Effect of isocapnic hypoxia on systolic time intervals in conscious man

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SUMMARY The effects of progressive isocapnic hypoxia on the systolic time intervals were studied in 10 healthy human subjects. We induced hypoxia by a rebreathing method and monitored the arterial oxygen saturation continuously and non-invasively by means of an ear oximeter. Arterial oxygen saturation (S_{aO_2}) was allowed to fall to a level of 75 per cent and was then held constant for five minutes. As S_{aO_2} fell, heart rate increased linearly, with a mean increase of 0.83 beats/min per one per cent fall in S_{aO_2} . The pre-ejection phase index decreased from a mean of 127.2 ms at full oxygen saturation to 120.1 ms at steady-state hypoxia levels, while the ratio of the pre-ejection phase to left ventricular ejection time decreased from a mean of 0.330 to 0.301. The left ventricular ejection time index increased from 417.4 ms to 429.3 ms, while no statistically significant difference was found in the length of electromechanical systole.

The use of systolic time intervals (STI) is a well-established method for assessing cardiovascular function non-invasively (Weissler and Garrard, 1971a, b; Lewis *et al.*, 1977; Weissler, 1977). As hypoxia is common in clinical practice, its effect on systolic time intervals (STI) has received considerable attention, but the reported findings are conflicting, as the duration of hypoxia was variable, and in most studies the PCO_2 was allowed to vary, making it difficult to assess the effect of hypoxia alone. We recently reported the effect of acute, progressive hypoxia on heart rate in healthy subjects using a technique that enabled us to study physiological responses independent of changes in PCO_2 (Slutsky and Rebeck, 1978). We found that heart rate was best fitted to an inverse linear relation to arterial oxygen saturation and a power function to PO_2 . The purpose of the present study was to extend these findings, determining whether the tachycardia induced by isocapnic hypoxia was associated with changes in electromechanical systole.

Subjects

Ten subjects (5 men, 5 women), aged 24 to 40, who were staff members of Toronto General

Hospital (laboratory personnel, nurses, and physicians) were studied. All subjects were physically fit, had normal ventilatory function, and no historical or physical evidence of cardiovascular disease. Subjects had not taken any drugs for the 24 hours before the experiment, and were asked not to smoke and not to drink coffee or tea within two hours of study. All studies were performed in the morning. Informed written consent was given by all subjects.

Methods

INDUCTION OF HYPOXIA

The principle of the technique was to have the subject rebreathe from a 6-litre bag which initially contained room air. Oxygen was added to the bag at a rate of 100 ml/min, that is less than the subject's oxygen consumption, so that the PO_2 fell progressively but slowly during rebreathing. End-tidal PCO_2 was held constant at a predetermined level by means of a variable-speed pump attached to a soda-lime CO_2 -absorbing bypass. Arterial oxygen saturation was measured continuously with a fiberoptic ear oximeter (HP 47201A) (Saunders *et al.*, 1976). Details of the experimental circuit have been described previously (Rebeck and Woodley, 1975).

When the subject had been lying comfortably for 15 minutes, he/she began breathing room air

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through the mouthpiece while end-tidal PCO_2 was monitored. After a stable end-tidal PCO_2 had been achieved (± 1 mmHg), the valve connecting the subject to the rebreathing circuit was turned at the end of a normal expiration to allow rebreathing and hence progressive lowering of the inspired Po_2 . When the subject's oxygen saturation reached a value of 70 to 75 per cent, he/she was maintained at that level for five minutes. Thereafter, the subject was disconnected from the circuit by turning the valve connecting the subject to the rebreathing bag. However, the subject continued to breathe room air via the mouthpiece until his/her oxygen saturation was equal to or greater than his/her prehypoxic level for at least five minutes.

Tidal gas was sampled at the mouth, passed through a Beckman LB-2 rapid CO_2 analyser (Beckman Instruments, I 11) and a Servomex oxygen analyser (Type OA 272), before being returned to the rebreathing bag. Inspired ventilation was measured with a Med. Sci. 570 wedge spirometer (St. Louis, Mo.). Ventilation, Po_2 , PCO_2 , and S_{aO_2} were recorded on an eight-channel graphic recorder (Astromed. Super 8).

