This is to certify that the

thesis entitled

THE ROLE OF H_1 AND H_2 HISTAMINE RECEPTORS IN THE PULMONARY MECHANICAL, GAS EXCHANGE AND CARDIOVASCULAR RESPONSES OF NEONATAL CALVES TO INTRAVENOUS HISTAMINE.

presented by

Ronald Francis Slocombe

has been accepted towards fulfillment
of the requirements for

Master's degree in Science

Department of Large Animal Surgery and Medicine

Major professor

Date August 6, 1979

THE ROLE OF H_1 AND H_2 HISTAMINE RECEPTORS IN THE PULMONARY MECHANICAL, GAS EXCHANGE AND CARDIOVASCULAR RESPONSES OF NEONATAL CALVES TO INTRAVENOUS HISTAMINE.

By

Ronald Francis Slocombe

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Large Animal
Surgery and Medicine

1979

ABSTRACT

THE ROLE OF H_1 AND H_2 HISTAMINE RECEPTORS IN THE PULMONARY MECHANICAL, GAS EXCHANGE AND CARDIOVASCULAR RESPONSES OF NEONATAL CALVES TO INTRAVENOUS HISTAMINE.

By

Ronald Francis Slocombe

Histamine was administered by continuous intravenous infusion to three groups of anesthetized ventilated calves. Group I received histamine alone, Group II was pretreated with H_1 antagonist and Group III with H_2 antagonist.

Histamine caused a decrease in cardiac output, increased heart rate and systemic and pulmonary hypotension. H_2 receptors mediated pulmonary and systemic vasodilation and caused tachycardia. H_1 receptor stimulation resulted in pulmonary vasodilation and decreased cardiac output without affecting heart rate. No H_1 mediated effect could be clearly demonstrated on the systemic vasculature.

In the lungs, histamine decreased dynamic compliance, increased airway resistance, increased lung pressure-volume hysteresis and increased alveolar-arterial oxygen differences.

It was concluded that the adverse effect of histamine on pulmonary mechanics and gas exchange results from H_1 mediated constriction of small and large airways. Weak H_2 mediated peripheral airway dilation was also demonstrated.

ACKNOWLEDGEMENTS

Special thanks to Drs. Mather, Coy, Riley and the Food Animal Faculty for their encouragement and support to allow completion of this work.

A friend as well as an exemplary advisor, Dr. Robinson provided inspiration, guidance and endurance to a fledgling graduate student. My deepest gratitude is extended to this special human being.

My appreciation is also extended to Roberta Milar for her painstaking efforts to teach technical skills to a graduate student with apparently many thumbs.

Lastly, to my wife, Judy, who in no small measure contributed to the completion of this work with her patience and enthusiasm.

TABLE OF CONTENTS

TABLE OF CONTENTS (Cont.)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (Cont.)

INTRODUCTION AND LITERATURE REVIEW

Pulmonary disease in cattle results in sickness and mortality, probably only second in importance to enteric disease. The development of lung disease may be favored by the environmental conditions typically encountered in calf rearing, and during normal management of the adult herd. There are, however, anatomical and physiological differences unique to cattle, that may favour the development of clinical disease. Some of these aspects are discussed in detail below.

1. Cattle have higher basal respiratory rates and minute ventilation than other animals probably as a result of a relatively small gas exchange surface area in relation to basal oxygen consumption (Altman and Dittmer, 1971; Veit and Farrel, 1978). Respiratory rates may be further accelerated in heat stressed cattle (Esmay 1969). The factors may not only facilitate exposure to environmental hazards but may jeopardize gas exchange in the face of relatively minor distrubances in lung function.

2. Bovine lung differs anatomically from many species in that lung parenchyma is divided into discrete lobules (McLaughlin et al, 1961; Mariassy et al, 1975). Interconnections between alveolar membranes, known as Pores of Kohn are of very limited number in cattle lungs (Mariassy et al, 1975).

Interconnections between adjacent lobules, known as collateral pathways have been described in dogs, cat, man and horses (Robinson and Sorenson, 1978; Woolcock and Macklem, 1971) but are absent in cattle.

Collateral pathways may deliver air to lung segments subtended by obstructed airways and maintain gas exchange. In species such as cattle, airway obstruction may have profound and lasting effects on gas exchange because of ensuing atelectasis.

3. In species with unlobulated lungs, collapse of a lobule tends to be prevented as a result of interdependence (tethering) by the surrounding lung (Mead et al, 1970). In calves with loose interlobular connective tissue, interdependence may not occur and atelectasis may develop more readily than in other species (Sylvester et al, 1975). As shown for isolated dog lung, (Robinson, manuscript in preparation) interdependence is least effective in the ventral lung fields.

4. During breathing, energy is required to stretch the lung and generate air flow. Work of breathing may become increased in pulmonary disease (Gillespie et at, 1964, 1966) and a decrease in specific conductance of cattle exposed to viral infection have been demonstrated (Kiorpes and Bisgard, 1978). Although studies on the work of breathing have not been conducted in naturally occurring cases of bovine pulmonary disease, it is likely that work of breathing increases. Increased work of breathing may limit growth and performance, and may compromise blood oxygen availability in species with a normally low total alveolar surface/basal oxygen uptake ratio. In addition, increased work of breathing may lead to respiratory muscle fatigue and further compromise lung function (Pardy et al, 1979).

5. The bovine lung has been shown to have relatively few alveolar macrophages (Mariassy et al, 1975; Rybicka et al, 1974). Alveolar macrophages function rely chiefly on energy generated by oxidative

phosphorylation, a process dependent on the availability of oxygen (Leak et al, 1964; Stossel, 1974). Thus, the bovine lung is likely to have a limited alveolar macrophage response due to the small numbers available and because hypoxia created by terminal bronchiolar obstruction may reduce phagocytic activity. In addition hypoxia may depress the activity of the mucociliary transport mechanism (Laurenzi and Yin, 1970).

That these effects of hypoxia are important in calves is supported by the finding that reduced bacterial clearance rates closely correspond to decreased regional oxygen tensions within the lung (Veit et al, 1978).

6. Lysozyme is important in body defense mechanisms, particularly against infection (Jolles 1975, Stossel 1974). Bovine granulocytes and ocular secretions do not contain lysozyme (Padgett and Hirsch, 1969) and its presence has yet to be demonstrated in bovine lung secretions (Veit and Farrel, 1978).

7. Bovine pulmonary vasculature shows marked reactivity upon exposure to hypoxia (Grover et al, 1963; Kuida et al, 1962; Jaenke and Alexander, 1973). This may be an adaptive measure for, if the bovine lung suffers from a propensity to develop atelectasis (for the reasons previously discussed), pulmonary blood flow should be shunted away from hypoxic lung tissue in order to maintain blood oxygenation, ie. to minimize mismatching of ventilation and perfusion (Grant et al, 1976). This response is thought to be under local control (Grant et al, 1976; Fishman, 1976) and chemical mediators, particularly histamine, have been incriminated in the rabbit, rat (Kay and Grover, 1975; Hauge and Melmon,

1968; Shaw, 1971), cat (Shaw, 1971; Hauge, 1969), mouse, guinea pig and sheep (Woods et al, 1976). The role of histamine in hypoxic pulmonary vasoconstriction of dogs (Tucker et al 1976, 1977; Giordano et al, 1977; Glazier and Murray, 1971), cats (Hoffman et al, 1977) and calves (Silove and Simcha 1973; Kay and Grover 1975) is currently controversial. The pulmonary hypoxic pressor response of calves has been shown to be modified by environmental (Will et al, 1978) genetic (Will et al, 1975; Weir et al, 1974) and pharmacological influences (Silove and Grover 1968; Silove and Simcha 1973, Reeves et al, 1972) and not to diminish with aging (Bisgard et al, 1972). The large numbers of mast cells in the bovine lung (Mariassy et al, 1975), with their attendant supply of mediators, may be a necessary component of vasoregulation in the face of local hypoxic stimuli (Fishman, 1976).

However, in cattle exposed to reduced atmospheric oxygen tensions (as in high altitude environments) these mechanisms lead to the inappropriate responses of pronounced pulmonary hypertension and right heart failure (Alexander and Jensen, 1963; Grover et al, 1963). It remains unknown whether pneumonia in cattle is complicated by mediators released in response to local hypoxia.

Cattle are exquisitely sensitive to histamine (Desliens, 1958; Nilsson, 1963.) Release of histamine as well as other mediators has been suspected in diverse disease conditions in cattle, including ruminal acidosis (Nilsson 1963; Ohga and Taneike, 1978) metritis and

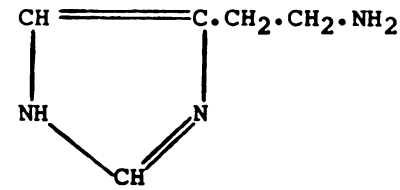
mastitis (Nilsson 1963, Zarkower and Norcross 1966) acute interstitial pneumonia (Wilkie 1976, 1977, 1978; Moulton et al, 1963), Brisket disease, passive cutaneous anaphylaxis (Wells and Eyre, 1972) and generalized anaphylaxis (Eyre et al, 1973).

Although antihistamines are commonly used in the treatment of hypomagnesaemia, an important role for histamine in this condition has not been substantiated (Henry et al, 1977). Not only is histamine one of the putative mediators of anaphylaxis in cattle, but the lung has been demonstrated as the principle target organ of bovine anaphylaxis (Wray and Thomlinson, 1974; Aitken and Sanford, 1972).

The importance of histamine and other chemical mediators remains to be determined for infectious bovine pulmonary disease. Histamine depresses the pulmonary clearance of bacteria (Gilka et al, 1974a, 1974b). The effects of histamine on gas exchange and the mechanical properties of the lung have not been studied in calves. Although a large volume of literature exists regarding the physiopharmacology of histamine in man, dog and guinea pig, cross species comparisons are likely to be inaccurate since the bovine lung exhibits marked anatomical and physiological differences as previously described.

Pharmacology of Histamine

Histamine was first synthesized in 1907 (Windaus and Vogt, 1907). It is a diacidic amine of molecular weight 111, readily soluble in water and stable under acidic conditions (Roth and Tabachnick, 1971). The first description of the pharmacological activity of histamine was made in 1910 (Dale and Laidlaw, 1910), and since that time there have been a great many reports concerning the biological activity of histamine.



Histamine M.W. 111.

Histamine is not uncommon in nature (Mettrick and Telford, 1963) and can be found in plants as well as most animal tissues (Aviado and Sadavongvivad, 1970; Brocklehurst 1960; Eliassen 1973). In mammals, it is chiefly synthesized by tissue mast cells and basophils, but can also be synthesized by other cells (Wicki and Schatzmann, 1977), particularly in the fetus (Green 1962; Harrison et al, 1974).

The biological importance of histamine is not well understood. It has widespread effects in most intact mammalian tissues, affecting smooth muscle in the cardiovascular, pulmonary, urinary, gastrointestinal and genital systems (Rocha e Silva, 1966) Histamine stimulates exocrine gland secretion and may cause release of catecholamines from the adrenal medulla (Ploy-Song-Sang et al, 1978, Roth and Tabachnick, 1971). It may have a physiological role in reproductive function (Marcus et al, 1963;

Lerner and Carminati, 1977) and has been documented to cause excitation in the central nervous system (Monnier et al, 1967; Schayer 1974; Rosenburg and Savarie, 1964) and peripheral nerves (Chiou et al, 1976; McGrath and Shepherd, 1978). In addition, it appears to be a growth promotent found in high concentration in fetal tissues (Harrison, Peat and Heese, 1974) and in recovering foci of inflammation (Boucek and Noble, 1973; Kahlson and Rosengren, 1968). It has been incriminated in fetal cardiovascular responses during parturition (Woods et al, 1976). However, histamine is most frequently incriminated as a mediator of allergic and anaphylactic disease in a wide variety of species (Austen and Orange, 1975; Piper, 1977; Brocklehurst, 1960; Collier and James, 1967).

Histamine release from mast cells is readily achieved using appropriate antigenic stimulation. A wide variety of known allergens, including moulds (Eyre, 1972), pollens (Bryant and Burns, 1976), pollutants (Said, 1978) bacterial toxins (Brown, 1965), venoms (Fredholm and Haegermark, 1968) and serum proteins (Metzger et al, 1978), may elicit mast cell degranulation under natural conditions. Many chemicals including 48/80 (Colebatch et al, 1966), dextrans (Vaage et al, 1978), radiographic contrast media (Cogen et al, 1978, Ring et al, 1978), surfactants, antibiotics (Raab, 1968) and calcium ionophor also trigger histamine release. In the intact animal, histamine release may be affected by a wide variety of entities, including immunoglobulins (Vijay

and Perelmutter, 1977; Grant et al, 1972; Ishizaka et al, 1978; Weyer et al, 1978), complement fragments (Grant et al, 1977), enzymes such as trypsin and chymotrypsin (Tolos et al, 1975; Uvnas, 1963), phospholipase A (Damerau et al, 1975) prostaglandins, prostacyclines and thromboxanes (Engineer et al, 1978; Ercan and Türker, 1972; Walker, 1972), catecholamines (Kaliner et al, 1972), kinins and serotonin (McGrath and Shepherd, 1978). Exposure to hypoxia may also affect histamine release (Fishman, 1976).

Control of the reactivity of basophils has recently been described in a number of species (Austen et al, 1976; Lichtenstein, 1976). The control mechanism is believed to operate by alteration of cyclic nucleotide levels (Ortez, 1976; Orange, 1976). Modulation of histamine release can occur through the action of other mediators such as prostaglandins (Orange, 1976) corticosteroids (Lee, 1977), catecholamines (Moore, 1977) and acetyl choline (Reed et al, 1978). Furthermore, a relationship between pulmonary airway reactivity and cyclic nucleotide content in the lung has been demonstrated in rabbits (Kaukel et al, 1978) but not clearly identified in dogs (Barnett et al, 1978).

There are at least two binding sites for histamine, termed H_1 and H_2 receptors, which are responsible for histamine's biological activity (Chand and Eyre, 1975). Early studies concerning the biological effects of histamine utilized the common antihistamines, such as mepyramine, to

block the conventional H_1 effect. In 1972, the H_2 receptor was described and found antagonized by a new series of inhibitors typified by cimetidine, metiamide and burimamide (Black et al, 1972, 1973). Recently, histamine was shown to exert an effect, in the face of both H_1 and H_2 antagonists, upon isolated equine tracheal muscle preparations (Chand and Eyre, 1977), suggesting the presence of an H_3 receptor. The responses elicited by H_1 and H_2 receptor stimulation have been extensively reviewed by Chand and Eyre (1975). Not only are these receptors found in varying numbers in different organs, but their selective activation results in marked alteration of organ function.

Histamine modulates cyclic nucleotide levels (Mathé et al, 1974; Lichtenstein and Gillespie, 1975; Polson et al, 1974; Lichtenstein, 1976; Kaliner, 1977; Reed et al, 1978). H_2 receptor stimulation in the guinea pig (Mathé et al, 1974) and human lung (Kaliner and Platshon, 1978) increases pulmonary levels of 3'5' adenosine monophosphate (cAMP). H_1 receptor stimulation decreases cAMP. However, in dogs, histamine causes a net increase in cAMP in the lung mediated via H_1 receptors (Barnett et al, 1978). H_1 receptor stimulation also causes increased 3'5' guanosine monophosphate (cGMP) in the lung (Barnett et al, 1978; Mathé et al, 1974; Kaliner and Platshon, 1978). Similar increases in cGMP are also produced upon cholinergic stimulation (Kaliner, 1977; Kaukel et al, 1978).

In general, H_1 receptor stimulation causes increases in cGMP and

decreases in cAMP, and H_2 receptor stimulation increases cAMP in most tissues of a number of domestic and laboratory animal species (Chand and Eyre, 1975; Platshon and Kaliner, 1978).

The implications of selective control of cyclic nucleotide levels, both in the release of and control by histamine within the lung, are far-reaching. The degree to which histamine participates in the various clinical forms of pulmonary disease remains to be clarified, and perhaps more importantly, it remains to be determined when participation of histamine in the pulmonary disease leads to exacerbation or amelioration of the condition.

Biologic effects of histamine

1. The lung

Anaphylaxis in the guinea pig produces intense bronchoconstriction and histamine is thought to mediate this response (Collier and James, 1967) primarily through H_1 stimulation (Bernauer et al, 1968). Histamine induces contraction of both large and small airways, resulting in increases in airway resistance and decreases in dynamic lung compliance (Popa et al, 1973; Drazen and Austen, 1974, 1975; Douglas et al, 1973). While the reversal of bronchospasm with anticholinergic drugs has been documented (Drazen and Austen, 1975; Douglas et al, 1973, 1976), histamine has been shown to produce a peripheral constrictive effect refractory to vagal blockade in the guinea pig (Drazen and Austen, 1975) and cat (Colebatch and Engel, 1974). In a study involving

three calves, Aitken and Sanford (1972,) observed that the clinical signs and postmortem findings of histamine given at 0.03 mg/kg intravenously did not appear to be reduced in severity after vagotomy in anesthetized calves. Similar studies do not entirely support this view, as it has been reported that vagotomy does prevent the initial apnea which occurs after histamine injection (Eyre et al, 1973). Alteration of the airway responses to histamine by interaction with catecholamines has also been demonstrated (Drazen, 1978; Collier and James, 1967; Popa et al, 1973; Douglas et al, 1973). In horses, similar H_1 effects were reported in 1947 (Obel and Schmiterlöw, 1947) and modification of the response to histamine by vagal blockade or catecholamine administration was noted. An H_2 receptor-mediated bronchodilation was later identified for the horse in an in vitro study (Chand and Eyre, 1977).

Studies on the intact and isolated dog lung also indicate that histamine H_1 receptor stimulation leads to constriction of both large and small airways and that effects on airway resistance can be counteracted by vagal antagonism (Kira and Rodbard, 1971; Jackson et al, 1978; Wasserman, 1975; Nisam et al, 1978). Variability in the tonic vagal activity influencing the airways at the time of histamine exposure may alter the airway response to histamine (Loring et al, 1977, 1978; Benson and Graf, 1977). Histamine directly stimulates dog (Bleecker et al, 1976; Dixon et al, 1978; Vidruk et al, 1977), cat and rabbit lung irritant receptors (Mills et al, 1969; Miserocchi et al, 1978; Karczewski

and Widdicombe, 1969; Kaukel et al, 1978) but stimulation of neural receptors indirectly is also likely via changes in the permeability of the respiratory epithelium and by alteration of the mechanical and gas exchange properties of the lung (Kaukel et al, 1978; Coon et al, 1978).

Cross-species variability in the pulmonary response to histamine is well known. The bronchoconstrictive effect of histamine aerosols, as well as its release upon antigenic exposure, is well documented for man, dogs and monkeys (Mathé et al, 1973; Frey and Gold, 1978; Michoud et al, 1979; Simon et al, 1977). The bronchoconstriction elicited upon antigen or histamine exposure is thought the result of H_1 receptor stimulation (Casterline and Evans, 1977). In contrast, evidence from isolated muscle strips indicates that, in sheep, histamine causes weak, central airway bronchoconstriction mediated by H_1 receptors and pronounced peripheral airway dilation as a result of H_2 receptor stimulation (Eyre, 1975). Rats appear relatively resistant to the bronchoconstrictive effects of histamine (Church, 1975; Kaukel et al, 1978).

In man, histamine-induced bronchoconstriction causes decreased maximal and partial forced expiratory flows, decreased specific airway conductance (Rosenthal et al, 1978), decreased vital capacity and increased closing volume and total lung resistance (Newball and Keiser,

1973; Mitchell and Bouhuys, 1976). Cats exposed to histamine develop decreased dynamic compliance and increased airway resistance (Colebatch et al, 1966a, 1966b). These observations would support the contention that, for most species studied to date, histamine can compromise lung function. In addition, histamine may cause these abnormalities to arise in naturally occurring cases of asthmatic lung disease in man. However, disagreement still exists for it has been reported that changes in lung function tests in asthmatics may reflect prechallenge abnormalities in lung function rather than alterations in histamine reactivity between control and asthmatic patients (Brown et al, 1977a, 1977b).

Studies on the pulmonary effects of histamine in cattle have not been extensive. Histamine is liberated in vitro from bovine lung undergoing anaphylaxis (Eyre, 1971) and the cardiovascular changes of intact cattle undergoing anaphylaxis have been extensively studied. These studies have not addressed changes in gas exchange or mechanical properties of the lung. Anaphylaxis results in dyspnea, coughing and hyperpnea frequently preceded by a period of apnea and cyanosis (Aitken and Sanford, 1968, 1969; Ladiges et al, 1974, Wells et al, 1973; Eyre et al, 1973). Typical pulmonary lesions are congestion, hemorrhage, edema and patchy atelectasis, with degeneration and desquamation of alveolar epithelial cells and lymphatic distension (Wells et al, 1973; Ladiges

et al, 1974). Sludging of granulocytes in the pulmonary capillary beds is also apparent (Wells et al, 1973). Similar clinical and pathological signs have been produced by intravenous injection of histamine (Wray and Thomlinson, 1974; Aitken and Sanford, 1972) and have been reported in isolated lung studies (Lewis and Eyre, 1972). After an initial period of apnea, both histamine injection and anaphylaxis increase minute ventilation, tidal volume and respiratory rate as measured by Wrights respirometer or volume transducer methods (Burka and Eyre, 1974; Aitken and Sandford, 1969, 1972; Lewis and Eyre, 1972; Eyre et al, 1973). Histamine has also been demonstrated as important in passive cutaneous anaphylaxis in the calf (Wells and Eyre, 1972). However, disagreement still exists as to whether histamine is primarily responsible for the pulmonary signs seen in cattle undergoing anaphylaxis. Plasma histamine levels were found to increase in cattle undergoing anaphylaxis (Eyre et al, 1973). However, this could not be demonstrated for other studies in cattle (Aitken 1970; Wray and Thomlinson, 1974). Furthermore, a protective role for the classic antihistamines was identified in two studies (Eyre & Wells, 1973; Eyre et al, 1973) but could not be supported by the findings of others (Aitken and Sanford, 1969, 1972; Wray & Thomlinson, 1974; Wells et al, 1974). Differences in challenge and sensitization procedures are unlikely to account for the current disagreement (Aitken et al, 1975).

In vitro studies indicate that the bovine trachea and bronchus contract when exposed to histamine (Eyre, 1975; Kirkpatrick et al, 1975; Bullock and Kirkpatrick, 1976). The respiratory effects of histamine infusion have been described in several studies, but none have addressed the problems of gas exchange and mechanical properties of the lung. In addition, some of the inferences concerning the respiratory effects of histamine are questionable. From clinical observations and measurement of minute volumes using a Wright respirometer, Aitken and Sanford (1972) concluded that H_1 antagonists blocked the respiratory effects of histamine, and that vagal activity was unimportant in the respiratory response. However, the studies were performed on pentobarbitol anesthetized calves. Pentobarbitol is known to depress the autonomic nervous system and has been demonstrated to alter the effects of histamine given to guinea pigs (Mordelet-Dambrine et al, 1977). In addition, studies measuring minute ventilation were performed on four calves, including one vagotomized calf, and one calf premedicated with mepyramine. These limited numbers were too small to allow statistical comparisons between treatment groups. This study also involved the administration of lethal doses of histamine (0.03 mg/kg) and may not reflect the response of the lung to a physiologically realistic exposure.

In a more extensive study, again with pentobarbitol anesthetized

calves (Eyre et als, 1973), similar conclusions regarding the effects of histamine on ventilation volume were made. However, this study did find that vagotomy reduced the apneic response caused by histamine. The studies by Wells, Eyre and Lumsden (1973) and Lewis and Eyre (1972) did not explore the mechanism whereby histamine induces the change in minute volume, or for the increased inspiratory resistance noted for one isolated calf lung (Eyre et al, 1973).

Finally, it has yet to be clearly demonstrated that the antihistamines as employed by Wray and Thomlinson (1974), Aitken and Sanford (1969, 1972), Wells, Eyre, and Lumsden (1973), Eyre, Lewis and Wells (1973) can adequately antagonize the high local concentrations of histamine that could conceivably be achieved in lung tissue during bovine anaphylaxis. The conclusion that histamine is unimportant in bovine anaphylaxis, based solely on the failure of H_1 antagonism to be protective for cattle undergoing anaphylaxis may be in error.

II Vascular effects of histamine

In vitro studies indicate that both the bovine pulmonary artery and vein constrict upon histamine exposure (Eyre, 1971, 1975). In vivo histamine causes a marked decrease in systemic arterial pressure and a rise in pulmonary artery pressure (Aitken and Sanford, 1972; Eyre et al, 1973; Eyre and Wells, 1975; Lewis and Eyre, 1972). Reduction in heart

rate was reported for one calf in a study by Aitken and Sanford (1972) and was accompanied by a reduction in cardiac output (reported for two calves). However, in vitro experiments using isolated perfused calf lung (Silove and Simcha, 1973) describe histamine induced pulmonary vasodilation, contrary to the findings of the above in vivo studies.

The systemic vasodepressive action of histamine in calves is largely, but not completely prevented by H_1 antagonists (Eyre & Wells, 1973; Aitken and Sanford, 1972) indicating that the principle systemic effects of histamine are via H_1 receptors (Elmes and Eyre, 1977). From studies on calves undergoing anaphylaxis, it was concluded that H_2 receptor blockade potentiated the systemic vasodepressor effects, suggesting a pressor response for systemic H_2 receptors (Eyre and Wells, 1973). Furthermore, it was suggested that the depressive action of histamine in calves that was unable to be blocked by H_1 antagonism is not due to H_2 receptors, but rather due to incomplete H_1 blockade. This view has yet to be substantiated.

Eyre and Wells (1973), and Chand and Eyre (1975) indicate that, from preliminary data, bovine pulmonary vasculature has H_1 and H_2 receptors that function with effects opposite to those found in the systemic vasculature. The only data published to substantiate this view appears to concern an in vitro experiment where H_1-mediated contraction of pulmonary vein strips has been demonstrated (Burka and Eyre, 1974).

Histamine given to intact calves has also been shown to produce pulmonary edema (Lewis and Eyre, 1972; Aitken and Sanford, 1972; Gilka et al, 1974; Ladiges et al, 1974). Similar edemogenic properties of histamine have been reported in sheep (Brigham, 1975; Harris et al, 1978) and in guinea pigs (Aarsen and Zeegers, 1972). In sheep, the ability of histamine to induce pulmonary edema was blocked by H_1 receptor antagonism (Brigham, 1975).

The role of H_1 and H_2 receptors in the pulmonary and systemic circulation of domestic animals has recently been reviewed (Chand & Eyre, 1975). Considerable species difference in the distribution and response of receptor types is apparent. In addition, receptor response has been shown to vary with the state of smooth muscle tone (Barer et al, 1976), histamine dosage (Barer et al, 1976), and the type of anesthetic agent employed (Woods et al, 1977). A systemic depressor response mediated via H_1 receptors and a systemic pressor response mediated via H_2 receptors suggested to exist for calves (Eyre and Wells, 1973) has also been described in horses (Hanna and Eyre, 1978) and guinea Pigs (Okpako, 1972a, 1972b; Türker, 1973; Goadby and Phillips, 1973). A similar role for H_1 and H_2 receptor responses has been described for the pulmonary vasculature of cats (Barer et al, 1976). Although histamine produces similar blood pressure changes in both dogs and calves (Borst et al, 1957), the response to H_1 and H_2 receptor stimulation in the systemic

vasculature appears opposite for these two species (Tucker et al, 1975). Systemic H_2 receptor responses also appear different from the calf, for the chicken (Chand and Eyre, 1975) and the cat (Flynn and Owen, 1974) where H_2 receptor stimulation causes systemic vasodilation.

