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Relief of the 'air hunger' of breathholding
A role for pulmonary stretch receptors

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Abstract

Fowler (Fowler, W.S., 1954, J. Appl. Physiol. 6:539–545) showed that rebreathing, despite worsening P_{CO_2} and O_2 saturation, relieved the distress of breathholding; he suggested a role for vagal input in the relief. We studied effects on respiratory sensation of breathholding and rebreathing in normals, patients with bilateral lung transplants (LT), who have a decrease in number of pulmonary stretch receptors (PSR), and heart transplant recipients (HT). Subjects held their breath until distress became intolerable, rebreathed various combinations of CO_2 and O_2, then performed another maximal breathhold. Respiratory distress was rated continuously (visual analog scale) by each subject. Both LT and HT had earlier onset of and more rapidly developing distress during breathholding, resulting in shorter breathhold times, than normals. Relief with rebreathing was neither as rapid nor as great in LT as in HT and normals. Our findings suggest that mechanisms that produce respiratory distress in HT and LT are similar, but differ from normals. However, reduction in distress on rebreathing is more rapid and greater in HT and normals than in LT. This is compatible with the loss during rebreathing of the inhibitory effect of PSR input on neural mechanisms that lead to respiratory distress.

Keywords: Breathing; Air hunger; Control of breathing; Respiratory sensation; Mammals; Humans; Rebreathing; Receptors; Pulmonary stretch; Sensation; Respiratory; Transplant; Heart; Lung; Vagus nerve

1. Introduction

The distressful sensation of dyspnea is a common symptom, yet the mechanisms underlying the sensation have not been fully elucidated. Some understanding has come from psychophysical studies but only recently have some potential neurophysiological mechanisms been demonstrated. Studies in cats have shown that neurons in reticular formations of mesencephalon (Chen et al., 1991) and thalamus (Chen et al., 1992) develop graded respiratory-associated rhythmic firings as respiratory drive rises above a threshhold level, firings which appear to be driven by a corollary discharge from the medulla that re-

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flects the level of neural respiratory activity (Chen et al., 1991). It has been suggested that these neurons in midbrain and thalamus are part of a pathway that, when activated, is involved in carrying information about respiration to the cortical level where it ultimately may be interpreted as the unpleasant sensation of dyspnea. Eldridge and Chen (1992) noted that inflation of the lungs inhibited the firing of the same midbrain neurons; this effect was dependent upon the integrity of the vagus nerves but was independent of the level of medullary respiratory drive. Their findings indicated that the inhibitory effect was related to activation of pulmonary stretch receptors (PSR).

Consistent with the above are studies in human beings in whom respiratory distress can be reduced by movement of the lungs. For example, Hill and Flack (1908) showed that a breathing person could tolerate a higher level of CO_2 than could a breath-holding subject. Opie et al. (1959) found that paralyzed poliomyelitis patients ventilated with large tidal volumes tolerated a greater level of hypercapnia than when they were ventilated with small tidal volumes. More recently, Manning et al. (1992) studied ventilated high-level (C1–C2) quadriplegics, whose respiratory sensation is clearly not dependent upon neural input from the chest wall or respiratory muscles, and found that a mild CO_2-induced 'air hunger' could be increased by reducing ventilator tidal volume and decreased by making tidal volume larger, even though P_{CO_2} was kept constant. The findings are consistent with the hypothesis that relief of the respiratory distress results from expansion of the lungs and activation of PSR.

The present study was an attempt to see if this potential mechanism could be demonstrated in other ways in human beings. We approached the problem using breathholding with a protocol similar to Fowler's now classic breathholding study (1954), a study that also supports the idea of modulation of respiratory sensation by movement of the lungs. Fowler had normal human subjects perform breathholds to the point of intolerable respiratory distress, then rebreathe a gas mixture that was high in CO_2 and low in O_2. The rebreathing, even though it caused no improvement in blood gases, did lead to an immediate reduction of the distress so that additional breathholds could be performed. We compared normal subjects to patients with bilateral lung transplants, persons who have lost a substantial number of PSR. We hypothesized that patients with bilateral lung transplants would, because of their reduced number of PSR, experience less relief of respiratory distress than normal subjects during rebreathing after a maximal breathhold. As an additional control group, we studied patients who had undergone heart transplantation. They are similar to lung transplant patients in that they take immunosuppressive medications, have had a surgical procedure to the chest wall, and have had a history of chronic dyspnea prior to transplantation, yet they differ from the lung transplant patients in that their vagi remain intact.

2. Methods

2.1. Subject selection

Patients who had undergone bilateral lung transplantation ($n = 9$) and heart transplantation ($n = 8$) with successful outcomes were recruited for participation in the study. All patients were studied at least six months after their operation and were required to have spirometric measurements within normal limits (FVC and FEV_1 greater than 80% of predicted). Ten normal subjects were recruited from a university hospital setting; they were also required to have normal spirometric measurements.

The lung transplant procedures were performed using the technique of Pasque et al. (1990), so that anastomoses were located in the mainstem bronchi. Heart transplantation was performed through a median sternotomy.

