An investigation of cardiovascular reflexes during a trimix saturation dive to 450 msw (GUSI 17)

F. BOWSER-RILEY, M. J. CORNISH, R. HAINSWORTH, C. KIDD, and R. C. LYONS

Division of Physiology, School of Biomedical Sciences, Marischal College, University of Aberdeen AB9 1AS, UK, and Department of Cardiovascular Studies, University of Leeds, Leeds LS2 9JH, UK (R. H.)

Bowser-Riley F, Cornish MJ, Hainsworth R, Kidd C, Lyons RC. An investigation of cardiovascular reflexes during a trimix saturation dive to 450 msw (GUSI 17). Undersea Biomed Res 1992; 19 (2):271–278.—The study examines the hypothesis that the carotid sinus heart rate baroreflex responses are changed in human subjects on exposure to 450 msw. Baroreceptor reflex changes in heart rate (expressed as ms/mmHg applied pressure) were evoked by application of negative or positive pressure to a cuff surrounding the neck. At 450 msw using trimix, the mean resting heart rate of divers slowed significantly from 64 ± 1.3 beats/min at surface to 55 ± 1.4 beats/min at 450 msw, respiratory rate decreased from 15 ± 1.4 at surface to 11 ± 2 at 450 msw, and sinus arrhythmia increased. There was no change in arterial blood pressure. Baroreceptor reflex sensitivity to an increased carotid sinus transmural pressure was reduced from 5.6 ± 2.9 (mean ± SEM) at surface to 2.4 ± 0.8 ms · $mmHg^{-1}$ at 450 msw; sensitivity to decreased carotid sinus transmural pressure increased from 2.2 ± 0.4 ms · $mmHg^{-1}$ at surface to 5.1 ± 0.2 ms · $mmHg^{-1}$ at 450 msw. A progressive shortening of cardiac interval during breath hold in expiration was also noted. When this shortening of interval was incorporated into the analysis of baroreceptor reflex sensitivity, no significant change in sensitivity was observed but the overall baroreflex stimulus-response relationship shifted downward.

hyperbaria
bradycardia
baroreceptor reflexes
sinus arrhythmia
blood pressure

Exposure of human subjects to hyperbaric conditions has been shown to cause a reduction in resting heart rate, the so-called "hyperbaric bradycardia" (1). Several factors have been postulated to contribute to the bradycardia, including raised partial pressure of oxygen, increased gas density, and raised hydrostatic pressure per se. Of these, gas density and pressure are claimed to be important (2), but the underlying mechanisms have not been defined.

Experiments on animal models have suggested that the reduction in heart rate may result from an enhanced responsiveness of baroreceptor reflex systems, possibly associated with a pressure-induced change in central neural function (3, 4). This

hypothesis has been examined in human subjects. Baroreceptor reflex heart rate responses have been assessed by changing transmural pressure across the carotid sinus by means of a neck collar and measuring subsequent reflex changes in cardiac interval (CI).

In a previous study (5) on human subjects at 450 msw breathing heliox, a decrease in sensitivity (i.e., a reduced slope, ms · $mmHg^{-1}$) in response to an increase in carotid sinus transmural pressure was observed, whereas an increase in sensitivity (i.e., a steeper slope ms · $mmHg^{-1}$) followed the application of a reduced transmural carotid sinus pressure. An enhanced sinus arrhythmia and a shortening of interval which persisted throughout voluntary apnea were also noted. Mean resting heart rate and mean arterial blood pressure were significantly reduced.

The current experiments were aimed to further investigate these cardiovascular changes during a simulated dive using trimix in an attempt to glean a clearer understanding of the effects of hyperbaric pressure and the gas regimen, i.e., heliox or trimix, on the cardiovascular system, and in particular to examine the effect of a progressive shortening of cardiac interval observed during the expiratory breath hold at depth on the baroreflex responses.

MATERIALS AND METHODS

Five saturation divers, ages 33–39 yr, were selected by GUSI to take part in the simulated dive on the basis of experience and upon achieving satisfactory results in a powerbike fitness program.

