**Acta physiol. scand. 1976. 97. 158–165**

From the Department of Physiology and Medical Biophysics, Biomedical Centre, the Department of Internal Medicine and the Department of Lung Medicine, University Hospital, Uppsala, Sweden

# Effects of Respiratory Alkalosis and Acidosis on Myocardial Excitation

By

ROLF G. SAMUELSSON and GYÖRGY NAGY

Received 7 October 1975

## Abstract

SAMUELSSON, R. G. and G. NAGY. *Effects of respiratory alkalosis and acidosis on myocardial excitation.* Acta physiol. scand. 1976. *97.* 158–165.

In anesthetized dogs electrocardiogram and monophasic action potentials (MAPs) were recorded from the right atrium and the right ventricle by intracardiac suction electrode technique. The animals were subjected, by means of ventilation with $CO_2$ and hyperventilation, to periods of respiratory acidosis and respiratory alkalosis, respectively. Pronounced respiratory acidosis induced an increased sympathetic activity followed by a decrease in heart rate and prolongation of the A–V conduction time whereas the shape and duration of the atrial and ventricular MAPs remained unaltered. Arterial hypoxia in combination with pronounced respiratory acidosis did not influence the MAP durations. Respiratory alkalosis resulted in an increased sympathetic influence on the heart activity whereas the shape and duration of the atrial and the ventricular MAPs remained unaffected. During pronounced hyperventilation with increasing central venous pressure an increased parasympathetic influence on the heart activity with decrease in the heart rate, prolongation of the A–V conduction time and shortening of the atrial MAP duration was recorded.

*Key words:* Monophasic action potentials; Electrocardiogram; Refractory period; Heart, suction electrode, cardiac catheter; Atrium; Ventricle, respiratory alkalosis, respiratory acidosis; Dogs

Clinical and experimental evidence has emphasized the frequent occurrence of cardiac arrhythmias in association with respiration-induced shifts in acid–base balance. It has been reported that patients with acute and chronic respiratory failure (Price 1960, Hudson *et al.* 1973, Kurt *et al.* 1973), critically ill, intensive-treated (Lawson *et al.* 1973) and respirator-treated (Yakaitis *et al.* 1971, Ayres and Grace 1969) patients have a high incidence of cardiac rhythm disturbances. Various types of animal experiments support these findings (*cf.* Cline *et al.* 1966, Dong *et al.* 1967). The precise role however that acid–base imbalances play in the genesis of arrhythmias is still poorly understood and different authors have been stressing different reasons for the cause of developement of the cardiac rhythm disturbances (Price 1960, Yakaitis *et al.* 1971, Lawson *et al.* 1973, Rodgers *et al.* 1973).

[1] Visiting Scientist of the Swedish Association for Chest and Heart Diseases. Permanent Address: Orszagos Koranyi Intezet, Budapest, XII ker., Pihenö ut 1., Hungary.

The effect of pH shifts on the action potential of cardiac muscle has previously been studied in isolated heart muscle preparations and it has been found that an increase of the pH will induce a shortening of the duration of the action potential (Hecht and Hutter 1964, Vaughan Williams and Whyte 1967). According to Watanabe and Dreifus (1968) and Vaughan Williams (1970), anything that shortens the refractory period of heart muscle cells favours the development of re-excitation and the induction of arrhythmias.

As far as is previously known, no study has been made concerning the influence of respiration-induced pH shifts on the action potential (AP) or the monophasic action potential (MAP) of the cardiac muscle in the heart *in situ*. The aim of this communication is to present studies of the influence of respiration-induced pH shifts on the MAP recorded from atrial and ventricular muscle in the dog's heart *in situ*. The intracardiac suction-electrode technique used for this purpose has been described in a previous work (Samuelsson and Sjöstrand 1971).

## Methods and Experimental Procedure

The experiments were performed on 12 mongrel dogs of both sexes, weighing between 12 and 16 kg. After the induction of anesthesia with pentobarbital (Nembutal®, 25 mg/kg), the dog was intubated and given artificial respiration with air (Jonzon *et al.* 1971). Maintenance doses of Nembutal, on the average 50 mg/h, were administered throughout the expts. The temperature was checked regularly during the expts. and kept constant by means of heat pads incorporated into the operating table.