All subjects were untrained and naive to the ultimate purpose of the study, although they did sign a consent form which noted that breathholding and respiratory discomfort would be measured. The experiments were approved by the local Committee on the Protection of the Rights of Human Subjects.

2.2. Equipment

The breathing and rebreathing circuit consisted of a mouthpiece and a three-way valve which allowed switching the subject from breathing room air to a bag containing one of four experimental gases. The

gases used included: (Gas A) room air; (Gas B) 8.2% O_2, 7.5% CO_2, 84.3% N_2; (Gas C) 21% O_2, 7.5% CO_2, 71.5% N_2; and (Gas D) 92.5% O_2, 7.5% CO_2. The subject's airflow was measured by means of a pneumotachograph (Hans Rudolph). Gas was continuously sampled near the mouthpiece and airway P_{CO_2} was measured by means of an infrared CO_2 analyzer (Beckman LB-2). Arterial O_2 saturation (Sa_{O_2}) was measured continuously in a finger by means of a pulse oximeter (Nellcor N-200).

The distressful respiratory sensation experienced by a subject was measured by means of a visual analogue scale (VAS). In our case, the VAS consisted of a box on the face of which were six horizontally oriented and equally spaced lights with labels of 'no discomfort' and 'intolerable' at the extremes; it was mounted at eye level. A subject rated the level of respiratory distress relative to these extremes by manipulating a 150 mm-long hand-held linear potentiometer to turn on the appropriate light.

2.3. Experimental protocol

Each subject was studied in a quiet room. All trials in that subject were performed on a single day. Breathholds were performed with the subject in a sitting position, wearing a nose clip and with a mouthpiece. After a short period of quiet breathing of room air, the subject performed a maximal breathhold (BH1). When the discomfort of the breathhold could not be tolerated for 'a second longer' (breakpoint), the subject rebreathed one of the gas mixtures for five breaths and then performed a second maximal breathhold (BH2). When the breakpoint was again reached, breathing of room air was allowed.

Breathholds were performed at both total lung capacity (TLC) and functional residual capacity (FRC). A practice trial at each lung volume was performed to acquaint the subject with the protocol and with the VAS device; these trials were not included in data analysis. Three trials with each of the four inspired gases at each lung volume were performed for a total of twenty-four trials for each subject. A period of five minutes passed between each trial to allow the subjects a return to baseline before the next trial.

The subject was blinded to the content of the gases being breathed and was asked to focus on the VAS throughout each trial. Instructions were given that the sensation felt prior to the breathhold was equivalent to the light labelled 'no discomfort', and the sensation at the breakpoint was equivalent to the light labelled 'intolerable'. The subject was instructed to rate the 'discomfort' relative to these extremes throughout each trial.

2.4. Questionnaire

After each experiment the subject was asked to describe the sensations experienced during the trials and to answer questions directed at the quality of the sensation at different junctures of the protocol; answers were recorded for later transcription. The subject was also asked to assess his or her ability to use the VAS to indicate the intensity of respiratory distress.

2.5. Data analysis

Airflow, airway P_{CO_2}, Sa_{O_2} and VAS rating were recorded continuously on either a multichannel analog Grass Recorder (lung transplant and normal subjects) or directly into the computer (heart transplant subjects) via an analog-to-digital converter (DATAQ, Inc.). For those trials recorded on the Grass Recorder, the data were converted into digital values by means of a digitizing tablet (SigmaScan, Jandel) and computer.

Breatholding times were extracted via the computer. VAS values were obtained by converting all VAS measured values to whole-number VAS scores (range 0 to 5), the conversion being based upon a calibration of the VAS potentiometer-light system performed at the beginning of the study. Values of PA_{CO2} and Sa_{O_2} used for analysis were the values just prior to BH1 and at the ends of both BH1 and BH2. Since the initial maneuver from TLC after a breathhold was an expiration, a valid measurement of alveolar P_{CO_2} could be obtained. However, in the FRC trials, the initial maneuver was an inspiration; the subsequent end-expiratory P_{CO_2} was therefore affected by the gas being rebreathed and was not representative of PA_{CO2} at the end of the breathhold. Therefore, only the PA_{CO2} measured at the end of the breathhold from the TLC trials is reported in the results.

2.6. Statistical methods

A repeated measures analysis of variance (ANOVA) was used to assess the relationship between outcome variables (or dependent variables) and patient classification (normal subject, lung transplant patient or heart transplant patient). The outcome variables consisted of time of onset of distress, time to each whole-number VAS score, breathhold times, and the effects of rebreathing for both TLC and FRC. The repeated measures were with respect to gas exposure (A, B, C, D). The repeated measures ANOVA was implemented with statistical software using a general linear model program (SAS PROC GLM, SAS Institute, Cary, NC).

For both TLC and FRC, a mean of the three measurements taken at each of the four gas exposures was computed for each subject. The four means (one for each gas exposure) were used as the repeated measures outcomes. In the repeated measures ANOVA, patient classification was analyzed as a between-subject main effect; gas effects were analyzed as within-subject main-effects.