Ethical approval and voluntary informed consent were obtained for the studies, which were all conducted in a dry pressure chamber. Subjects breathed oxyhelium gas at pressure (P_{O_2} 0.4 ± 0.5 atm abs) with 5% nitrogen (trimix) and were studied during a 34-day dive to 450 msw (46 atm abs) at specific times allocated by the dive schedule. In two predive training sessions the divers were instructed in blood pressure measurement, ECG recording, use of the respiratory monitor, baroreflex testing, and the operation and maintenance of the equipment within the chamber. After these sessions the divers were studied in the chamber at 1 atm abs 6 days and 2 days before compression to obtain control data.

After a compression to 450 msw, which took 34 h 16 min, initial tests were carried out on Day 3 during the sojourn at 450 msw, and a second set of tests was performed on Day 6 at the end of the 450-msw phase. On Day 7, decompression began and the divers were tested again on Day 8 during decompression between 450 and 360 msw (decompression rate 0.016 m · min^{-1}). During the isobaric pressure phase at 360 msw (Days 11–15) the divers were tested on Days 12, 13, and 15. A 4-day decompression to 265 msw (decompression rate 0.016 m · min^{-1}) followed, and two further tests were performed on Days 20 and 22 during the plateau phase at 265 msw.

Divers worked in pairs, one as subject, one as tender. Blood pressure was estimated by auscultation of the brachial artery using a calibrated aeronoid sphygmomanometer, respiration was monitored using a stethograph connected to a Gould DTX pressure transducer, heart rate was measured by conventional surface ECG electrodes (lead II), and CI was obtained from the R-R interval. Baroreceptor reflexes were evoked using a tailored orthopedic neck collar (6) to apply brief pulses of positive or negative pressure to the neck in the area over the carotid sinuses, thus causing transient

decreases and increases, respectively, in carotid sinus transmural pressure and eliciting reflex heart rate responses. Changes in pressure to the collar were controlled by a solenoid valve, and pressure was supplied from a 50-liter ballast reservoir charged by a self-contained mechanical pump (7) capable of supplying both positive and negative pressures. The solenoid valve controlling pressure application was remotely operated via a 24-V DC isolated transformer controlled from the surface. Pressure within the collar was monitored using a Gould DTX patient-isolated transducer. Signals were passed through the chamber hull penetrators into conventional amplifiers and collected, monitored, and analyzed on a Fastdaq Data Acquisition and Analysis system (CSS LEEDS).

Protocol

Subjects rested in supine position for 15 min preceding each experiment, after which the ECG and respiration were recorded for 90 s; arterial blood pressure was then measured. A neck collar was applied to facilitate the measurement of baroreflexes. During each test, subjects held their breath for 10 s in expiration, and 5 s into the breath hold a pressure pulse lasting 5 s was applied to the collar. A series of pressure pulses of different magnitudes were applied. The sequence of pulses was $-40, +40, +20 -20, 0, -20, +20, +40, -40, 0$ mmHg. Between each pulse, heart and respiratory rates were allowed to return to prestimulus values, approximately 1 min. After the final application, the neck collar was removed, blood pressure measured, and ECG and respiration recorded for a further 90 s.

Sinus arrhythmia was assessed as the difference between maximum and minimum CI (8) during the 90-s periods before and after the application of the series of pressure pulses to the collar.

Baroreceptor heart rate reflex responses were calculated as the difference between the mean CI in the 5 s before application of the pressure pulse and the longest or shortest cardiac interval after the application of the pressure pulse. Mean changes in cardiac interval at each applied neck-collar pressure were evaluated. A least squares linear regression of the data enabled an expression of baroreceptor sensitivity in ms · $mmHg^{-1}$.

Results are expressed as mean ± SEM. Significance was tested using a repeated measure analysis of variance ($P < 0.05$ being considered significant).

RESULTS

Heart rate, respiratory rate, sinus arrhythmia, and arterial blood pressure at specified stages during the course of the dive are illustrated in Fig. 1.