The thorax was opened by splitting the sternum in order to control the position of the tip of the suction electrode catheter. The artificial respiration was regulated, after the thorax had been opened, so that the arterial $P_{O_2}$ was about 100 mmHg and the acid–base status was within the following limits: pH $7.40 \pm 0.05$, $P_{CO_2}$ $40 \pm 5$ mmHg. For the measurement of the arterial pH, $P_{CO_2}$ and $P_{O_2}$, an Acid–Base Analyzer, Type 71. connected to a Blood Micro System, Type BMS 2b, a $P_{CO_2}$ electrode, Type E 5036 and a $P_{O_2}$ electrode, Type E 5046 (Radiometer, Copenhagen), were used. Arterial blood samples were performed by a catheter introduced into the thoracic aorta from the femoral artery.

Respiratory alkalosis was induced by lowering the frequency, increasing the relative insufflation time and increasing the respiratory minute volume. The central venous pressure (CVP) was measured via a catheter introduced from the femoral vein to the level of the atrium throughout the hyperventilation expts. Respiratory acidosis was induced by a gradual adding of $CO_2$ to the ventilation gas. Hypoxia was induced by gradually replacing the air in the ventilation gas by Nitrogen until the desired oxygenation level was reached. The ECG (standard lead II), the right atrial and the right ventricular MAPs were recorded during the expts. These recordings were made on an oscilloscope (Tektronix, Type 561) and filmed with an oscilloscope recording camera, Model C 4 (Grass Instruments, Mass., USA). A pacemaker (USCI No. 5652), localized in the upper part of the right atrium, was used to keep the heart rate constant and thereby to avoid variations in the MAP duration due to changes in the heart rate.

Qualitative changes in the shape and duration of the MAP were determined by superimposing the control recordings on the experimental recordings.

## Results

### *Respiratory alkalosis*

The experiments were performed on 6 dogs. In the first series of expts., respiratory alkalosis was induced by a successive increase in hyperventilation until a point was reached where an increase in the CVP was recorded. At that point the hyperventilation was interrupted in order to avoid the influence of hemodynamic alterations upon the heart performance due to the artificial respiration (Morgan *et al.* 1966, Andersen and Kuchiba 1967, Nordström 1972). In these expts. an increase in pH, range: 7.55–7.61, slight increase in $P_{O_2}$, range:

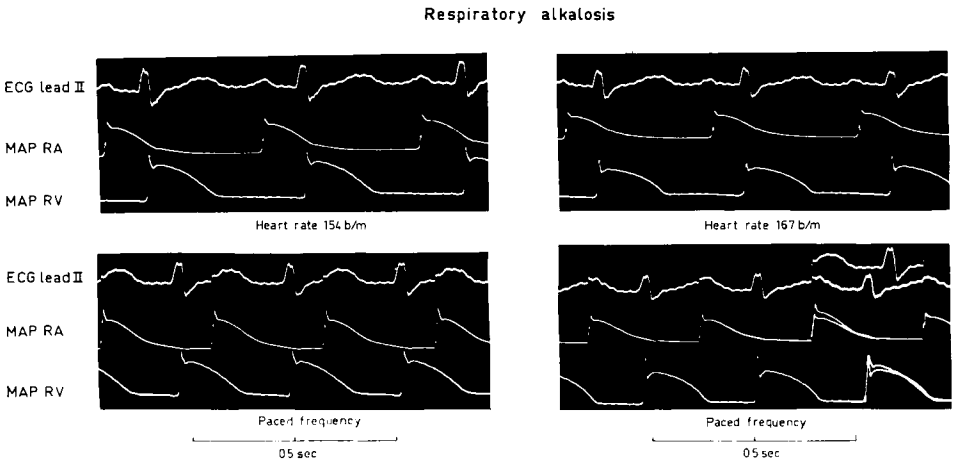


Fig. 1. ECG, atrial MAP and ventricular MAP recordings made before and during respiratory alkalosis, recorded during spontaneous and paced, constant, heart rate. Control recordings have been superimposed on the recordings made during constant heart rate (bottom, right).