All P-values reported are a result of the repeated measures ANOVA unless otherwise stated; all averages are reported as mean ± SEM unless stated otherwise. A Bonferroni multiple comparison correction procedure was used where indicated.

3. Results

3.1. Subject characteristics

Specific information regarding the three groups is listed Table 1. The groups were generally similar although there were proportionally more males in the heart transplant group. The heart transplant patients were older and heavier than either of the other two groups. Spirometric measurements and lung volumes are also listed in Table 1. All of the subjects met the criteria for normal spirometric measurements though the normal subjects had a somewhat greater FVC and FEV_1, in absolute terms and as a per cent of predicted. The heart transplant patients had the greatest lung volumes of the three groups; however, the lung volumes as a per cent of predicted were generally similar. Both lung and heart transplant patients were maintained on a standard regimen of immunosuppressive medications (cyclosporin, prednisone, azathioprine) and prophylactic antibiotics (acyclovir, nystatin, trimethoprim-sulfamethoxazole); at the time of each subject's study, there were no clinical findings suggestive of infection or organ rejection.

Table 1
Subject characteristics

	Normals	LT	HT
Number	10	9	8
Gender (M:F)	4:6	4:5	7:1
Age (yrs)	31.0 ± 2.4 [c]	25.0 ± 2.5 [b]	46.1 ± 4.2
Height (in)	67.4 ± 1.4	64.1 ± 1.7 [b]	69.3 ± 1.3
Weight (lbs)	152.0 ± 14.3 [a]	109.0 ± 12.7 [b]	182.9 ± 10.6
FVC (L)	4.56 ± 0.36 [a]	3.38 ± 0.34	4.04 ± 0.31
FEV1 (L)	3.68 ± 0.23 [a]	2.79 ± 0.27	3.33 ± 0.24
FVC (% pred)	105.0 ± 4.3 [a,c]	86.7 ± 4.1	86.8 ± 5.2
FEV1 (% pred)	101.0 ± 2.3 [a]	85.6 ± 4.1	92.3 ± 5.3
TLC (L)	5.80 ± 0.34 [a]	4.54 ± 0.34 [b]	6.91 ± 0.45
FRC (L)	2.81 ± 0.14 [c]	2.77 ± 0.25	3.74 ± 0.41
RV (L)	1.24 ± 0.07 [c]	1.35 ± 0.18 [b]	2.52 ± 0.40
TLC (% pred)	97.0 ± 3.7	86.7 ± 4.1	98.4 ± 6.6
FRC (% pred)	89.0 ± 6.1	100.0 ± 9.9	99.1 ± 11.5
RV (% pred)	78.0 ± 8.4 [a,c]	104.4 ± 12.6	119.9 ± 20.4

All data are mean ± SEM. LT, bilateral lung transplant patients; HT, heart transplant patients. Asterisks indicate significant differences: [a] between normals and LT, [b] between LT and HT, [c] between normals and HT.

3.2. Representative tracing

A recording of one experimental trial by a lung transplant patient is shown in Fig. 1. The trial was performed at TLC and with rebreathing of Gas B (the low O_2/high CO_2 gas mixture). After a short period during which there was no discomfort (VAS = 0), the subject showed a progressive increase of distress throughout BH1, reaching a maximum VAS score of 5 at approximately the same time as the breakpoint of breathholding. During rebreathing of the gas mixture this subject recorded moderate relief of the respiratory distress that did not begin until after the second breath. The relief was short-lived and the subject was capable of performing only a brief second breathhold (BH2). The airway P_{CO_2} rose during BH1, but was less than the P_{CO_2} in the gas