III Cardiac effects of histamine

Bradycardia often accompanies anaphylaxis in cattle (Aitken and Sanford, 1969). The cardiac responses to histamine have not been critically evaluated in calves. Results quoted by Aitken and Sanford (1972), were limited to single measurements performed once on two calves. Results were not subjected to statistical analysis. In dogs, H_2 receptors exert a positive ionotropic effect as well as produce tachycardia, while H_1 receptors exert a mild negative ionotropic effect (Tucker et al, 1975). These findings are similar to those found in guinea pigs (Zavecz and Levi, 1978), but disagree with the conclusions of Woods et al (1977), based on studies in sheep.

IV Immunological modulation by Histamine

Histamine has been demonstrated to modulate the inflammatory reaction and development of an immune response (Chand and Eyre, 1975). Histamine alters the responsiveness of neutrophils (Busse and Sosseman, 1976), eosinophils (Clarke et al, 1977), lymphocytes (Verhagen et al, 1977; Fox et al, 1979; Rocklin and Greineder, 1978; Plaut and Berman, 1978) and platelets (Allen and Eakens, 1978). Viral infections have

also been demonstrated to directly affect inflammatory responses (Buss et al, 1978), but it is not known whether they do so via alteration of mediator receptor sensitivity.

In cattle, histamine is released from antigen-exposed leukocytes and lung fragments (Holroyde and Eyre, 1975, 1976a, 1976b, 1977). The release of histamine in bovine lung and leukocyte preparations is enhanced by H_2 receptor stimulation (Holroyde and Eyre, 1977), unlike in man (Lichtenstein and Gillespie, 1973). The bovine granulocyte is also notably different from other species in that β-adrenergic stimulation enhances rather than inhibits granulocyte release of histamine. The bovine granulocyte is also different in that it is inhibited by α-adrenergic stimulation (Holroyde and Eyre, 1976). This is the reverse of the findings for catecholamine modulation of histamine release in human and guinea pig basophils (Melmon and Bourne, 1974; Bourne et al, 1974).

Because of the unique modulation found in bovine granulocytes, blood borne leukocytes may serve to intensify inflammatory responses via a positive histamine feedback mechanism, rather than to lessen it as suggested in other species (Chand and Eyre, 1975).

The bovine lung may thus be exposed to histamine released under allergic or infectious inflammatory processes, and perhaps exacerbated by involvement of basophils.

Exposure to histamine may also be increased due to abnormal ruminal function (Wicki & Schatzmann, 1977), estrus (Crouch and Godke, 1978), parturition and mastitis (Zarkower and Norcross, 1966; Zarkower, 1967a, 1967b).

As discussed, clinical respiratory disease is of major economic importance in cattle. Physiological and anatomical differences in cattle may make them comparatively susceptible to the development and extension of pneumonia. Participation of histamine and other mediators has been described for a wide variety of conditions in cattle, but the importance of these mediators in the development and extension of disease states in the lung remains to be determined. In addition, pulmonary mechanical and gas exchange properties of the neonatal calf lung have not been studied in detail. There is a need to develop non-invasive pulmonary function tests for clinical and research purposes. Many of the techniques currently employed in human medicine are unsuitable for cattle, as these tests require alteration of patient breathing patterns upon request.

The purposes of this study were to

a. determine the normal pulmonary mechanical, gas exchange and cardiovascular properties of anesthetized neonatal calves,

b. describe changes in cardiovascular, gas exchange and pulmonary mechanical properties of calves exposed to intravenous histamine diphosphate.

c. determine the relative roles of H_1 and H_2 receptors in the bovine response to intravenously infused histamine.

d. develop a suitable experimental system for further research regarding mediator effects on lung function, and for development of pulmonary function tests suitable for adaptation to clinical situations.

Anesthetized, fixed-volume-ventilated calves were instrumented for the study of the cardiorespiratory effects of intravenously infused histamine (Group I), histamine infused after H_1 blockade (Group II) or histamine infused after H_2 blockade (Group III).

MATERIALS AND METHODS

Purebred Holstein bull calves less than two weeks of age and weighing less than 55 kg were purchased locally. The absence of respiratory disease was confirmed by clinical examination prior to anesthesia, measurement of arterial oxygen tension (PaO_2) prior to experimental studies, and by postmortem examination immediately following completion of data collection. Animals were not fed for 12 hours prior to an experiment. Two hours before anesthesia was induced calves received 1.5 liters of an oral multi-electrolyte preparation.[1] Animals were anesthetized by intravenous administration of chloralose (100 mg/kg) and urethane (500 mg/kg) via a short catheter[2] placed percutaneously in the right jugular vein. Induction of anesthesia was quiet if urethane were administered prior to the chloralose. Additional anesthetic was not required during the course of the experiment.

After anesthetic induction, animals were promptly intubated using a cuffed endotracheal tube, and ventilated with a fixed-volume ventilator.[3] Tidal volume was approximately 15 ml/kg body weight and respiratory rate was adjusted to provide an end expiratory carbon dioxide concentration of 4% to 5% as measured by an infrared analyzer which continuously sampled gas from the endotracheal tube.[4] Animals were

---

[1]Ion-aid, Diamond Laboratories
[2]Venocath, Abbott
[3]Harvard Ventilator, Harvard Appliance Co., Dover, Mass.
[4]Beckman LB-2 CO_2 Analyzer, Fullerton, Calif.

placed in sternal recumbency and given intermittent deep breaths to prevent atelectasis. With the exception of these maneuvers and during measurement of static compliance, tidal volume and ventilatory frequency were constant throughout the experiment. The left jugular vein and the left carotid artery were surgically exposed. A polyethylene catheter[5] was placed in the carotid artery and a number 4 French, four side hole, Teflon catheter[6] placed in the left jugular vein. Catheters were connected to pressure transducers[7] and pressures were displayed on a oscilloscope and continuously recorded[8] after signal amplification.[9] Transducers were calibrated prior to each experiment against a mercury manometer. The jugular vein catheter was advanced until the tip lay in the pulmonary artery as verified by characteristic pulmonary arterial pressure tracings displayed on the oscilloscope. In two cases where difficulty was encountered in catheter positioning, placement was performed under fluoroscopic guidance. Catheters were periodically flushed with heparinized saline.[10,11] Pressure tranducers were placed at the level of the heart base (between the central and lower thirds of the chest).

Transpulmonary Pressure Measurement

An esophageal balloon catheter was made by perforating the distal 10 cm of a 100 cm Teflon catheter[12] and attaching a 10 mm diameter, 10 cm

---

[5]Intramedic PE 190, Clay-Adams, Parsippany, N.J.
[6]United States Catheter and Instrument Corp., No. 5441, Glen Falls, N.Y.
[7]Statham P_{23} Db, Statham, Hato Rey, Puerto Rico
[8]Soltec Multipen Recorder Model B-38 II, Soltec, Sun Valley, Calif.
9PDV-22 Amplifier, Electronics for Medicine VR 6 Recorder, White Plains, N.Y.
[10]Sodium heparin, Sigma Chemical Co., St. Louis, Miss.
[11]Particle free saline, Fisher Scientific, Livonia, Mich.
[12]Cordis No. 8 French femoral catheter, Cordis Corp., Miami, Florida

long, thin walled, latex balloon to the distal end. The proximal 90 cm of the catheter were encased in a polethylene sleeve[13] to provide sufficient rigidity to pass the catheter via the external nares into the esophagus. The balloon catheter was connected to a differential pressure transducer[14] which was calibrated prior to each experiment against a water manometer. In order to measure transpulmonary pressure the other transducer port was connected via a similar 100 cm catheter to the endotracheal tube at the level of the animal's muzzle. A small volume of air (0.5 ml) was injected into the esophageal balloon, and the balloon positioned at the point in the distal esophagus where excursions of transpulmonary pressure were greatest during tidal breathing. Balloon construction, placement and response times to an effective square wave of 0-30 cm H_2O (100% in .030 seconds) were similar to that described by Mead and Whittenburger (1953) and Milic-Emili et al (1964). In addition, frequency response characteristics of the esophageal balloon were balanced with those of the pneumotachograph, to minimize errors in dynamic compliance measurements attributable to phase lag between flow and pressure (Macklem, 1974)

Transpulmonary pressures, systemic arterial pressure and pulmonary arterial pressure were continuously recorded using a multichannel pen recorder.[8]

Measurement of Gas Flows and Tidal Volume

Inspired and expired gas flows were measured using a pneumotachograph[15] attached to the endotracheal tube and connected to a

---

[13]Intramedic PE 320, Clay Adams, Parsippany, N.J.
[14]Statham PM 131, Statham, Hato Rey, Puerto Rico
[8]Soltec Multipen Recorder, Model B-38 II, Soltec, Sun Valley, Calif.
[15]Fleisch #1, Dynasciences, Bluebelle, Penn.

differential pressure transducer,[16] amplifier and recorder.[9] The pneumotachograph was calibrated at the termination of each experiment with a rotameter[17] and blower. Tidal volume was measured by electronic integration of the flow signal. Volume calibration was obtained by injecting known volumes of air through the pneumotachograph. Transpulmonary pressure, gas flow rates and tidal volume were recorded simultaneously on a light recorder for subsequent calculation of static compliance ($C_{stat.}$), dynamic complicance (C_{dyn}), airway resistance (R_{aw}) and the difference between maximal and resting transpulmonary pressure (P_{tp}).

Mechanics of Ventilation

1. C_{dyn} and R_{aw} were measured by the method described by Mead and Whittenberger, (1953). Briefly, dynamic compliance was calculated as the ratio of tidal volume and the change in transpulmonary pressure between points of zero air flow (figure 1a), at end inspiration and end expiration. Pulmonary resistance was calculated as the ratio of the change in transpulmonary pressures and change in flow rates between mid-inspiratory and mid-expiratory points of equal volume (figure 1b).

2. Static compliance. During recording of transpulmonary pressure, 200 ml. boluses of air, up to 1500 ml total, were injected[18] then withdrawn from the lung. A pause of a least two seconds between each bolus allowed air flow to cease in the respiratory tract. The

---

[16]Statham PM5, Statham, Hato Rey, Puerto Rico
[9]PDV-22 Amplifier, Electronics for Medicine VR 6 Recorder, White Plains, N.Y.
[17]Rotameter, Fischer and Porter Co., Warminster, Penn.
[18]Hamilton Syringe Company, Whittier, Calif.

FIGURE 1

Method for calculation of dynamic compliance (C_{dyn}) and airway resistance (R_{aw}) from recorded tracings of transpulmonary pressures (P_{tp}), airflow, ($\dot{V}$) and lung volume (V) during the respiratory cycle. Cardiac artifact on all tracings is present.

Figure 1A illustrates the methods used to calculate C_{dyn}, where $\triangle P_{tp}$ and $\triangle V$ are measured from projected points of zero air flow. The ratio of $\triangle V/\triangle P$ is then computed to give C_{dyn}.

Figure 1B illustrates the methods used in calculating R_{aw}. From points of equal lung volume, differences in $\triangle \dot{V}$ and $\triangle P_{tp}$ are measured and the ratio $\triangle P_{tp}/\triangle \dot{V}$ is determined to give R_{aw}.

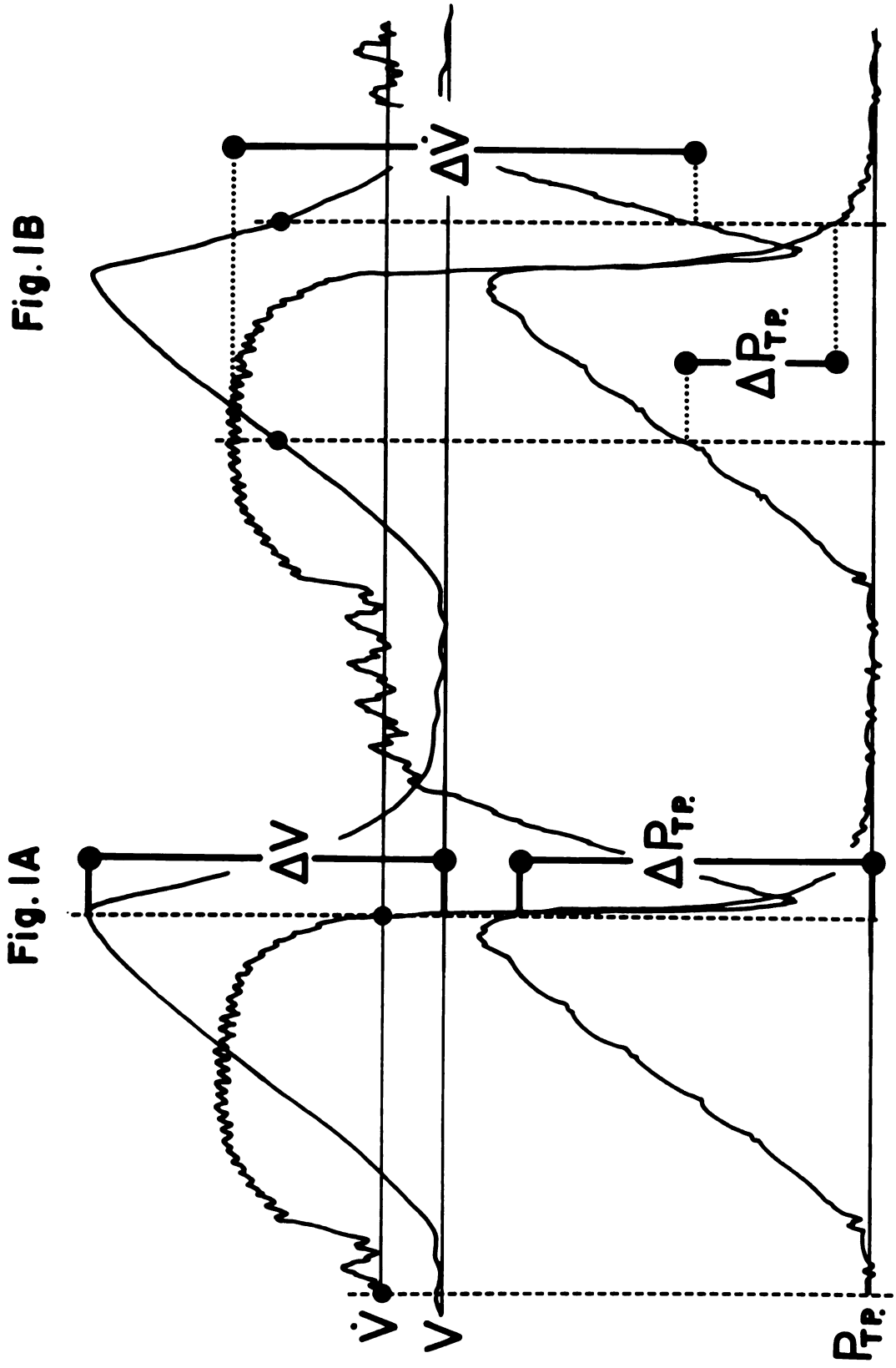


FIGURE 1

procedure was also repeated after three vital capacity maneuvers in which the lungs were inflated to a transpulmonary pressure of 30 cm H_2O (Fig. 2a). From the transpulmonary pressure data and lung volume, a lung pressure volume curve was plotted. Static compliance was calculated from the slope of the expiratory limb between functional residual capacity (FRC) and FRC + 800 ml (Robinson et al, 1972). The area enclosed by the static pressure-volume plot was measured by planimetry[19] (Fig. 2b).

Pulmonary Gas Exchange and Cardiac Output

Alveolar oxygen tension (PAo_2), dead space/tidal volume ratio (Vd/Vt), alveolar-arterial oxygen difference (A-a Do_2) and cardiac output were calculated using blood gas tensions, blood oxygen content, and mixed expired gas composition.

1. Expired Gas Composition. Exhaled gases were collected in a Krogh Spirometer.[20] The spirometer was flushed by twice collecting exhaled gas, before a third collection was taken for measurement of the mixed expired oxygen fraction[21] (FEo_2) and mixed expired carbon dioxide fraction[4] ($FEco_2$) (see Fig. 3). Oxygen and carbon dioxide analyzers were calibrated prior to each experiment using standard gases of known composition.

---

[19]K & E Compensating Polar Planimeter, Keuffel and Esser Co., Detroit, Mich.
[20]Warren-Collins Co., Braintree, Mass.
[21]Beckman OM-14 Oxygen Analyzer, Fullerton, Calif.
[4]Beckman LB-2 CO_2 Analyzer, Fullerton, Calif.

FIGURE 2

Method used in the calculation of static compliance (C_{stat}) from recorded pressure-volume tracings.

Figure 2A illustrates a typical tracing of changes in transpulmonary pressure (P_{tp}) and airflow ($\dot{V}$) during inflation and subsequent deflation of the lung with known volumes of air (V).

Figure 2B describes the method for calculation of C_{stat} from a static pressure volume loop and illustrates the effect of vital capacity maneuvers on the hysteresis behavior of the lung. Changes in P_{tp} (horizontal axis) are plotted against V (vertical axis).

Fig. 2A

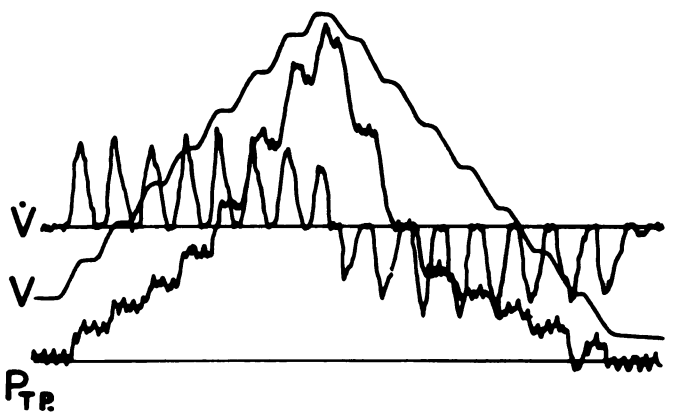


Fig. 2B

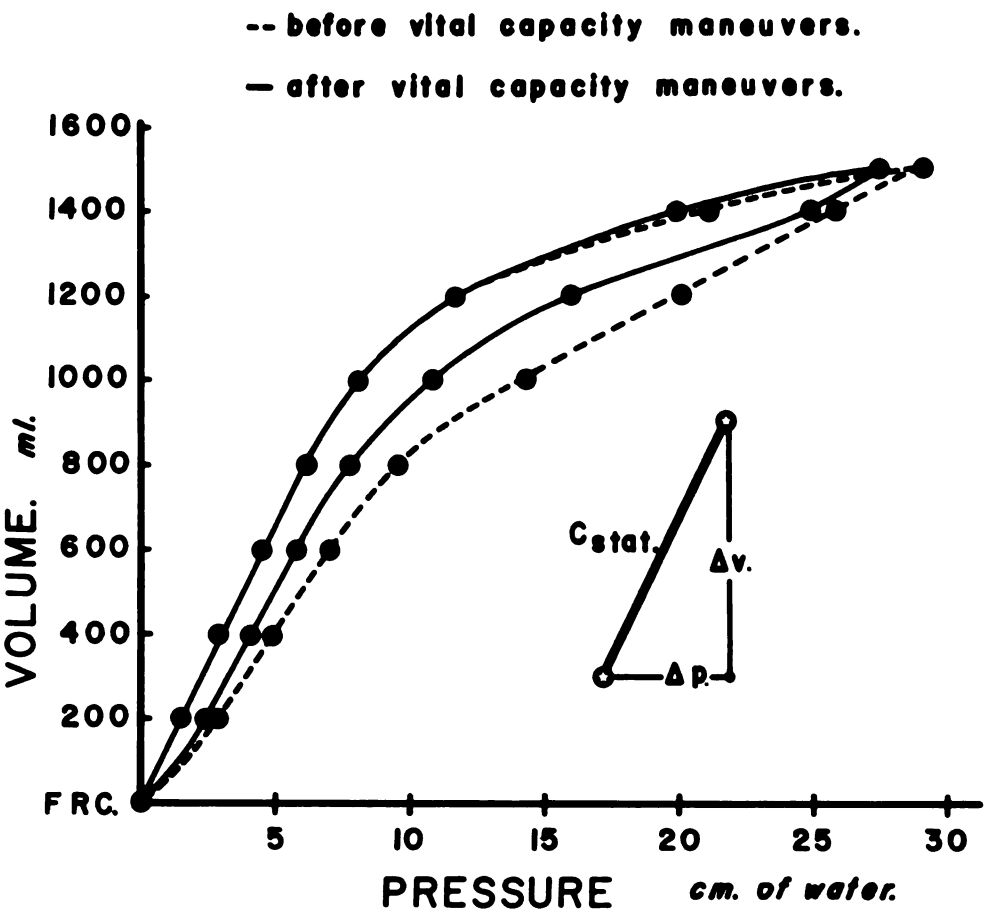


FIGURE 2

FIGURE 3

Schematic diagram of calf instrumentation for measurement of pulmonary mechanical and gas exchange variables. The shaded area represents air flow during normal respiration. Continuous recordings of gas flow using the pneumotachograph were integrated to also give tidal volume. Transpulmonary pressure was recorded as the difference between pressures at the muzzle and in the thorax, measured by esophageal ballon. The syringe and spirometer were linked to the system during respective measurement of static compliance and gas exchange variables.

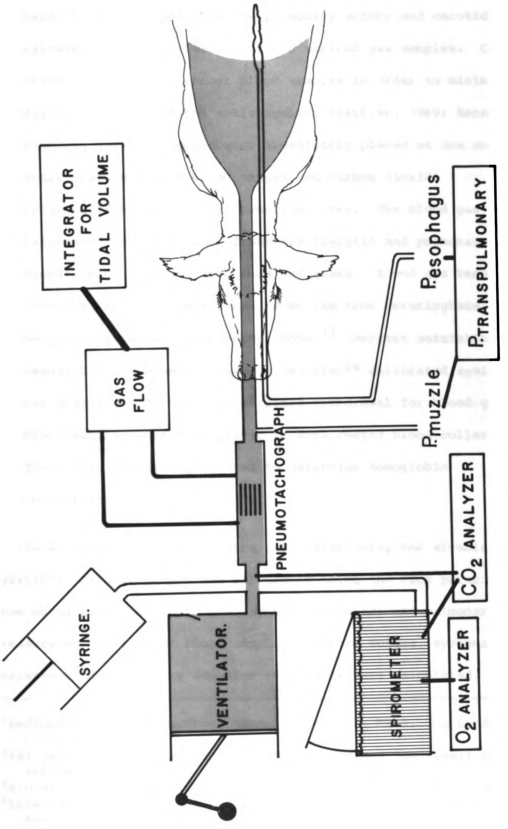

INTEGRATOR FOR TIDAL VOLUME
GAS FLOW
PNEUMOTACHOGRAPH
SYRINGE.
VENTILATOR.
SPIROMETER
O_2 ANALYZER
CO_2 ANALYZER
Pmuzzle
Pesophagus
PTRANSPULMONARY

FIGURE 3

2. Blood Gas Measurements. Blood samples were drawn anerobically into heparinized syringes from the pulmonary artery and carotid artery catheters during collection of the expired gas samples. Care was taken to draw large enough blood samples in order to minimize dilution effects of the anticoagulant (Sattler, 1969; Hansen and Simmons, 1977). Samples were immediately placed on ice and chilled until measurement of blood oxygen and carbon dioxide tensions,[22] usually within twenty minutes. The blood gas analyzer was calibrated for each pair of samples (carotid and pulmonary arterial blood) using standard solutions and gases. Blood gas tensions were corrected to body temperature (Nomogram from Severinghaus, J.W.) as measured by rectal thermometer probe.[23] Percent saturation of hemoglobin was measured with an oximeter[24] calibrated against an optical standard. At the time of blood withdrawal for blood gas analysis, blood samples were also placed in EDTA coated blood collection vials. These samples were later used to determine hemoglobin concentration.[25,26]

Alveolar oxygen tensions were calculated using the alveolar gas equation. Cardiac output was calculated using the Fick principle, and from measurement of heart rate, systemic arterial and pulmonary arterial pressure at the time of blood sampling, stroke volume, systemic vascular resistance and pulmonary vascular resistance were calculated.

---

[22]Radiometer Copenhagen Blood Micro System BMS_3 Mk 2, The London Company, Cleveland, Ohio

[23]YSI Telethermometer Model 41 TF, Yellow Springs Instrument Company, Inc Yellow Springs, Ohio

[24]A.O Micro-Oximeter SM 2700, American Optical Co., Buffalo, N.Y.

[25]Internaltional Microcapillary Centrifuge Model MB., International Equipment Company, Inc., Boston, Mass.

[26]Fisher Haemophotometer, Fisher Scientific Co., Pittsburgh, Penn.

Alveolar-arterial oxygen differences and dead space/tidal volume ratios were also determined. (Equations used in all calculations are listed in Appendix 1).

Experimental Design

All animals were anesthetized and instrumented as described. All measurements described above were made repeatedly in the three groups of calves as outlined below.

Statistical Analysis

Data were analysed in a two way analysis of variance using each animal as its own control, in a completely randomized block experimental design. All calculations were based on the .01 significance level. Mean differences were statistically compared using Tukey's w procedure (Steel R.G.D and Torrie J.H. 1960).

Group I

After control measurements were taken, histamine diphosphate was continuously infused[27] via the previously placed right jugular indwelling catheter using a constant rate infusion pump.[28] Infusion rates were increased until at least a 50% increase in transpulmonary pressures was noted during tidal breathing. Once a steady state was reached, data were collected. Further measurements were taken 15, 30 and 60 minutes after cessation of histamine infusion. In four animals, blood was taken,

---

[27]Histamine diphosphate, Sigma Chemical Co., St. Louis, Miss.
[28]Infusion Pump Model 940, Harvard Apparatus Co., Millis, Mass.

immediately centrifuged[29] and the plasma separated and frozen for subsequent histamine analysis. (Courtesy: Dr. Ken Mathews, Allergy Section, Medical School, University of Michigan, Ann Arbor, Mich.). In all group I calves, peak expiratory flows were determined by measurement of the maximal flows recorded during passive exhalation.

Group II

After control measurements were taken, calves were given a single intravenous bolus of the H_1 antagonist, Tripelennamine, at a dosage of 5 mg/kg. Measurements were repeated 15 minutes after the bolus was injected. Adequacy of H_1 antagonism was assumed when the rapid intravenous administration of the H_1 agonist PEA[31] at a dosage of 50 mcg/kg produced no observable change in either systemic or pulmonary arterial blood pressure, or transpulmonary pressure. Histamine was then infused at a dose similar to that used in the first group of calves. Once steady-state conditions were achieved, measurements were repeated. The infusion rate of histamine was doubled, and further measurements taken. Additonal measurements were made 15, 30 and 60 minutes after the infusion of histamine ceased.

Group III

Following control measurements, calves were given a single intravenous bolus of the H_2 antagonist, Metiamide[32] at a dosage of 5

---

[29]International Clinical Centrifuge Model CL, International Equipment Co., Needham Heights, Mass.
[30]Tripelennamine, CIBA Chemical Co.
[31]PEA, Courtesy: Smith Kline & French, Philadelphia, Penn.
[32]Metiamide, Courtesy: Smith, Kline and French Laboratories, Philadelphia, Pa.

mg/kg. Fifteen minutes after the injection, measurements were made. Adequacy of H_2 antagonism was assumed when the rapid intravenous administration of the H_2 agonist, Dimaprit[33] (Schaff and Beaven, 1977) at a dosage of 50 mcg/kg produced no observable change in blood pressures or transpulmonary pressure. Histamine was infused as previously described, and the rate adjusted until at least a 50% increase in transpulmonary pressure occurred. Additional measurements were made at 15, 30 and 60 minutes after the infusion of histamine had ceased. Blood samples withdrawn for measurement of hemoglobin content, as previously described, were also used in the determination of haematocrit[25] and total solids, as measured by refractometer.[34]

---

[33]Dimaprit, Courtesy: Smith, Kline and French Laboratories, Philadelphia Pa.