A significant decrease in mean resting heart rate from 64 ± 1.3 beats/min (CI 945 ± 54 ms) at surface to 55 ± 1.4 beats/min (CI 1091 ± 32 ms; $P = 0.01$) at 450 msw was observed; this bradycardia became less marked during decompression. The maximum reduction in heart rate, observed during the second tests at 450 msw (Day 6), was accompanied by the largest decrease in respiratory rate from 15 ± 1.4 at surface to 11 ± 2 at 450 msw. There was no significant change in arterial blood pressure throughout the dive.

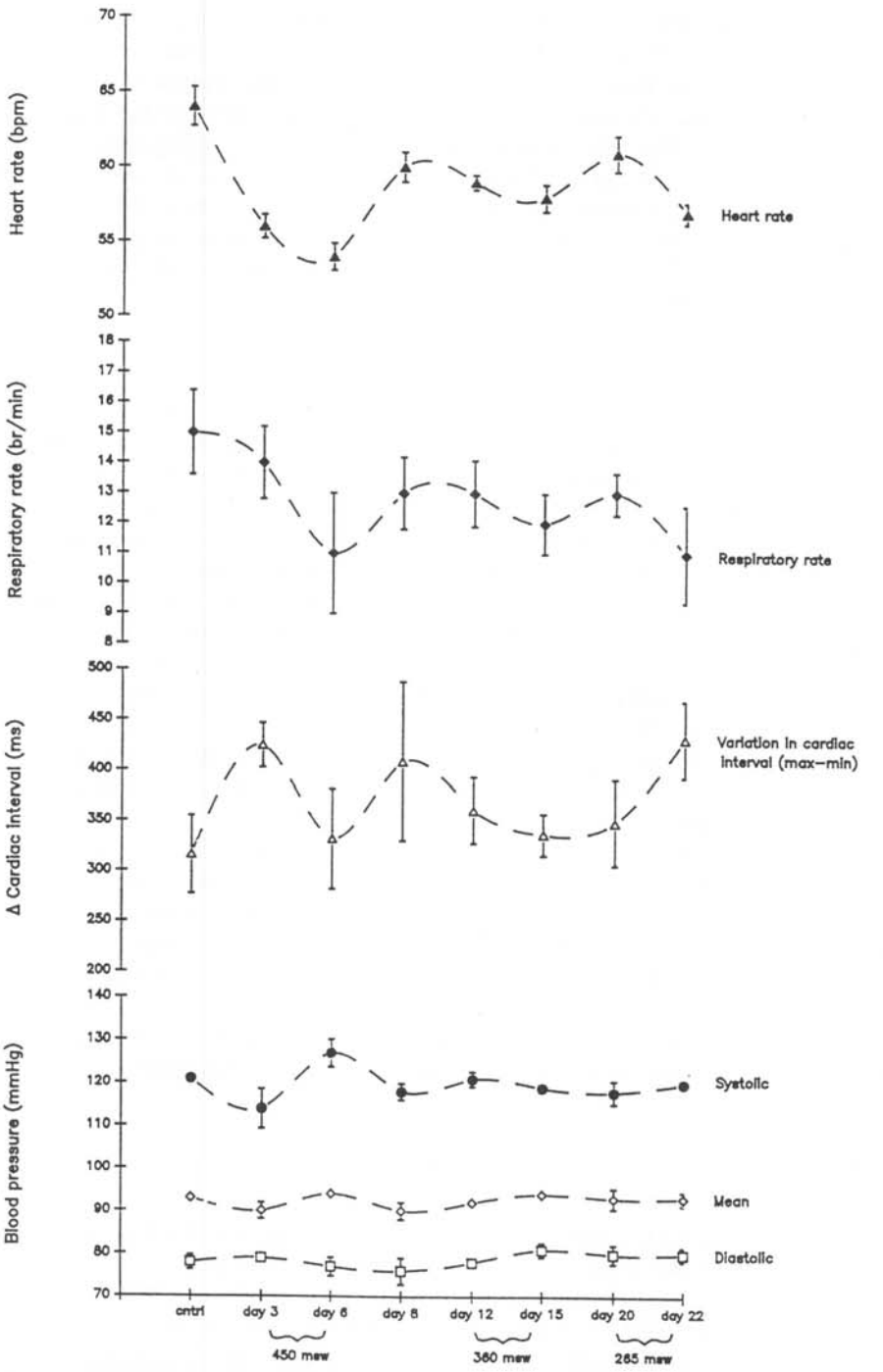

Fig. 1. Mean values (± SEM) for heart rate, respiratory rate, and variation in cardiac interval and arterial blood pressure observed in 5 subjects at rest during the course of a simulated dive to 450 msw.