106–122 mmHg and a decrease in $P_{CO_2}$ to less than 14 mmHg were recorded. The effects on the heart performance constituted of an increase in heart rate, on the average 11 ±3% (Mean ±S.D.) and a decrease in the A–V conduction time. As was recorded during paced, constant heart rate, no change in the shape or duration of the atrial or ventricular MAPs, except a slight decrease in the amplitude (Samuelsson and Sjöstrand 1971), was notified (see Fig. 1). When the hyperventilation was interrupted and the acid–base status restored to normal, the effects on the heart rate and the A–V conduction time also were restored. The same expt. has been repeated with similar effects on the heart performance several times.

In a second series of expts. the artificial ventilation was increased to maximal hyperventilation. This caused a continuous increase in the CVP. The hyperventilation was maintained until the CVP reached a value of 50 mmHg where the expt. was interrupted. This resulted in an increase in pH, range: 7.64–7.75, increase in $P_{O_2}$, range: 118–132 mmHg and a decrease of $P_{CO_2}$ to less than 10 mmHg.

The effects on the heart performance were an initially slight increase in heart rate that quickly changed to a pronounced decrease in the heart rate on the average 21 ±4% (Mean ±S.D.) and a pronounced prolongation of the A–V conduction time. The shape of the atrial MAP was markedly altered as a consequence of an acceleration of the repolarization course with a pronounced shortening of the MAP duration (see Fig. 2). As was recorded during paced, constant heart rate, the ventricular MAP remained unaltered except for a slight decrease in the amplitude (Samuelsson and Sjöstrand 1971). When a normal acid–base status was restored, a normalization of the heart rate, A–V conduction time and shape and duration of the atrial MAP was recorded.

*Respiratory acidosis*

The expts. were performed on 6 dogs. In a first series of expts. the dogs were ventilated by 20% $CO_2$ until a severe state of respiratory acidosis was reached. A decrease in pH, range:

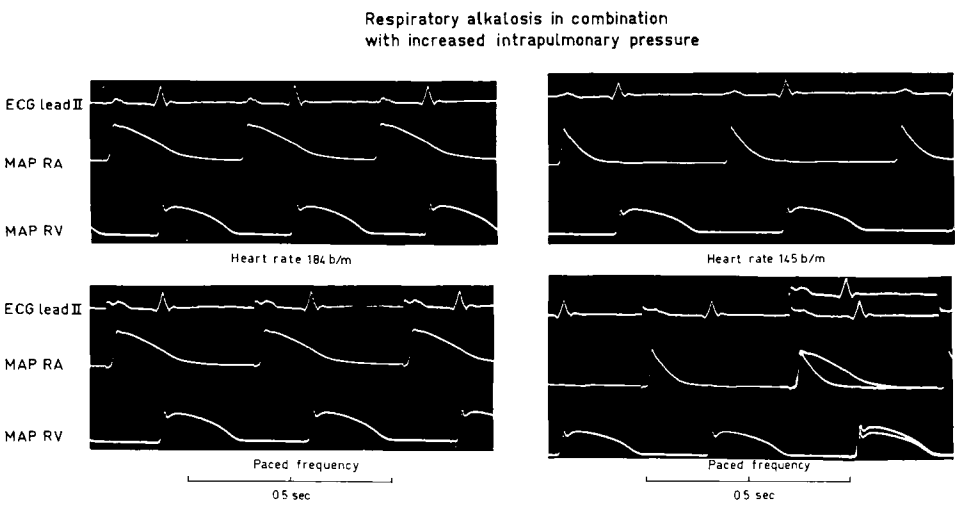


Fig. 2. ECG, atrial MAP and ventricular MAP recordings made before and during respiratory alkalosis in combination with increased intrapulmonary pressure. The recordings have been made during spontaneous and paced, constant, heart rate.

6.91–7.02, increase in $P_{CO_2}$, range: 81–118 mmHg was recorded whereas the $P_{O_2}$ remained in the range: 89–103 mmHg.

The effects on the heart performance constituted an initially slight increase that rapidly changed to a marked decrease in the heart rate, on the average $16 \pm 4\%$ (Mean $\pm$S.D.) and a prolongation of the A–V conduction time. No alternation in the shape or duration of the atrial or ventricular MAPs, except a slight decrease in the amplitudes was recorded during the paced, constant heart rate (see Fig. 3). When the supply of $CO_2$ gas was interrupted and the acid–base status was restored to normal, the heart rate and A–V conduction time also were restored to normal.