[25]International Microcapillary Centrifuge Model MB, International Equipment Co., Boston, Mass.

[34]American Optical Co., Buffalo, N.Y.

RESULTS

A. Group I

Histamine diphosphate was infused into five calves, at an average dose rate of 24.4 mcg/kg/min of histamine base (range 15.2 to 38.0 mcg/kg/min). Cardiovascular, gas exchange and pulmonary mechanics variables were measured during five periods, designated as follows:

"Control" - prior to histamine infusion.

"Histamine" - during histamine infusion, after steady state conditions had been reached.

"15-PH", "30-PH" and "60-PH" - respectively 15, 30 and 60 minutes after the infusion of histamine had ceased. All comparisons between means were conducted at the .01 significance level.

1) Effect on Pulmonary Mechanics

Infusion of histamine failed to alter C_{stat} (for mean values of all measurements see Appendix B) but decreased $C_{dyn.}$ to less than half its control value. After vital capacity maneuvers (v.c.) "histamine" and control $C_{dyn.}$ values did not differ (see Fig. 4, table 1a).

Histamine caused a greater than two fold increase in R_{aw} (Fig. 5) and P_{tp} (Fig. 6). Vital capacity maneuvers did not alter the effects of histamine on R_{aw} (table 1b) and after vital capacity maneuvers, P_{tp} measurements were not significantly different from mean "control" P_{tp} values.

TABLE 1

Statistical comparison between means for C_{dyn}, R_{aw}, and P_{tp} in group I calves.

a. C_{dyn} (ml/cm H_2O)

Histamine*	15-PH	30-PH	Histamine-VC	60-PH	Control	Control V C	30-PH VC	15-PH VC	60-PH VC
37.6	76.5	90.2	92.0	95.0	95.1	116.9	123.8	125.7	128.5

b. R_{aw} (cm H_2O/litre.min^{-1})

Control	Control VC	60-PH	60-PH VC	30-PH	15-PH	30-PH VC	15-PH VC	Histamine VC	Histamine
.053	.062	.068	.072	.081	.085	.090	.091	.116	.119

c. P_{TP} (cm H_2O)

60-PH VC	30-PH VC	Control VC	15-PH VC	60-PH	Control	30-PH	Histamine VC	15-PH	Histamine
6.68	7.40	7.45	7.84	8.23	8.89	9.04	10.20	10.40	20.14

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 4

Effect of histamine and vital capacity maneuvers on dynamic compliance (C_{dyn}) in Group I calves. C_{dyn} is plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

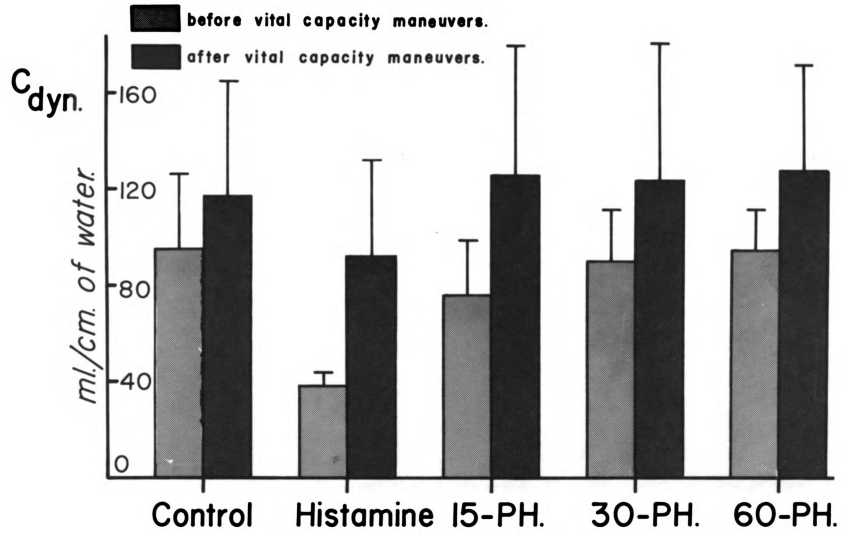

before vital capacity maneuvers.
after vital capacity maneuvers.
$C_{dyn.}$
ml./cm. of water.
160
120
80
40
0
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 4

FIGURE 4

Effect of histamine and vital capacity maneuvers on dynamic compliance (C_{dyn}) in Group I calves. C_{dyn} is plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

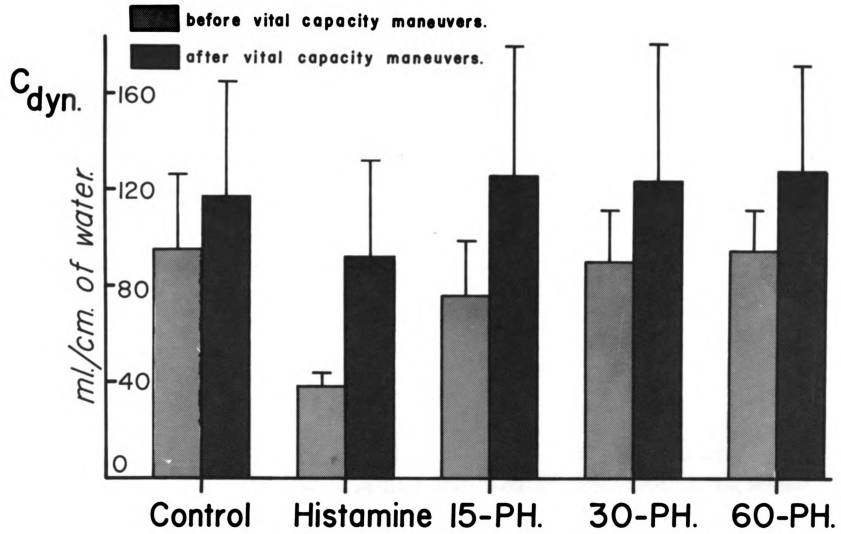

before vital capacity maneuvers.
after vital capacity maneuvers.
$C_{dyn.}$
ml./cm. of water.
160
120
80
40
0
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 4

FIGURE 5

Effect of histamine infusion and vital capacity maneuvers on airway resistance (R_{aw}) in Group I calves.

R_{aw} is plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

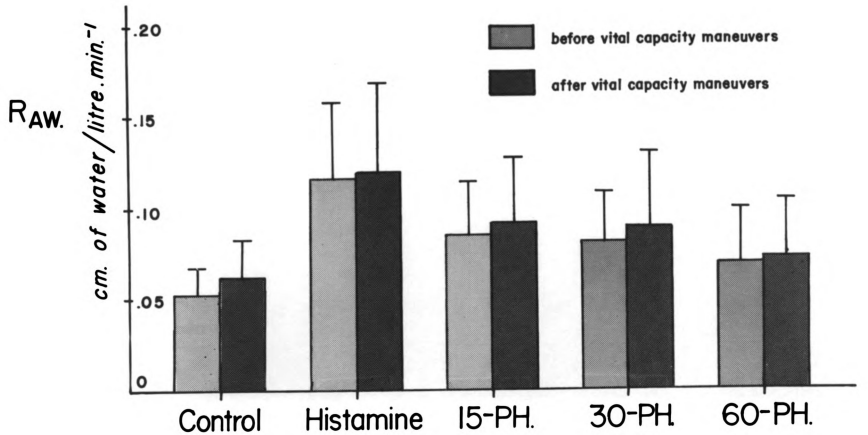

$R_{AW.}$
cm. of water/litre.min.$^{-1}$
.20
.15
.10
.05
0
before vital capacity maneuvers
after vital capacity maneuvers
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 5

FIGURE 6

Effect of histamine infusion and vital capacity maneuvers on maximal transpulmonary pressure (P_{tp-Max}) in Group I calves.

P_{tp-MAX} is plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

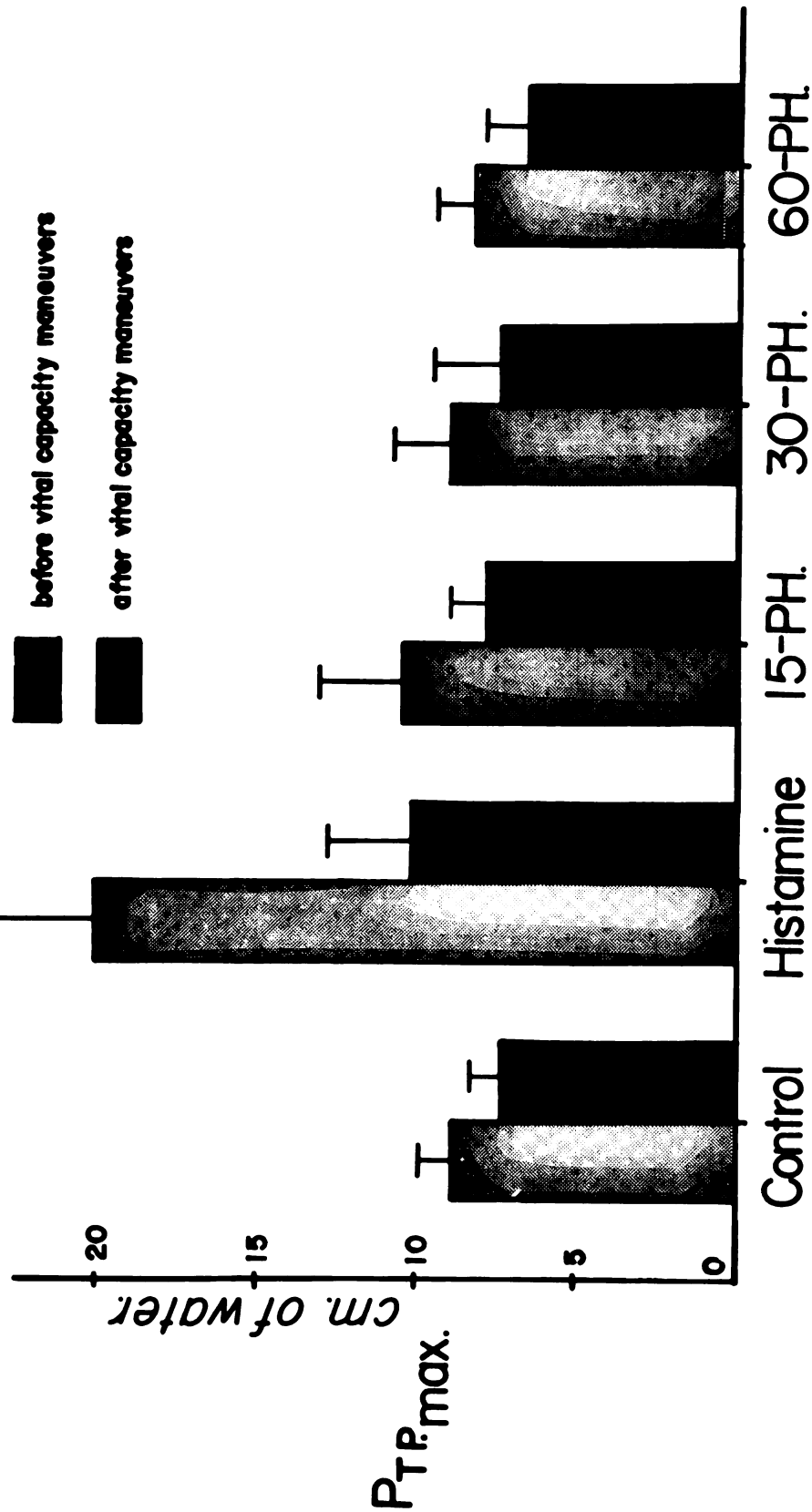

before vital capacity maneuvers
after vital capacity maneuvers
$P_{T.P._{max.}}$
cm. of water
20
15
10
5
0
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 6

Histamine increased P-V hysteresis (Fig. 7) and peak expiratory flow rates ($P\dot{V}_{EX}$) (Fig. 8) but these effects were significantly reduced by vital capacity maneuvers (table 2).

FIGURE 7

Effect of histamine infusion and vital capacity maneuvers on pressure-volume hysteresis (P-V hysteresis) in Group I calves.

P-V hysteresis is plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

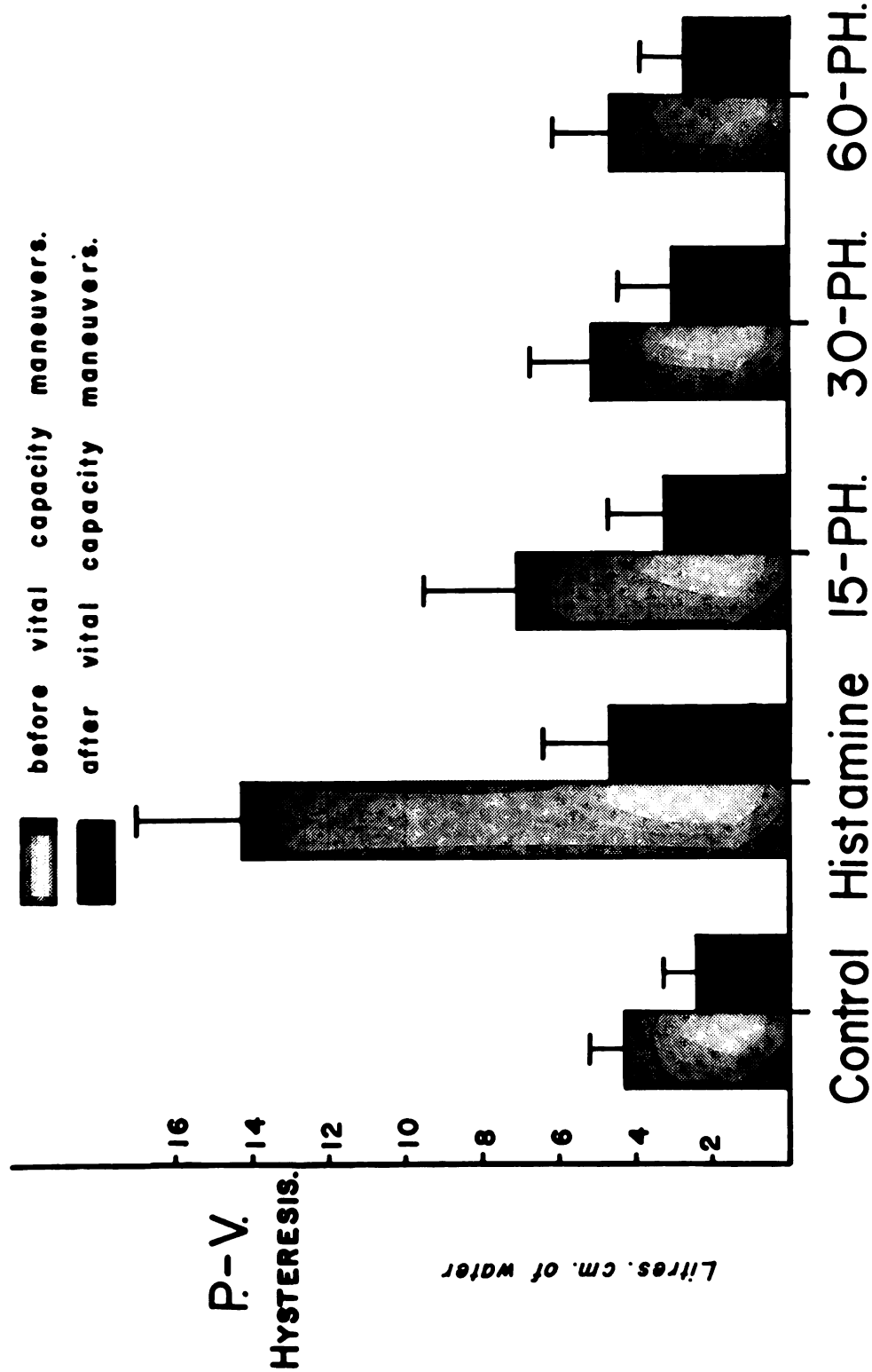

before vital capacity maneuvers.
after vital capacity maneuvers.
P.-V. HYSTERESIS.
Liters. cm. of water
16
14
12
10
8
6
4
2
Control
Histamine 15-PH.
30-PH.
60-PH.

FIGURE 7

FIGURE 8

Effect of histamine infusion and vital capacity maneuvers on peak expiratory flow ($P\dot{V}_{EX}$) in Group I calves.

$P\dot{V}_{(EX)}$ is plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

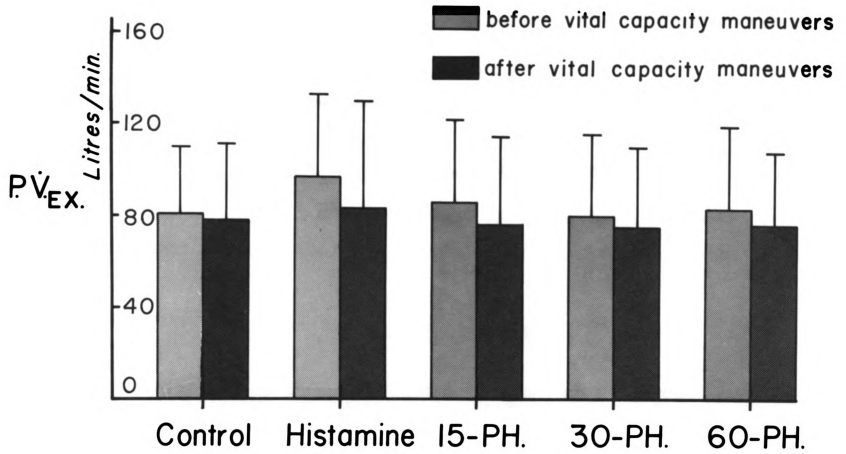

before vital capacity maneuvers
after vital capacity maneuvers
P.V̇EX. Litres/min.
160
120
80
40
0
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 8

TABLE 2

Statistical comparison between means for P-V hysteresis and P.E.V. in group I calves.

a. $P\text{-}V_{hysteresis}$ (liters.cm H_2O)

Control VC	60-PH VC	30-PH VC	15-PH VC	Control	60-PH	Histamine VC	30-PH	15 PH	Histamine
2.41	2.67	3.03	3.22	4.25	4.57	4.66	5.10	7.08	14.22

b. $P.E.\dot{V}.$ (liters/min)

30-PH VC	15-PH VC	60-PH VC	Control VC	30-PH	Control	60-PH	Histamine VC	15-PH	Histamine
74.6	76.1	76.3	78.1	79.5	81.4	82.7	83.3	86.3	96.9

* Means underscored by same line are not statistically significant at the .01 level

ii) Gas Exchange

PaO_2 decreased 38 mm Hg below control values, due to a 34 mm Hg rise in the (A-a) O_2 difference (Fig. 9, table 3). Changes in PAO_2 and $VD/_{VT}$ were not significant.

TABLE 3

Statistical comparison between means for PaO_2 and (A-a) O_2 differences in Group I calves.

a. PaO_2 (mm.Hg)

Histamine	15-PH	30-PH	60-PH	Control
28.7	52.8	63.2	65.3	66.6

b. (A-a) O_2 Difference (mm.Hg)

60-PH	30-PH	Control	15-PH	Histamine
39.7	40.5	43.1	54.5	77.0

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 9

Effect of histamine infusion on gas exchange in Group I calves. Alveolar-arterial oxygen differences and systemic arterial oxygen tension are plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

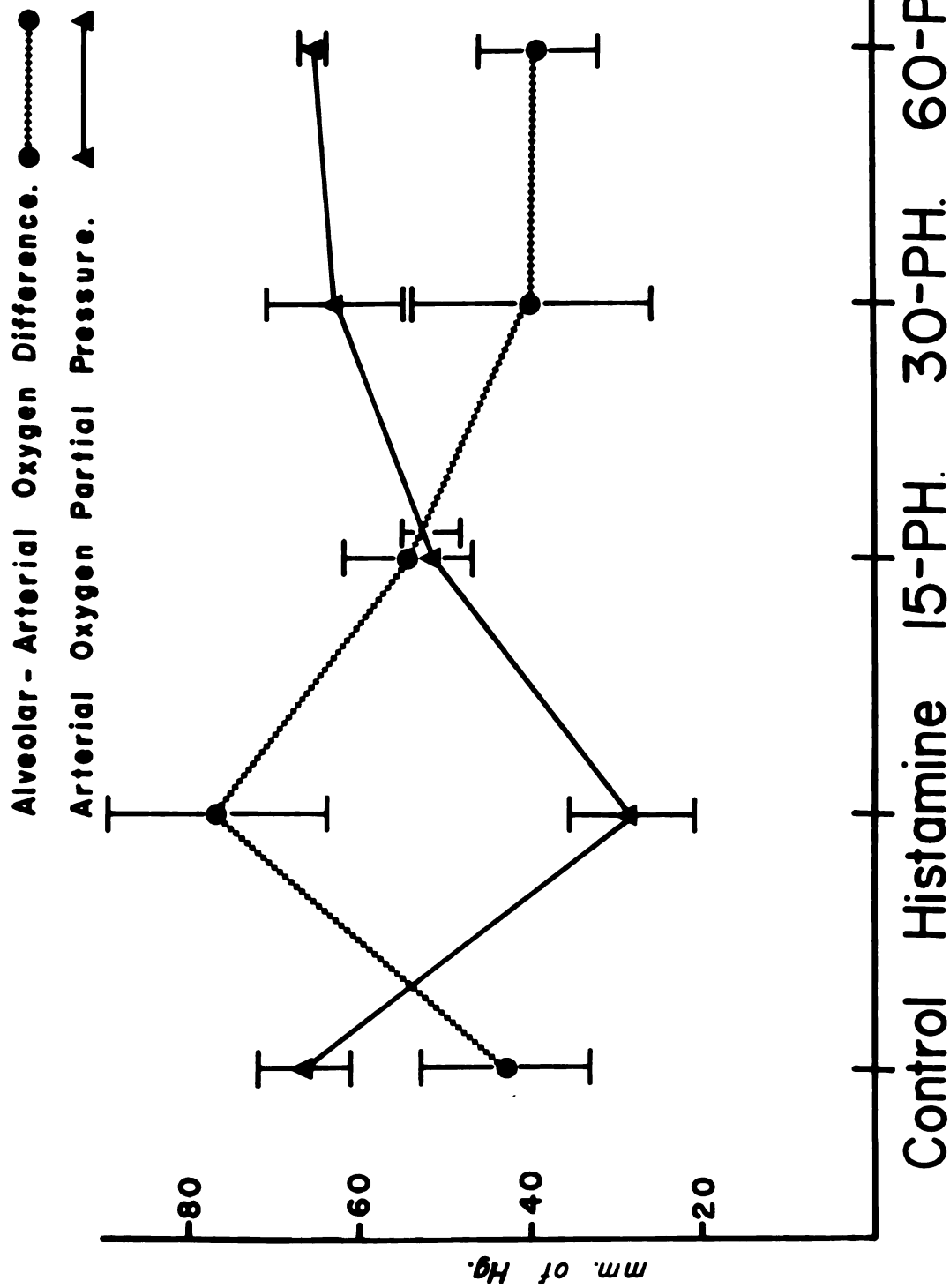

Alveolar - Arterial Oxygen Difference.
Arterial Oxygen Partial Pressure.
mm. of Hg.
80
60
40
20
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 9

iii) Cardiovascular Effects of Histamine

Cardiac output decreased by an average of 8.3 liters/min during histamine infusion, and did not significantly recover in the hour following the infusion (table 4a). The decrease in cardiac output was accompanied by a decrease in pulmonary artery pressure (Fig. 10, table 4b). Significant increases in pulmonary vascular resistance could only be demonstrated between "control" and "60-PH" mean values (table 4c).

Mean systemic arterial pressure decreased by an average of 74 mm Hg during histamine infusion and failed to recover significantly over the following hour (Fig. 11, table 5a). Systemic vascular resistance did not change. Increases in heart rate occurred during histamine infusion, and were accompanied by corresponding decreases in stroke volume (Fig. 12, table 5).

TABLE 4

Statistical comparison between means for cardiac output, pulmonary artery pressure and pulmonary vascular resistance in group I calves.

a) Cardiac Output (liters/min)

15-PH	60-PH	Histamine	30-PH	Control
4.99	5.38	5.42	5.63	13.70

b) Pulmonary Artery Pressure (mm Hg)

Histamine	15-PH	30-PH	60-PH	Control
19.8	23.8	28.2	30.0	30.6

c) Pulmonary Vascular Resistance (mm Hg/Liter min^{-1})

Control	Histamine	15-PH	30-PH	60-PH
2.48	3.85	5.07	5.27	6.19

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 10

Effect of histamine infusion on pulmonary vasculature in Group I calves. Cardiac output, pulmonary vascular resistance and pulmonary artery pressure are plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

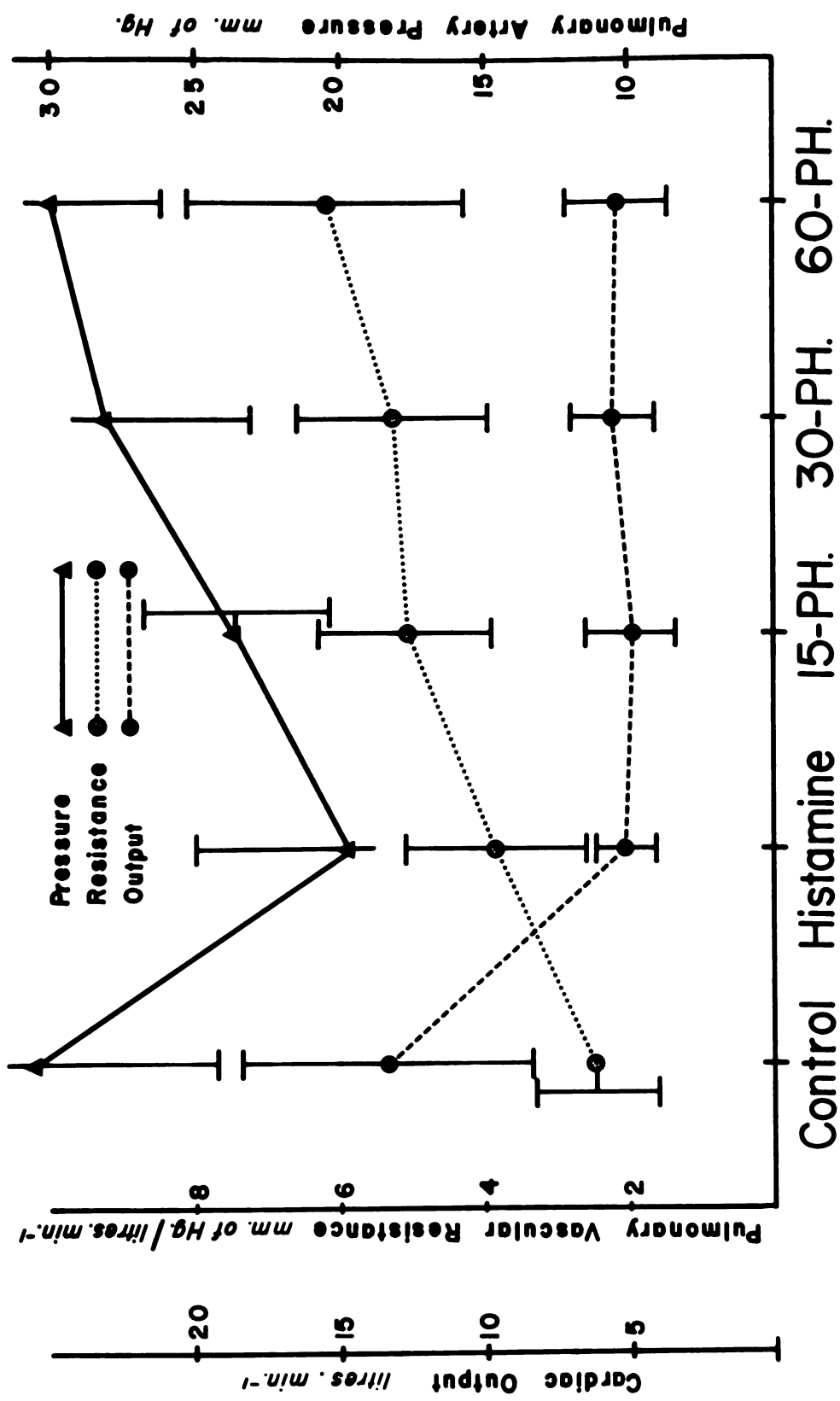

Cardiac Output litres . min.-1
20
15
10
5
Pulmonary Vascular Resistance mm. of Hg. / litres. min.-1
8
6
4
2
Pulmonary Artery Pressure mm. of Hg.
30
25
20
15
10
Pressure
Resistance
Output
Control
Histamine 15-PH.
30-PH.
60-PH.

