter is proportional to V_T^2. As a result, Wel was increased much less than would have been the case if V_T has remained normal. In fact, if V_T has equalled 0.5 l, the elastic work per breath would amount to about 280% of the observed values. On the other hand, all subjects exhibited increased respiratory frequency. As a consequence, the elastic work per minute was increased. In fact, if the respiratory frequency had remained normal (say 15 breaths per min), the average elastic work per min should amount to only about 56% of the observed value. Thus, as a result of rapid and shallow breathing, the elastic work per min amounted to about 164% of the corresponding value that would have been obtained had the breathing pattern remained normal (V_T=0.5 l and f = 15 breaths/min).

In spite of the relatively high flow-resistance offered by the endotracheal tube, the inspiratory flow-resistive work amounted to only about 24% of the total inspiratory work. This reflects the fact that the inspiratory flows were relatively low, the peak flows not exceeding 0.5 $l.s^{-1}$. Because of the curvilinear nature of the pressure-flow relationship of the endotracheal tube, with increasing minute ventilation (and hence increased inspiratory flow) the flow-resistive work should increase very markedly, as previously pointed out (Chapter II). As a result, the ventilatory response to CO_2 in anesthetized subjects should be reduced even in the absence of decreased activity of the respiratory muscles (i.e., without depression of the output of the respiratory centers). The increased respiratory system elastance during anesthesia should also contribute to depressed ventilatory response to chemical stimulation of breathing. These factors have not been sufficiently stressed in the past.

The total work per min during anesthesia (Table VII.3) was increased relative to normal, awake adults in whom, according

F. REFERENCES

1. Agostoni, E., and J. Mead. Statics of the respiratory system. In Handbook of Physiology. Respiration. Washington D.C.: Am. Physiol. Soc., sect. 3, vol.I, chapt.13, p. 387-409, 1964.

2. Berger, R., and N.K. Burki. The effects of posture on total respiratory compliance. Am. Rev. Respir. Dis. 125: 262-263, 1982.

3. Dohi, S., And M.I. Gold. Pulmonary mechanics during general anesthesia. The influence of mechanical irritation on the airway. Br. J. Anaesth. 51:205-213, 1979.

4. Frank, N.R., J. Mead, and B.G. Ferris, Jr. The mechanical behaviour of the lungs in healthy elderly persons. J. Clin. Invest. 36:1680-1687, 1957.

5. Ferris, B.G., Jr., J. Mead, and L.H. Opie. Partitioning of respiratory flow resistance in man. J. Appl. Physiol. 19:653-658, 1964.

6. Gold, M.I., and M. Helrich. Pulmonary compliance during anesthesia. Anesthesiology 26:281-288, 1965.

7. Goldman, H.I., and M.R. Becklake. Respiratory function tests: normal values of median altitudes and the prediction of normal results. Am. Rev. Tuberc. 79:457-467, 1959.

8. Goldman, M.D., G. Grimby, and J. Mead. Mechanical work of breathing derived from rib cage and abdominal V-P partitioning. J. Appl. Physiol. 41:752-763, 1976.

9. Grimby, G., G. Hedenstierna, and B. Lofstrom. Chest wall mechanics during artificial ventilation. J. Appl. Physiol. 38:576-580, 1975.

10. Grimby, G., T. Takishima, W. Graham, P. Macklem, and J. Mead. Frequency dependence of flow resistance in patients with obstructive lung disease. J. Clin. Invest. 47:1455-1465, 1968.

11. Hedenstierna, G., and G. McCarthy. Mechanics of breathing, gas distribution and functional residual capacity at different frequencies of respiration during spontaneous and artificial ventilation. Br. J. Anaesth. 47:706-711, 1975.

12. Katz, R.L., and J.F. Ryan. The neuromuscular effects of suxamethonium in man. Brit. J. Anaesth. 41:381-390, 1969.

to Petit et al., (1961), it averaged 2.9 joules.min^{-1} during resting breathing at $\dot{V}_E$ of 8.3 l.min^{-1}. In spite of the marked increase of overall elastance and flow-resistance, $\dot{W}$tot in the anesthetized subjects was only about 28% higher than in awake individuals. This modest increase of $\dot{W}$tot in the face of markedly altered mechanical properties of the respiratory system was due to the fact that breathing was rapid and shallow.

Finally, it should be noted that neither present data of mechanical work of breathing nor those of Petit et al. (1961) include the component required to overcome Rw (which, however, should represent a relatively small portion of $\dot{W}$tot) nor that resulting from distortion of the chest wall during active inspiration (Goldman et al., 1976). The latter should increase during halothane anesthesia (Tusiewicz et al., 1977).

13. Mead, J.: Mechanical properties of lungs. Physiol. Rev. 41:281-330, 1961.

14. Mead, J., and E. Agostoni. Dynamics of breathing. In Handbook of Physiology, Respiration. Washington D.C.: Am. Physiol. Soc., 1964, sect.3, vol. I, chapt. 14, p. 411-427.