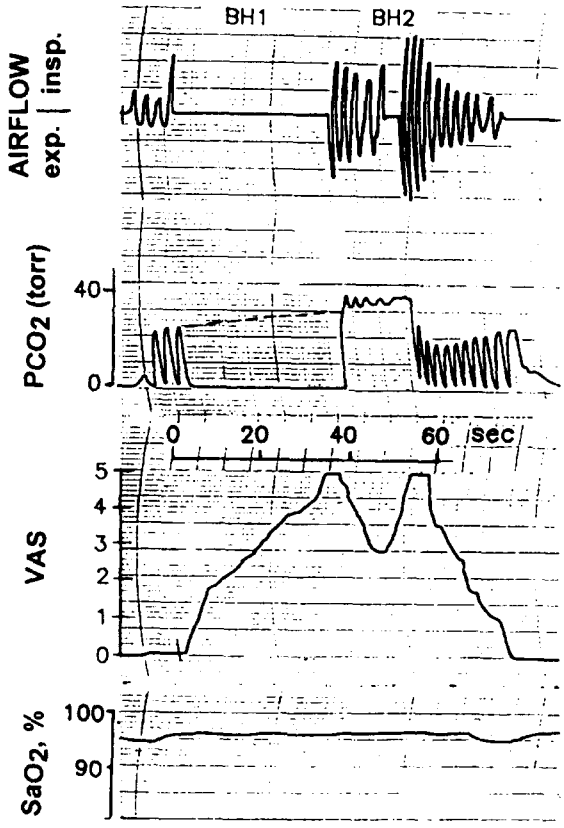

Fig. 1. Recording in a bilateral lung transplant patient of respiratory airflow, airway P_{CO_2}, respiratory distress as measured by a visual analog scale (VAS) and O_2 saturation (Sa_{O_2}). Subject performed maximal breathhold (BH1) at total lung capacity, then rebreathed five breaths of Gas B (high CO_2 /low O_2), and then performed a second breathhold (BH2). There was a progressive increase in respiratory distress during both BH1 and BH2. Dashed line represents estimated pathway of rising PA_{CO2} during BH1. Note partial relief of distress (reduction in VAS score) after the third breath despite increased P_{CO_2} and decreased Sa_{O_2} followed by rapid development of distress during BH2.

mixture, and then increased with rebreathing. There was minimal further change in the airway P_{CO_2} after BH2 because of its short duration. There was little change in the Sa_{O_2}, also because of the short breathhold durations. Resumption of breathing (air) after BH2 led to a slow reduction in respiratory distress.

3.3. Reproducibility of the visual analog scale

The high reproducibility (low intrasubject variability) of the VAS as a continuous measurement of respiratory sensation has been shown in a prior study of normal subjects (Flume et al., 1994). In this study, reproducibility of the VAS for all subjects was very high at both TLC and FRC (reliability coefficient > 0.95).

3.4. Development of respiratory distress

Development of respiratory distress during BH1 in all groups is shown in Fig. 2. There was a short period at the start of the breathhold when the distress level remained zero (no discomfort) for all groups. Each group then experienced a progressive increase in distress until maximal distress was reached resulting in termination of the breathhold. The development of distress and the resultant breathhold duration were similar in both heart and lung transplant groups. However, the onset of distress, the time that an increase in VAS was first recorded, occurred earlier in lung transplant patients than in the normals at both lung volumes ($P < 0.05$). Both heart and lung transplant patients developed maximal distress more rapidly than did the normal subjects resulting in a shorter breathhold duration than normals at TLC ($P < 0.001$, $P < 0.01$ respectively) and FRC ($P < 0.01$, $P < 0.05$ respectively), (see Table 2 for specific values). All subjects were able to hold their breath longer at TLC than at FRC.

3.5. Effects of rebreathing

All subjects reached the maximum VAS score of 5 at approximately the breakpoint of breathholding. The correlation coefficient between these two times was high for all subjects at both TLC ($r = 0.99$) and FRC ($r = 0.99$). Upon rebreathing, and regardless of the gas that was rebreathed, all of the subjects rated a reduction of respiratory distress. There was a difference, however, in the rapidity of relief among the groups (Fig. 3). The relief with rebreathing for the trials at TLC occurred more rapidly in the normal subjects ($P < 0.001$) and heart transplant patients ($P = 0.0001$) than in the lung transplant patients. Both the normal and heart transplant groups recorded substantial relief after the first and second breaths, yet the lung transplant group did not record any relief after the first breath. For the trials at FRC, the

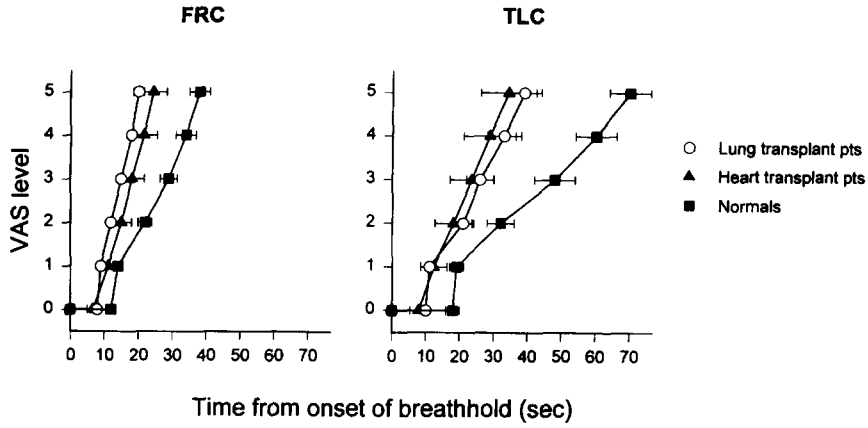

Fig. 2. Development of respiratory distress during breathholds at FRC and TLC for bilateral lung transplant patients, heart transplant patients and normal subjects. Values plotted are average (± SEM) time for onset of distress (i.e. when subjects first rated an increase in VAS) and average (± SEM) time for each level of distress (corresponding to each light on VAS device). Note earlier onset and more rapid progression of distress in both heart and lung transplant patients than in normals resulting in shorter breathhold durations for both transplant groups at both FRC and TLC.

heart transplant patients recorded more rapid relief ($P < 0.001$) with rebreathing than did the lung transplant patients; the normal subjects also recorded more rapid relief than did the lung transplant patients although this did not meet statistical significance ($P = 0.1$).