FIGURE 10

FIGURE 11

Effect of histamine infusion on systemic vasculature in Group I calves. Cardiac output, systemic vascular resistance and systemic arterial pressure are plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

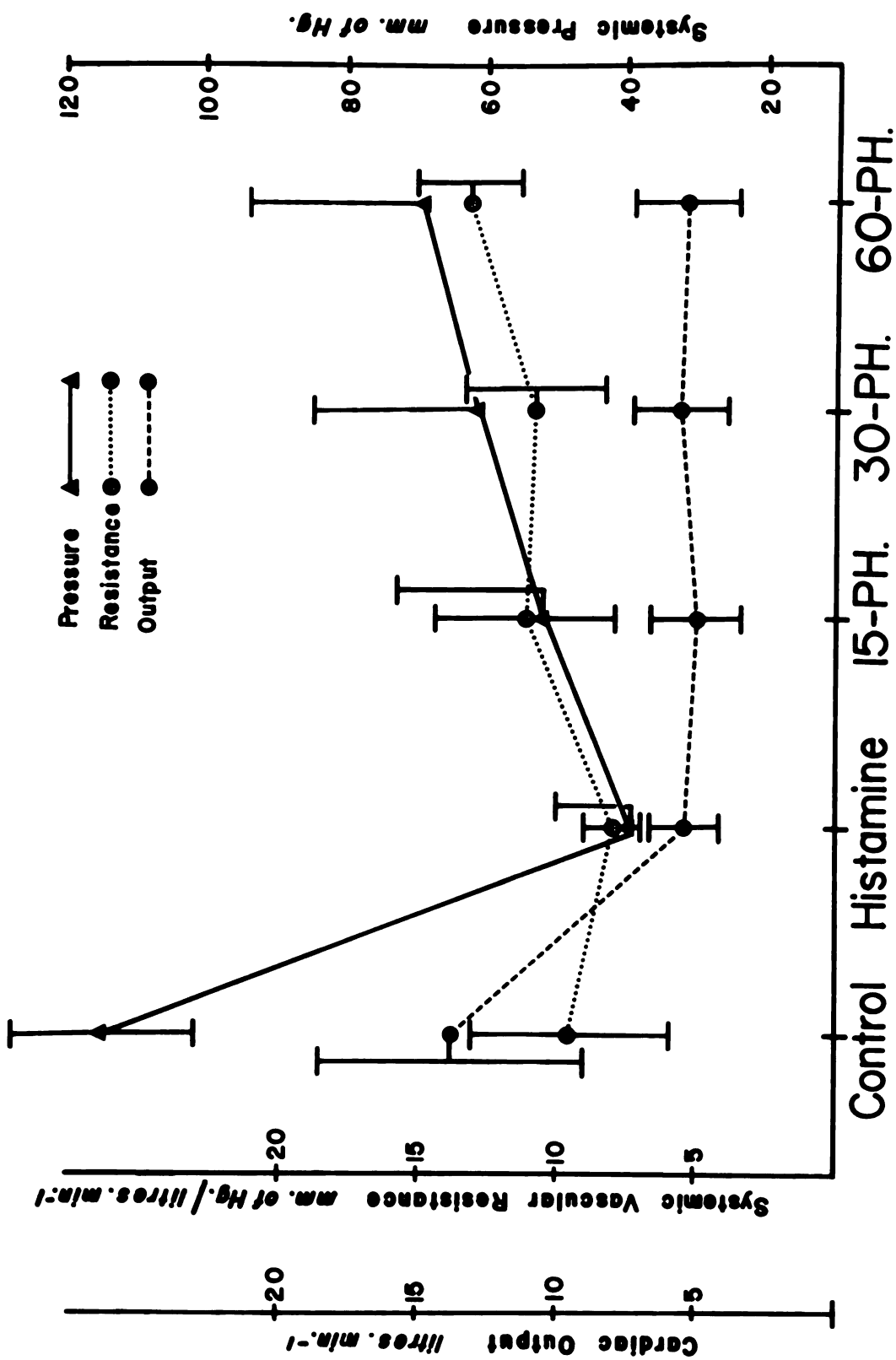

Cardiac Output litres. min.-1
Systemic Vascular Resistance mm. of Hg./ litres. min.-1
Systemic Pressure mm. of Hg.
Pressure
Resistance
Output
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 11

FIGURE 12

Effect of histamine infusion on cardiac output, stroke volume and heart rate in Group I calves. The measured variables are plotted on the vertical axis. The different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

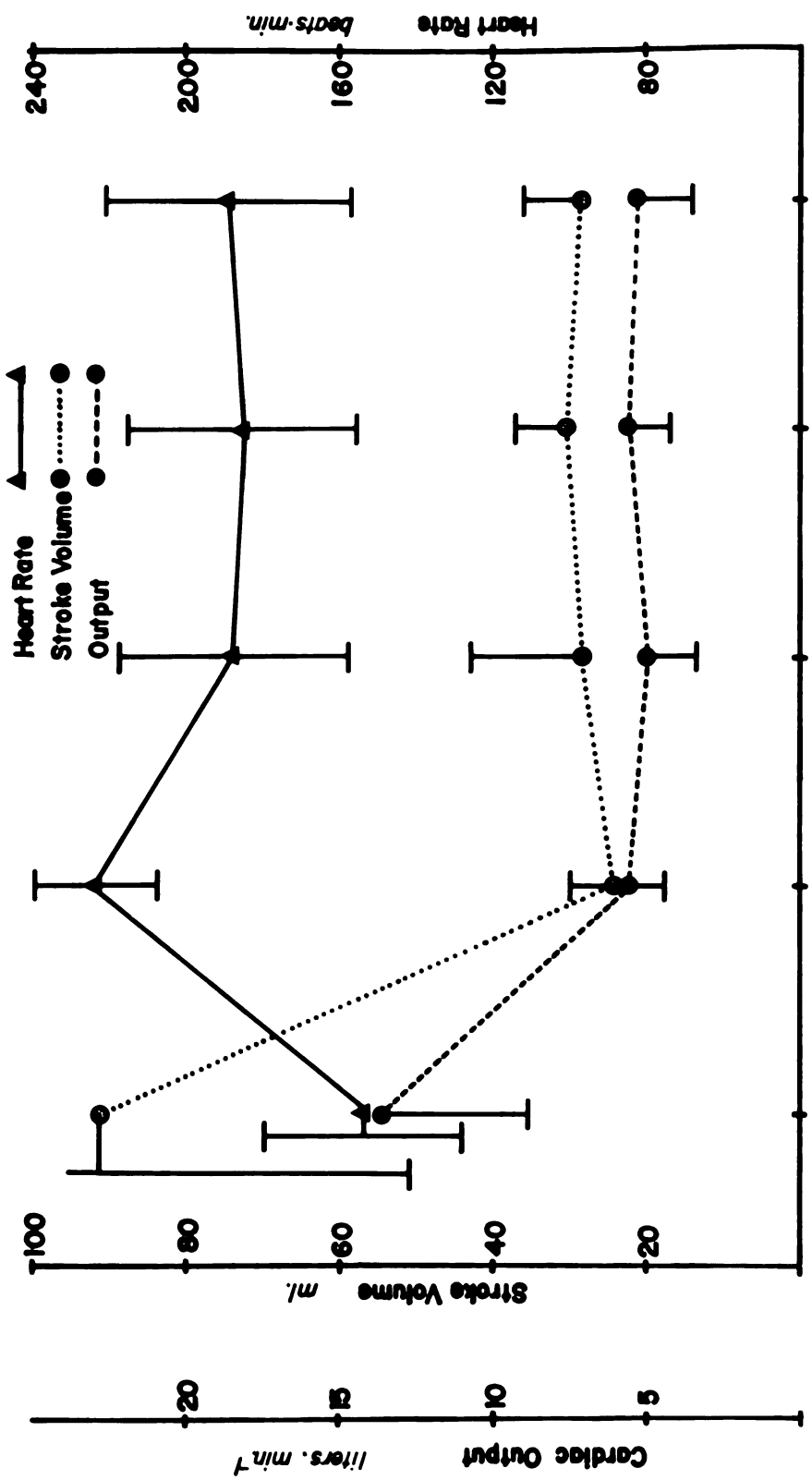

Heart Rate
Stroke Volume
Output
Heart Rate beats·min.
240
200
160
120
80
Stroke Volume ml.
100
80
60
40
20
Cardiac Output liters. min.⁻¹
20
15
10
5
Control
Histamine
15-PH.
30-PH.
60-PH.

FIGURE 12

TABLE 5

Statistical comparison between means for systemic arterial pressure, heart rate and stroke volume in group I calves.

a) Systemic Arterial Pressure (mm Hg)

Histamine	15-PH	30-PH	60-PH	Control
41.4	54.6	63.0	69.2	115.4

b) Heart rate (beats/min)

Control	30-PH	15-PH	60-PH	Histamine
154.4	185.2	189.2	189.8	224.8

c) Stroke Volume (ml)

Histamine	60-PH	15-PH	30-PH	Control
24.3	28.3	28.4	30.5	91.6

* Means underscored by same line are not statistically significant at the .01 level

Significant differences were found to exist between animals for the following variables:

a) Pulmonary mechanics - C_{stat}, C_{dyn}, R_{aw}, P_{tp}, $\dot{PV}_{EX}$, $PV_{Hysteresis}$

b) Gas exchange - $VD/_{VT}$, PAO_2, $(A\text{-}a)O_2$ Difference

c) Cardiovascular variables - $P_{syst.}$, Heart rate, Systemic vascular resistance

iv) General Observations

Calves died soon after removal from the ventilator despite resuming spontaneous respiration. At post-mortem, the small and large intestines were frequently distended with gas and fluid and the lungs failed to collapse completely. There was no gross evidence of atelectasis or pulmonary edema.

v) Blood histamine levels

Mean plasma histamine levels rose from an average of 5.3 ng/ml prior to histamine infusion to 196.9 ng/ml during histamine infusion. Histamine levels had fallen to an average of 11.1 ng/ml by one hour after cessation of histamine infusion.

B. Group II

Measurements were taken during seven periods, as indicated below. Studies were conducted on six calves.

"Control" - control measurement prior to H_1 antagonist administration.

"H_1 Block" - 15 minutes after the infusion of the H_1 antagonist.

"Lo Hist" - during infusion of a low dose of histamine diphosphate when steady state conditions were reached.

"Hi Hist" - during infusion of a high dose of histamine diphosphate when steady state conditions were reached.

"15-PH", "30-PH" and "60-PH" - measurement periods at 15, 30 and 60 minutes after the cessation of histamine infusion.

Rapid injection of the H_1 antagonist, Tripelennamine (5 mg/kg I/V) resulted in transient increases in resting and maximal P_{TP}, and a biphasic decrease/increase systemic arterial pressure response. Spontaneous return to pre-injection values occurred within several minutes (Fig. 13). No observed changes in blood pressures or transpulmonary pressure occurred following subsequent rapid intravenous administration of the H_1 agonist PEA (50 mcg/kg). Histamine diphosphate was infused at a mean "low dose rate" of 44.4 mcg/kg/min (range 42.0 to 52.9 mcg/kg/min). The average "high dose rate" was 88.6 mcg/kg/min (range 84.1 to 105.9 mcg/kg/min).

FIGURE 13

Typical tracing from a calf given a rapid intravenous bolus of the H_1 antagonist, tripelennamine. Displayed on the vertical axis are systemic pressure (P_{syst}), pulmonary artery pressure (P_{pa}) and transpulmonary pressure (P_{tp}). The time after injection is plotted on the horizontal axis.

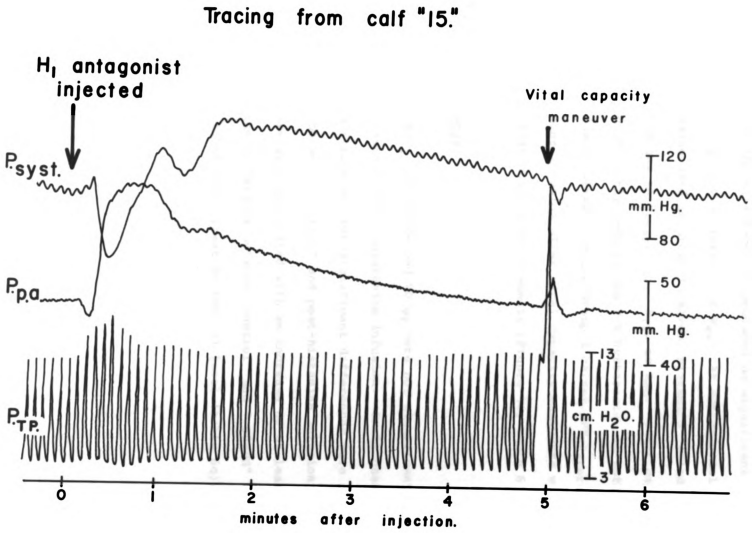

Tracing from calf "15."
H1 antagonist injected
Vital capacity maneuver
Psyst.
120
mm. Hg.
80
Ppa
50
mm. Hg.
40
PT.P.
13
cm. H2O.
3
0
1
2
3
4
5
6
minutes after injection.

FIGURE 13

i) Pulmonary Mechanics

Infusion of the H_1 antagonist produced no significant change in $C_{stat.}$, C_{dyn}, P_{TP}, P-V Hysteresis or R_{aw}. At approximately six times the dose of histamine used in Group I calves, histamine failed to produce significant changes in C_{stat}, C_{dyn}, P_{TP}, or R_{aw}. Vital capacity maneuvers significantly reduced the P-V hysteresis, in both control and histamine infused calves. Unlike Group I calves, $PV_{Hysteresis}$ values during histamine infusion after vital capacity maneuvers were significantly lower than control measurements (Figure 14, table 6).

ii) Gas Exchange

PaO_2, $(A-a)O_2$ difference and $VD/_{VT}$ were not significantly affectd by either the H_1 antagonist or histamine infusion. Small changes in PAO_2 occurred (table 6b) but significant differences were only demonstrated between "control" and post-histamine infusion measurement periods. These were associated with an increase of at least 6.5 mm Hg in $PaCO_2$, with the difference between "control" and " 30-PH" values for $PaCO_2$ found to be significant at the .01 level (table 6c).

FIGURE 14

Effect of H_1 blockade (tripelennamine) and histamine following H_1 antagonism on pressure-volume hysteresis (P-V hysteresis) in Group II calves. The effect of vital capacity maneuvers is also shown.

P-V hysteresis is displayed on the vertical axis and the different measurement periods are plotted on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

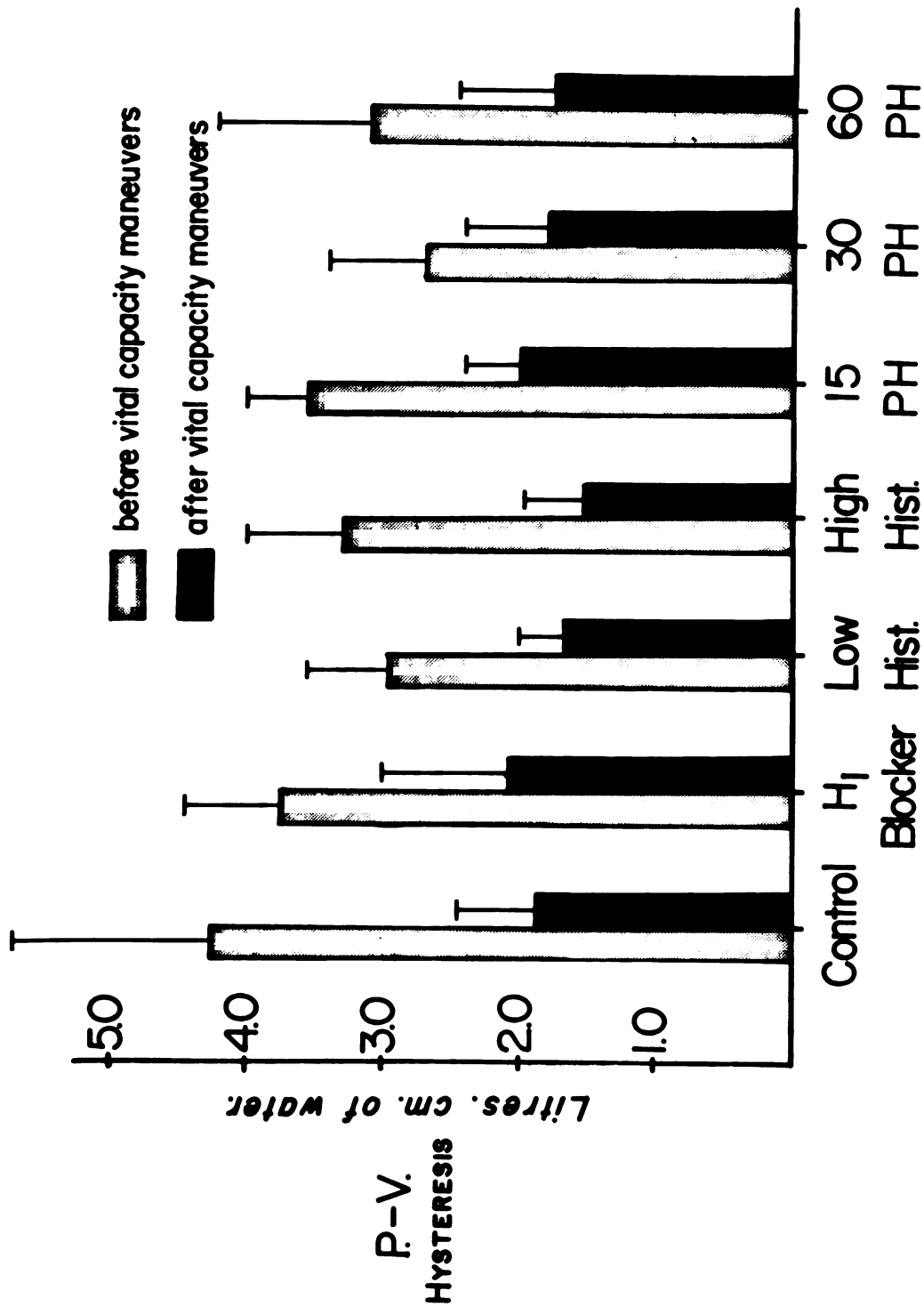

before vital capacity maneuvers
after vital capacity maneuvers
P.-V. HYSTERESIS
Litres. cm. of water
5.0
4.0
3.0
2.0
1.0
Control
H1 Blocker
Low Hist.
High Hist.
15 PH
30 PH
60 PH

FIGURE 14

Table 6

Statistical comparison between means for P-V hysteresis, PAO_2 and $PaCO_2$, Group II calves.

a) P-V hysteresis (litre.cm H_{20})

High HistVC	Low HistVC	60 PH VC	30 PH VC	Control VC	H_1 Block VC	15 PH VC	30PH	Low Hist	60PH	High Hist	15PH	H_1 Block	Control
1.53	1.67	1.77	1.79	1.88	2.09	2.10	2.70	2.97	3.10	3.31	3.56	3.76	4.27

b) PAo_2 (mm Hg)

60-PH	30-PH	15-PH	H_1 Block	High Hist	Low Hist	Control
89.82	91.32	91.85	93.60	94.67	95.38	99.99

c) $PaCO_2$ (mm Hg)

Control	Low Hist	H_1 Block	High Hist	15-PH	30-PH	60-PH
32.5	36.7	37.5	37.9	39.1	40.6	40.7

* Means underscored by same line are not statistically significant at the .01 level

iii) Cardiovascular Effects

There was no change in cardiac output during histamine infusion but, at the high dose rate, histamine halved systemic vascular resistance and decreased systemic arterial pressure by an average of 42 mm Hg (Fig. 15, table 7). Heart rate increased in all measurement periods subsequent to H_1 antagonist administration (Table 8a). Changes in stroke volume were not significant. Decreased pulmonary vascular resistance following histamine infusion was accompanied by decreased pulmonary artery pressure (Fig. 16, table 8b).

TABLE 7

Statistical comparison between means for systemic vascular resistance and systemic pressure, Group II calves.

a) Systemic Vascular Resistance (mm Hg/Litre min^{-1})

High Hist	Low Hist	15-PH	30-PH	H_1 Block	60-PH	Cont.
5.50	5.64	8.28	9.39	10.51	10.86	11.31

b) Systemic Pressure (mm Hg)

H_1 Hist	Lo Hist	Cont.	15-PH	30-PH	60-PH	H_1 Block
78.3	91.7	110.7	111.3	118.5	120.0	121.7

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 15

Effect of H_1 blockade (tripelennamine) and histamine following H_1 antagonism on systemic vasculature in Group II calves. Systemic pressure and systemic vascular resistance are displayed on the vertical axis, and the different measurement periods on the horizontal axis, where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Standard error bars are calculated for the .01 significance level.

Systemic Pressure. (mm. Hg.)
160
120
80
40
0
Systemic pressure.
Systemic vascular resistance.
Control
H1 Blocker
Low Hist.
High Hist.
15 P.H.
30 P.H.
60 P.H.
16
12
8
4
0
Systemic Vascular Resistance. (mm. Hg./Litre.min.-1)

FIGURE 15

TABLE 8

Statistical comparison between means for heart rate, pulmonary vascular resistance and pulmonary artery pressure, Group II calves.

a) Heart rate (beats/min)

Control	H_1 block	60-PH	30-PH	15-PH	High Hist	Low Hist
165.0	189.8	194.2	195.0	202.6	228.0	234.5

b) Pulmonary Vascular Resistance (mm Hg/litre min^{-1})

Lo Hist.	Hi Hist	15-PH	30-PH	60-PH	H_1 Block	Cont
1.71	1.97	2.28	2.56	2.74	3.15	3.45

c) Pulmonary Artery Pressure (mm Hg)

Hi Hist	Lo Hist	15-PH	60-PH	30-PH	Cont.	H_1 Block
27.0	27.8	30.3	30.5	32.7	35.7	38.2

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 16

Effect of H_1 blockade (tripelennamine) and histamine following H_1 antagonism on pulmonary vasculature in Group II calves. Pulmonary artery pressure and pulmonary vascular resistance are displayed on the vertical axis, and the different measurement periods on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Low Hist. and High Hist. designate measurement periods at which time histamine was infused at two different dose rates.

Standard error bars are calculated for the .01 significance level.

Pulmonary artery Pressure.
(mm. Hg.)
40
30
20
10
Pulmonary Artery Pressure.
Pulmonary Vascular Resistance.
Pulmonary vascular Resistance.
(mm. Hg. Litre min.-1)
4
3
2
1
Control
H1 Blocker
Low Hist.
High Hist.
15 PH.
30 PH.
60 PH.

FIGURE 16

iv) General Observations

Significant animal to animal variation was found in Group II calves in all variables measured. Unlike Group I calves, animals did not die when removed from the ventilator despite receiving over six times the dose of histamine as the first group. No lesions were observed on post-mortem.

C. Group 3

Histamine diphosphate was infused into six calves at an average dose rate of 11.9 mcg/kg/min (range 4.55 to 18.4 mcg/kg/min). Measurements of pulmonary mechanical, gas exchange and cardiovascular variables were performed during six periods designated as follows:

"Control" - prior to administration of H_2 antagonist.

"H_2 Blocker" - 15 minutes after the rapid intravenous injection of metiamide (5 mg/kg).

"Hist" - during histamine infusion, after steady state conditions had been reached.

"15-PH, "30-PH" and "60-PH" - 15, 30 and 60 minutes after cessation of histamine infusion.

i) Effect on Pulmonary Mechanics

Histamine infusion caused a decrease of 30 ml/cm H_2O in C_{dyn} (Fig 17, table 9). This effect was reversed by vital capacity maneuvers. R_{aw} doubled during histamine infusion (Fig. 18). Vital capacity maneuvers failed to return R_{aw} to control values. Increases in P_{TP} (Fig. 19) and P-V Hysteresis (Fig. 20) caused by histamine, were reversed by vital capacity maneuvers. No significant changes occurred in C_{stat}.

FIGURE 17

The effect of H_2 blockade (metiamide) and histamine following H_2 antagonism on dynamic compliance (C_{dyn}) in Group III calves. The effects of vital capacity maneuvers are also illustrated. $C._{dyn}$ is plotted on the vertical axis, and the different measurement periods on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Hist. = measurement during histamine infusion.

Standard error bars are calculated for the .01 significance level.

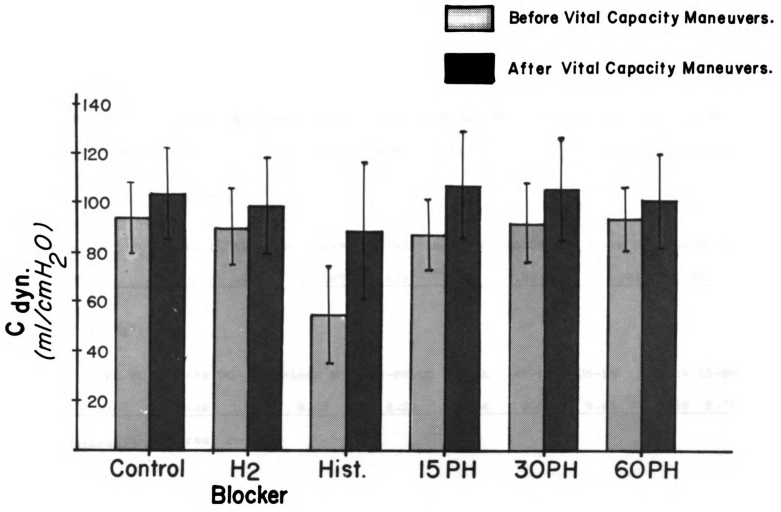

Before Vital Capacity Maneuvers.
After Vital Capacity Maneuvers.
C dyn.
(ml/cm H2O)
140
120
100
80
60
40
20
Control
H2
Hist.
15 PH
30PH
60PH
Blocker

FIGURE 17

TABLE 9

Statistical comparison between means for C_{dyn}, R_{aw}, P_{tp} and P-V hysteresis, group III calves.

a) C_{dyn} (ml/cm H_2O)

Hist	15-PH	Hist VC	H_2 Block	30-PH	60-PH	Cont	H_2 Block VC	60-PH VC	Cont. VC	30-PH VC	15-PH VC
54.9	87.4	89.1	90.5	92.5	94.2	94.4	99.7	101.2	104.9	106.2	107.8

b) R_{aw} (cm H_2O/liter min^{-1})

Cont.	Cont VC	H_2 Block	H_2 Block VC	60-PH	30-PH	30-PH VC	60-PH VC	15-PH VC	15-PH	Hist VC	Hist
.064	.067	.068	.072	.077	.078	.079	.081	.084	.085	.127	.142

c) P_{TP} (cm. H_2O)

Cont VC	30-PH VC	15-PH VC	H_2 Block VC	60-PH VC	Cont	60-PH	30-PH	H_2 Block	15-PH	HistVC	Hist
8.01	8.22	8.28	8.28	8.29	8.74	9.01	9.05	9.06	9.70	10.00	16.98

d) $P\text{-}V_{hysteresis}$ (litres. cm H_2O)

Cont VC	H_2 Block VC	30-PH VC	60-PH VC	15-PH VC	H_2 Block	Cont.	30-PH	60-PH	Hist VC	15-PH	Hist
2.23	2.30	2.36	2.40	2.52	3.41	3.45	3.63	3.87	3.95	4.40	12.2

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 18

The effect of H_2 blockade (metiamide) and histamine following H_2 antagonism on airway resistance (R_{aw}) in Group III calves. The effects of vital capacity maneuvers are also illustrated. R_{aw} is plotted on the vertical axis, and the different measurement periods on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Hist. = measurement during histamine infusion.

