work and oxygen consumption. In patients with appreciable valvular stenosis or constrictive pericarditis the compensatory increase in cardiac output may be limited by mechanical factors and the hypotension consequently more pronounced. Similarly, patients who are unable to respond with a tachycardia may suffer disproportionately severe hypotension; this group would include those taking large amounts of digitalis and those with heart block. The risk may be increased in patients receiving beta-adrenergic blocking agents (Norman and Atkinson, 1970) and in those with myxoedema. Some patients with cardiomyopathy suffer a fall in cardiac output in response to tachycardia (Goodwin, 1964) and constitute another group at risk.

The likelihood and extent of the fall in blood pressure can be minimized by ensuring adequate preoperative hydration and by careful blood replacement during the preliminary stages of the operation. The content of free monomer in the mixture varies inversely with its hardness, and Charnley (1970) recommended that the cement should not be applied until it is of a firm and doughy consistency. He also recommended that excess monomer should be allowed to evaporate by kneading and rolling the cement after mixing so as to expose as large a surface area as possible to the air. It has been suggested that venting the femoral canal during the insertion of the cement and prosthesis may reduce the intramedullary pressure and the likelihood of air and fat embolism; it may also diminish the seepage of free monomer into the circulation, but the evidence for this is at present inconclusive (Phillips *et al.*, 1971).

Conclusion

The existence of a syndrome of acute hypotension associated with the application of acrylic cement to raw bone surfaces has been substantiated by this investigation. An understanding of the mechanisms involved in the production of the cardiovascular disturbance enables a high-risk group of patients to be defined to whom this syndrome constitutes a real and serious hazard. It is arguable that hip surgery involving the use of currently available cements should rarely, if ever, be performed on these individuals. Alternative operations for the total replacement of diseased hip joints without the use of cement have been developed and are reported to give satisfactory results in practised hands (Ring, 1971; J. L. Sbarbaro, jun., personal communication). Recent suggestions for the more widespread use of acrylic cement in large quantities (Welsh *et al.*, 1971) should be viewed with caution.

We thank Dr. A. M. C. Jennings for his helpful advice and criticism and for his statistical analysis. The assistance of the technical staff of the London Hospital Anaesthetic Research Laboratories is gratefully acknowledged, as is the invaluable help of Mr. Jeffrey Huntingdon, of Electronic and X-ray Applications Ltd., Basingstoke.

Reprints are available from Dr. Richard H. Ellis, Department of Anaesthesia, St. Bartholomew's Hospital, London EC1A 7BE.

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PRELIMINARY COMMUNICATION

Effect of Mechanical Loading on Ventilatory Response to CO_2 and CO_2 Excretion

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British Medical Journal, 1972, 1, 351-353

Summary

The ventilatory response to CO_2 (S) and respiratory exchange ratio have been measured in 10 healthy subjects breathing naturally and through added resistive loads. The changes in these values produced by the added loads were shown to be correlated with the unloaded CO_2 responsiveness. The results indicated that poorly responsive individuals had a greater depression of ventilatory response to CO_2 and were more liable to retain CO_2.

These observations raise the possibility that the constitutional CO_2 responsiveness of an individual influences the alveolar ventilation achieved in the presence of airways obstruction. The propensity to develop respiratory failure may thus be conditioned by the premorbid CO_2 responsiveness.

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Introduction

Retention of CO_2 occurs in some patients with airways obstruction but the mechanical abnormality does not appear to be entirely responsible for the development of respiratory failure (Clark, 1968; Lane, Howell, and Giblin, 1968). The poor correlation observed between the forced expiratory volume in one second (FEV_1) and CO_2 tension suggests that in addition to airflow obstruction other important factors modify the drive to

breathe when ventilation is hindered. Previous work has shown the importance of personality in modifying the patient's response to chronic airways obstruction (Clark and Cochrane, 1970) and the present study sets out to examine the hypothesis that the premorbid CO_2 sensitivity also influences the alveolar ventilation achieved in the presence of airflow obstruction.

Subjects and Methods

Ten healthy men aged 20-33 were studied who had some knowledge of the techniques employed, being medical students or doctors working in the physiology department. None were known to suffer any abnormality of the respiratory system and all had a normal FEV_1, vital capacity, and mixed venous CO_2 tension.

Ventilatory Response to CO_2.—This was measured using a rebreathing technique (Read, 1967) and the results were expressed in terms of total ventilation (l./min) produced by a change of 1 mm Hg in end-tidal CO_2 tension; the notation S is used as an abbreviation for CO_2 responsiveness.

Excretion of CO_2.—Changes in CO_2 excretion were sought by measuring the respiratory exchange ratio. Expired air was collected in a Douglas bag with the subjects seated and resting. Once a steady state had been reached expired air was collected for 15 minutes and analysed for CO_2 and O_2 by using a rapid CO_2 analyser (URAS) and a paramagnetic analyser (Servomex DC 131) previously calibrated with known gas mixtures of CO_2 and O_2. The respiratory exchange ratio was calculated and at rest breathing air was assumed to equal the respiratory quotient.

