LOW VENTILATORY RESPONSE TO CARBON DIOXIDE NOT ASSOCIATED WITH INCREASED DEPRESSION BY MORPHINE

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SUMMARY

Ventilation ($\dot{V}E$), end-tidal ($P\dot{E}'CO_2$), mixed venous $P^{CO_2}$ ($P\dot{V}CO_2$) and the ventilatory response to carbon dioxide ($\Delta\dot{V}E/\Delta PCO_2$) were measured before and within 90 min after morphine 0.15 mg kg$^{-1}$ i.m. given to 17 adult patients undergoing elective surgery under general anaesthesia. The hypothesis that patients with a low ventilatory response to carbon dioxide are more susceptible to the ventilatory depressant effects of morphine was tested. Morphine induced increases in $P\dot{E}'CO_2$ and $P\dot{V}CO_2$ were not correlated with either the slope or the position of the preinjection response to carbon dioxide. Mean $\Delta\dot{V}E/\Delta PCO_2$ was depressed after morphine ($P<0.05$), but individual responses varied widely. Seven patients whose control $\Delta\dot{V}E/\Delta PCO_2$ was 9.9 litre min$^{-1}$ kPa$^{-1}$ or less decreased $\Delta\dot{V}E/\Delta PCO_2$ after morphine. In four patients, $\Delta\dot{V}E/\Delta PCO_2$ increased after morphine; however, in each case, $P\dot{E}'CO_2$ and $P\dot{V}CO_2$ increased also. Morphine displaced the carbon dioxide response to the right ($P<0.001$) but no correlation was found between either the magnitude of the displacement or change in slope and control $\Delta\dot{V}E/\Delta PCO_2$. The results suggest that patients with a low value for $\Delta\dot{V}E/\Delta PCO_2$ are not more susceptible to the ventilatory depressant action of morphine.

Patients with chronic airways obstruction are more likely to develop hypercapnia if they have a low rather than a high ventilatory response to carbon dioxide (Lane and Howell, 1970). Similarly, patients with asthma and known to have a small response to carbon dioxide when their airways resistance is normal, are more likely to develop hypercapnia during an acute exacerbation than are those who have a large carbon dioxide response (Rebuck and Read, 1971).

These observations confirmed the original suggestion of Lambertsen that a low sensitivity to carbon dioxide might predispose patients to the development of carbon dioxide retention in various clinical conditions (Lambertsen, 1960). He suggested also that individuals with low ventilatory response to carbon dioxide might be more susceptible to ventilatory depression by narcotic agents (Lambertsen, 1960). Although the rebreathing method for the measurement of ventilatory response to carbon dioxide (Read, 1967) has been used in clinical studies (Jennett, Barker and Forrest, 1968; Rebuck et al., 1973; Rigg, Rebuck and Campbell, 1974) this hypothesis has not been tested, except in a small group of volunteer subjects in whom recovery of ventilatory response to carbon dioxide was assessed following thiopentone, morphine and fentanyl, when the results were inconclusive (Rigg and Goldsmith, 1976). There remains the important possibility that measurement of the ventilatory response to carbon dioxide might be used to predict an increased risk of ventilatory depression after anaesthesia. The hypothesis has now been tested in a group of surgical patients with no history of lung disease, and who received morphine i.m. as premedication before elective surgery.

METHODS

Ventilation ($\dot{V}E$), end-tidal and mixed venous carbon dioxide partial pressure ($P\dot{E}'CO_2$ and $P\dot{V}CO_2$) and ventilatory response to carbon dioxide ($\Delta\dot{V}E/\Delta PCO_2$) were measured before and within 90 min after morphine 0.15 mg kg$^{-1}$ i.m., given to 17 adult patients (American Society of Anesthesiologists' physical status I and II) before elective surgery under general anaesthesia.

Details of the experimental procedure are given by Rigg (1978).

The slope of the ventilatory response to carbon dioxide was determined by least squares regression, using the procedure of Read (1967). The positions of the response curves before and after morphine were compared in each subject using the procedure described by Rigg (1978) to determine the response curve position variables $\dot{V}E_H$ and $\dot{V}E_L$.

To test the hypothesis that response to carbon dioxide before injection determines the magnitude of morphine-induced changes in $\dot{V}E$ and $\Delta\dot{V}E/\Delta PCO_2$, control $\Delta\dot{V}E/\Delta PCO_2$, $\dot{V}E_H$ and $\dot{V}E_L$ were plotted...
against per cent changes of $P_{t}C_{02}$, $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$, $V_{E_{H}}$ and $V_{E_{L}}$ after morphine. The relationships between these variables were explored using least squares regression analysis. The significance of all changes following injection was determined using paired $t$ tests.