Standard error bars are calculated for the .01 significance level.

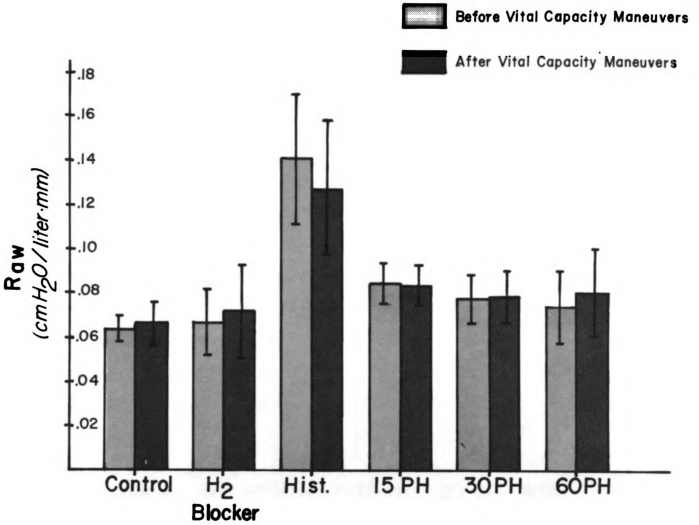

Before Vital Capacity Maneuvers
After Vital Capacity Maneuvers
Raw
(cm H2O / liter·mm)
.18
.16
.14
.12
.10
.08
.06
.04
.02
Control
H2 Blocker
Hist.
15 PH
30 PH
60 PH

FIGURE 18

FIGURE 19

The effect of H_2 blockade (metiamide) and histamine following H_2 antagonism on transpulmonary pressure (P_{tp}) in Group III calves. The effects of vital capacity maneuvers are also illustrated. P_{tp} is plotted on the vertical axis, and the different measurement periods on the horizontal axis, where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Hist. = measurement during histamine infusion.

Standard error bars are calculated for the .01 significance level.

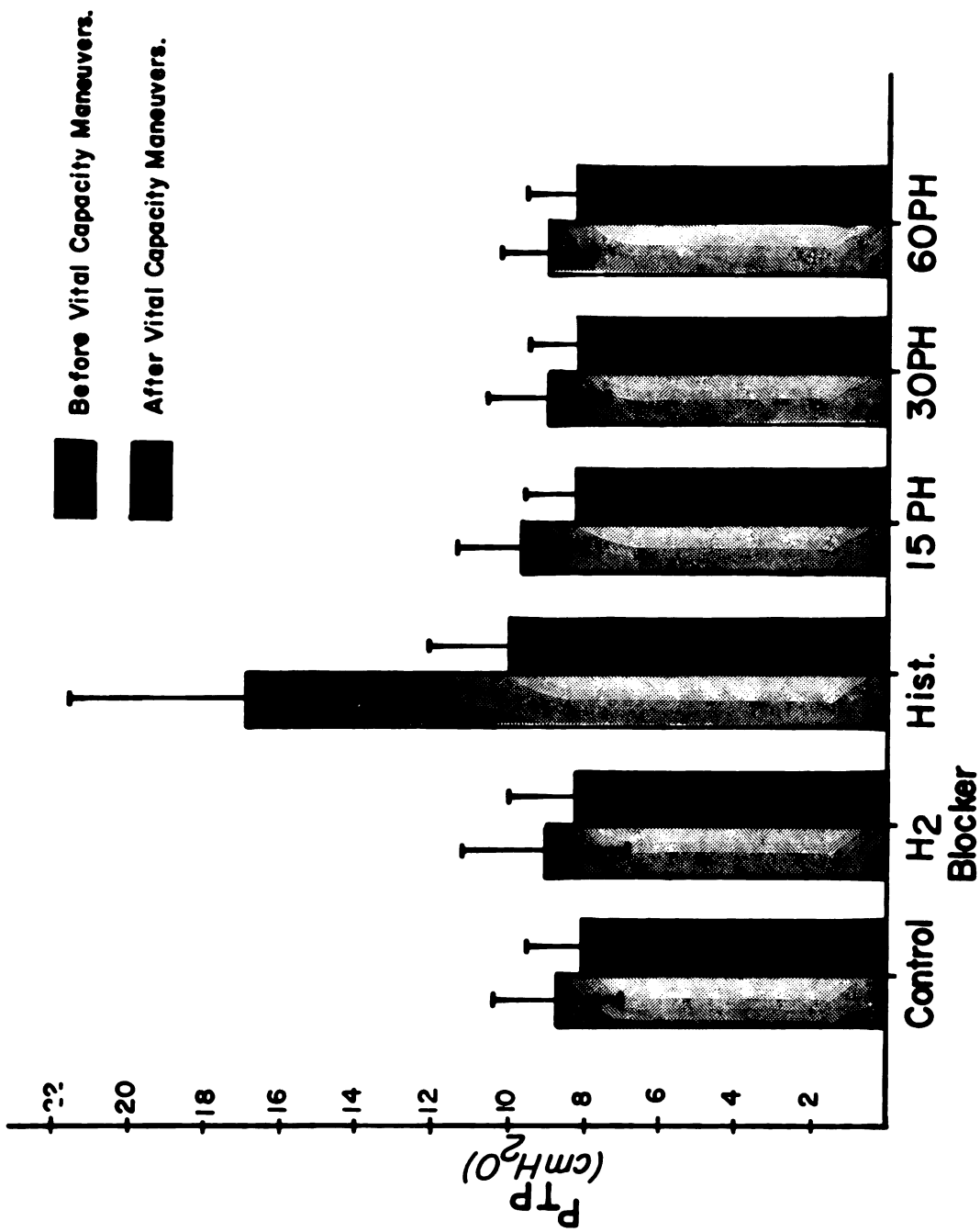

Before Vital Capacity Maneuvers.
After Vital Capacity Maneuvers.
P_{TP} (cmH_2O)
22
20
18
16
14
12
10
8
6
4
2
Control
H2 Blocker
Hist.
15 PH
30PH
60PH

FIGURE 19

FIGURE 20

The effect of H_2 blockade (metiamide) and histamine following H_2 antagonism on pressure-volume hysteresis (P-V hysteresis) in Group III calves. The effects of vital capacity maneuvers are also illustrated. P-V hysteresis is plotted on the vertical axis, and the different measurement periods on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Hist. = measurement during histamine infusion.

Standard error bars are calculated for the .01 significance level.

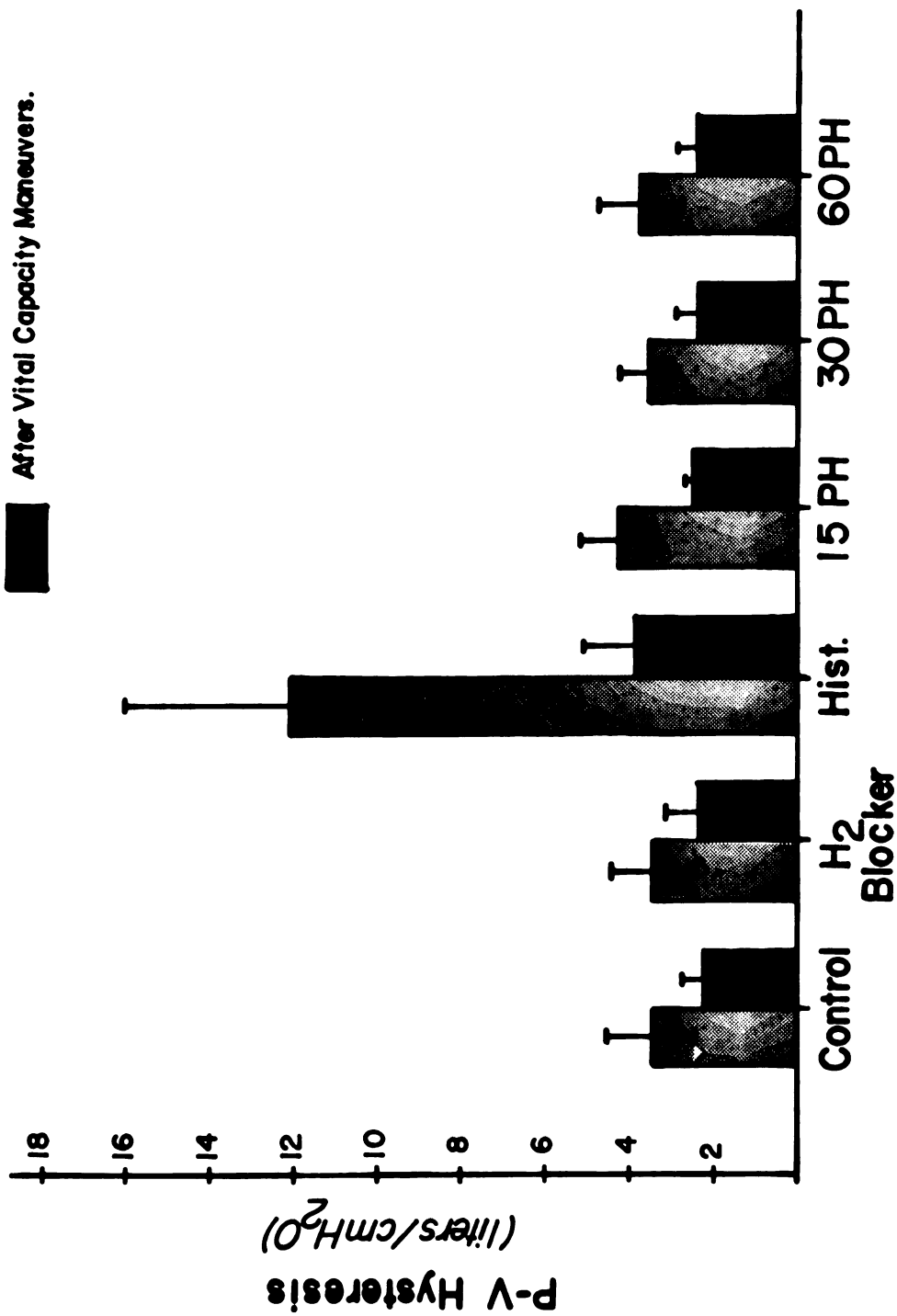

Before Vital Capacity Maneuvers.
After Vital Capacity Maneuvers.
P-V Hysteresis
(liters/cmH2O)
18
16
14
12
10
8
6
4
2
Control
H2 Blocker
Hist.
15 PH
30PH
60PH

FIGURE 20

ii) Effects on Gas Exchange

Histamine decreased PaO_2 by an average of 41 mm Hg below control values, with a concurrent increase in $(A-a)O_2$ difference of 44 mm Hg. (Fig. 21, table 10). No significant change in PAO_2 or $VD/_{VT}$ was found.

TABLE 10

Statistical comparison between means for PaO_2 and $(A-a)O_2$ differences, group III calves.

a) PaO_2 (mm Hg)

Hist.	60-PH	15-PH	30-PH	Cont.	H_2 Block
34.7	67.8	68.7	70.5	76.1	76.8

b) (A-a) O_2 Difference (mm Hg)

H_2 Block	Cont.	30-PH	60-PH	15-PH	Hist.
36.9	38.3	45.0	45.2	46.8	81.3

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 21

The effects of H_2 blockade (metiamide) and histamine following H_2 antagonism on gas exchange in Group III calves. Alveolar-arterial oxygen differences, (A-a) O_2 difference, and systemic arterial pressure are plotted on the vertical axis, and the different measurement periods on the horizontal axis, where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Hist. = measurement during histamine infusion.

Standard error bars are calculated for the .01 significance level.

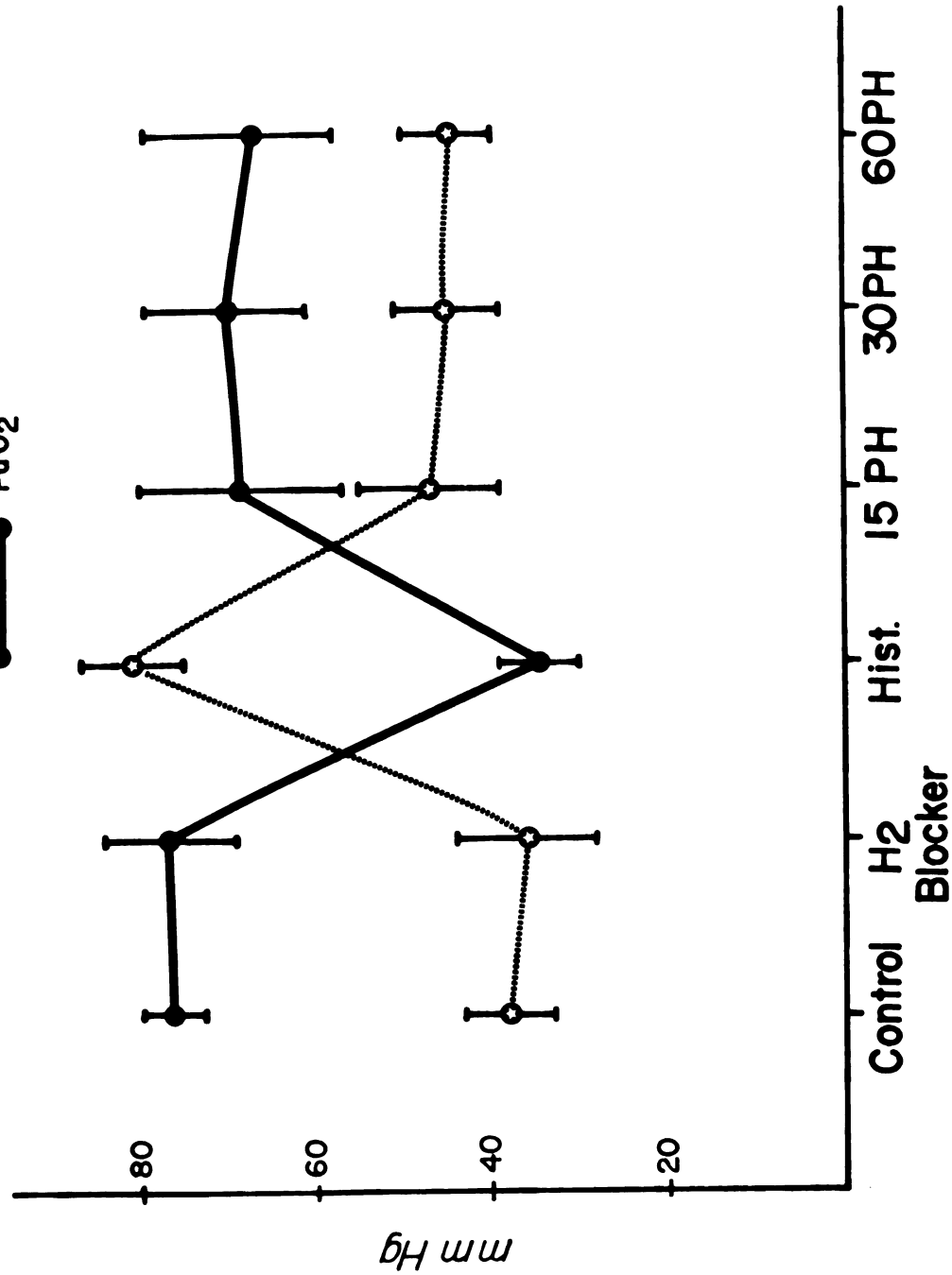

(A-a) O2 difference
PaO2
mm Hg
80
60
40
20
Control
H2 Blocker
Hist.
15 PH
30PH
60PH

FIGURE 21

iii Cardiovascular Effects

Cardiac output and stroke volume were significantly lower at "60-PH" than at control levels but "histamine"values were not significantly different from those of the "control" period (Fig. 22). Histamine did not change heart rate (Table 11).

TABLE 11

Statistical comparison between means for cardiac output and stroke volume, group III calves.

a) Cardiac Output (litres/min)

60-PH	Histamine	30-PH	15-PH	H_2 Block	Control
6.52	7.32	7.35	7.40	9.63	11.52

b) Stroke Volume (ml.)

60-PH	30-PH	Histamine	15-PH	H_2 Block	Control
37.0	43.2	43.8	47.0	60.9	68.3

* Means underscored by same line are not statistically significant at the .01 level

FIGURE 22

The effects of H_2 blockade (metiamide) and histamine following H_2 antagonism on cardiac output and stroke volume in Group III calves. Cardiac output and stroke volume are plotted on the vertical axis, and the different measurement periods on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Hist. = measurement during histamine infusion.

Standard error bars are calculated for the .01 significance level.

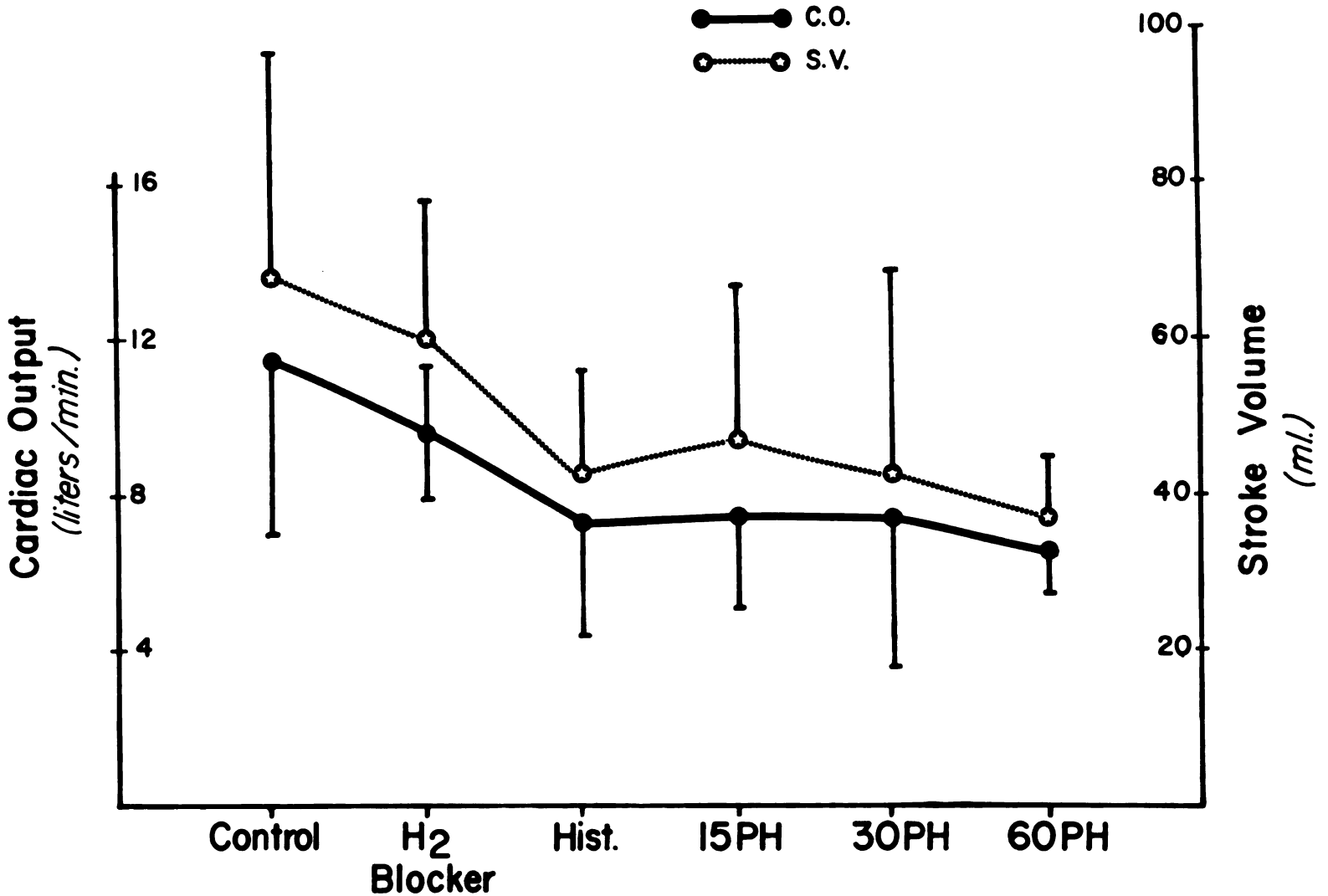

C.O.
S.V.
Cardiac Output
(liters/min.)
16
12
8
4
100
80
60
40
20
Stroke Volume
(ml.)
Control
H2
Blocker
Hist.
15PH
30PH
60PH

FIGURE 22

Injection of the H_2 antagonist had no significant effect on pulmonary or systemic arterial pressures and resistances. Systemic arterial pressure decreased by an average of 62 mm Hg from "control" upon histamine infusion and failed to recover to control levels even at "60-PH" (table 12). Although highly significant differences were obtained for systemic vascular resistance using the 2-way analysis of variance, these differences could not be demonstrated as significant using Tukey's w procedure. The largest difference between means was between "histamine" and 60-PH.

A 10 mm Hg reduction in pulmonary artery pressure occurred during histamine infusion (table 12) without any significant change in pulmonary vascular resistance.

TABLE 12

Statistical comparison between means for systemic arterial pressure and pulmonary artery pressure, group III calves.

a) Systemic Arterial Pressure (mm Hg)

Histamine	15-PH	30-PH	60-PH	H_2 Block	Control
59.5	72.2	88.0	92.2	111.0	122.2

b) Pulmonary Artery Pressure (mm Hg)

Histamine	15-PH	60-PH	30-PH	Control	H_2 Block
23.5	27.2	29.0	32.0	32.8	33.2

* Means underscored by same line are not statistically significant at the .01 level

Histamine infusion elevated packed cell volume (PCV) and hemoglobin concentration (Hgb) and both remained significantly different from control values at "60-PH" (Fig. 23, table 13). Significant differences in plasma total solids were also found. "Histamine" was not significantly different from the control group mean of 4.61 gm/100 ml. Mean total solids for the "15-PH" and "30-PH" periods were significantly reduced from the control group, and the "30-PH" group was also less than during histamine infusion (Table 13c).

General Observations

As in Group I calves, animals died shortly after removal from the ventilator and had similar lesions upon post mortem examination.

Significant differences between animals existed for all variables, except systemic arterial pressure, PaO_2, $VD/_{VT}$ and (A-a) O_2 difference.

FIGURE 23

The effects of H_2 blockade (metiamide) and histamine following H_2 antagonism on packed cell volume (PCV) total solids and hemoglobin concentration in Group III calves. PCV, total solids and hemoglobin concentration are plotted on the vertical axis, and the different measurement periods on the horizontal axis where

15-PH = 15 minutes after histamine infusion had ceased.

30-PH = 30 minutes after histamine infusion had ceased.

60-PH = 60 minutes after histamine infusion had ceased.

Hist. = measurement during histamine infusion.

Standard error bars are calculated for the .01 significance level.

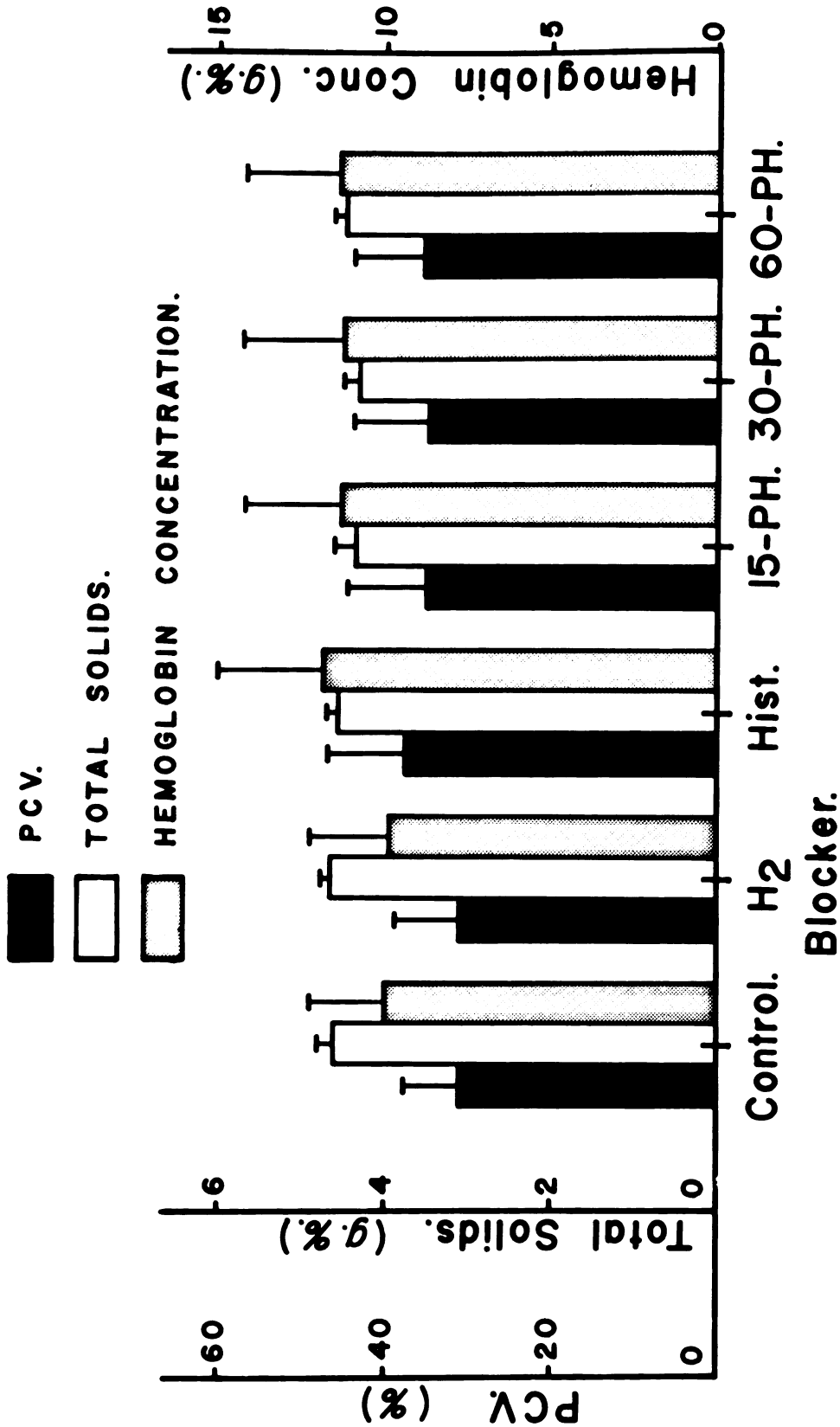

PCV.
TOTAL SOLIDS.
HEMOGLOBIN CONCENTRATION.
PCV (%)
Total Solids. (g.%.)
Hemoglobin Conc. (g.%.)
Control.
H2 Blocker.
Hist.
15-PH.
30-PH.
60-PH.