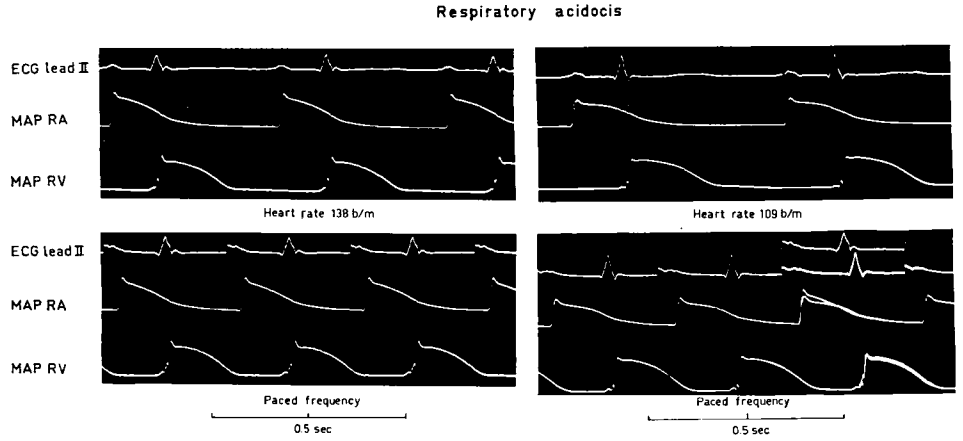


Fig. 3. ECG, atrial MAP and ventricular MAP recordings made before and during respiratory acidosis, recorded during spontaneous and paced, constant, heart rate.

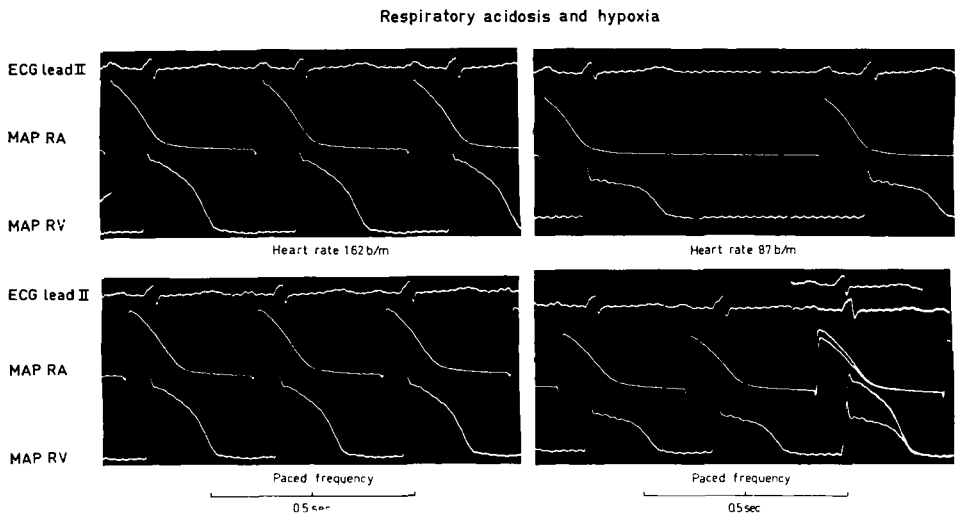


Fig. 4. ECG, atrial MAP and ventricular MAP recordings made before and during respiratory acidosis in combination with hypoxia. The recordings have been made during spontaneous and paced, constant, heart rate.

In a second series of expts. the ventilation air was partly replaced by nitrogen gas until a $P_{O_2}$ in the range: 40–50 m Hg was achieved. Thereafter carbon dioxide was added to the ventilating gas to a concentration about 20%. The dogs then were ventilated until a severe state of respiratory acidosis was induced. In these expts. a decrease in pH, range: 6.83–6.97 and a increase in $P_{CO_2}$, range: 86–128 mmHg was recorded.

The effects on the heart performance were a moderate increase in the heart rate when the arterial $P_{O_2}$ was reduced to 40–50 mmHg. When respiratory acidosis was induced, a decrease in heart rate and a prolongation of the A–V conduction time was recorded. The shape and duration of the atrial and ventricular MAPs, except for a decrease in the amplitudes, remained unaltered (see Fig. 4).