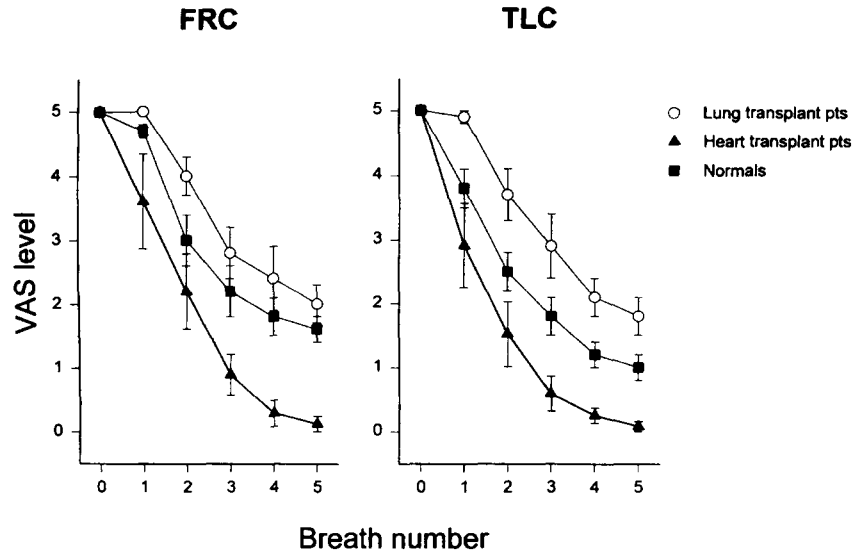

Fig. 3. Relief of respiratory distress with rebreathing for bilateral lung transplant patients, heart transplant patients and normal subjects at both FRC and TLC. Values plotted are average (± SEM) VAS scores at breakpoint of breathholding and after each inspiration. These results are from all trials. Note rapid onset of relief with rebreathing. Onset of relief occurred earlier and was greater for both heart transplant patients and normal subjects than for the lung transplant patients.

Table 2
Breathhold durations

	Normals	LT	HT
BH1 duration			
TLC	70.5 ± 5.8 [a,c]	39.2 ± 3.9	41.8 ± 7.5
FRC	37.5 ± 3.2 [a,c]	22.5 ± 1.6	27.5 ± 3.5
BH2 duration			
TLC			
Gas A	55.7 ± 4.0 [a,c]	31.5 ± 3.1	29.0 ± 5.8
Gas B	17.3 ± 1.2 [a,c]	7.9 ± 1.5	12.5 ± 1.7
Gas C	24.9 ± 1.6 [a,c]	12.1 ± 1.9	14.8 ± 1.9
Gas D	36.0 ± 3.6 [a,c]	22.0 ± 4.1	18.3 ± 2.6
FRC			
Gas A	33.2 ± 2.6 [a,c]	24.1 ± 2.4	23.5 ± 3.0
Gas B	9.3 ± 1.1	6.7 ± 1.3	10.7 ± 3.0
Gas C	16.7 ± 1.4 [a]	11.7 ± 1.8	13.2 ± 2.4
Gas D	32.3 ± 4.5 [c]	21.5 ± 3.8	16.7 ± 3.3

All data are mean ± SEM. LT, bilateral lung transplant patients; HT, heart transplant patients. BH1, breathhold one; BH2, breathhold two. Asterisks indicate significant differences: [a] between normals and LT, [b] between LT and HT, [c] between normals and HT. Gas A, air; Gas B, 8.2% O_2, 7.5% CO_2, 84.3% N_2; Gas C = 21% O_2, 7.5% CO_2, 71.5% N_2; Gas D = 92.5% O_2, 7.5% CO_2.

Table 3
PA_{CO_2} and Sa_{O_2}

	Normals	LT	HT
PA_{CO_2} (mm Hg)			
Initial	33.5 ± 1.7	35.2 ± 1.6	34.6 ± 1.7
End BH1	48.1 ± 1.8 [c]	45.4 ± 2.2	40.7 ± 2.2
Change	14.6 ± 1.0 [a,c]	10.2 ± 1.1 [b]	6.0 ± 1.2
Sa_{O_2} (%)			
TLC			
Initial	98.0 ± 0.3	97.4 ± 0.4	97.3 ± 0.3
End BH1	94.7 ± 0.6	95.8 ± 0.6	96.4 ± 0.6
Change	−3.3 ± 0.5 [a,c]	−1.5 ± 0.5	−0.9 ± 0.5
FRC			
Initial	98.0 ± 0.3	97.4 ± 0.4	97.5 ± 0.3
End BH1	94.4 ± 0.7	94.2 ± 1.3	93.2 ± 1.3
Change	−3.6 ± 0.7	−3.2 ± 1.2	−4.2 ± 1.2

All data are mean ± SEM. LT = bilateral lung transplant patients; HT = heart transplant patients. BH1 = breathhold one. Asterisks indicate significant differences: [a] between normals and LT, [b] between LT and HT, [c] between normals and HT.