15. Milic-Emili, J., and J.M. Tyler. Relation between work output of respiratory muscles and end-tidal CO_2 tension. J. Appl. Physiol. 18:497-504, 1963.

16. Munson, E.S., C.P. Larson, Jr., A.A. Babad, M.J. Regan, D.R. Buichel, and E.I. Eger. The effects of halothane, fluroxene and cyclopropane on ventilation: A comparative study. Anesthesiology 27:716-728, 1966.

17. Petit, J.M., L. Delhez, and J. Daimoiseau. Signification de quelques valeurs de mēchanique ventilatoire chez l'adulte normal au repos. Acta Tuberc. Belg. 52:356-372, 1961.

18. Radford, E.P., Jr.: The physics of gases. In Handbook of Physiology, Respiration. Washington, D.C.: Am. Physiol. Soc., 1964, sect.3, Vol.I, chapt.3, p. 125-152.

19. Rehder, K., J.E. Mallow, E.E. Fibuch, D.R. Krabill, and A.D. Sessler. Effects of isoflurane anesthesia and muscle paralysis on respiratory mechanics in normal man. Anesthesiology 41:477-485, 1974.

20. Rich, C.R., K. Rehder, T.J. Knopp, and R.E. Hyatt. Halothane and enflurane anesthesia and respiratory mechanics in prone dogs. J. Appl. Physiol: Respirat Environ Exercise Physiol 46:646-653, 1979.

21. Tusiewicz, K., A.C. Bryan, and A.B. Froese. Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anesthesia. Anesthesiology 47:327-337, 1977.

22. Van Lith, P., F. Johnson, and J.T. Sharp. Respiratory elastances in relaxed and paralyzed states in normal and abnormal men. J. Appl. Physiol. 23:475-486, 1967.

23. Vincent, N.J., R. Knudson, D.E. Leith, P.T. Macklem, and J. Mead. Factors influencing pulmonary resistance. J. Appl. Physiol. 29:236-243, 1970.

24. Westbrook, P.R., S.E. Stubbs, A.D. Sessler, K. Rehder, and R.E. Hyatt. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J. Appl. Physiol. 34:81-86, 1973.

25. Wu, N., W.F. Miller, and N.R. Luhn. Studies of breathing in anesthesia.Anesthesiology 17:696-707, 1956.

CHAPTER VIII

CONCLUSIONS AND CLAIM OF ORIGINALITY

A. CONCLUSIONS AND CLAIM OF ORIGINALITY

This Thesis provides the first systematic study of respiratory mechanics in anesthetized humans. Both the passive and active mechanical properties of the respiratory system were examined, and the post-inspiratory decay of inspiratory muscle pressure was quantified. In order to obtain valid measurements of pulmonary and chest wall mechanics, the "occlusion test" was used.

The following results specifically represent original contributions to the fields of respiratory mechanics and anesthesia:

1. A simple method, namely the "occlusion test", has been applied for the first time in both awake and anesthetized human adults in order to assess the validity of the indirect measurement of pleural surface pressure with the esophageal balloon technique. Using this test, valid measurements of the changes in esophageal pressure could be obtained in both awake and anesthetized supine humans. In the past, it was thought that in supine position the esophgeal balloon technique was not valid.

2. Measurements of lung mechanics in normal awake subjects showed significant changes with body position. The increase in pulmonary flow resistance in decubitus positions (supine, right and left lateral) is not due solely to a decrease in lung volume but positional changes in upper airway resistance are also involved

3. Based on analysis of passive expirations and measurements of passive elastance of the total respiratory system, it was possible to obtain the first systematic measurements of the passive pressure-flow (P-$\dot{V}$) relationship of the total respiratory system in anesthetized humans. A curvilinear P-$\dot{V}$ relationship was found in all subjects, the curvilinarity being due entirely to the enotracheal tubes. After correction for enotracheal tube resistance, the intrinsic P-$\dot{V}$ 1relationship was found to be linear, the resistance values being close to normal.

4. This Thesis provides the first systematic study of partitioning of respiratory mechanics into lung and chest wall components in anesthetized humans.

5. The present results provide the first quantification of the decay of the pressure developed by the inspiratory muscles during expiration (post-inspiratory activity) in anesthetized humans. Considerable expiratory braking is caused by this activity, and as a result, only about 48% of the elastic work done during total inspiration is used to overcome expiratory flow resistance, the remainder (52%) representing negative work done by the inspiratory muscles during expiration.

6. The present results represent the first measurements of the active inspiratory impedance in anesthetized humans. During active(spontaneous) inspiration, the respiratory system

elastance is 34% greater than its passive value, while active flow resistance exceeds the passive intrinsic resistance by about 17%.

7. Apart from the new instrumental and analytical approaches described in this Thesis, the present results provide a systematic account of the effects of a common anesthesia mode (halothane-N_2O) on respiratory mechanics. In the available literature there is only one study which gives values of pulmonary flow resistance (uncorrected for endotracheal tube resistance) during halothane-N_2O anesthesia.

8. Most important, the present Thesis provides the kernel for future assessment of respiratory mechanics (both active and passive) in humans anesthetized with different anesthetics.