SYSTOLIC TIME INTERVALS

Simultaneous recording of the electrocardiogram, phonocardiogram, indirect carotid artery pulse tracing, and arterial oxygen saturation were recorded using an Elema-Schonander eight-channel recorder at a paper speed of 100 mm/s. The carotid pulse was obtained by holding a pressure cup over the right carotid artery. The pressure cup was connected through polyethylene tubing in series with an air-coupled transducer whose frequency response was 0.1 to 40 Hz. An Elema-Schonander piezo-microphone with a low band pass filter was used to record the heart sounds; the frequency response of the phonocardiograph was 100 to 400 Hz. A standard electrocardiogram (lead II) was used to identify the Q wave. All subjects were studied in the resting supine position, and carotid pulse tracings were taken at full oxygen saturation and at approximately 4 per cent decrements as arterial oxygen saturation decreased. Tracings were also obtained at one-minute intervals during the five minutes of steady-state hypoxia at a saturation of approximately 75 per cent.

Analysis of data

The arterial oxygen saturation and the duration of the components of the STI were calculated from these tracings using a digitiser (Model no. HP-9864A) connected to a calculator (Model no. 9820A). The digitiser had an accuracy of 0.01 inch in the X and Y co-ordinates. This system has been

considered by others to be the most accurate means of calculating STI (Lewis *et al.*, 1977). Heart rate was calculated from the Q-Q interval of the electrocardiogram. Electromechanical systole (QS2) was measured from the initial QRS deflection of the electrocardiogram to the initial high-frequency vibrations of the aortic component of the second heart sound. Left ventricular ejection time (LVET) was measured from the onset of the rapid upstroke to the trough of the incisura. Pre-ejection phase (PEP) was obtained by subtracting the LVET from the QS2. The STI were then corrected for heart rate according to sex of the subject, using the previously-described equations (Weissler *et al.*, 1968) to obtain the STI indices: QS2I, LVETI, and PEPI.

Linear regression was used to determine the effect of saturation on each of the dependent variables. The paired *t* test was used to determine whether any statistical differences existed in the dependent variables at full saturation and during hypoxia.

Results

Heart rate increased linearly in all subjects as arterial oxygen saturation fell, with a mean heart rate increase of 0.83 beats/min per 1 per cent fall in saturation and mean correlation coefficient of 0.92 (Table).

The ratio, PEP/LVET, decreased in all subjects as progressive hypoxia was induced (Fig.). The mean value of PEP/LVET was 0.330 at full saturation, well within the accepted range (0.350 ± 0.04) for healthy subjects (Weissler and Garrard, 1971a). The value of PEP/LVET at the steady-state hypoxia level ($\text{S}_{\text{aO}_2} \sim 75\%$) was 0.301, a value which was statistically different, using a paired *t* test, from the value at full saturation ($P < 0.01$) (Table).

LVETI increased in all but one subject with a mean value of 417.4 ± 10.39 ms to 429.3 ± 9.14 ms as saturation was decreased to steady-state hypoxia levels ($P < 0.01$) (Fig.). This increase in LVETI during arterial desaturation was well described by linear equations in all but two subjects. The average correlation coefficient for all subjects was 0.77. The decrease in PEPI from a mean value of 127.2 ± 7.15 ms to 120.0 ± 8.80 ms was also statistically significant ($P < 0.05$) (Fig.).

The changes in PEPI and LVETI, which were in opposite directions, were such that the mean value of QS2I (=PEPI + LVETI) at full saturation (544.6 ± 13.07 ms) and at the steady-state hypoxia levels (549.6 ± 12.21 ms) were almost the same (Fig.). These changes in QS2I were not statistically significant (Table).

Table Mean heart rates ($\pm$ SD) and STI ($\pm$ SD) at full arterial oxygen saturation ($S_{aO_2} \sim 97\%$), at a steady-state hypoxia ($S_{aO_2} \sim 75\%$)

	Full saturation (97%)	Steady-state hypoxia (75%)	t value	Statistical significance (P)
Heart rate (beats/min)	71.4 (± 8.13)	91.8	12.23	P < 0.001
PEP/LVET	0.330 ± 0.020	0.301 ± 0.029	4.03	P < 0.01
PEPI (ms)	127.2 ± 7.15	120.1 ± 8.80	2.96	P < 0.05
LVETI (ms)	417.4 ± 10.39	429.3 ± 9.14	4.42	P < 0.01
QS2I (ms)	544.6 ± 13.07	549.6 ± 12.21	1.76	NS

Note: There is a significant increase in heart rate and LVETI, a significant decrease in PEP/LVET and PEPI, with no significant difference in QS2I.