**RESULTS**

Increases in $P_{t}C_{02}$ and $P_{v}C_{02}$ induced by morphine were not correlated with preinjection $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$, $V_{E_{L}}$ or $V_{E_{H}}$ (fig. 1). Similarly, the magnitude of changes in $V_{E_{L}}$ and $V_{E_{H}}$ were not related to control $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$ (fig. 2).

The mean slope of the ventilatory response to carbon dioxide decreased from 12.3 to 10.05 litre min$^{-1}$ kPa$^{-1}$ after morphine ($P<0.05$) but individual responses varied widely. Seven patients with preinjection $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$ of 9.9 litre min$^{-1}$ kPa$^{-1}$ or less showed a decrease in $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$ after morphine; the largest per cent decrease occurred in three patients with control $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$ less than 7.5 litre min$^{-1}$ kPa$^{-1}$. Of 10 patients in whom the value before injection ranged from 10.2 to 23.0 litre min$^{-1}$ kPa$^{-1}$, four increased and six decreased $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$ after morphine. All four of the patients with increased $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$ after morphine had typical ventilatory depression on the basis of increases of $P_{t}C_{02}$ and $P_{v}C_{02}$. Comparison $\Delta \dot{V}_{E}/\Delta P_{CO_{2}}$ before and after injection did not suggest a greater susceptibility to morphine in individuals with a low response (fig. 3).


**DISCUSSION**

Many studies have defined the effect of narcotics and other central nervous depressant drugs on ventilation in man (Dripps and Dumke, 1943; Eckenhoff and Helrich, 1958; Bellville and Seed, 1960; Severinghaus and Larson, 1965; Munson et al., 1966; Larson et al., 1969). The present study differs in its method in that morphine was used in an attempt to characterize differences in ventilatory control that might have an important bearing on the recovery of adequate spontaneous ventilation following general anaesthesia. The findings support those of Bellville and Seed (1960) who concluded that opiates caused a large displacement of the carbon dioxide response and little alteration in slope.

The results of the present study suggest that patients with normal lungs and a low ventilatory response to carbon dioxide are not more susceptible to the depressant action of morphine, as judged by the effect on $\frac{P_CO_2}{PE'}$, $\frac{PV_{CO_2}}{PVCO_2}$ and $\frac{A\bar{V}E}{APCO_2}$. However, caution should be exercised in extending this conclusion to the general population or to the effects of other narcotics or depressant drugs.

Few attempts have been made previously to define a “normal” “low” or “high” carbon dioxide response. This problem has been compounded by the identification of several characteristics that influence ventilatory response to carbon dioxide. These include body size, athleticism and personality (Avery et al., 1963; Rebuck and Read, 1971; Saunders, Heilpern and Rebuck, 1972; Rebuck et al., 1974; Rigg, Rebuck and Campbell, 1974; Hirshman, McCullough and Weil, 1975; Irsigler, 1976). Hirshman, McCullough and Weil reported data obtained from 44 normal non-athletic subjects aged between 21 and 51 yr (Hirshman, McCullough and Weil, 1975). They compared their findings (Δ$\bar{V}E$/Δ$P_{CO_2}$ and $\Delta P_{CO_2}$) with those of previous reports (Read, 1967; Byrne-Quinn et al., 1971; Forster et al., 1971; Kallos et al., 1972; Saunders, Heilpern and Rebuck, 1972; Kronenberg and Drage, 1973; Rebuck et al., 1973), in which mean $\Delta \bar{V}E$/Δ$P_{CO_2}$ ranged from 1.84 to 3.4 litre min$^{-1}$ mm Hg$^{-1}$. * They concluded that it is difficult to characterize an individual as abnormal because of the large tolerance limits of the ventilatory response to hypercapnia. More recently, Irsigler studied 126 healthy medical students and found mean $\Delta \bar{V}E$/Δ$P_{CO_2}$ and SEM = 2.60 ± 0.11 litre min$^{-1}$ mm Hg$^{-1}$ (Irsigler, 1976). Eighty per cent of these subjects had ventilatory response curve slopes between 1.5 and 5.0, 16% less than 1.5 and 4% greater than 5.0 litre min$^{-1}$ mm Hg$^{-1}$. Rebuck and Read (1971) found champion sprint and endurance athletes at the high and low extremes of the range of carbon dioxide response curve slopes, with limits of 0.4 and 8.0 litre min$^{-1}$ mm Hg$^{-1}$ in their subjects; the range of $\Delta \bar{V}E$/Δ$P_{CO_2}$ in the present study of 4.3–23.0 litre min$^{-1}$ kPa$^{-1}$ (0.58–3.07 litre min$^{-1}$ mm Hg$^{-1}$) is within these limits. Thus, it seems reasonable to define “low” $\Delta \bar{V}E$/Δ$P_{CO_2}$ as less than 7.5 litre min$^{-1}$ kPa$^{-1}$ (1.0 litre min$^{-1}$ mm Hg$^{-1}$) and “high” $\Delta \bar{V}E$/Δ$P_{CO_2}$ as greater than 52.5 litre min$^{-1}$ kPa$^{-1}$ (7.0 litre min$^{-1}$ mm Hg$^{-1}$). The three subjects in the present study who had control $\Delta \bar{V}E$/Δ$P_{CO_2}$ of less than 7.5 litre min$^{-1}$ kPa$^{-1}$ all had response slopes of less than 60% of control following morphine. However, the decrease in absolute levels of ventilation during the latter part of rebreathing after morphine in these patients was less than that of the remaining patients in whom control $\Delta \bar{V}E$/Δ$P_{CO_2}$ was greater. Furthermore, in none of the three patients with $\Delta \bar{V}E$/Δ$P_{CO_2}$ less than 7.5 litre min$^{-1}$ kPa$^{-1}$ was the increase in $P_{CO_2}$ substantially greater than that of the other patients. However, these changes in $P_{CO_2}$ during air breathing were small and close to the limits of precision of infra-red capnography. It is possible that a greater likelihood of hypercapnia might be found in patients with low carbon dioxide responses if a larger dose of a narcotic was studied.