3.6. Effect of inspired gases

The differences in the magnitude and rapidity of the relief with rebreathing were not affected by the gas that was rebreathed. However, the rebreathed gas had an effect on the duration of the second breathhold (BH2). BH2 durations for all groups are shown in Table 2. The increased level of P_{CO_2} in Gases B, C and D resulted in shorter BH2 durations than did rebreathing of room air. The shortest BH2 occurred after rebreathing Gas B (low O_2/high CO_2), and BH2 progressively increased with the higher levels of P_{O_2} in Gases C and D. BH2 was consistently greater in the normal subjects than in both heart and lung transplant patients at TLC ($P < 0.001$, $P < 0.001$ respectively) and FRC ($P < 0.05$, $P < 0.05$ respectively).

3.7. PA_{CO2} and Sa_{O_2}

All three groups started the initial breathhold with a similar PA_{CO2} (see Table 3). The average increase

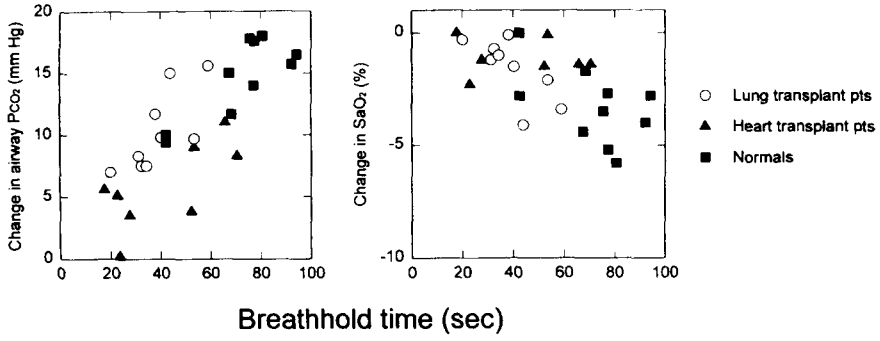

Fig. 4. Changes in alveolar P_{CO_2} (left panel) and O_2 saturation (Sa_{O_2}, right panel) at end of first breathhold for bilateral lung transplant patients, heart transplant patients and normal subjects. Values plotted are average breathhold times vs. average changes in P_{CO_2} (left panel) and Sa_{O_2} (right panel) for trials performed at TLC.

in PA_{CO2} after BH1 was significantly greater in the normal subjects than both heart and lung transplant patients; the average increase in PA_{CO2} compared to the average breathhold time for each subject is shown in Fig. 4 (left panel).

The initial Sa_{O_2} was similar in all groups at TLC. Sa_{O_2} did not decrease much during BH1 in any group; however, the average decrease in Sa_{O_2} was greater in the normal subjects than both heart and lung transplant patients. The average decrease in Sa_{O_2} for each subject at the end of BH1 is shown in Fig. 4 (right panel). In the trials at FRC, there was no difference among the groups in Sa_{O_2} at the start of BH1 or in the change in Sa_{O_2} upon completion of BH1.

Rebreathing of the gases had different effects on PA_{CO2} and Sa_{O_2} at the end of BH2. We are not reporting all of these values, but the results were as would be expected from the composition of the inspired gases.

3.8. Questionnaire

Subjects in all groups stated that they were able to rate accurately their level of discomfort (respiratory distress) using the VAS. Various descriptors were given freely by the normal subjects when asked to relate the sensation they felt at the end of BH1. These included 'tired,' 'hungry for air,' 'suffocating,' and 'short of breath.' Similar responses were given freely by both transplant groups including 'I needed air,' 'real tight,' and 'uncomfortable'. All subjects noted relief of distress with rebreathing, although their comments suggested a difference in rapidity of onset. For example, normal subjects and heart transplant recipients offered comments such as 'instant relief,' 'within a second or two,' and 'after a second or so, I was back to baseline.' The lung transplant patients stated that their relief occurred 'by the third breath,' 'probably in about three or four breaths,' and 'it took a few breaths.'

4. Discussion

4.1. Relief of distress with rebreathing

The hypothesis for this study was that patients with bilateral lung transplants would, because of the reduction of pulmonary stretch receptors, experience less relief during rebreathing of the respiratory distress generated during a maximal breathhold than would normal subjects or recipients of heart transplants. The bases for our hypothesis were 1) the studies in humans of Fowler (1954) and Manning et al. (1992) which suggested that volume-related input from the lungs inhibits hypercapnia-induced 'air hunger' and 2) the neurophysiological studies of Eldridge and Chen (1992) which demonstrated that neurons in the midbrain involved in transmitting respiratory-related information to higher brain, information that may ultimately be interpreted as dyspnea or respiratory distress, are inhibited by vagally-mediated input from pulmonary stretch receptors.