Fig. Values of PEP/LVET, LVETI, PEPI, and QS2I at full arterial oxygen saturation ($S_{aO_2} \sim 97\%$) and at steady-state hypoxia ($S_{aO_2} \sim 75\%$). All subjects showed a decrease in PEP/LVET and an increase in LVETI when arterial oxygen saturation was reduced to 75 per cent. In nine of 10 subjects PEPI decreased and in seven of 10 subjects QS2I decreased during hypoxia. The changes in PEP/LVET, LVETI, and PEPI were statistically significant.

Discussion

Analysis of the systolic time intervals (STI) provides a non-invasive method for investigating the cardiovascular system. The indices determined using these methods are primarily measures of left ventricular performance (Weissler *et al.*, 1969; Lewis *et al.*, 1976). Though STI have limited use in differential diagnosis, they serve to quantify the

effects on the cardiovascular system of various pharmacological interventions (Harris *et al.*, 1966, 1967) or disease states (Weissler *et al.*, 1968; Toutouzas *et al.*, 1969; Lewis *et al.*, 1976), as multiple observations in the same individual are possible.

Some studies have reported the effects of hypoxia on the STI in conscious man, but in these studies the PCO_2 was allowed to vary as a consequence of alveolar ventilation. Thus the effects of hypoxia alone on the STI could not readily be assessed. As hypocapnia and alkalosis have important effects on the circulatory system (Richardson *et al.*, 1972), it is likely that they may also influence the STI independently of the effect of hypoxia. The purpose of the present study was to isolate the effects of hypoxia on the STI by inducing progressive isocapnic hypoxia in conscious humans using a technique developed by us that combines re-breathing, oximetry, and precise control of PCO_2 (Rebuck and Woodley, 1975). The linear increase in heart rate that we found with decreasing levels of arterial oxygen saturation is in agreement with our previous study in which we found that isocapnic hypoxia induced a mean increase in heart rate of 0.98 beats/min per 1 per cent fall in saturation (Slutsky and Rebuck, 1978). This tachycardia was accompanied by a decrease in PEP/LVET and PEPI, an increase in LVETI, while QS2I remained the same.

It emerges that our findings concerning the STI are in agreement with those of Kowalsky and Anthony (1972), who induced hypoxia in their subjects by taking them to simulated altitudes of 15 000 and 18 000 ft at a rate of 3000 ft/min in a hypobaric chamber. Values for PCO_2 were not given in their study, but no attempt was made to monitor or control alveolar ventilation. On the other hand, these results contrast with those of Balasubramanian *et al.* (1975) who studied the effects of high-altitude hypoxia on the STI by exposing healthy sea-level residents to high altitude over several days. They found an increase in PEP/LVET and PEPI with a decrease in LVETI. In their study, the first measurements of the STI were performed one day after the subjects had been at the high altitude so that the process of acclimatisation may have started to develop. Furthermore, the greatest changes in the STI occurred on the second and third days at high altitude and, though changes decreased by the tenth day, the mean PEP/LVET were significantly lower than the baseline readings. As these changes are found characteristically in patients with left ventricular failure, it was proposed that they might relate to the pathophysiology of high-altitude pulmonary oedema.

The only studies on the effects of isocapnic hypoxia on the STI that we are aware of are those of Rasmussen and Bech-Jansen (1974) and Rasmussen *et al.* (1975) in anaesthetised, artificially ventilated dogs. They found that there was a slight decrease in PEP/LVET and a slight increase in $1/PEP^2$ when the arterial partial pressure of oxygen (P_{aO_2}) fell from 120 to 80 mmHg and that these changes were not obvious until the P_{aO_2} had fallen below 40 mmHg. After approximately 25 minutes of severe hypoxia ($P_{aO_2}=20$ mmHg), PEP/LVET started to increase towards their initial values as $1/PEP^2$ started to decrease. This observation in anaesthetised dogs may explain, in part, the similarity in results observed by us and by Kowalsky and Anthony (1972), as both studies used relatively short periods of hypoxia, as opposed to Balasubramanian *et al.* (1975) in whose subjects the stimulus persisted for days rather than minutes. However, caution is required in extrapolating the results from severe hypoxia in anaesthetised ventilated animals to conscious man, as in rabbits (Korner, 1959; Korner and Edwards, 1960) and in artificially ventilated dogs (Bernthal *et al.*, 1951) hypoxia induced bradycardia rather than an increase in heart rate.