There was wide variation in the plasma concentrations of morphine in individual patients, both in the maximum plasma concentrations and in the time course of the concentrations (Rigg, 1978). These differences reflect, presumably, wide inter-individual differences in absorption of morphine from the i.m. site of injection (all 17 patients were injected in the right gluteal region) and in the distribution to the brain. It is possible that after a single dose of morphine i.m., different effects on ventilation and ventilatory response to carbon dioxide may reflect differences between individuals in the pharmacokinetics of the drug. That there was no correlation between the magnitude of the effect of morphine on ventilatory variables and plasma concentration of the drug argues against this possibility (Rigg, 1978). Nevertheless, it remains possible that, if plasma concentrations of morphine were maintained constant by i.v. infusion, patients with a low response to carbon dioxide might be more susceptible to ventilatory depression.

* 1 mm Hg = 0.13 kPa.
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REFERENCES


FAIBLE REPONSE VENTILATOIRE AU GAZ CARBONIQUE NON ASSOCIE A UNE AUGMENTATION DE LA DEPRESSION PAR LA MORPHINE

RESUME

La ventilation ($V_e$), le volume courant final ($P_{CO_2}$), le $PCO_2$ (PAO,) veines-mixte et la réponse ventilatoire au gaz carbonique ($\Delta V_e/\Delta PCO_2$) ont été mesurés avant et dans un délai de 90 min après qu’une injection de morphine à raison de 0,15 mg kg⁻¹ ait été administrée par voie intramusculaire à 17 malades adultes subissant une intervention chirurgicale à froid sous anesthésie générale. On a procédé à des tests pour vérifier l’hypothèse supposant que les malades ayant une faible réponse ventilatoire au gaz carbonique sont plus susceptibles aux effets ventilatoires déprimants de la morphine. Les augmentations du $P_{CO_2}$ et du $P_{CO_2}$ provoquées par la morphine n’ont été reliées ni au coefficient angulaire ni à la position de la réponse de la pré-injection au gaz carbonique. La $\Delta V_e/\Delta PCO_2$ moyenne s’est trouvée déprimée après la morphine ($P<0,05$), mais les réponses individuelles ont accusé de vastes variations. Sept malades, dont la valeur témoing de $\Delta V_e/\Delta PCO_2$ était de 9,9 litre min⁻¹ kPa⁻¹ ou moins, ont vu leur $\Delta V_e/\Delta PCO_2$ diminuer après la morphine. Sur quatre malades, la $\Delta V_e/\Delta PCO_2$ a augmenté après la morphine; mais dans chaque cas le $P_{CO_2}$ et le $P_{CO_2}$ ont aussi augmenté. La morphine a déplacé la réponse au gaz carbonique vers la droite ($P<0,001$) mais on n’a trouvé aucune corrélation entre l’importance du déplacement et les variations du coefficient angulaire et de la valeur témoin $\Delta V_e/\Delta PCO_2$. Les résultats obtenus laissent penser que les malades ayant une faible valeur de $\Delta V_e/\Delta PCO_2$ ne sont pas plus susceptibles à l’action ventilatoire déprimante de la morphine.
GERINGE BELÜFTUNGSREAKTION AUF KOHLENSTOFFDIOXYD NICHT VERBUNDEN MIT ERHÖHTER UNTERDRÜCKUNG DURCH MORPHIUM