We therefore studied effects of breathholding and rebreathing on respiratory sensation (distress) in normal subjects, patients who had undergone heart transplants, and patients who had undergone bilateral lung transplantation. We used lung transplant patients because the transplanted lungs have lost, and do not regain, afferent innervation. Dogs which had undergone reimplantation of an excised lung (Edmunds et al., 1971; Lall et al., 1973) showed some return of efferent neural responses but no return of afferent activity. Trimble et al. (1967) demonstrated the persistent absence of the Hering-Breuer reflex in dogs after lung reimplantation. There is also no evidence that human lungs develop afferent reinnervation; for example, Hathaway et al. (1991) demonstrated in patients with heart-lung transplantation the persistent absence of the cough reflex, i.e., an absence of response to nebulized distilled water. We studied heart transplant patients as an additional control group because of their similarities to lung transplant patients (similar history of breathlessness prior to transplant, a thoracic procedure, and similar medications) but with the difference that vagal innervation of the lungs was intact.

Under the hypothesis, relief of the distress of breathholding should occur quickly after the onset of rebreathing. We allowed our subjects five breaths, as did Fowler (1954), but this was clearly not necessary, for in all groups there was substantial relief of distress with only a few breaths, consistent with a neural mechanism. It turns out to be irrelevant which rebreathing gas is used because the relief of distress occurs before any potential gas changes in the lungs

can have reached the chemoreceptors. This is similar to the findings of another study in which one-breath and five-breath rebreathings led to similar relief of distress (Flume et al., 1994) and with studies which showed that one breath was as effective as up to five in allowing subsequent breathhholds of the same duration (Flume et al., 1994; Godfrey and Campbell, 1969).

The major difference among the groups during rebreathing was the less rapid and smaller relief of the distress in the patients with lung transplants, compared to the normal subjects and those with heart transplants, which were similar. We believe this is consistent with our hypothesis and therefore suggest that the difference is due to the loss of vagally-mediated afferent information from the pulmonary stretch receptors in the lung transplant patients.

If the lung transplant patients have denervated lungs, then why did they obtain any relief by rebreathing? There are several potential explanations. 1) We noted previously that anastomoses were made in the mainstem bronchi. Afferent innervation of the lungs was therefore lost but innervation of the native extrapulmonary airways remained. In animals, it has been shown that a major proportion of the stretch receptors, ranging from about 40% to greater than 50% in various studies, are located in extrapulmonary airways, mainly in carina and proximal mainstem bronchi (Coleridge and Coleridge, 1986). Thus, it is probable that the lung transplant patients have lost only some of their pulmonary stretch receptors and may retain some of the sensory inhibitory effect of stretch receptor activation. The actual number of stretch receptors left in a given patient and the relation between them and the level of their input cannot be determined. 2) There may be other mechanisms associated with movement and changes in chest volume that lead to relief during rebreathing of the distress of a breathhold. For example, we have shown recently that after a breathhold at TLC, an expiration alone leads to some reduction of the distress, albeit not as much as with an inspiration (Flume et al., 1995). The mechanisms are uncertain, but could involve stretch receptors activated during expiration, or changes of inputs from upper airway and chest wall. Mechanisms not involving pulmonary stretch receptors, if they exist, are not relevant to our present findings, because they could be expected to be the same in all three groups, and not affected by the lung transplant procedure.

4.2. Other findings

Breathhold durations were longer at TLC than at FRC in all groups, a well-known finding in normal subjects (Mithoefer, 1965). The larger volume at TLC provides a greater store of O_2 than at FRC, as well as a larger volume for distribution of CO_2 returning to the lung during a breathhold; this would lead to slower changes with time of both alveolar and arterial P_{O_2} and P_{CO_2}. Nevertheless, because of disproportionately longer breathhold duration at TLC, the ultimate increase of P_{CO_2} is greater than at FRC and there is a greater decrease of P_{O_2}. These findings led Mithoefer (1965) to conclude that chemoreceptor input alone could not account for the difference in breathhold durations at the two volumes and to postulate that there must be an additional mechanism. One such mechanism could be related to the greater lung volume and activation of pulmonary stretch receptors at TLC, that in turn inhibit the neurons in midbrain and higher brain that activate the distressful sensation (Eldridge and Chen, 1992). The inhibition of these neurons would thus allow a longer breathhold and a greater respiratory drive level to develop before maximal distress and breakpoint occurs.

If the above were true, we would expect that heart transplant patients, still having a full complement of PSRs, would have longer breathhold durations than lung transplant patients. This is not what we found; heart transplant patients had similar breathhold durations as did lung transplant patients. It may be that other mechanisms are more important in the increase in respiratory distress during a breathhold in transplant patients (see below).

In addition, the time to onset of respiratory distress was shorter at FRC than at TLC in all groups of subjects. The distress did not start immediately upon onset of the first breathhold in any group but only developed after a period during which respiratory drive would have been increasing along with rising P_{CO_2}. This is consistent with a threshold level, involving neurons that transmit the sensation, below which conscious perception of respiratory distress

does not develop. It is also consistent with findings from the previously quoted human studies (Banzett et al., 1989; Manning et al., 1992) and the neurophysiological studies of midbrain and thalamic neurons (Chen et al., 1991, 1992).