## Discussion

*Respiratory alkalosis*

In the first series of expts. with hyperventilation and an uninfluenced CVP, an increase in heart rate and a decrease in the A–V conduction time was recorded. These effects are in agreement with findings reported by other authors due to an increased sympathetic activity (Yu *et al.* 1959, Donevan *et al.* 1962, Thompson *et al.* 1962). No influence upon the shape or duration of the atrial and ventricular MAPs was recorded during the alkalotic state.

In the second series of expts. with hyperventilation and an increasing CVP, initially a rise in heart frequency was recorded. This seems to be due to an increased sympathetic activity (Little and Smith 1964, Feisal *et al.* 1967). The following decrease in heart rate, prolongation of the A–V conduction time and shortening of the atrial MAP duration that was recorded are in agreement with findings previously reported in the literature, due to an increased vagal influence upon the heart (Hoffman and Suckling 1953, Samuelsson 1973).

It is well known that artificial ventilation by intermittent positive pressure ventilation will result in an increase in CVP and a decrease in CO (Morgan *et al.* 1966, Nordström 1972). The pronounced increase in hyperventilation in these expts. obviously not only induced a marked increase in the CVP but also in the vagal nerve activity. The reason for the increased parasympathetic nerve activity is unclear but might be due to a marked reduction in CO resulting in systemic hypoxia (*cf.* Samuelsson 1973). It is notable that despite the pronounced alkalotic state induced, no influence upon the shape or duration of the ventricular MAP was recorded.

These findings thus indicate that respiratory alkalosis induced by artificial ventilation with no influence on the CVP might result in an increased sympathetic influence upon the heart performance. A pronounced hyperventilation with an increased CVP on the contrary might result in an increased vagal nerve influence upon the heart. A pronounced alkalotic state in itself however does not seem to alter the shape or duration of the atrial and ventricular MAPs.

*Respiratory acidosis*

In the first series of expts. with respiratory acidosis, initially a slight increase in heart rate was recorded. This finding has been reported by other authors, considering it to be due to an increased sympathetic influence on the heart performance (Price 1960, Blackburn *et al.* 1972, Cullen *et al.* 1969). Following that, a decrease in heart rate and prolongation of the A–V conduction time was recorded. These depressing effects on the heart function that previously has been reported in the literature (McElroy *et al.* 1958, Noble *et al.* 1966) are considered to depend on a direct effect of $CO_2$ on the heart. No influence during the pronounced acidotic state upon the shape or duration of the atrial or ventricular MAPs was recorded except for a slight decrease in the amplitudes, related to the recording technique (Samuelsson and Sjöstrand 1971).

In the second series of expts. the hypoxia resulted in an increase in heart rate (*cf.* Keys 1943, Comroe 1964). As a consequence of the $CO_2$-ventilation a decrease in the heart rate and prolongation of the A–V conduction time was recorded. As in the first series of experiments, the shape and duration of the atrial as well as the ventricular MAPs remained unaffected.

From these findings the conclusions can be drawn that pronounced respiratory acidosis will induce a decrease in heart rate and a prolongation of the A–V conduction time, whereas the shape and duration of the atrial and the ventricular MAPs remain unaltered. Even arterial hypoxia compounded by pronounced respiratory acidosis do not influnce on the shape and duration of the atrial and ventricular MAPs.

*Implications*

As has been pointed out in the introduction, different reasons have been postulated as the cause of development of cardiac rhythm disturbances induced by respiratory induced acid–base imbalances. Basically the initiation and maintenance of cardiac arrhythmias originates from alterations in the fundamental properties of the cardiac tissue including enhanced automaticity, delayed conduction, decreased excitability threshold and shortened refractory

period. The mechanisms operative in the alterations of these properties in respiration-induced acid–base distrubances may be shifts in concentration and distribution of calcium, sodium and potassium between the intracellular and the extracellular compartments (Yakaitis *et al.* 1971, Lawson *et al.* 1973), increased activity in the sympathetic or parasympathetic nervous system (Price 1960, Noble *et al.* 1966) or effects of $CO_2$, $HCO_3^-$ or $H^+$ ions on the cell membranes or enzyme systems (McElroy *et al.* 1958, Noble et *al.* 1966).