ZUSAMMENFASSUNG
Belüftung ($V_e$), Ausatmungsvolumen ($P_{\text{CO}_2}$), venöses Gemisch $PCO_2$ ($Pv\text{CO}_2$) und die Belüftungsreaktion auf Kohlendioxid ($\Delta V_e/\Delta PCO_2$) wurden vor und innerhalb von 90 min nach Verabreichung von 0,15 mg kg$^{-1}$ intramuskulär an 17 erwachsene Patienten gemessen, die verschiedenen chirurgischen Eingriffen unter allgemeiner Narkose unterzogen wurden. Die Hypothese, dass Patienten mit geringer Belüftungsreaktion auf Kohlendioxid anfälliger auf die Belüftungsunterdrückungswirkung von Morphium sind, wurde geprüft. Morphium führte Anstiege von $P_{\text{CO}_2}$ und von $Pv\text{CO}_2$ herbei, die weder auf Gefälle oder Position der Vorinjektionsreaktion auf Kohlendioxid bezogen waren. Der Mittelwert von $\Delta V_e/\Delta PCO_2$ war nach Morphium unterdrückt ($P<0,05$), doch die individuellen Reaktionen variierten stark. Sieben Patienten der Kontrollwert von $\Delta V_e/\Delta PCO_2$ 9,9 liter min$^{-1}$ kPa$^{-1}$ oder weniger war, senkte $\Delta V_e/\Delta PCO_2$ nach dem Morphium. Bei vier Patienten stieg $\Delta V_e/\Delta PCO_2$ nach Morphium; in jedem Falle aber stiegen auch $P_{\text{CO}_2}$ und $Pv\text{CO}_2$. Morphium verschob die Kohlendioxidreaktion nach rechts ($P<0,001$), doch konnte man keine Korrelation mit der Grösse der Verschiebung oder mit einer Veränderung in Abfall oder Kontrollwert von $\Delta V_e/\Delta PCO_2$ feststellen. Daraus schliesst man, dass Patienten mit niedrigen Werten für $\Delta V_e/\Delta PCO_2$ nicht anfälliger auf die Belüftungsunterdrückungswirkung von Morphium sind.

REDUCIDA RESPUESTA VENTILATORIA AL DIOXIDO DE CARBONO NO ASOCIADA CON UNA MAYOR DEPRESIÓN CAUSADA POR MORFINA

SUMARIO
Se midieron la ventilación ($V_e$), marel final ($P_{\text{CO}_2}$), $P_{\text{CO}_2}$ venoso mezclado ($Pv\text{CO}_2$) y la respuesta ventilatoria al dióxido de carbono ($\Delta V_e/\Delta PCO_2$) antes y al cabo de 90 min de haberse suministrado morfina 0,15 mg kg$^{-1}$ a 17 pacientes adultos sometidos a cirugia electiva bajo anestesia general. Se examinó la hipótesis según la cual los pacientes con una respuesta ventilatoria baja al dióxido de carbono son más susceptibles a los efectos deprimentes ventilatorios de la morfina. Los aumentos inducidos por morfina en el $P_{\text{CO}_2}$ y $Pv\text{CO}_2$, no se correlacionaron con la inclinación ni la posición de la respuesta de preinyeccion al dióxido de carbono. El $\Delta V_e/\Delta PCO_2$ medio se deprimió después de suministrar morfina ($P<0,05$), pero las respuestas individuales variaron en gran medida. En siete pacientes cuyo $\Delta V_e/\Delta PCO_2$ de control fue de 9,9 litros min$^{-1}$ kPa$^{-1}$ o menos disminuyeron su $\Delta V_e/\Delta PCO_2$ después de la administración de morfina. En cuatro pacientes, el $\Delta V_e/\Delta PCO_2$ aumentó después de la morfina; sin embargo, en cada caso, el $P_{\text{CO}_2}$ y el $Pv\text{CO}_2$ también aumentaron. La morfina desplazó la respuesta de dióxido de carbono a la derecha ($P<0,001$) pero no se descubrió una correlación, ya sea entre la magnitud del desplazamiento o un cambio en la inclinación y el $\Delta V_e/\Delta PCO_2$ de control. Los resultados sugieren que los pacientes con un valor bajo de $\Delta V_e/\Delta PCO_2$ no son más susceptibles a la acción de presiva ventilatoria de la morfina.