FIGURE 23

TABLE 13

Statistical comparison between means for PCV, Hgb and T.S., group III calves.

a) PCV (%)

Control	H_2 Block	30-PH	15-PH	60-PH	Histamine
30.9	31.1	34.8	35.3	35.6	37.5

b) Hgb (g/100 ml)

Control	H_2 Block	30-PH	15-PH	60-PH	Histamine
9.91	9.98	11.22	11.25	11.30	11.88

c) T.S. (g/100 ml)

30-PH	15-PH	60-PH	Histamine	Control	H_2 Block
4.31	4.33	4.46	4.55	4.61	4.65

* Means underscored by same line are not statistically significant at the .01 level

DISCUSSION AND CONCLUSIONS

I. Pulmonary mechanics

Histamine infusion in calves greatly increased the maximal transpulmonary pressure difference between onset and end inspiration, in anesthetized, fixed volume ventilated calves. The mechanical forces that lead to the development of changes in transpulmonary pressure have been previously described (Mead and Whittenburger, 1953), and include inertial, elastic and flow-resistive forces within the lung. Since flow-resistive forces are chiefly influenced by the calibre of large airways (Macklem et al, 1969; Macklem, 1976) changes in R_{aw} indicate changes in large airway calibre. The calculation of C_{stat} requires a cessation of air flow within the respiratory tree and thus reflects chiefly the elastic properties of the lung parenchyma (Macklem, 1975). Dynamic compliance is calculated from points of zero flow in the respiratory cycle, as measured at the mouth. A reduction in small airway calibre may result in prolonged time constants for the lung segments affected by the change in airway calibre, and flow may not have ceased in these segments, when it approaches zero in the upper airways. As a result, inequalities in time constants between lung segments lead to incomplete participation of the lung units during the respiratory cycle and results in a decrease in C_{dyn}. Dynamic compliance will also be influenced by changes in the elasticity of lung parenchyma.

Histamine infusion, in the presence or absence of antagonists, failed to alter C_{stat}, indicating that the elastic properties of the lung parenchyma were not altered. The values reported for C_{dyn} in adult cattle are considerably larger than those determined in our study (Musewe et al, 1979), as would be expected because of the larger lung volume in adult cattle. Our values are smaller than those reported in healthy awake calves (Kiorpes et al, 1978). In our study, animals were maintained under anesthesia, in sternal recumbency using a V trough for support. Compression of the lower thorax and the dependent portions of lung as a result of this restraint may have led to atelectasis and restriction of lung expansion resulting in decreased lung compliance. Values for C_{stat} have not been previously reported for calves, but were similar to values reported for dogs and humans compared on the basis of equal body weight or vital capacity (Altman, P.L. and Dittmer, D.S., 1971).

Histamine infusion decreased C_{dyn} to less than half control values. The response was not affected by H_2 antagonism but was completely blocked by H_1 antagonism indicating principally an H_1 receptor response.

Control values for R_{aw} in our studies were in good agreement with those reported previously for calves (Kiorpes et al, 1978). Histamine caused two-fold increases in R_{aw} that could be completely blocked by H_1 antagonism but R_{aw} was unaffected by H_2 antagonism. The changes in C_{dyn} and R_{aw}, but not C_{stat} indicate that histamine causes both small and

large airway constriction in calves, and that these responses are due to H_1 receptor stimulation.

Vital capacity maneuvers were effective in reversing the effect of histamine on C_{dyn} but not R_{aw}. The effect of vital capacity maneuvers in increasing C_{dyn} is thought to be related to the opening of previously collapsed terminal airways and the redistribution of surfactant within the lung, resulting in a lessening of surface tension forces (Mead et al, 1957). Since these changes occur chiefly in the lung periphery, central airway dynamics and hence R_{aw} are little affected. The beneficial effects of forced inflation of the lungs on compliance have previously been described in guinea pigs undergoing anaphylaxis (Collier and James, 1967). Generally, we found small increments in R_{aw} occurred after vital capacity maneuvers were performed. These are probably related to minor large airway constriction initiated as a vagal reflex resulting from lung distension.

Pressure-volume hysteresis was calculated as the area enclosed by the static pressure-volume loop and reflects, in part, the work of breathing. It differs, however, from the work of breathing in that P-V hysteresis does not include work required to overcome flow resistive forces within the lung. The P-V hysteresis is affected by the elastic properties of the peripheral airways and lung parenchyma and depends chiefly on the critical opening pressure of small airways and surface tension forces. All determinations of C_{stat} and P-V hysteresis were performed by

injecting known volumes of air into the lung and always starting at functional residual capacity. P-V hysteresis is affected by the volume history of the lung, since large lung inflations open previously collapsed terminal airways. Care was taken to measure P-V hysteresis and C_{stat} only after the lungs had been inflated to the same tidal volume for several minutes. Values for P-V hysteresis were then compared, before and after vital capacity maneuvers. An increase in P-V hysteresis is thus further evidence for small airway closure, and such increases should be reduced by vital capacity maneuvers which would reopen collapsed airways.

Histamine infusion increased P-V hysteresis. The response was not blocked by H_2 receptor antagonism, but was significantly reduced by vital capacity maneuvers. H_1 antagonism prevented the rise in P-V hysteresis caused by histamine. Similar changes in hysteresis curves for isolated cat and dog lungs exposed to histamine, and then given forced lung inflations, have also been reported (Colebatch and Mitchell, 1971; Colebatch and Engel, 1974). These findings support the conclusion that histamine causes peripheral airway constriction via an H_1 mediated response. Our results indicate that H_2 receptor-stimulated calves, (histamine infused after H_1 blockade) given vital capacity maneuvers had significantly less P-V hysteresis values than those of the control group, suggesting a weak H_2 receptor mediated peripheral bronchodilation occurred.

The airway constrictive effects of histamine have been extensively

studied in many species and the species differences in pulmonary responses to histamine have been recently reviewed (Chand and Eyre, 1975; Persson and Ekman, 1976). Our results in calves, which indicate that central and peripheral airway constriction induced by histamine is an H_1 mediated response, are similar to those reported for man (Casterline and Evans, 1977; Laitinen et al, 1976), dogs (Drazen et al, 1978; Krell, 1978; Nisam et al, 1978; Bradley and Russel, 1977; Irvin and Dempsey, 1978), and guinea pigs (Bernauer et al, 1969; Collier and James, 1967; Drazen and Schneider, 1977).

A possible relaxant effect of histamine on peripheral airways of calf lungs mediated by H_2 receptors has not been previously reported. H_2 mediated relaxation of peripheral airways has been described for sheep (Eyre, 1973) and dogs (Drazen et al, 1978) using isolated muscle strips, but could not be identified in guinea pig muscle strips (Drazen and Schneider, 1977). H_2 antagonists given to intact guinea pigs undergoing anaphylaxis results in a lessening of the severity of respiratory distress, suggesting a similar role for H_2 receptors in the guinea pig lung (Drazen et al, 1978). H_2 receptor stimulation in dogs lessens the histamine induced changes in peripheral airway resistance and C_{dyn} when animals are concurrently exposed to α and β adrenergic blockade (Irvin and Dempsey, 1978). These results suggest a similar weak H_2 mediated response in dogs as we report for calves.

II Gas Exchange

The Pco_2 values described for systemic arterial blood from unanesthetized cattle (Musewe et al, 1979) were in excellent agreement with those found during control measurement periods in our experiments, indicating that the controlled ventilation we provided was adequate for normal CO_2 elimination. However, studies on young and adult cattle (Bisgard et al, 1973; Donawick and Baue, 1968; Musewe et al, 1979) found PaO_2 values which were about 10 mmHg larger than the values we describe. These differences are probably related to the effect of anesthesia in our calves. Our results were in good agreement with the PaO_2 values described in older, unanesthetized calves (Kiorpes et al, 1978).

Histamine profoundly affected the gas exchange properties of the lung. Large decreases in PaO_2 (average decrease 38 mmHg) were accompanied by a similar increment in the (A-a) O_2 difference from 43 $\pm$ 10 to 77 $\pm$ 13 mmHg, during histamine infusion. The (A-a) O_2 difference reported for 4-6-week-old unanesthetized calves (Kiorpes et al, 1978) is considerably less than noted in our study on younger, anesthetized calves. Anesthesia results in chest compression, inhibition of sighing and terminal airway closure, leading to an increase in the number of lung units with low ventilation/perfusion ratios and the subsequent development of impaired gas exchange. Differences between our results and those of Kiorpes et al, (1978) may also have arisen because of age differences in the animals used, since younger animals have higher (A-a) O_2 differences. Histamine

reduces PaO_2 in sheep (Brigham et al, 1976) and dogs when given intravenously (Robinson and Slocombe, unpublished observations) or by aerosol (Diamond, 1969). Inhaled histamine also reduces PaO_2 in rabbits and cats (Miserocchi et al, 1978; Kaukel et al, 1978). PaO_2 and (A-a) O_2 differences were unaffected by histamine when calves were premedicated with the H_1 antagonist, but H_2 antagonism failed to exert any protective effect. These results indicate that the effect of histamine on gas exchange properties of the lung is principally mediated by H_1 receptors, and in this respect, calf lungs behave in a similar fashion to that of sheep (Brigham et al, 1976).

Impairment of gas exchange within the lung may result from alteration of the alveolar membrane permeability to oxygen, decreased mixed venous oxygen saturation, right to left vascular shunts, and ventilation/perfusion inequalities. The cardinal sign for the existence of ventilation-perfusion ($\dot{V}/\dot{Q}$) inequalities is the development of enlarged (A-a) O_2 differences (West, 1969, 1977). Extensive airway constriction induced by histamine is likely to generate lung units with low $\dot{V}/\dot{Q}$ ratios. Hypoxic vasoconstrictive responses are unlikely to be effective in maintaining gas exchange in the face of such generalized airway constriction, or reduced alveolar oxygen tension, as demonstrated for the coati-mundi, an animal with lungs anatomically similar to cattle lungs (Grant et al, 1976).

$\dot{V}/\dot{Q}$ abnormalities may also arise in the lung as a result of decreased pulmonary perfusion. Histamine has been shown to decrease the pulmonary

blood volume in isolated perfused cat lungs (Dawson et al, 1975). As might be anticipted by a reduction in pulmonary blood flow, high $\dot{V}/\dot{Q}$ lung units are likely to develop. However, high $\dot{V}/\dot{Q}$ lung units do not greatly affect the gas exchange properties of the lung, unlike low $\dot{V}/\dot{Q}$ units (West, 1977). Histamine-induced decreases in cardiac output and alteration of pulmonary vascular tone may disturb mechansims (currently unknown) by which ventilation and perfusion are matched.

It remains to be determined to what degree $\dot{V}/\dot{Q}$ abnormalities in calves develop as a result of histamine induced alterations in cardiovascular function.

(A-a) O_2 differences may also increase as a result of decreases in the permeability of the alveolar membrane to oxygen. Histamine has been demonstrated both in vivo and in vitro to alter the pulmonary vascular permeability to fluids, in sheep (Brigham, 1975; Brigham et al, 1976; Harris et al, 1978), cats (Dawson et al, 1975), guinea pigs (Aarson and Zeegers, 1972) and dogs (Propst et al, 1978). Histamine produced pulmonary edema in a small number of calves given lethal doses (Aitken and Sanford, 1972; Gilka et al, 1974). These studies for calves did not measure rates of fluid flux within the lung as was done for the other species indicated, but were based on autopsy examinations.

Histamine-induced pulmonary edema is an unlikely cause of the impaired gas exchange we observed after histamine infusion for the following reasons.

a) Retention of CO_2 did not occur in the histamine-exposed calf. Although the solubility of oxygen is much less than that of CO_2, and O_2 exchange across edematous lung is likely to be more severely impaired than for CO_2, the lack of CO_2 retention during histamine infusion indicates that if edema does exist, it is not sufficient to reduce alveolar ventilation enough to impair the elimination of CO_2.

b) In sheep, H_1 blockade failed to prevent decreases in PaO_2 caused by histamine infusion (Brigham et al, 1976), but completely prevented the ability of histamine to increase pulmonary vascular permeability and cause lung edema. This indicates that impairment of gas exchange, at least in the sheep, occurs independently from the development of pulmonary edema.

Reduction in the mixed venous oxygen tension ($P_{\bar{v}}O_2$) may result in increased (A-a) O_2 differences (West, 1977). Factors which may contribute to a decline in $P_{\bar{v}}$ O_2 include a decrease in cardiac output, increase in tissue metabolic rates and a "right displacement" of the oxyhemoglobin dissociation curve. Histamine infusion decreased cardiac output and systemic pressure and was accompanied by an average fall of 11 mmHg in the $P_{\bar{v}}O_2$. However, histamine did not alter, significantly, mixed venous pH, or CO_2 tensions. Premedication with H_2 antagonist failed to prevent histamine-induced changes in PaO_2, (A-a) O_2 difference, cardiac output or systemic pressure, but prevented significant decreases in $P_{\bar{v}}O_2$. These results indicate that the decrease in $P_{\bar{v}}O_2$ experienced with histamine

infusion alone, had little influence on the development of large (A-a) O_2 differences.

The dead space/tidal volume ratio ($VD/_{VT}$) did not significantly change for any measurement period. This would seem inconsistent with the conclusion that histamine causes airway constriction, a response which is expected to reduce $VD/_{VT}$. However, histamine may reduce alveolar membrane permeability to gases or, as believed more likely in these calves, induce $\dot{V}/\dot{Q}$ inequalities. The latter influences tend to increase $VD/_{VT}$ and may obscure decreases in $VD/_{VT}$ caused by bronchoconstriction.

Our results demonstrate from studies of pulmonary mechanics variables, that histamine causes both large and small airway constriction as a result of H_1 receptor stimulation. The reduction in C_{dyn} and increased P-V hysteresis without change in C_{stat} demonstrates the presence of small airway closure, which leads to the development of $\dot{V}/\dot{Q}$ inequalities within the lung, and the subsequent development of hypoxemia as a result of impaired gas exchange.

III Cardiovascular effects

Control values of arterial pressures and resistances, cardiac output, stroke volume and heart rate were in excellent agreement with previously reported studies on normal unanesthetized calves (Kuida et al, 1961; Reeves et al, 1962).

a) Systemic vasculature

Previous studies have demonstrated the systemic hypotensive effect of histamine (Aitken and Sanford, 1972; Lewis and Eyre, 1972; Burka and Eyre, 1974; Eyre et al, 1973; Eyre and Wells, 1973). Our results indicate that the decrease in systemic arterial pressure was principally the result of a decrease in cardiac output, as no significant change in systemic vascular resistance could be demonstrated, as a result of histamine infusion. Antagonism by H_2 antagonists appeared to potentiate the effects of intravenous histamine, producing similar decreases in systemic pressure and cardiac output, as in group I calves at half the dose rate. Systemic vascular resistance did not change significantly in the presence of H_2 antagonism.

These changes indicate that the principle effect of H_1 receptor stimulation on the systemic circulation of the intact calf is to reduce systemic pressure as a result of depression in cardiac output. Our results support the conclusion that H_2 receptors exert a beneficial effect in cardiac output, as evidenced by the finding that H_2 receptor blockade

potentiates the effect of histamine without changing systemic vascular resistance significantly. Our results are similar to those of Eyre and Wells (1973) who reported a hypotensive effect of histamine which was exacerbated by H_2 receptor blockade. However, in their study, changes in cardiac output were not evaluated, and their conclusion that H_1 receptor stimulation causes vasodilation, and H_2 receptors cause vasoconstriction did not account for the large changes in cardiac output which occur. Our results do not provide conclusive evidence that systemic H_1 receptor stimulation causes vasodilation. Passive changes in transmural pressure would be expected to increase systemic vascular resistance in the face of decreasing blood flow. Since these changes were not detected in either group I or group III calves, these results suggest the presence of an H_1 receptor-mediated systemic vasodilation. Furthermore, concurrent catecholamine release at the time of histamine infusion may oppose any systemic histamine induced vasodilation and mask any concurrent H_1 mediated vasodilation.

Under the influence of H_1 antagonism, large doses of histamine caused a decrease in systemic pressure and systemic vascular resistance, but were not accompanied by a reduction in cardiac output. A decrease in systemic pressure without change in cardiac output, subsequent to meypramine administration, was observed in a study on one calf (Aitken and Sanford, 1972). Their results demonstrated the presence of a weak H_2 receptor mediated systemic vasodilation. An H_2 mediated, systemic vasodilatory

response has been demonstrated in cats (Hoffman et al, 1977; Tucker et al, 1977) and dogs (Tucker et al, 1977).

This conclusion does not agree with that of Eyre and Wells (1973) who concluded that the effects of H_2 stimulation are vasoconstrictive. However, the inability of Eyre and Wells (1973) to demonstrate a pressor response in H_1 receptor-antagonized calves when exposed to histamine, may not be the result of incomplete H_1 blockade, as they contend, but may also be explained in terms of an H_2 receptor mediated vasodilation.

The results we describe, and those of Eyre and Wells (1973) support the conclusion that histamine causes systemic hypotension also via an H_1 mediated vasodilation. This conclusion disagrees with the findings of an in vitro and isolated perfused limb study by Elmes and Eyre (1979) who concluded that the vasoconstrictive effects they noted as a result of histamine infusion were mediated by H_1 receptors. They were unable to demonstrate any H_2 mediated vascular responses.

Differences in animal age, dosage of histamine, method of anesthesia and blood oxygen content all influence receptor responsiveness (Barer et al, 1976; Hoffman et al, 1977; Therman et al, 1975, 1977; Tucker et al, 1977; Wood et al, 1977) and may account for these differences.

b) Cardiac effects

A profound, histamine-induced decrease in cardiac output observed in Group I calves, was accompanied by significantly increased heart rate and

decreased stroke volume. Aitken and Sanford (1972) report bradycardia in one calf, in a study composed of two calves. Heart rate was not measured in the other calf, nor in a calf premedicated with mepyramine. Lewis and Eyre (1973) examined cardiovascular responses in six calves exposed to histamine, but did not report any changes in heart rate, stroke volume or cardiac output. Our results indicate that the depressant effects of histamine on cardiac output are chiefly mediated by H_1 receptors since H_1 blockade prevented decreases in cardiac output. The results from group II calves are conflicting to some degree, as significant increases in heart rate were noted but no significant differences in cardiac output or stroke volume were detected. H_2 antagonism prevented the development of tachycardia but did not protect against the reduction in cardiac output or stroke volume induced by histamine. These findings would support the contention that H_2 receptor stimulation principally causes histamine induced tachycardia, and H_1 receptor stimulation causes a negative ionotropic effect. Similar roles for these receptors have been described for the cat, dog (Tucker et al, 1975, 1977), guinea pig (Zavecz and Levi, 1978), and sheep (Woods et al, 1977) cardiac responses to histamine, but have not been previously reported in cattle.

c) Pulmonary vasculature

Disagreement exists in the current literature concerning the effects of histamine upon the bovine pulmonary vasculature. In constant flow,

isolated neonatal calf lung preparations histamine induces vasodilation, even under hypoxic conditions (Silove and Simcha, 1973). As in the results we report, histamine was found to decrease pulmonary artery pressure in anesthetized calves (Burka and Eyre, 1974). However, it is also reported that histamine infusion causes increased pulmonary artery pressure in pentobarbitol anesthetized calves (Aitken and Sanford, 1972; Lewis and Eyre, 1972; Eyre and Wells, 1973). The reasons for the disparity remain obscure, apparently not related to differences in anesthesia, histamine dosage or degree of hypoxia. Of interest, the studies we report, and those of Silove and Simcha (1973) employed neonatal animals, in comparison to the older calves used in studies reported by others. Unidentified factors which alter the vascular tone of the preparation also may profoundly alter responsiveness to histamine (Woods et al, 1976; Barer et al, 1976).

Experiments in vitro, using muscle strips, have demonstrated constriction of both bovine pulmonary artery and vein preparations upon histamine exposure (Burka and Eyre, 1974; Eyre, 1971, 1975; Lewis and Eyre, 1972). The results from in vitro experiments do not correlate well with our results in which a constriction of pulmonary vasculature (and hence an increase in pulmonary vascular resistance) could not be demonstrated. The principle cause for a decrease in pulmonary artery pressure appeared to be the large decrease in cardiac output. Our results regarding pulmonary vascular resistance must be interpreted with

some caution, since they reflect resistance to flow as measured at the pulmonary artery catheter tip, and because measurement of left atrial pressures was not performed.

Because of the great compliance of the pulmonary vascular bed, a reduction in pulmonary artery pressure normally increases pulmonary vascular resistance, as a result of passive vessel collapse (Burton, 1965). Our results indicate concurrent histamine induced vasodilation is probably occurring, thus maintaining pulmonary vascular resistance at control values, in the face of a decreasing cardiac output and pulmonary artery pressure. The response to histamine was unaffected by premedication with metiamide, indicating that stimulation of H_1 receptors probably causes pulmonary vascular dilatation.

Blockade of H_1 receptors prevented the decrease in cardiac output induced by histamine but resulted in a decrease in pulmonary vascular resistance and pulmonary artery pressure, indicating a vasodilatory effect mediated by H_2 receptors. A similar conclusion for the role of H_2 receptors in the bovine pulmonary vascular bed was reached by Eyre and Wells (1973) based on preliminary work yet to be published. Of interest, based on the same information, Eyre and Wells concluded that H_1 receptors cause vasoconstriction and that mepyramine blocks this effect. From a single observation in one anesthetized calf premedicated with mepyramine, Aitken and Sanford (1972) came to a similar conclusion.

Our conclusions regarding the effects of histamine on the bovine

pulmonary vascular bed support those by Silove and Simcha (1973) and indicate that the vasodilation caused by H_1 and H_2 receptor stimulation in the bovine pulmonary vascular bed appears similar to that described in cats (Black et al, 1972). However, in most other species, including the cat (Tucker et al, 1977; Hoffman et al, 1977), H_1 receptors are thought to cause pulmonary vasoconstriction.

d) Vascular permeability

Hemoglobin concentration rose significantly after histamine infusion in group I and group III calves but not group II.

Measurement of plasma total solids and packed cell volume were also performed on group III calves. Plasma total solids were significantly lower than control values, in the measurement periods subsequent to histamine infusion, but packed cell volume increased.

These results indicate that there was a net loss of protein from the vascular compartment. The increase in packed cell volume and hemoglobin concentration may have been the result of splenic contraction subsequent to catecholamine release, but may also have developed as a result of fluid loss from the vascular bed. Affected calves were noted to have increased fluid content in the gut and the lungs upon postmortem examination. Our results indicate that the vascular effects of histamine are not antagonized by H_2 receptor blockade, suggesting that the effects of histamine on vascular permeability in the calf are due to H_1 receptor

stimulation. A similar role for H_1 receptors has been reported in sheep (Brigham et al, 1976) and in dogs and horses (Kozlowski et al, 1979; personal communication). The production of edema in the isolated bovine foot, as a result of histamine infusion, has also been shown to be the result of an H_1 mediated effect (Elmes and Eyre, 1977).

From our results, it would appear that stimulation of H_1 receptors in the cardiovascular system of the neonatal calf resulted in systemic and pulmonary vasodilation, increased vascular permeability and marked negative ionotropic effects on the heart. Stimulation of H_2 receptors also produced systemic and pulmonary vasodilation, but resulted in mild positive ionotropic effects on the heart as well as the development of tachycardia. It is not yet known to what degree autonomic reflexes influenced the development of cardiovascular abnormalities induced by histamine infusion.

SUMMARY

The results of the present study indicate that:

1. The detrimental effect of intravenous histamine on pulmonary mechanical function and gas exchange in the calf relate chiefly to H_1 receptor stimulation.
2. Histamine causes both small and large airway constriction, via the H_1 receptor.
3. Stimulation of lung H_2 receptors results in a small degree of peripheral airway dilation.
4. The impaired gas exchange which develops following histamine infusion probably occurs as a result of peripheral airway constriction and the subsequent development of ventilation/perfusion inequalities in obstructed lung segments.
5. Stimulation of H_1 receptors in the cardiovascular system causes systemic and pulmonary hypotension, predominantly by a negative ionotropic effect on cardiac output, although some H_1 mediated vasodilation of the pulmonary and systemic vascular beds is also suspected.
6. Stimulation of H_2 receptors in the vascular system causes pulmonary and systemic vasodilation and subsequent hypotension.
7. Stimulation of cardiac H_2 receptors results in tachycardia.

LIST OF REFERENCES

LIST OF REFERENCES

1. Aarsen, P.N. and Zeegers, A.: Effects of histamine, 5 hydroxytryptamine and bradykinin on the vascular system of isolated lungs of the guinea-pig and the influence of phenylbutazone on these effects. Br J. Pharmacol. 45:284-98, 1972.

2. Aitken, M.M., Deline, T.R. and Eyre, P.: Influence of the method of sensitization on some features of anaphylaxis in calves. J. Comp. Path. 85:351-360, 1975.

3. Aitken, M.M.: Studies on the mechanism of anaphylaxis in cattle. PhD Thesis (1970). Glasgow.

4. Aitken, M.M. and Sanford, J.: Experimentally induced anaphylaxis in cattle. Vet. Rec. 82:418-19, 1968.

5. Aitken, M.M. and Sanford, J.: Experimental Anaphylaxis in Cattle. J. Comp. Path. 79:131-139, 1969.

6. Aitken, M.M. and Sanford, J.: Protection of cattle against experimentally induced anaphylaxis. Nature 223:314-316, 1969.

7. Aitken, M.M. and Sanford, J.: Effects of histamine, 5-hydroxytryptamine and bradykinin on cattle and their modification by antagonists and by vagotomy. J. Comp. Path. 82:257-266, 1972.

8. Alexander, A.F. and Jensen, R.: Pulmonary arteriographic studies of bovine high mountain disease. Am. J. of Vet Res. 24:1094-1097, 1963.

9. Allan, G. and Eakins, K.E.: Burimamide is a selective inhibitor of Thromboxane A biosynthesis in human platelet microsomes. Prostaglandins 15:659-661, 1978.

10. Altman, P.L. and Dittmer, D.S. Eds. Respiration and Circulation. FASEB. 110-111, 1971. Bethesda, Maryland

11. Austen, K.F. and Orange, R.P.: Bronchial asthma: The possible role of the chemical mediators of immediate hypersensitivity in the pathogenesis of subacute chronic disease. Am. Rev. Respir. Dis. 112:423-436, 1975.

12. Austen, K.F., Wasserman, S.I. and Goetzl, E.J.: 'Mast cell-derived mediators: Structural and functional diversity and regulation of expression.' Molecular and Biological Aspects of the acute allergic reaction. Eds. Johansson, S.G.O., Strandberg, K. Uvnas, B. p293-318, N.Y., 1976.

13. Aviado, D.M. and Sadavongvivad, C.: Pharmacological significance of biogenic amines in the lungs: histamine. Br. J. Pharmac. 38:366-373, 1970.

14. Barer, G.R., Emery, C.J., Mohammed, F.H., Mungall, I.P. and Thompson, B.: H_1 and H_2 histamine receptors in the pulmonary circulation. J. Physiol. (Lond.) 259:41P-42P, 1976.

15. Barnett, D.B., Chesrown, S.E., Zbinden, A.F., Nisam, M., Reed, B.R., Bourne, H.R., Melmon, K.L. and Gold, W.M.: Cyclic AMP and cyclic GMP in canine peripheral lung: regulation in vivo. Am. Rev. Respir. Dis. 118:723-733, 1978.

16. Benson, M.K. and Graf, P.D.: Bronchial reactivity: Interaction between vagal stimulation and inhaled histamine. J. Appl. Physiol. 43:643-647, 1977.