Alterations in the magnitude of sinus arrhythmia (RSA) were not consistent: on Day 3 there was a significant ($P = 0.03$) increase in RSA at 450 msw, followed by a return to control values on Day 6. RSA increased again during decompression to 360 msw, returned to control values during the period at 360 msw, and remained stable until the final day of measurement at 265 msw.

Figure 2*a* shows the mean baroreceptor reflex responses to neck collar pressure pulses of approximately +40, +20, −20, −40 mmHg at surface and 450 msw. The responses to negative and positive neck-collar pressure pulses were plotted and separately fitted with a least squares linear regression through the origin. At 450 msw the baroreceptor reflex responses to increased carotid sinus transmural pressure were attenuated, and responses to a decrease in carotid sinus transmural pressure were significantly enhanced ($P = 0.0002$). Baroreceptor sensitivity to decreased carotid sinus transmural pressures significantly increased from 2.2 ± 0.4 ms · $mmHg^{-1}$ at 1 atm abs to 5.1 ± 0.2 ms · $mmHg^{-1}$ at 46 atm abs ($P = 0.001$) but sensitivity to increased transmural pressures decreased from 5.6 ± 2.9 to 2.4 ± 0.8 ms · $mmHg^{-1}$ between 1 and 46 atm abs.

In this and other analyses (9) it was assumed that the cardiac intervals during the expiratory pause remain constant. However, during these studies it became clear that early in the period of breath hold in expiration, in the absence of any stimulus, a progressive shortening of the cardiac interval (increase in heart rate) occurred. This became statistically significant ($P = 0.006$) at depth. A shortening in cardiac interval of 88 ± 16.9 ms during the expiratory pause at 450 msw is shown on Fig. 2*b*. To take