Hypoxia induces a number of physiological changes which may, in part, explain our findings. The mechanism by which hypoxia causes an increase in heart rate is thought to be an integration of carotid body reflexes and reflexes secondary to the hyperpnoea induced by hypoxia (Daly, 1972). When the carotid body is perfused with hypoxic blood, a decrease in myocardial contractility occurs (Downing *et al.*, 1962, 1963), while isolated cerebral hypoxia or total body hypoxia causes an increase in myocardial contractility. This is in keeping with our findings of a decrease in PEP/LVET, a ratio which is considered to reflect left ventricular performance (Lewis *et al.*, 1977) and which correlates well with angiographic ejection fraction (Garrard *et al.*, 1970).

Our studies may allow some speculation as to the relative roles of adrenergic and mechanical factors in the tachycardia of hypoxia. Acute hypoxia stimulates the adrenal medulla either directly or via the sympathetic nervous system (Van Liere and Stickney, 1963), and beta-receptor stimulation has been shown to cause a decrease in PEP/LVET (Weissler, 1977) and a decrease in PEPI. However, positive inotropic agents generally shorten the LVETI and QS2I (Harris *et al.*, 1967; Salzman *et al.*, 1971; Lewis *et al.*, 1972), while we found that LVETI increased and QS2I remained approximately the same. Since QS2I is felt to be the most useful of the STI in judging the presence of positive

inotropic stimulation (Lewis *et al.*, 1977), it is unlikely that the effects we have observed are solely the result of catecholamine release though this may play some role. This finding is in agreement with those of Richardson *et al.* (1967) who found no increases in plasma concentrations of adrenaline or noradrenaline during hypoxia. Decreased vagal tone does not seem to be the mechanism causing the changes we observed as it causes both QS2I and LVETI to shorten while PEPI remains the same (Raab *et al.*, 1958).

The levels of hypoxia we have used have little effect on blood pressure, but more profound hypoxia can cause a decrease in peripheral resistance (Van Liere and Stickney, 1963). Though Shaver *et al.* (1968) showed that an increase in afterload causes an increase in PEPI, LVETI, and QS2I, in the two subjects they studied in greater detail, they also found that left ventricular end-diastolic pressure had also increased significantly. The STI are sensitive both to changes in preload (Sawayama *et al.*, 1969; Shah *et al.*, 1969) and to alterations in posture. A change from lying to standing induces significant increases in PEPI and PEP/LVET. Shah *et al.* (1969) showed that decreasing preload in normal subjects by the application of venous cuffs on both thighs was associated with an increase in PEPI and PEP/LVET, while systemic artery systolic and diastolic pressures did not change significantly. Though in dogs hypoxia causes an increase in pulmonary wedge pressure, an increase in left atrial pressure does not occur, perhaps because there is constriction between the site of arterial wedging and the left atrium (Braunwald *et al.*, 1958).

Acute hypoxia has been shown to cause a decrease in total peripheral resistance and an increase in stroke volume (Van Liere and Stickney, 1963). The latter causes an increase in LVETI, a decrease in PEPI, while leaving QS2I unaltered (Weissler *et al.*, 1961; Willems and Kesteloot, 1967; Greenfield *et al.*, 1968). As these are precisely the findings we obtained in our study, it is likely that our results may be explained by a combination of changes in peripheral resistance and stroke volume. We conclude that in conscious man, heart rate increases linearly, with falls in arterial oxygen saturation, and that the tachycardia is not associated with a shortening of electromechanical systole, corrected for heart rate. Since catecholamines are known to shorten QS2I, this finding that QS2I remained constant suggests that increased adrenergic activity is not responsible for the tachycardia induced by isocapnic hypoxia. It is more likely that the tachycardia is associated with an increased stroke volume, possibly combined with an increase in preload. However,

these findings may be much influenced by the duration of exposure to hypoxia and may be obscured if the hypoxia is combined with respiratory alkalosis.

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