17. Bernauer, W., Hahn, F. and Giertz, H.: Comparison of the antilethal, broncholytic, and antiemphysematous activities of mepyramine in anaphylactic, histamine and anaphylatoxin shock of guinea-pigs. Arch. Int. Pharmacodyn. 178:137-151, 1969.

18. Bisgard, G.E., Ruiz, A.V., Will, J.A. and Filley, G.F.: Ventilatory response to acute and chronic hypoxia in the calf. Federation Proc. 31:389, 1972.

19. Bisgard, G.E., Ruiz, A.V. and Grover, R.F.: Ventilatory control in the Hereford calf. J. Appl. Physiol. 35:220-226, 1973.

20. Black, J.W., Duncan, A.M., Durant, C.J., Ganellin, C.R. and Parsons, E.M.: Definition and antagonism of histamine H_2-receptors. Nature 236:385-390, 1972.

21. Black, J.W., Duncan, W.A.M., Emmett, J.C., Ganellin, C.R., Hesselbo, T., Parsons, M.E. and Wyllie, J.H.: Metiamide-An orally active histamine H_2-receptor antagonist. Agents and actions 3:133-137, 1973.

22. Bleecker, E.R., Cotton, D.J., Fischer, S.P., Graf, P.D., Gold, W.M. and Nadel, J.A.: The mechanism of rapid, shallow breathing after inhaling histamine aerosol in exercising dogs. Am. Rev. Respir. Dis. 114:909-916, 1976.

23. Borst, H.G., Berglund, E. and McGregor, M.: The effects of pharmocologic agents on the pulmonary circulation in the dog. Studies on epinephrine, norepinephrine, 5-hydroxytryptamine, acetylcholine, histamine and aminophylline. J. Clin. Invest. 36:669-675, 1957.

24. Boucek, R.J. and Noble, N.L.: Histamine, norepinephrine, and bradykinin stimulation of fibroblast growth and modification of serotonin response. Proc. Soc. Exp. Biol. Med. 144:929-933, 1973.

25. Bourne, H.R., Lichtenstein, L.M., Melmon, K.L., Henney, C.S., Weinstein, Y. and Shearer, G.M.: Modulation of inflammation and immunity by cyclic AMP. Receptors for vasoactive hormones and mediators of inflammation regulate many leukocyte functions. Science 176:19-28, 1974.

26. Bradley, S.L. and Russel, J.A.: Distribution of Histamine H_1 and H_2 receptors in dog airway smooth muscle. Physiologist 20:11, 1977.

27. Brigham, K.L., Bowers, R.E. and Owen, P.J.: Effects of antihistamines on the lung vascular response to histamine in unanaesthetized sheep. Diphenhydramine prevention of pulmonary edema and increased permeability. J. Clin. Invest. 58:391-398, 1976.

28. Brigham, K.L.: Effects of histamine on lung transvascular fluid and protein movement in awake sheep. Chest 67:505-525, 1975 Suppl.

29. Brocklehurst, W.E.: The release of histamine and formation of a slow-reaching substance (SRS-A) during anaphylactic shock. J. Physiol. 151:416-435, 1960.

30. Brown, D.A.: The release of histamine by the alpha toxin of Staphylococcus pyogenes. Br. J. Pharmacol 25:771-780, 1965.

31. Brown, N.E., McFadden, E.R., Jr., Ingram, R.H., Jr.: Airway responses to inhaled histamine in asymptomatic smokers and nonsmokers. J. Appl. Physiol. 42:508-513, 1977.

32. Brown, R., Ingram, R.H., Wellman, J.J. and McFadden, E.R.: Effects of intravenous histamine on pulmonary mechanics in non-asthmatic and asthmatic subjects. J. Apl. Physiol. 42:221-227, 1977.

33. Bryant, D.H. and Burns, M.W.: Bronchial histamine reactivity: Its relationship to the reactivity of the bronchi to allergens. Clin. Allergy 6:523, 1976.

34. Bullock, C.G. and Kirkpatrick, C.T.: Effects of histamine on ionic distribution in bovine tracheal smooth muscle. J. Physiol. 254:63P-64P, 1976.

35. Burka, J.F. and Eyre, P.: A study of prostaglandins and prostaglandin antagonists in relation to anaphylaxis in calves. Can. J. Physiol. Pharmacol. 52:942-951, 1974.

36. Burton, A.C.: Physiology and Biophysics of the Circulation. Year Book Medical Publishers, Inc. Chicago, 1965.

37. Busse, W.W. and Sosman, J.: Histamine inhibition of neutrophil lysozomal enzyme release: An H_2 histamine receptor response. Science 194:737, 1976.

38. Busse, W., Cooper, W., Warshauer, D., Dick, E. and Albrecht, R.: Altered granuloctye isoproterenol and H_2 histamine response by in vitro influenza virus. J. Allergy Clin. Immunol. 61 Abst. 68. 149, 1978.

39. Casterline, C.L. and Evans, R.: Further studies on the mechanism of human histamine induced asthma. J. Allergy Clin. Immunol. 59 No. 6, 420-424, 1977.

40. Chand, N. and Eyre, P.: Cardiovascular histamine receptors in the domestic chicken. Arch. Int. Pharmacodyn Ther. 216:197-207, 1975.

41. Chand, N. and Eyre, P: Histamine relaxes constricted trachea and bronchi of horse. Veterinary Science Communications 1:85-90, 1977.

42. Chand, N. and Eyre, P: Classification and biological distribution of histamine receptor sub-types. Agents Actions 5:277-95, 1975.

43. Chiou, C.Y., Trzeciakowski, J. and Klein, D.C.: Histamine mediation of nicotine effects on postganglionic sympathetic neuroeffector junctions. Neuropharmacology 15:689-693, 1976.

44. Church, M.K.: Response of rat lung to humoral mediators of anaphylaxis and its modification by drugs and sensitization. Br. J. Pharmac. 55:423-430, 1975.

45. Clark, R., Sandler, J.A., Gallin, J.I. and Kaplan, A.P.: Histamine modulation of eosinophil migration. J. Immunol. 118:137, 1977.

46. Cogen, F.C. Hirshfield, J., Dunsky, E., Norman, M. and Zweiman, B.: Radiocontrast media-induced histamine release and complement consumption in humans. J. Allergy Clin. Immunol. Abstract No. 55. 61:145, 1978.

47. Colebatch, H.J. and Mitchel, C.A.: Constriction of isolated living liquid-filled dog and cat lungs with histamine. J. Appl. Physiol. 30:691-702, 1971.

48. Colebatch, H.J.H., Olsen, C.R. and Nadel, J.A.: Effect of histamine, seratonin and acetylcholine on the peripheral airways. J. Appl. Physiol. 21:217-266, 1966.

49. Colebatch, H.J.H., Olsen, C.R. and Nadel, J.A.: Effects of 48/80 on the mechanical properties of the lung. J. Appl. Physiol. 21:379-382, 1966.

50. Colebatch, H.J. and Engel, L.A.: Constriction of the lung by histamine before and after adrenalectomy in cats. J. Appl. Physiol. 37:798-805, 1974.

51. Collier, H.O.J. and James, G.W.L.: Humoral factors affecting pulmonary inflation during acute anaphylaxis in the guinea-pig in vivo. Br. J. Pharmac. Chemother. 30:283-301, 1967.

52. Coon, R.J., Nilsestuen, J., Hopp, F., Igler, F.O. and Kampine, J.P.: Respiratory effects of Acetylcholine and histamine administered to an isolated canine lung preparation. The Physiologist 21:23, 1978.

53. Crouch, M.D. and Godke, R.A.: Estrogen induced peaks in bovine plasma histamine. Federation Proc. No. 945, March, 1978.

54. Dale, H.H. and Laidlaw, P.P.: The physiological action of β -Iminozolyethylamine. J. Physiol. 41:318-344, 1910.

55. Damerau, B., Lege, L., Oldigs, H.D. and Vogt, W.: Histamine release, formation of prostaglandin-like activity (SRS-C) and mast cell degranulation by the direct lytic factor (DLF) and phospholipase A of cobra venom. Naunyn Schmiedebergs Arch Pharmacol 287:141-156, 1975.

56. Dawson, C.A., Forrester, T.E. and Hamilton, L.H.: Effects of hypoxia and histamine infusion on lung blood volume. J. Appl. Physiol 38:811-816, 1975.

57. Desliens, P.L.: Contribution à l'étude pharmacodynamique de l'Histamine et des Antihistaminiques sur les grand animaux. La Presse Medicale 66:563-565, 1958.

58. Dixon, M., Jackson, D.M., Richards, I.M. and Vendy, K.: The effects of acetylcholine and histamine on total lung resistance, dynamic compliance and lung irritant receptor discharge in the anaesthetized dog. J. of Physiol. 275 Proceedings. 79P, 1978.

59. Donawick, W.J. and Baue, A.E.: Blood gases, acid-base balance, and alveolar-arterial oxygen gradient in calves. Am. J. Vet. Res. 29:561-567, 1968.

60. Douglas, J.S., Brink, C. and Bouhuys, A.: 'Actions of histamine and other drugs on guinea-pig airway smooth muscle.' Lung Cells in Disease. Bouhuys, A. Ed. Elsevier/North-Holland Biomedical Press, p245-259, 1976.

61. Douglas, J.S.M., Dennis, M.W., Ridgway, P. and Bouhuys, A.: Airway constriction in guinea pigs: interaction of histamine and autonomic drugs. J. Pharmacol. Exp. Therap. 184:169-179, 1973.

62. Drazen, J.M., Schneider, M.W. and Venugopalan, C.S.: Modulation of central and peripheral airway contractile activity of histamine in vitro by H_2 receptor activation. The Physiologist 21:31, 1978.

63. Drazen, J.M., Venugopalan, C.S. and Soter, N.A.: H_2-receptor mediated inhibition of immediate type hypersensitivity reactions in vivo. Am. Rev. Respir. Dis. 117:479-484, 1978.

64. Drazen, J.M. and Schneider, M.W.: Comparative responses of tracheal spirals and parenchymal strips to histamine and carbachol in vitro. J. Clin. Invest. 61:1441-1447, 1978.

65. Drazen, J.M. and Austen, K.F.: Effects of intravenous administration of slow-reaching substance of anaphylaxis, histamine, bradykinin, and prostaglandin $F_2\alpha$ on pulmonary mechanics in the guinea-pig. J. Clin. Invest. 53:1679-1985, 1974.

66. Drazen, J.M. and Austen, K.F.:Atropine modification of the pulmonary effects of chemical mediators in the guinea-pig. J. Appl. Physiol. 38:834-838, 1975.

67. Drazen, J.M.: Adrenergic influences on histamine-mediated bronchoconstriction in the guinea-pig. J. Appl. Physiol. 44:340-345, 1978.

68. Eliassen, K.A.: A comparative study of in vitro metabolism of histamine in various tissues from domestic animals. (Cow, sheep, horse and pig.) Aeta. Physiol. Scand. 88:317-329, 1973.

69. Elmes, P.J. and Eyre, P.: Vascular reactivity of the bovine foot to neurohormones, antigens, and chemical mediators of anaphylaxis. Am. J. Vet. Res. 38:107-112, 1977.

70. Engineer, D.M., Jose, P.J., Piper, P.J. and Tippins, J.R.: Modulation of slow reacting substance of anaphylaxis and histamine release by prostacyclin and thromboxanes. J. Physiol. 281:42P (proceedings), 1978.

71. Ercan, Z.S. and Türker, R.K.: Potentiation of the effect of histamine by PGE_2 in the isolated perfused rabbit kidney and guinea-pig lung. Experentia 31:333-335, 1975.

72. Esmay, M.L.: Principles of the Animal Environment. The AVI Publishing Co. Inc., Westport Connecticut. 14-42, 83-85, 1969.

73. Eyre, P.: Equine pulmonary emphysema: A bronchopulmonary mould allergy. Vet. Rec. 91:134-140, 1972.

74. Eyre, P.: Histamine release from calf lung in vitro by specific antigen and compound 48/80. Arch. Int. Pharmacodyn. 192:347-352, 1971.

75. Eyre, P.: Comparisons of reactivity of pulmonary vascular and airway smooth muscle of sheep and calf to tryptamine analogues, histamine, and antigen. Am. J. Vet. Res. 36:1081-1084, 1975.

76. Eyre, P. and Wells, P.W.: Histamine H_2-receptors modulate systemic anaphylaxis: a dual cardiovascular action of histamine in calves. Br. J. Pharmacol. 49:364-367, 1973.

77. Eyre, P.: Pharmacology of bovine pulmonary vein anaphylaxis in vitro. Br. J. Pharmac. 43:302-311, 1971.

78. Eyre, P., Lewis, A.J. and Wells, P.W.: Acute systemic anaphylaxis in the calf. Br. J. Pharmac. 47:504-516, 1973.

79. Fishman, A.P.: Hypoxia on the pulmonary circulation-how and where is acts. Circulation Research 38:221-223, 1976.

80. Flynn, S.B. and Owen, D.A.A.: Vascular histamine receptors in the cat. Br. J. Pharmac. 51:15-16P, 1974.

81. Fox, B., Gordon, D. and Toledo-Pereyra, L.H.: The effect of cimetidine, an H_2 receptor antagonist, on murine splenocyte responses to mitogens, syngeneic and allogenic stimulation. Federation Proc. 38 No. 3 1102, 1979. Abst. 4629.

82. Fredholm, B. and Haegermark, O.: Histamine release from lung tissue of rat induced by bee venom fractions and compound 48/80. Br. J. Pharmacol. 34:236P, 1968.

83. Frey, M.J. and Gold, W.M.: Antigen induced release of histamine from lung compared in vitro and in vivo in natively allergic dogs. The Physiologist 21:40, 1978.

84. Gilka, F., Thomson, R.G. and Savan, M.: The effect of edema, hydrocortisone acetate, concurrent viral infection and immunization on the clearance of pasteuralla haemolytica from the bovine lung. Can. J. Comp. Med. 38:251-259, 1974.

85. Gilka, F., Thomson, R.G. and Savan, M.: Microscopic findings in the lungs of calves aerosolized with Pasteurella haemolytica and treated to alter pulmonary clearance. Zbl. et. Med. B. 21:774-786, 1974.

86. Gillespie, J.R., Tyler, W.S. and Eberly, V.E.: Blood pH, O_2 and CO_2 tensions in exercised, control and emphysematous horses. Am. J. Physiol. 207 (5):1067-1072, 1964.

87. Gillespie, J.R., Tyler, W.S. and Eberly, V.E.: Pulmonary ventilation and resistance in emphysematous and control horses. J. Appl. Physiol. 21:416-422, 1966.

88. Giordano, J., Zinner, M., Goba, A. and Lynch, N.: Effects of H_1 and H_2 histamine antagonists on the pulmonary pressor response to alveolar hypoxia. J. Surg. Res. 22:392-397, 1977.

89. Glazier, J.B. and Murray, J.F.: Sites of pulmonary vasomotor reactivity in the dog during alveolar hypoxia and serotonin and histamine infusion. J. of Clin. Invest. 50:2550-2558, 1971.

90. Goadby, P. and Phillips, E.A.: Some effects of burimamide on the isolated perfused pulmonary circulation of the guinea-pig. Br. J. Pharmac. 49:368-369, 1973.

91. Grant, J.A., Lichtenstein, L., Ishizaka, K. and Marsh, D.: Histamine release from human leucocytes by anti-IgG. Federation Proc. 31:747, 1972. (Abstr.)

92. Grant, J.A., Dupree, E. and Thueson, D.O.: Complement mediated release of histamine from human basophils. J. Allergy Clin Immunol. 60:306-311, 1977.

93. Grant, B.J.B., Davies, E.E., Jones, H.A. and Hughes, J.M.B.: Local regulation of pulmonary blood flow and ventilation-perfusion ratio in the coatimundi. J. Appl. Physiol 40:216-228, 1976.

94. Green, J.P.: Binding of some biogenic amines in tissues. Advanc. Pharmacol. 1:349-422, 1962.

95. Grover, R.F., Reeves, J.T., Will, D.H. and Blount, S.G.: Pulmonary vasoconstriction in steers at high altitude. J. Appl. Physiol 18:567-574, 1963.

96. Hanna, C.J. and Eyre, P.: Pharmcological studies on the pulmonary vein of the horse. I. Effects of selected spasmogens. Can. J. Physiol. Pharmacol. 56:812-817, 1978.

97. Hansen, J.E. and Simmons, D.H.: A systematic error in the determination of blood Pco_2. Am. Rev. Respir. Dis. 115:1061-1063,

98. Harris, T.R., Brigham, K.L. and Rowlett, R.D.: Pressure, serotonin, and histamine effects on lung multiple indicator curves in sheep. J. Appl. Physiol. 44:245-253, 1978.

99. Harrison, V.C., Peat, G. and Deheese, H.V.: Fetal growth in relation to histamine concentration in urine. J. Obstet. Gynaecol. Br. Commonw. 81:686-690, 1974.

100. Hauge, A. and Staub, N.C.: Prevention of hypoxic vasoconstriction in cat lung by histamine-releasing agent 48/80. J. Appl. Physiol. 26:693-699, 1969.

101. Hauge, A. and Melmon, K.L.: Role of histamine in hypoxic pulmonary hypertension in the rat: II. Depletion of histamine, senotonin, and catecholamines. Circulation Research 22:385-392, 1968.

102. Henry, P.R., Smith W.H. and Cunningham, M.D.: Effect of histamine and ammonia on hypomagnesemia in ruminants. J. of Animal Science 44:276-281, 1977.

103. Hoffman, E.A., Monroe, M.L., Tucker, A, Reeves, J.T.: Histamine H_1 and H_2 receptors in the cat and their roles during alveolar hypoxia. Respir. Physiol. 29:255-264, 1977.

104. Holroyde, C. and Eyre, P.: Immunologic release of histamine from bovine polymorphonuclear leukocytes. Am. J. Vet. Res. 36:1801-1802, 1975.

105. Holroyde, M.C. and Eyre, P.: Immunological release of histamine from bovine luekocytes. Unusual adrenergic modulation. Immunology 31:167-170, 1976.

106. Holroyde, M.C. and Eyre, P.: Inhibition by 5-hydroxytryptamine of anaphylactic histamine release from bovine granulocytes. Eur. J. of Pharmacol. 37:397-399, 1976.

107. Holroyde, M.C. and Eyre, P.: Modulation of antigen-induced histamine release from bovine granulocytes by several anti-allergic agents. Int. Archs. Allergy Appl. Immun. 53:515-519, 1977.

108. Irvin, C.G. and Dempsey, J.A.: Role of H_1 and H2 receptors in increased small airways resistance in the dog. Respiration Physiology 35:161-176, 1978.

109. Ishizaka, T., Ishizaka, K., Conrad, D.H. and Froese, A.: A new concept of triggering mechanisms of IgE mediated histamine release. J. Allergy Clin. Immunol. 61:320-330, 1978.

110. Jackson, A.C., Loring, S.H. and Drazen, J.M.: Serial distribution of bronchoconstriction due to vagal stimulation and histamine aerosol. The Physiologist 21:58, 1978.

111. Jaenke, R.S. and Alexander, A.F.: Fine structural alterations of bovine peripheral pulmonary arteries in hypoxia-induced hypertension. Am. J. Pathol. 73:377-398, 1973.

112. Jolles, P.: A possible physiological function of lysozyme. Biomedicine 25:275-276, 1975.

113. Kahlson, G. and Rosengren, E.: New approaches to the physiology of histamine. Physiol. Revue 48:155-196, 1968.

114. Kaukel, E., Lanser, K., Völkel, N., Beier, W. and Sill, V.: Cyclic nucleotide metabolism in experimental bronchial constriction in rabbits. Respiration 35:158-164, 1978.

115. Kaliner, M. and Platshon, L.: The effects of histamine on human lung anaphylaxis. J. Allergy Clin. Immunol 61 Mar. 1978. (Abstr.)

116. Kaliner, M.: Human lung tissue and anaphylaxis. I. The role of cyclic GMP as a moderator of the immunologically induced secretory process. J. Allergy Clin. Immunol. 60 (3), 204-211, 1977.

117. Kaliner, M. Orange, R.P. and Austen, K.F.: Immunological release of histamine and slow reacting substance of anaphylaxis from human lung. J. of Exp. Med. 136:556-567, 1972.

118. Karczewski, W. and Widdicombe, J.G.: The role of the vagus nerves in the respiratory and circulatory responses to intravenous histamine and phenyl diguanide in rabbits. J. Physiol. (Lond.) 201:271-291, 1969.

119. Kay, J.M. and Grover, R.F.: Lung mast cells and hypoxic pulmonary hypertension. Prog. Resp. Res. 9:157:164, 1975.

120. Kira, S. and Rodbard, S.: Effects of histamine and acetylcholine on the isolated perfused lung lobe. Q. Jl. Exp. Physiol 56:1-11, 1971.

121. Kirkpatrick, C.T., Jenkinson, H.A. and Cameron, A.R.: Interaction between drugs and potassium-rich solutions in producing contraction in bovine tracheal smooth muscle: studies in normal and calcium-depleted tissues. Clinical and Expt. Pharmacol and Physiol. 2:559-570, 1975.

122. Krell, R.D.: Investigation of the role of histamine in antigen-induced bronchoconstriction in the ascaris-hypersensitive dog. Br. J. Pharmacol. 62:519-528, 1978.

123. Kiorpes, A.L., Bisgard, G.E., Manohar, M. and Hernandez, A.: Pathophysiologic studies of infectious bovine rhinotracheitis in the Holstein-Fresian calf. Am. J. Vet Res. 39 (5): 779-783, 1978.

124. Kiorpes, A.L., Bisgard, G.E. and Manohar, M.: Pulmonary function values in healthy Holstein-Fresian calves. Am. J. Vet. Res. 39 (5):773-778, 1978.

125. Kuida, H., Brown, A.M., Thorne, J.L., Lange, R.L. and Hecht, H.H.: Pulmonary vascular response to acute hypoxia in normal, unanesthetized calves. Am. J. Physiol. 203:391-396, 1962.

126. Kuida, H., Brown, A.M., Lange, R.L. and Hecht, H.H.: Cardiovascular studies on normal calves. Am. J. Physiol. 200:247-252, 1961.

127. Ladiges, W.C., Dickinson, E.O. and Gorham, J.R.: Clinical and pathologic comparison of the pulmonary response during experimentally induced anaphylaxis in sheep and cattle. Am. J. Vet. Res. 35:389-392, 1974.

128. Laitinen, L.A., Empey, D.W., Poppius, H., Lemen, R.J., Gold, W.M. and Nadel, J.A.: Effects of intravenous histamine on static lung compliance and airway resistance in normal man. Am. Rev. Respir. Dis. 114:291-295, 1976.

129. Laurenzi, G.A. and Yin, S.: Studies of mucus flow in the mammalian respiratory tract I. The beneficial effects of acetyl ovabain on respiratory tract mucus flow. Am. Rev. Respir. Dis. 103:800-807, 1971.

130. Leak, E.S., Gonzales-Ojeda, D. and Myrvik, Q.N.: Enzymatic differences between normal alveolar macrophages and oil induced peritoneal macrophages obtained from rabbits. Exp. Cell Res. 33:553-561, 1964.

131. Lee, T: Effects of histamine sensitizing factor and cortisol on lymphocyte adenyl cyclase responses. J. Allergy Clin. Immunol. 59 (1): 79-82, 1977.

132. Lerner, L.J. and Carminati, P.: Effect of day on pregnancy and pregnancy terminating agents on prostaglandin synthesis and metabolism and histamine metabolism in the rat utero-placental fetal complex and lung. J. Steroid Biochem. 8:395-402, 1977.

133. Lewis, A.J. and Eyre, P.: Some cardiorespiratory effects of histamine, 5-hydroxytryptamine, and compound 48/80 in the calf. Can. J. Physiol. Pharmacol. 50:545-553, 1972.

134. Lichtenstein, L.M.: 'Hormone receptor modulation of cAMP in the control of allergic and inflammatory responses.' The Role of Immunological Factors in Infectious, Allergic, and Autoimmune Processes. Eds. R.F. Beers, Jr. and E.G. Bassett. Raven Press, N.Y., p 339-354, 1976.

135. Lichtenstein, L.M. and Gillespie, E.: Inhibition of histamine release by histamine controlled by H_2 receptor. Nature 244:287-288, 1973.

136. Lichtenstein, L.M. and Gillespie, E.: The effects of the H_1 and H_2 antihistamines on "allergic" histamine release and its inhibition by histamine. J. Pharmacol. Exp. Ther. 192:441-450, 1975.

137. Loring, S.H., Drazen, J.M. and Ingram, R.H.: Canine pulmonary response to aerosol histamine: direct versus vagal effects. J. Appl. Physiol. 42:946-952, 1977.

138. Loring, S.H., Drazen, J.M., Snapper, J.R. and Ingram, R.H.: Vagal and aerosol histamine interactions on airway responses in dogs. J. of Appl. Physiol. 45 (1):40-44, July, 1978.

139. McGrath, M.A. and Shepherd, J.T.: Histamine and 5-hydroxytryptamine inhibition of transmitter release mediated by H_2 and 5-hydroxytryptamine receptors. Federation Proc. 37:195-198, 1978.

140. McLaughlin, R.F., Tyler, W.S. and Canada, R.O.: A study of subgross pulmonary anatomy in various species. Am. J. Anat. 108:149-165, 1961.

141. Macklem, P.T.: Procedures for standardized measurements of lung mechanics. National Heart and lung Institute Division of Lung Diseases. Nov. 1974.

142. Macklem, P.T.: New tests to assess lung function. New Eng. J. of Med. 293:339-342, 1975.

143. Macklem, P.T.: Disease in small airways. American Thoracic Society Basis of Respiratory Disease. 4 (5):26-31, 1976.

144. Macklem, P.T., Woolcock, A.J., Hogg, J.C., Nadel, J.A. and Wilson, N.J.: Partitioning of pulmonary resistance in the dog. J. Appl. Physiol. 26:798-805, 1969.

145. Marcus, G.J., Kraicer, P.F. and Shelesnyak, M.C.: Studies on the mechanism of decidualization. II Histamine releasing action of pyrathiazine. J. Reprod. Fertility. 5:409-415, 1963.

146. Mariassy, A.T., Plopper, C.G. and Dungworth, D.L.: Characteristics of bovine lung as observed by scanning electron microscopy. Anatomical Records 183:13-26, 1975.

147. Mathé, A.A., Volicer, L. and Puri, S.K.: Effect of anaphylaxis and histamine, pyrilamine and buramide on levels of cyclic AMP and cyclic GMP in guinea-pig lung. Research Communications in Chem., Path. and Pharmac. 8:635-651, 1974.

148. Mathé, A.A., Hedqvist, P., Holmgren, A. and Svanborg, N.: Bronchial hyperreactivity to prostaglandin $F_2\alpha$ and histamine in patients with asthma. Br. Med. J. 1:193-196, 1973.

149. Mead, J., Takishima, T. and Leith, D.: Stress distribution in lungs: a model of pulmonary elasticity. J. Appl. Physiol. 28:595-608, 1970.

150. Mead, J., Whittenberger, J.L. and Radford, E.P.: Surface tension as a factor in pulmonary volume-pressure hysteresis. J. Appl. Physiol. 10(2):191-196, 1957.

151. Mead, J., Whittenberger, J.L.: Physical properties of human lungs measured during spontaneous respiration. J. Appl. Physiol. 5:779-796, 1953.