From these experiments it has become apparent that the cellular electrical activity of the cardiac tissue as reflected in the atrial and the ventricular MAPs is remarkably resistant to respiration-induced alkalosis and acidosis. The duration of the MAPs that constitutes a reliable index of the refractory period of the myocardial cells (Olsson 1971) remained unchanged during pronounced acid–base disturbances. Even the combination of arterial hypoxia and pronounced respiratory acidosis did not affect the MAP durations. It also has become apparent that respiratory alkalosis as well as acidosis induce an increased sympathetic influence on the heart activity. During pronounced artificial hyperventilation also an increased parasympathetic nerve activity was established resulting in a shortened atrial MAP duration.

It is well known that increased sympathetic (Han and Moe 1964) as well as parasympathetic (Alessi *et al.* 1958) nerve activity exert an arrhythmogenic influence on the heart activity due to an increased asynchrony of the recovery of the excitability of the cardiac cells. From the results of this investigation the conclusions can be drawn that in the study of the genesis of cardiac arrhythmias associated with respiration-induced acid–base disturbances, alterations in the autonomic nerve activity constitutes an important factor. Whereas the direct effect of the acid–base shifts on the refractory period of the myocardial cells seem to be insignificant. Furthermore in the increasing use of artificial ventilation it can be concluded that in an inappropriate use of the mechanical ventilators resulting in cardiac rhythm disturbances, imbalances in the autonomic nerve system has to be taken into account.

This investigation was supported financially by the Swedish Medical Research Council (Grant B76-14X-04768-01), Tore Nilssons foundation for Medical Research and the Swedish Medical Association.

## References

ALESSI, R., M. NUSYNOWITZ, J. A. ABILDSKOV and G. K. MOE, Nonuniform distribution of vagal effects on the atrial refractory period. *Amer. J. Physiol.* 1958. *194* (2). 406–410.

ANDERSEN, M. N. and K. KUCHIBA, Depression of cardiac output with mechanical ventilation. *J. thorac. Surg.* 1967. *54.* 182–190.

AYRES, S. M. and W. J. GRACE, Inappropriate ventilation and hypoxemia as causes of cardiac arrhythmias. *Amer J. Med.* 1969. *46.* 495–505.

BLACKBURN, J. P., C. M. CONWAY, J. M. LEIGH, M. J. LINDOP and J. A. REITAN, $Paco_2$ and the pre-ejection period: the $Paco_2$/inotropy response curve. *Anesthesiology* 1972. *37.* 268–276.

CLINE, R. E., A. G. WALLACE, W. GLENN YOUNG, JR, and W. C. SEALY, Electrophysiologic effects of respiratory and metabolic alkalosis on the heart. *J. thorac. Surg.* 1966. *52.* 769–776.

COMROE, J. H., JR, The peripheral chemoreceptors. In *Handbook of physiology*, Section 3, Respiration, vol. 1. Eds. W. O. Fenn and H. Rahm. American Physiological Society. Washington D.C. 1964.

CULLEN, D. J., E. J. EGER and G. A. GREGORY, The cardiovascular effects of carbon dioxide in man, concious and during cyclopropane anesthesia. *Anesthesiology* 1969. *31.* 407–413.

DONEVAN, R. D., N. M. ANDERSON, P. SEKELJ, O. PAPP and M. MCGREGOR, Influence of volontary hyperventilation on cardiac output. *J. appl. Physiol.* 1962. *17.* 487–491.

DONG, E. JR, E. B. STINSON and N. E. SHUMWAY, The ventricular fibrillation threshold in respiratory acidosis and alkalosis. *Surgery* 1967. *61*. 602–607.

FEISAL, K. A., F. M. ABBOUD and J. W. ECKSTEIN, Effects of adrenergic blockade on cardiovascular responses to increased airway pressure. *Amer. J. Physiol.* 1967. *213*. 127–133.

HAN, J. and G. K. MOE, Nonuniform recovery of excitability in ventricular muscle. *Circulat. Res.* 1964. *14*. 44–60.

HECHT, H. H. and O. F. HUTTER, Action of pH on cardiac purkinje fibers. In *Electrophysiology of the heart*. Ed. by B. Taccardi. Pergamon Press. London. 1964.

HOFFMAN, B. F. and E. E. SUCKLING, Cardiac cellular potentials: Effect of vagal stimulation and acetylcholine. *Amer. J. Physiol.* 1953. *173*. 312–320.