Added Airways Resistance.—The subjects breathed through two added flow resistive loads, R_1 and R_2, with respective resistances of 10 cm H_2O and 24 cm H_2O at 0·5 l./sec. The resistances were shown to be linear up to 1·0 l./sec. In rebreathing studies the subjects performed a ventilatory response to CO_2 without resistance and then repeated the procedure breathing in and out through R_1, which was inserted into the circuit close to the mouth. R_2 was not used after preliminary experiments had shown that few subjects could tolerate this load long enough to complete the rebreathing procedure. The ventilatory response to CO_2 was measured three times unloaded (S) and twice loaded (S_1) in the order S, S_1, S, S_1, S and the mean values of S and S_1 were calculated (see Fig. 1). In studies of CO_2 excretion each subject completed a preliminary unloaded gas collection to allow calculation of respiratory exchange ratio. The resistance was then inserted into the circuit close to the mouth and the subject continued to breathe in and out through it. The added dead space was 30 ml for R_1 and 25 ml for R_2. A 10-minute gas collection was made immediately while breathing through each resistance and the respiratory exchange ratio calculated. An unloaded expired gas collection was made at intervals between each loading experiment.

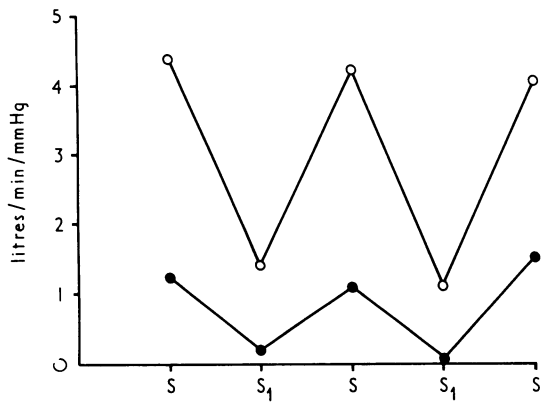

FIG. 1—Effect of breathing through resistance R_1 on ventilatory response to CO_2 in two subjects. S represents unloaded CO_2 response and S_1 the loaded CO_2 response

Results

Ventilatory Response to CO_2.—The relation between the responsiveness to CO_2 and the change in responsiveness (S_1/S) expressed as a percentage is shown in Fig. 2. The regression line is significant ($P < 0·01$) and suggests that a greater percentage fall in responsiveness occurs in individuals who are normally least responsive to CO_2. If the effect produced by breathing through a resistance was not related to the responsiveness to CO_2 one would expect a random reduction.

Excretion of CO_2.—The mean respiratory exchange ratio at rest was 0·83 and the mean values produced breathing through R_1 and R_2 were 0·80 and 0·77 respectively. If underventilation were produced by breathing through a resistance a transient fall in exchange ratio would be expected, and in Fig. 3 the fall in exchange ratio seen in eight subjects breathing through R_2 is related to their CO_2 responsiveness (S). The correlation is probably significant ($P < 0·05$) with a greater reduction in respiratory exchange ratio in those subjects with the lower CO_2 responsiveness.

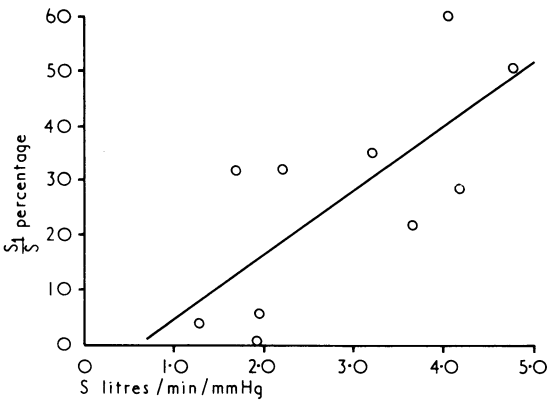

FIG. 2—Relation between unloaded ventilatory response to CO_2 (S) and the change in responsiveness (S_1/S %) observed breathing through a resistance (R_1).

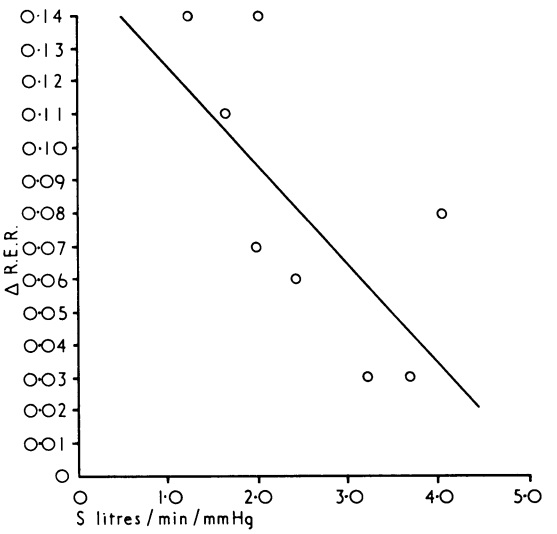

FIG. 3—Relation between unloaded ventilatory response to CO_2 (S) and the fall in Respiratory Exchange Ratio (R.E.R.) observed breathing through a resistance (R_2).