Besides the differences noted above, three other findings became clear: 1) both lung and heart transplant patients felt an earlier onset of distress after the onset of breathholding than did the normal subjects; 2) during breathholds, respiratory distress reached the maximal tolerated level more quickly in both transplant groups than in the normals; and, 3) not surprisingly, both transplant groups had shorter breathhold durations than normals. The findings were consistent at both lung volumes.

Because these findings were similar in the heart and lung transplant patients, the differences cannot be explained solely by activation of PSR, or lack thereof. We have considered other possible factors for our results. We attempted to select three groups of subjects to be, except for the transplant procedures, as similar as possible (see Table 1); nevertheless, there were small differences. Weight was significantly lower in the lung transplant patients and greater in the heart transplant patients compared to normals, although it is difficult to see how this could have affected the findings. All spirometric variables were within normal limits (> 80% predicted) in all three groups, although FVC and FEV_1 (as a per cent of predicted) were significantly lower in both heart and lung transplant patients than in normals. It is unlikely that dynamic measures would affect breathholding durations performed at static volumes. More important for this study, the three groups did not have significantly different lung volumes when normalized to body size, i.e. as a per cent of predicted, which do have a relation with breathhold duration (Mithoefer, 1965).

All subjects started with similar levels of chemical stimulation. The rise of PA_{CO2} in all our subjects was similar to that reported by Hong et al. (1971), i.e. PA_{CO2} rises rapidly (within 30 sec) to venous levels and then more slowly (3-5 mm Hg over the next 30 sec) as more CO_2 returns to the lungs. Therefore, a breathhold that is of longer duration than another will result in a greater rise in PA_{CO2}. We have already noted that the differences in chemoreceptor stimulation between the two groups were in the wrong direction to explain the differences in breathhold durations, i.e., a tendency to higher P_{CO_2} and lower P_{O_2} but longer breathholds in normals.

What about inputs from receptors of the upper airways, chest wall and respiratory muscles, especially the diaphragm? The lung transplant procedure performed on our patients involved anastomoses in the mainstem bronchi (Pasque et al., 1990). The airways are left untouched during a heart transplant procedure. Therefore, input from tracheal and upper airway receptors in both of these groups should have remained unchanged. The lung transplant operation is performed through a transverse incision across the chest, while the heart transplant procedure is performed through a vertical sternotomy incision. It is conceivable that some restriction of the chest wall results; however, our subjects were without serious limitation. Innervation of the chest wall is essentially unaffected by the operation. The transplant surgeon is cautious to avoid the phrenic nerve (Egan, 1992), although injury to the phrenic nerve is conceivable, resulting in reduced neural input both to and from the diaphragm. The patients in our study had no clinical findings of phrenic nerve injury and they had normal lung volumes, so there is no evidence to support a loss of diaphragmatic innervation.

The transplant patients were on medications, some of which have been reported to affect neural function. High levels of cyclosporin have been associated with tremors and seizures (Kahan et al., 1986); the seizures have been attributed to concomitant bolus methylprednisilone therapy. Neurologic symptoms typically represent motor rather than sensory disorders (Kahan et al., 1986). Corticosteroids may also have an effect upon the central nervous system, primarily presenting as neuropsychiatric symptoms such as affective disorders (Truhan and Ahmed, 1989; Stiefel et al., 1989). There was no evidence of cyclosporin toxicity in our patients and the dose of steroids they were taking at the time of the study was considerably lower than those reported to cause central nervous system effects.

It might be suggested that the transplant patients have a 'memory' of respiratory distress that could affect their ability to tolerate a breathhold. There are respiratory neural mechanisms that cause the effects of respiratory stimulatory (and inhibitory) inputs to

outlast the period of stimulation, i.e. a respiratory memory (Eldridge and Millhorn, 1986). These memories have been demonstrated to have both short and long (> 1 hour) durations; it is possible that prolonged chronic stimulation of respiratory-associated neurons prior to lung or heart transplantation may have resulted in a more permanent change in the neurons. They may now have a lower threshold for firing, resulting in earlier and more rapid respiratory distress.

In conclusion, we have reconfirmed that the respiratory distress of a maximal breathhold is relieved by respiratory movement despite worsening blood gases. We have shown that the relief of distress after the onset of rebreathing is more rapid and more substantial in normal subjects and recipients of heart transplants than it is in patients with bilateral lung transplants, who have lost afferent innervation of their lungs. This finding is consistent with the partial loss in lung transplant patients of the effects of vagally mediated pulmonary stretch receptor input to the brain that has an inhibitory effect on the sensation of respiratory distress. We also found earlier onset and more rapid development of respiratory distress during breathholding, resulting in shorter breathhold durations, in both heart and bilateral lung transplant recipients when compared to normal subjects. These findings are probably not related to the loss of vagal receptors in the lung; possible mechanisms are discussed above.

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