152. Melmon, K.L. and Bourne, H.R.: Mechanisms of inflammation. Clin. Pharmac. Ther. 16:886-891, 1974.

153. Mettrick, D.F. and Telford, J.M.: Histamine in non-vertebrate animals. J. Pharm. Pharmacol. 15:694-697, 1963.

154. Metzger, W.J., Fish, J., Kelly, J.F., Rosenburg, M. and Patterson, R.: Hypersensitivity lung disease early diagnosis. J. Allergy Clin. Immunol. 61 (2):67-72, 1978.

155. Michoud, M.C., Pare, P.D., Orange, R.P. and Hogg, J.C.: Airway sensitivity to slow-reaching substance of anaphylaxis, histamine, and antigen in Ascaris sensitive monkeys. Am. Rev. of Resp. Dis. 119:419-424, 1979.

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

157. Mills, J.E., Sellick, H. and Widdicombe, J.G.: Activity of lung irritant receptors in pulmonary microembolism, anaphylaxis and drug-induced bronchoconstrictions. J. Physiol. (Lond.) 203:337-357, 1969.

158. Miserocchi, G., Trippenback, T., Mazzarelli, M., Jaspar, N. and Hazucha, M.: The mechanism of rapid shallow respiration due to histamine and phenyldiguanide in cats and rabbits. Respiration Physiology 32:141-153, 1978.

159. Mitchell, C. and Bouhuys, A: Interaction between bronchoconstrictor stimuli on human airway smooth muscle. The Yale J. of Biol. and Med. 49:317-325, 1976.

160. Monnier, M., Fallert, M. and Bhattacharya, I.C.: The waking action of histamine. Experientia 23:21-26, 1967.

161. Moore, J.B.: Regulation of intracellular cyclic GMP and cyclic AMP levels in mouse lung fragments by disodium cromoglycate, β-adrenergic agonists, cholinergic activators, and histamine. Research Communications in Clin. Path. and Pharmac. 17:639-647, 1977.

162. Mordelet-Dambrine, M., Gateau, O., Hartmann, C.H., Treize, G. and Parrot, J.L.: Does the pneumogastric nerve intervene the bronchopulmonary effects of histamine in anaesthetized and ventilated guinea-pig? Acta Allergol (KBH) 32:218-219, 1977. Proceedings.

163. Moulton, J.E., Cornelius, C.E. and Osburn, B.I.: Acute pulmonary emphysema in cattle. J.A.V.M.A. 142:133-137, 1963.

164. Musewe, V.O., Gillespie, J.R. and Berry, J.D.: Influence of ruminal insufflation on pulmonary function and diaphragmatic electromyography in cattle. Am. J. Vet. Res. 40:26-31, 1979.

165. Newball, H.H. and Keiser, H.R.: Relative effects of bradykinin and histamine on the respiratory system of man. J. Appl. Physiol. 35:552-555, 1973.

166. Nilsson, S.A.: Clinical, morphological and experimental studies of laminitis in cattle. Acta Veterinaria Scandinavica 4:1-307, 1963.

167. Nisam, M.R., Zbinden, A., Chesrown, S., Barnett, D. and Gold, W.M.: Distribution and pharmacological release of histamine in canine lung *in vivo*. J. Appl. Physiol. 44:455-463, 1978.

168. Obel, N.J. and Schmiterlöw, C.G.: The action of histamine and other drugs on the bronchial tone in horses suffering from alveolar emphysema (Heaves). Acta Pharmacol. 4:71-80, 1948.

169. Ohga, A. and Taneike, T.: H_1- and H_2-receptors in the smooth muscle of the ruminant stomach. Br. J. Pharmac. 62:333-337, 1978.

170. Okpako, D.T.: A dual action of histamine on guinea-pig lung vessels. Br. J. Pharmac. 44:311-321, 1972.

171. Okpako, D.T.: The actions of histamine and prostaglandins $F_{2\alpha}$ and E_2 on pulmonary vascular resistance of the lung of the guinea-pig. J. Pharm. Pharmac. 24:40-46, 1972.

172. Orange, R.P.: The immunological response of chemical mediators from human lung: Approaches to pharmacological antagonism. The Role of Immunological Factors in Infectious, Allergic, and Autoimmune Processes. Eds. R.F. Beers, Jr. and E.G. Bassett. Raven Press, N.Y. pp223-227, 1976.

173. Ortez, R.A.: Effect of histamine on lung cyclic AMP levels in normal and pertussis-vaccinated mice. Biochemical Pharmacology 25:523-526, 1976.

174. Padgett, G.A. and Hirsch, J.G.: Lysozyme: Its absence in tears and leukoctes of cattle. Aust. J. Exp. Biol. Med. Sci. 45:569-570, 1969.

175. Pardy, R.L., Rivington, R.N., Jardim, J., Despas, P.J. and Macklem, P.T.: Assessment of inspiratory pressures and resistances required to produce inspiratory muscle fatigue in chronic airflow limitation. Am. Rev. Respir. Dis. 119 (4):346, 1979.

176. Persson, G.A. and Ekman, M.: Contractile effects of histamine in large and small respiratory airways. Agents Actions 6:389-393, 1976.

177. Piper, P.J.: Anaphylaxis and the release of active substance in the lungs. Pharmac. and Ther. 3:75-98, 1977.

178. Plaut, M. and Berman, I.J.: Histamine receptors on human and mouse lymphocytes. Abstract No. 13. J. Allergy Clin. Immunol. 61 (3), 1978.

179. Platshon, L.F. and Kaliner, M.: The effects of the immunologic release of histamine upon human cyclic nucleotide levels and prostaglandin generation. J. Clin. Invest. 62:1113-1121, 1978.

180. Ploy-Song-Sang, Y., Corbin, R.P. and Engel, L.A.: Effects of intravenous histamine on lung mechanics in man after beta-blockade. J. Appl. Physiol. 44:690-695, 1978.

181. Polson, J.B., Krzanowski, J.J. and Szentivanyi, A.: Histamine induced changes in pulmonary guanosine-3', 5'-cyclic monophosphate (cGMP) and adenosine-3', 5'-cyclic monophosphate (cAMP) levels in mice following sensitization by Bordetella pertussis and/or propranolol. Research Communications in Chem. Path. and Pharmac. 9:243-251, 1974.

182. Popa, V., Douglas, J.S. and Bouhuys, A.: Airway responses to histamine, acetylcholine, and propranolol in anaphylactic hypersensitivity in guinea-pigs. J. Allergy Clin. Immunol. 51:344-356, 1973.

183. Propst, K., Millen, J.E. and Glauser, F.L.: The effects of endogenous and exogenous histamine on pulmonary alveolar membrane permeability. Am. Rev. Respir. Dis. 117:1063-1068, 1978.

184. Raab, W.P.: Mast cell depleting properties of neomycin. J. Invest. Dermatol. 50:138-140, 1968.

185. Reed, R., Bourne, H.R., Melmon, K.L. and Gold, W.M.: Cyclic AMP and cyclic GMP in canine peripheral lung: regulation in vivo. Am. Rev. Respir. Dis. 118:723-733, 1978.

186. Reeves, J.T., Daoud, F.S. and Estridge, M.: Pulmonary hypertension caused by minute amounts of endotoxin in calves. J. Appl. Physiol. 33:739-743, 1972.

187. Reeves, J.T., Grover, R.F., Will, D.H. and Alexander, A.F.: Hemodynamics in normal cattle. Circulation Research 10:166-171, 1962.

188. Ring, J., Arroyave, C.M., Fritzler, M.J. and Tan, E.M.: In vitro histamine and seratonin release by radiographic contrast media (RCM) in man. J. Allergy Clin. Immunol. 61:145, 1978.

189. Robinson, N.E., Gillespie, J.R., Berry, J.D. and Simpson, A.: Lung compliance, lung volumes, and single-breath diffusing capacity in dogs. J. Appl. Physiol. 33:808-812, 1972.

190. Robinson, N.E. and Sorenson, P.R.: Collateral flow resistance and time constants in dog and horse lungs. J. Appl. Physiol. 44:63-68, 1978.

191. Rocha e Silva: Histamine and antihistamines. Handbook of Experimental Pharmacology. Vol. XVIII, 1966.

192. Rocklin R.E. and Greineder, D.: Histamine induced suppressor factor (HSF): Nature of stimulus and effect. J. Allergy Clin. Immunol. 61: Abstract 54, 1978.

193. Rosenburg, M. and Savarie, P.J.: Histamine and the reversal of chlorpromazine induced depression. J. Pharmacol. Exp. Therap. 146:180-185, 1964.

194. Rosenthal, R.R., Bleeker, E.R., Laube, B., Norman, P.S. and Permutt, S.: Cholinergic response to histamine challenge. J. Allergy Clin. Immunol. (Ab. 36) 61:139, 1978.

195. Roth, F.E. and Tabachnick, I.I.A.: Histamine and antihistamines. Drills Pharmacology in Medicine. 4th edition. J.R. DiPalma editor. McGraw-Hill Book Co., N.Y. 1971.

196. Rybicka, K., Daly, B.D.T., Migliore, J.J. and Norman, J.C.: Ultrastructure of pulmonary alveoli of the calf. Am. J. Vet. Res. 35:213-222, 1974.

197. Said, S.I.: Environmental injury to the lung: role of humoral mediators. Federation Proc. 37:2504-2507, 1978.

198. Sattler, F.P.: Measuring ventilation, pH, and blood gases in the surgical patient. J.A.V.M.A. 154:511-517, 1969.

199. Schayer, R.W.: Evidence for a specific function of histamine in brain. Adv. Neurol. 5:111-114, 1974.

200. Severinghaus, J.W.: Blood gas concentrations. In Handbook of Physiology-Respiration II American Physiological Society, Washington D.C., p 1475-1487, 1965.

201. Shaff, R.E. and Beaven, M.A.: Inhibition of histamine-N-methyltransferase and histamine (diamine oxidase) by a new histamine H_2-receptor agonist, Dimaprit. Biochem. Pharmacol. 26:2075-2078, 1977.

202. Shaw, J.W.: Pulmonary vasodilator and vasoconstrictor actions of histamine. J. Physiol. 215:34P-35P, 1971.

203. Silove, E.D. and Grover, R.F.: Effects of alpha adrenergic blockade and tissue catecholamine depletion on pulmonary vascular response to hypoxia. J. Clin. Invest. 47:274-285, 1968.

204. Silove, E.D. and Simcha, A.J.: Histamine-induced pulmonary vasodilation in the calf: relationship to hypoxia. J. Appl. Physiol. 35:830-836, 1973.

205. Simon, R.A., Stevenson, D.D., Arroyave, C.M. and Tan, E.M.: The relationship of plasma histamine to the activity of bronchial asthma. J. Allergy Clin. Immunol. 60:312-316, 1977.

206. Steel, R.G.D. and Torrie, J.H.: Principles and Procedures of Statistics. McGraw-Hill Book Co. Inc. N.Y., 1960.

207. Stossel, T.P.: Phagocytosis (parts I, II and III). New Eng. J. of Med. 290:717-723, 774-780, 833-839, 1974.

208. Sylvester, J.T., Menkes, H.A. and Stitik, F.: Lung volume and interdependence in the pig. J. Appl. Physiol. 38 (3):395-401, 1975.

209. Thermann, M., Lorenz, W., Schmal, A., Schingale, F., Dormann, P. and Hamelmann, H.: Alterations in the circulatory system of anaesthetized dogs following administration of histamine and histamine H_1- and H_2-receptor antagonists in relation to plasma histamine levels. Agents Actions 5:450-454, 1975.

210. Thermann, M., Lorenz, W., Schmal, A., Schingale, F., Dormann, P. and Hamelmann, H.: Influence of H_1- and H_2-receptor antagonists on the circulatory system and on the endogenous plasma histamine concentrations in dogs. Agents Actions 7:97-101, 1977.

211. Tolos, W.P., Richards, D.E. and Scheel, L.D.: Histamine induction and release following proteolytic enzyme exposure. Am. Ind. Hyg. Assoc. J. 36:272-277, 1975.

212. Tucker, A., Weir, E.K., Reeves, J.T. and Grover, R.F.: Histamine H_1 and H_2 receptors in pulmonary and systemic vasculature in the dog. Am. J. Physiol. 229:1008-1013, 1975.

213. Tucker, A., Weir, E.K., Grover, R.F. and Reeves, J.T.: Oxygen tension dependent pulmonary vascular responses to vasoactive agents. Can. J. Physiol. Pharmacol. 55:251-257, 1977.

214. Tucker, A., Hoffman, E.A. and Weir, E.K.: Histamine receptor antagonism does not inhibit hypoxic pulmonary vasoconstriction in dogs. Chest. 71, 2 Suppl:261-262, 1977.

215. Tucker, A., Weir, E.K., Reeves, J.T. and Grover, R.F.: Failure of histamine antagonists to prevent hypoxic pulmonary vasoconstriction in dogs. J. Appl. Physiol. 40:496-500, 1976.

216. Türker, R.K.: Presence of histamine H_2-receptors in the guinea-pig pulmonary vascular bed. Pharmacology 9:306-311, 1973.

217. Uvnas, B.: Mechanism of histamine release in mast cells. Ann. N.Y. Acad. Sci. 103:278-283, 1963.

218. Vaage, J., Scott, E. and Wiberg, T.: Dextran induced release of prostaglandins (PG's) from lungs, and its inhibition by a histamine receptor blocker. Prostaglandins (Abstr.) 15:713, 1978.

219. Veit, H.P. and Farrell, R.L.: The anatomy and physiology of the bovine respiratory system relating to pulmonary disease. Cornell Vet. 68:555-581, 1978.

220. Veit, H.P. Farrell, R.L. and Troutt, F.: Pulmonary clearance of Serratia marcescens in calves. Am. J. Vet. Res. 39:1646-1650, 1978.

221. Verhaegen, H., DeCock, W. and DeCree, J.: Histamine receptor-bearing peripheral T lymphocytes in patients with allergies. J. Allergy Clin. Immunol. 59:266-268, 1978.

222. Vidruk, E.H., Hahn, H.L., Nadel, J.A. and Sampson, S.R.: Mechanisms by which histamine stimulates rapidly adapting receptors in dog lungs. J. Appl. Physiol. 43:397-402, 1977.

223. Vijay, H.M. and Perelmutter, L.: Inhibition of reagin-mediated PCA reactions in monkeys and histamine release from human leucocytes by human IgG_4 subclass. Int. Arch. Allergy Appl. Immunol. 53:78, 1977.

224. Walker, J.L.: The regulatory function of prostaglandins in the release of histamine and SRS-A from passively sensitized human lung tissue. Advances in the Biosciences. 9 International conference on Prostaglandins 235-240, 1972.

225. Wasserman, M.A.: Bronchopulmonary responses to $PGF_2\alpha$, histamine and acetylcholine in the dog. Eur. J. Pharmacol. 32:146-155, 1975.

226. Weir, E.K., Tucker, A., Reeves, J.T., Will, D.H. and Grover, R.F.: The genetic factor influencing pulmonary hypertension in cattle at high altitude. Cardiovascular Research 8:745-749, 1974.

227. Wells, P.W. and Eyre, P.: The pharmacology of passive cutaneous anaphylaxis in the calf. Can. J. Physiol. Pharmacol. 50:255-262, 1972.

228. Wells, P.W., Eyre, P. and Lumsden, J.H.: Hematological and pathological changes in acute systemic anaphylaxis in calves: Effects of pharmacological agents. Can. J. Comp. Med. 37:119-129, 1973.

229. West, J.B.: Ventilation perfusion inequality and overall gas exchange in computer models of the lung. Resp. Physiol. 7:88-110, 1969.

230. West, J.B.: Ventilation-perfusion relationships. Am. Rev. Respir. Dis. 116:919-943, 1977.

231. Weyer, A., David, B., Laurent, M. and Henocq, E.: Cellular histamine release, specific and total serum IgE levels in hay fever patients and controls. Clinical Allergy 8:187-194, 1978.

232. Wicki, A. and Schatzmann, H.J.: Histamine formation by ruminal fluid from cattle in vitro. Experentia 33:422-423, 1977.

233. Wilkie, B.N.: Experimental hypersensitivity pneumonitis. Humoral and cell mediated immune response of cattle to Micropolysporum faeni and clinical response to aerosol challenge. Int. Arch. Allergy Appl. Immunol. 50:359-373, 1976.

234. Wilkie, B.N.: Hypersensitivity pneumonitis: Experimental production in calves with antigens of Micropolyspora faeni. Can. J. Comp. Med. 40:221-227, 1977.

235. Wilkie, B.N.: Bovine allergic pneumonitis: An acute outbreak associated with mouldy hay. Can. J. of Comp. Med. 42:10-13, 1978.

236. Will, D.H., McMurtry, I.F., Reeves, J.T. and Grover, R.F.: Cold induced pulmonary hypertension in cattle. J. Appl. Physiol. 45: (3):469-473, 1978.

237. Will, D.H., Hicks, J.L., Card, C.S. and Alexander, A.F.: Inherited susceptibility of cattle to high altitude pulmonary hypertension. J. Appl. Physiol 38:491-495, 1975.

238. Windaus, A. and Vogt, W.: Synthesis of Imidazolethylamines. Ber. Deut. Chem. Ges. 40:3691-3793, 1907.

239. Woods, J.R., Brinkman, C.R., Dandavino, A., Murayama, K. and Assali, N.S.: Action of histamine and H_1 and H_2 blockers on the cardiopulmonary circulation. Am. J. Physiol. 232: Ph73-78, 1977.

240. Woods, J.R., Brinkman, C.R., Assali, N.S.: Fetal and neonatal cardiopulmonary response to histamine. Obstetrics and Gynecology 48:195-202, 1976.

241. Woolcock, A.J. and Macklem, P.T.: Mechanical factors influencing collateral ventilation in human dog and pig lungs. J. Appl. Physiol. 30:99-115, 1971.

242. Wray, C. and Thomlinson, J.R.: Investigations into the role of pharmacologically active amines in calves. Br. Vet. J. 130:466-474, 1974.

243. Zarkower, A.: Histamine in the cow: Effect of histamine and estradiol administration on protein concentrations in milk. Am. J. Vet. Res. 28:1757-1762, 1967.

244. Zarkower, A.: Histamine in the cow: Pre and post-parturition histamine concentrations in plasma, milk and tissue. Am. J. Vet. Res. 28:1751-1755, 1967.

245. Zarkower, A. and Norcross, N.L.: Histological changes in the bovine mammary gland after infusion with Streptococcus agalactiae extract. Cornell Vet. 56:555-566, 1966.

246. Zavecz, J.M. and Levi, R.: Histamine-induced negative inotropism: Mediation by H_1-receptors. J. Pharmacol. Exp. Ther. 206:274-280, 1978.

APPENDICES

APPENDIX A

Equations used in calculation of indices described under the section "Materials and Methods."

1. Alveolar oxygen tension (PAO_2)[1]

$$PAO_2 = PIO_2 - \frac{PACO_2}{R} + PACO_2 \cdot FIO_2 \cdot \frac{I-R}{R}$$

where PIO_2 is inspired oxygen partial pressure

$PACO_2$ is alveolar carbon dioxide partial pressure

FIO_2 is the oxygen fraction in inspired air and

R is defined as

$$R = \frac{P_ECO_2}{\frac{P_IO_2 \cdot P_EN_2}{P_IN_2} - P_EO_2}$$

where $PECO_2$ is expired carbon dioxide partial pressure and PIN_2, PEN_2 are the inspired and expired nitrogen partial pressures.

Since it was assumed that

a) inspired CO_2 concentration was negligible,

b) $PACO_2$ equalled $PaCO_2$ where $PaCO_2$ was defined as systemic arterial carbon dioxide pressure then the working form of the alveolar Gas Equation was reduced to

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R} + PaCO_2 \cdot FIO_2 \frac{I-R}{R}$$

---

1 From Alveolar Gas Equation "Respiratory Physiology" - The essentials J.B. West. Williams & Wilkins. 1975.

2. Dead space/tidal volume ratio $\frac{V_D}{V_T}$

$$\frac{V_D}{V_T} = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

$PaCO_2$ Systemic arterial carbon dioxide tension.

$PECO_2$ Partial pressure of expired carbon dioxide.

3. Cardiac output ($\dot{Q}$)

From the Fick principle $\dot{Q} = \frac{\dot{V}O_2}{C_aO_2 - C_{\bar{v}}O_2}$ [1]

where $\dot{V}O_2$ = net oxygen uptake

C_{aO_2} = arterial oxygen content

$C_{\bar{v}}O_2$ = mixed venous oxygen content

$\dot{V}O_2$ = Minute Ventilation ($FIO_2 - FEO_2$) where FIO_2 = fraction of oxygen in inspired air.

FEO_2 = fraction of oxygen in expired air.

---

1 West, J.B.: Respiratory Physiology-The essentials. Williams & Wilkins, 1975.

Oxygen content = 1.34 x % sat. x Hgb. + .003 x PO_2

where PO_2 = O_2 partial pressure.

% sat = % saturation of hemoglobin,

Hgb. = hemoglobin concentration.

The constant 1.34 relates the volume of oxygen that will be bound by 1 gm of hemoglobin, under standard conditions of temperature and pressure.[2]

% sat, Hgb and PO_2 are determined for arterial and mixed venous samples in order to calculate ($C_aO_2 - C\bar{v}O_2$).

---

[2] Slonim, N.B. and Hamilton, L.H.: Respiratory Physiology, 3rd edition, 1976. C.V. Mosby Co., Saint Louis.

APPENDIX B

Tabulated values of the means for all variables measured at the designated measurement periods.

Means for variables which failed to change significantly in response to histamine are also presented in this Appendix.

Group I Calves

Variable	Control		Histamine		15-PH		30-PH		60-PH	
	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc
C_{stat} (ml/cm H_2O)	153.2	153.2	140.0	146.4	164.6	171.2	155.1	162.1	152.6	154.0
**C_{dyn} (ml/cm H_2O)	75.0	116.9	37.6	92.0	76.5	125.7	90.2	123.8	95.0	128.5
** R_{aw} (cm H_2O/liter.min^{-1})	.053	.062	.116	.119	.085	.091	.081	.090	.068	.072
**P-V hysteresis (liter.cm H_2O)	4.25	2.41	14.22	4.77	7.06	3.22	5.10	3.03	4.57	2.67
**P_{tp} max. (cm. H_2O)	8.89	7.45	20.14	10.20	10.40	7.84	9.04	7.40	8.23	6.68
**$\dot{V}_{max.}$ (liter/min)	81.4	78.1	96.9	83.3	86.3	76.1	79.5	74.6	82.7	76.3
VD/V_T (%)	32.7		47.2		36.2		41.4		37.3	
PAO_2 (mm Hg)	109.7		105.8		107.5		103.7		105.0	
**PaO_2 (mm Hg)	66.6		28.7		52.8		63.2		65.3	
**(A-a) DO_2 (mm Hg)	43.1		77.0		54.7		40.5		39.7	
**Cardiac Output (liters/min)	13.70		5.42		4.99		5.63		5.38	
**Stroke Vol. (ml)	91.6		24.3		28.4		30.5		28.3	
**Heart Rate (beats/min)	154.4		224.8		189.2		185.2		189.8	
**$P_{syst.}$ (mm Hg)	115.4		41.4		54.6		63.0		69.2	
**P_{pa} (mm Hg)	30.6		19.8		23.8		28.2		30.0	
PVR (mm Hg/litre.min^{-1})	2.48		3.85		5.07		5.27		6.19	
SVR (mm Hg/liter.min^{-1})	9.62		7.59		11.01		10.78		13.12	

** Significant differences between means at the .01 level

Group II Calves

Variable †	Control	H_1 Block	Low Hist.	High Hist.	15-PH	30-PH	60-PH
**PAO_2	100.0	93.6	95.4	94.7	91.9	91.2	89.8
$Pa0_2$	82.2	78.3	77.1	75.4	74.2	79.5	77.4
(A-a) DO_2	23.4	21.2	23.7	24.4	23.6	17.1	17.7
V_D/V_T	23.2	24.8	22.6	23.0	20.7	25.2	29.6
Cardiac Output	10.76	12.62	19.32	15.29	16.10	13.71	11.47
Stroke Vol.	65.7	66.3	83.3	67.7	81.7	71.3	59.3
**Heart Rate	165.2	189.8	234.5	228.0	202.2	195.0	194.2
**$P_{syst.}$	110.7	121.7	91.7	78.3	111.3	118.5	120.0
**P_{pa}	35.7	38.2	27.8	27.0	30.3	32.7	30.5
PVR.	3.45	3.15	1.71	1.97	2.28	2.56	2.74
**SVR.	11.31	10.51	5.64	5.50	8.28	9.39	10.86

† Units for variables are as listed for group I calves.

** Significant differences between means at the .01 level.

Group II Calves

Variable ††	Control		H_1 blocker		Low Hist.		High Hist.		15-PH		30-PH		60-PH	
	before vc †	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc
C_{stat}	107.6	111.0	108.9	108.9	103.4	106.8	107.8	107.7	104.5	104.5	98.9	104.6	109.2	117.2
C_{dyn}	80.2	91.7	78.4	83.1	80.7	87.7	81.0	83.4	80.0	83.5	83.6	87.1	85.5	90.8
R_{aw}	.090	.089	.076	.074	.068	.074	.087	.078	.074	.091	.075	.089	.072	.083
P_{tp} Max	10.72	9.65	10.34	10.06	10.25	9.56	10.46	9.90	10.79	10.40	9.85	9.99	9.66	9.33
** P-V Hysteresis	4.27	1.88	3.76	2.09	2.97	1.67	3.31	1.53	3.56	2.10	2.70	1.79	3.10	1.77

† vc - Vital capacity maneuvers
** Significant differences between means at .01 level
†† - Units for variables are as listed for group I calves

Group III Calves

Variable †	Measurement Period											
	Control		H_2 Block		Histamine		15-PH		30-PH		60-PH	
	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc
C_{stat}	127.3	129.4	129.9	129.9	136.7	134.2	130.5	133.7	128.4	128.4	129.0	129.0
**C_{dyn}	94.4	104.9	90.5	99.7	4.9	89.1	87.4	107.8	92.5	106.2	94.2	101.3
**R_{aw}	.064	.067	.067	.072	.142	.127	.085	.084	.078	.079	.077	.081
**P-V hysteresis	3.45	2.23	3.41	2.30	12.19	3.95	4.40	2.52	3.63	2.36	3.87	2.40
**P_{tp} max.	8.74	8.01	9.06	8.28	16.98	10.00	9.70	8.28	9.05	8.22	9.01	8.29

† Units for variables are as listed for group I calves.

** Significant differences between means at the .01 level.

Group III Calves

Variable †	Measurement Period											
	Control		H_2 Block		Histamine		15-PH		30-PH		60-PH	
	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc	before vc	after vc
VD/VT	28.4		28.2		34.8		28.7		27.8		28.3	
PAO_2	114.3		113.7		116.1		115.5		115.4		113.0	
**PaO_2	76.1		76.8		34.7		68.7		70.5		67.8	
**(A-a) DO_2	38.3		36.9		81.3		46.8		45.0		45.2	
**Cardiac Output	11.52		9.63		7.32		7.40		7.35		6.52	
**Stroke Vol.	68.3		60.9		43.8		47.0		43.2		37.0	
**Heart Rate	170.7		163.2		170.2		162.7		176.0		179.2	
**$P_{syst.}$	122.2		111.0		59.5		72.2		88.0		92.2	
**P_{pa}	32.8		33.2		23.5		27.2		32.0		29.0	
PVR	3.26		3.53		3.37		3.95		5.23		4.61	
SVR	12.17		11.97		8.77		10.59		14.57		14.56	
**PCV	30.9		31.1		37.5		35.2		34.8		35.3	
*Hgb.	9.98		9.92		11.88		11.25		11.22		11.30	
*T.P.	4.62		4.65		4.55		4.33		4.32		4.47	

† Units for variables are as listed for group I calves.

** Significant differences between means at the .01 level.