Discussion

Previous work has shown that added airway resistance reduces the ventilatory response to CO_2 (Cherniack and Snidal, 1956; Milic-Emili and Tyler, 1963; Clark and Godfrey, 1969) but the

fall in responsiveness has not been related to the unloaded ventilatory response. Our results suggest that the fall in ventilatory response to CO_2 produced by loading is partly dependent on the initial responsiveness, with unresponsive individuals showing the greatest percentage fall in slope.

These observations are in accord with the hypothesis that the premorbid CO_2 responsiveness modifies a patient's adaptation to airways obstruction. A patient who when healthy is poorly responsive to CO_2 might therefore be expected to underventilate more readily when airways obstruction develops and thus CO_2 retention will be facilitated. A similar line of argument has been postulated to explain the origins of chronic mountain sickness in terms of previous insensitivity to hypoxia (Severinghaus, Bainton, and Carcelen, 1966). A corollary of this argument might be that unresponsive individuals tolerate greater rises in P_{CO_2}, but we failed to observe any correlation between the maximum P_{CO_2} achieved during rebreathing and the unloaded CO_2 responsiveness.

The resistances used were high and noticeably reduced FEV_1 (R_1 approximately halved FEV_1 and R_2 reduced it by 75%). They were the same for inspiration and expiration and were used throughout the respiratory cycle as it seems likely that CO_2 retention can be produced by obstruction either during expiration or during inspiration (Clark, 1970).

We thought it also desirable to examine the relation between CO_2 responsiveness, added airways resistance, and CO_2 excretion. The effect of added respiratory loads is not easy to interpret in terms of alveolar CO_2 tension (Pope, Holloway, and Campbell, 1968; Freedman and Campbell, 1970) and it was thought undesirable to examine changes in arterial blood gas tensions. As well as raising P_{CO_2} in arterial blood and alveolar air an inability to maintain normal CO_2 excretion might also be seen as a transient fall in respiratory exchange ratio ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) which would return to normal values once a new steady state has been achieved in response to the sustained added load. We therefore examined the immediate changes in respiratory exchange ratio while breathing through a resistance and were able to show impaired CO_2 excretion which appeared to bear a relation to the initial CO_2 responsiveness. This relation was consistent with that observed in terms of changes in responsiveness and lends support to the idea that relatively unresponsive subjects are more liable to retain CO_2 in the presence of acute airways obstruction.

The idea that CO_2 retention is not explicable purely in terms of the mechanical abnormality is well established in chronic airways obstruction (Lane and Howell, 1970) and obesity (Lourenco, 1969) and the discrepancies observed have largely been explained in terms of an abnormal CO_2 responsiveness. This explanation still leaves the problem of deciding whether the abnormal CO_2 responsiveness is a primary or a secondary phenomenon. Our results support the hypothesis that part of the explanation for CO_2 retention may lie in the constitutional CO_2 responsiveness of the patient who develops airways obstruction.

Requests for reprints should be sent to Dr. T. J. H. Clark.

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MEDICAL MEMORANDA

Cerebrotendinous Xanthomatosis

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British Medical Journal, 1972, 1, 353-354

Tendon xanthomas are a reliable indication of hypercholesterolaemia and warn of an increased risk of coronary heart disease (Beaumont *et al.*, 1963). The case reported here is an exception to the rule. The patient's tendon xanthomas were associated with mental defect and a barely raised serum cholesterol. This combination is rare and apparently has not been described in the British medical literature.

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Case Report

A white woman aged 47 had been in the Alexandra Institution (for mentally defective people) from the age of 25. At that time her I.Q. was assessed as 38 though according to her family she appeared to have been mentally normal until she was about 14. Her birth was said to have been normal. A visit to the family in the Ceres district of the Cape province provided the additional information that she was probably retarded from early childhood. Though she attended a farm school and learnt to write her name she could never read. She was the sixth of nine children. Her parents were first cousins and so were her father's parents. One of her brothers, who was dead, had been mentally defective and lumps had been present on his elbows and knees. Her father had died of myocardial infarction. Her mother suffered from rheumatoid arthritis.

Fatty tumours on both Achilles tendons were excised in 1952. Similar tumours appeared in both patellar tendons and were excised in 1967. Histologically they were xanthomas. The Achilles tendon xanthomas recurred and extensive excisions were performed in 1969. Histological examination showed sheets of xanthoma cells, large cholesterol spaces, foreign body giant cells, and fibrosis. The same year bilateral dense nuclear and cortical cataracts were found and the right lens was extracted.

On examination she was found to have a moderately severe mental defect; she could speak some English and Afrikaans and was left eye and asteroid hyalitis in the right eye. The right fundus was normal. There were scars in front of both knees and behind