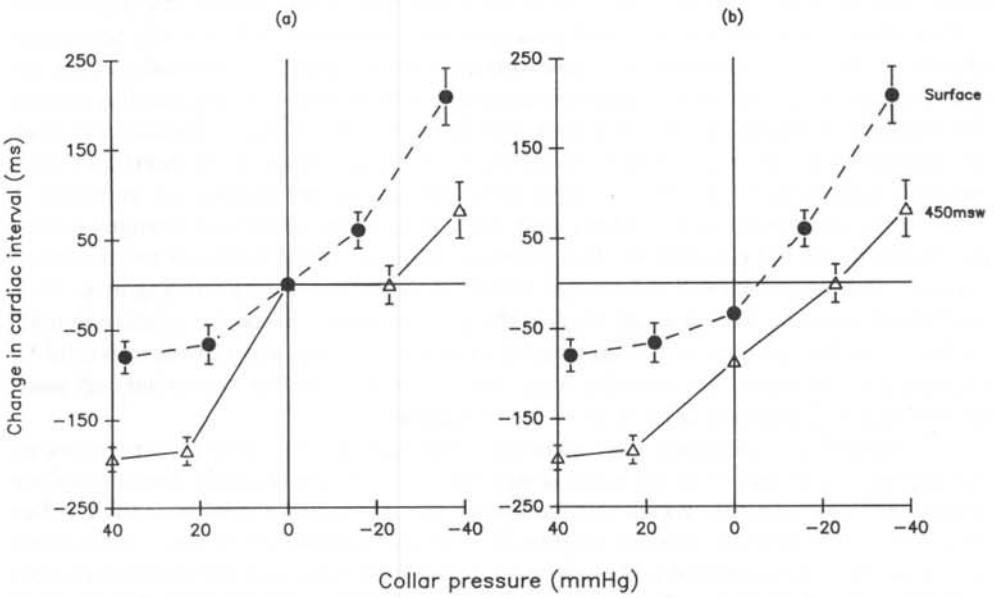

Fig. 2. Baroreflex responses ±SEM to ±20 and 40 mmHg applied to the neck collar measured in 5 subjects at surface (*solid circles*) and 450 msw (*open triangles*). *a*, Shows the relationship obtained if the change in cardiac interval during the breath hold in the absence of a stimulus was ignored. *b*, Demonstrates the downward shift in the relationship at 450 msw when the variability of cardiac interval during expiratory pause is included.

such an effect into account, the form of analysis used to estimate baroreceptor sensitivity was modified. Mean changes in cardiac interval during breath hold in the absence of a stimulus were calculated as the difference between mean cardiac interval in the first and second 5-s periods of the expiratory pause and used to define a baseline for baroreceptor reflex responses. When such a different baseline at zero cuff pressure was incorporated into the baroreceptor sensitivity curves, the calculated baroreflex sensitivity to increased carotid sinus transmural pressure was not significantly reduced (6.4 ± 2.8 ms · $mmHg^{-1}$ to 3.8 ± 1.4 ms · $mmHg^{-1}$) at 450 msw. There was no significant alteration in sensitivity to decreased carotid sinus transmural pressure (1.2 ± 0.4 ms · $mmHg^{-1}$ to 3.5 ± 1.0 ms · $mmHg^{-1}$) at 450 msw. Overall, the effect of the incorporation of the shortening of cardiac interval during breath hold was to induce a parallel downward shift in the baroreceptor response curve without a statistically significant effect on baroreflex sensitivity (Fig. *2b*).

DISCUSSION

A number of mechanisms have been postulated to explain the slowing of the mean resting heart rate in divers exposed to increased ambient pressures. It is said to be due to direct effects of increased hydrostatic pressure and inert gas on the cardiac tissue itself (10, 11). This was on the basis of observations made on isolated tissue at very high pressures which would be lethal to the intact animal. The P_{O_2} of the respired gas has been linked with the occurrence of the bradycardia, although the evidence is indirect and unconvincing (e.g., 1, 2). Nevertheless, in the present study any possible effect was minimized by keeping P_{O_2} at the same level throughout the experiments.

Gas density has been implicated as a possible contributory factor via secondary effects. At 46 atm abs the respired gases are more dense and therefore both inspiration and expiration require more vigorous muscular contractions: consequently, greater fluctuations in intrathoracic pressures are likely to occur. Such fluctuations may, through several direct and reflex effects on pressure and flow in the heart and great vessels, contribute to an altered sinus arrhythmia. Further studies are required to assess this. However, it is unlikely that the whole of the observed changes can be attributed to altered gas density. In a previous study (5) using heliox as the breathing mixture, the magnitudes of the change in baroreceptor sensitivity, resting heart rate, and blood pressure were greater than in the present study. Since the relative density of heliox at 46 atm abs is 6.5 compared to 8.8 for trimix, the converse would be expected if increased gas density were solely responsible for the enhanced sinus arrhythmia and possible effects on reflex responses.

An alternative explanation may lie in the existence of direct effects of pressure on autonomic components of the central nervous system, particularly those involved with heart rate control, which are manifested as attenuated cardiovascular reflex responses. The central neurons responsible for the generation of sinus arrhythmia are exposed to both central and peripheral inputs from lung and chest wall receptors (12). We speculate that a direct effect of high pressure on these central autonomic neurons results in wider and more erratic variations in cardiac interval (sinus arrhythmia), which persist during the expiratory breath hold to appear as the early progressive shortening of cardiac interval. In human subjects at 1 atm abs, a sinus arrhythmia that persisted during voluntary expiratory pause has been reported, and baroreflex