HUDSON, L. D., T. L. KURT, T. L. PETTY and E. GENTON, Arrhythmias associated with acute respiratory failure in patients with chronic airway obstruction. *Chest* 1973. *63*. 661–665.

JONZON, A., P. Å. ÖBERG, G. SEDIN and U. SJÖSTRAND, High frequency positive pressure ventilation by endotracheal insufflation. *Acta anaesth. scand.* 1971. *15*. Suppl. 43.

KEYS, A., J. P. STAPP and A. VIOLANTE, Responses in size, output and efficiency of the human heart to acute alteration in the composition of inspired air. *Amer. J. Physiol.* 1943. *138*. 763–771.

KURT, T. L., L. D. HUDSON, T. L. PETTY and E. GENTON, Arrhythmias in respiratory failure. *New Engl. J. Med.* 1973. *288*. 470.

LAWSON, N. W., G. HARRISON BUTLER and C. THORPE RAY, Alkalosis and cardiac arrhythmias. *Anesth. Analg. Curr. Res.* 1973. *52*. 951–962.

LITTLE, R. C. and C. W. SMITH, Cardiovascular response to acute hypocapnia due to overbreathing. *Amer. J. Physiol.* 1964. *206*. 1025–1030.

LORKOVIC, H., Influence of changes in pH on the mechanical activity of cardiac muscle. *Circulat. Res.* 1966. *19*. 711–720.

MCELROY, W. T., A. J. GERDES and E. B. BROWN, Effects of $CO_2$, bicarbonate and pH on the performance of isolated perfused guinea pig hearts. *Amer. J. Physiol.* 1958. *195*. 412–416.

MORGAN, B. C., W. E. MARTIN, T. F. HORNBEIN, E. W. CRAWFORD and W. G. GUNTHEROTH, Hemodynamic effects of intermittent positive pressure respiration. *Anesthesiology* 1966. *27*. 584–590.

NOBLE, M. I. M., E. TRENCHARD and A. GUZ, Effect of changes in $P_{aCO_2}$ and $P_{aO_2}$ on cardiac performance conscious dogs. *J. appl. Physiol.* 1966. *22*. 147–152.

NORDSTRÖM, L., On automatic ventilation. *Acta anaesth. scand.* 1972. Suppl. 47.

OLSSON, S. B., *Monophasic action potentials of right heart*. Elanders Boktryckeri AB. Gothenburg. 1971.

PRICE, H. L., Effects of carbon dioxide on the cardiovascular system. *Anesthesiology* 1960. *21*. 652–663.

RODGERS, R. M., J. F. SPEAR, E. N. MOORE, L. H. HOROWITS and J. E. SONNE, Vulnerability of canine ventricle to fibrillation during hypoxia and respiratory acidosis. *Chest* 1973. *63*. 986–994.

SAMUELSSON, R., Effects of severe systemic hypoxia on myocardial excitation. *Acta physiol. scand.* 1973. *88*. 267–280.

SAMUELSSON, R. and U. SJÖSTRAND, Endocardial recording of monophasic action potentials in the intact dog. *Acta Soc. Med. upsalien.* 1971. *76*. 191–210.

THEYE, R. A., J. H. MILDE and J. D. MICHENFELDER, Effect of hypocapnia on cardiac output during anesthesia. *Anesthesiology* 1966. *27*. 778–782.

THOMPSON, H. K., J. N. BERRY, H. D. MCINTOSH and N. C. DURHAM, Circulatory responses to hyperventilation and exercise in normal subjects. *Amer. Heart J.* 1962. *63*. 106–114.

VAUGHAN WILLIAMS, E. M. and J. M. WHYTE, Chemosensitivity of cardiac muscle. *J. Physiol.* (Lond.) 1967. *189*. 119–137.

YAKAITIS, R. W., J. E. COOKE and J. S. REDDING, Re-evaluation of relationships of hyperkalemia and $P_{CO_2}$ to cardiac arrhythmias during mechanical ventilation. *Anesth. Analg. Curr. Res.* 1971. *50*. 368–373.

YU, P. N., B. J. B. YIM and C. A. STANFIELD, Hyperventilation syndrome. *Arch. intern. Med.* 1959. *103*. 902–913.