responses were attenuated during cardioacceleration and enhanced during cardiac slowing (12, 13). We observed cardioacceleration during the early phase of breath hold, which became more marked at 46 atm abs. Using a form of analysis that did not take into account the changes in cardiac interval during a breath hold, baroreflex sensitivity in response to increased transmural pressure showed a significant decrease ($P = 0.001$), whereas an increase was observed in response to decreased transmural pressure. However, it is clear that even in the absence of a stimulus, the baselines for responses to changes in carotid sinus transmural pressure at 1 and 46 atm abs are neither the same nor zero. The second analysis incorporates changes in baseline heart rate preceding and predictably during the pressure pulse; under these circumstances there is no significant change in baroreceptor sensitivity but a definite downward shift in the baseline. In other words, the analysis indicates a resetting of the baroreceptor reflex baseline although baroreceptor sensitivity itself remains constant, irrespective of underlying variations in resting heart rate.

In light of the unstable cardiac interval during apnea, further experiments and analyses are in progress (14) to examine the effect it may have on baroreflex sensitivities. Further experiments are also planned to attempt to elucidate the mechanisms underlying the changes brought about by an increased ambient pressure on the cardiovascular system of man.

Gratitude is also extended to the divers and surface personnel, whose voluntary and skillful assistance made the research possible, and to GUSI, GKSS, Germany, for the extensive support and access to their high pressure facility.

We acknowledge the financial support of the Wellcome Trust, Medical Endowments Aberdeen University, the European Social Fund, and COMMET.—*Manuscript received July 1991; accepted April 1992.*

REFERENCES

1. Fagraeus L. Cardiorespiratory and metabolic functions during exercise in the hyperbaric environment. Acta Physiol Scand Suppl 1974; 414:1–40.
2. Flynn ET, Berghage TE, Coil EF. Influence of increased ambient pressure and gas density on cardiac rate in man. Experimental Diving Unit report 4-72. Washington, DC: Washington Navy Yard, 1972:35.
3. Bowser-Riley F, Kidd C. Hydrostatic pressure enhances baroreceptor reflexes in rat. Q J Exp Physiol 1988; 73:785–788.
4. Bowser-Riley F, Kidd C. The effects of raised hydrostatic pressure on cardiovascular function in the ferret. J Physiol (Lond) 1989; 409:87.
5. Bowser-Riley F, Kidd C, Al-Timman JKA, Hainsworth R. Report on 450 msw dive, Igloo '88. Aberdeen: National Hyperbaric Centre, 1989; 2:203–211.
6. Al-Timman JKA, Hainsworth R, Vakasovic JL. A modified neck chamber for the study of carotid baroreceptors in humans. J Physiol (Lond) 1988; 399:14.
7. Al-Timman JKA, Bowser-Riley F, Kidd C, Hainsworth R. A device for the generation of fixed negative and positive pressures for application to a neck chamber for the study of baroreceptor reflexes in humans. J Physiol (Lond) 1989; 416:11.
8. Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. J Appl Physiol 1983; 54:961–966.
9. Eckberg DL. Temporal response patterns of the human sinus node to brief carotid baroreceptor stimuli. J Physiol (Lond) 1976; 258:769–782.
10. Doubt TJ, Hogan PM. Effects of hydrostatic pressure on conduction and excitability in rabbit atria. J Appl Physiol 1978; 45:24–32.
11. Gennser M, Örnhagen H.C. Effects of hydrostatic pressure and inert gases on twitch tension. Undersea Biomed Res 1989; 16:415–426.

12. Trzebski A, Raczkowska M, Kubin L. Influence of respiratory activity and hypocapnia on the carotid baroreflex in man. In: Sleight P, ed. Atrial baroreceptors and hypertension. England: Oxford University Press, 1980:282–290.
13. Shepherd JT, Mancia G. Reflex control of the human cardiovascular system. Rev Physiol Biochem Pharmacol 1986; 105:1–99.
14. Bowser-Riley F, Cornish MJ, Farqhuar J, Hainsworth R, Kidd C. The influence of breath hold tachycardia on human baroreflex heart rate responses to changes in carotid transmural pressure at 37 ATA. J Physiol (Lond) 1992; 466:215.