lower output, so your findings do not in any way negate this neural mechanism which decays slowly.

Dr. Dutton: I agree. However, the time constants of the reverberations that you showed were something like 45 seconds. The time constants in our study for all 3 types of flow were higher than 175 seconds for ventilation and for tidal volume they're all higher than 250 seconds. For frequency, of course, they are very high, so that in any one of these conditions we are not approaching the kind of time constant that you describe as a purely neural reverberation mechanism.

Dr. Eldridge: Probably both neural and chemical factors contribute.

Dr. Edelman: Dr. Dutton, I have a question. In this preparation you're setting up a large gradient between cortical PCO2 and brain stem PCO2. That might produce a time constant due to the flux of CO2 through the brain. Now if that's true, I don't see that your time constants, although real, can be interpreted in the physiologic sense.

Dr. Dempsey: Dr. Cotton, is the decrease in ventilation with hypoxia in your babies true hypoventilation or does metabolic rate fall in these babies rather easily? That is, is ventilation simply following metabolic rate?

Dr. Cotton: I don't know. I don't think that's ever been measured.

Dr. Eldridge: This study demonstrates some of the problems using ventilation in response to a change in the gas which is given and trying to make any conclusion as to what's doing it. It seems to me that some of those changes that you showed at the beginning of giving high oxygen could very well be a change in the timing of the appearance of an oscillation at the carotid body.

Dr. Edelman: Do we know whether or not the depression of ventilation is due to brain hypoxia? In children with familial dysautonomia you see exactly the same pattern—hyperventilation followed by hypoventilation. If you measure their blood pressure you see that it has fallen enough to probably decrease brain blood flow.

Dr. Cotton: In these babies, blood pressure stays constant and heart rate stays constant, but I agree that brain blood flow may be the deciding element.

**Intrapulmonary and Neuromuscular Receptor Factors**

Respiratory Muscle Function in Amyotrophic Lateral Sclerosis*

Stephen M. Kreitzer, M.D.; Nicholas A. Saunders, M.D.; H. Richard Tyler, M.D.; and Roland H. Ingram, Jr., M.D.

Patients with neuromuscular disorders often exhibit an unhalting progression in paralysis and die from respiratory failure, yet how respiratory muscle weakness contributes to abnormal pulmonary function remains poorly defined.

We studied the relationships between lung volume, flow and intrathoracic pressure in 32 patients with amyotrophic lateral sclerosis (ALS), who had a large range of respiratory muscle weakness. Total lung capacity (TLC) and its subdivisions were measured by plethysmography or helium dilution. Specific conductance, dynamic compliance and static deflation pressure-volume curves of the lung were measured by standard techniques. Maximum expiratory flow-volume curves were obtained spirometrically. Respiratory muscle function was assessed in two ways: first, mouth pressure was measured during maximal static inspiratory (MIPS) and expiratory (MEPS) efforts at least 4 lung volumes: total lung capacity, residual volume, functional residual capacity, and approximately 1/3 inspiratory capacity. Second, transdiaphragmatic pressure was measured in 9 patients able to swallow both esophageal and gastric balloons.

Among the 32 patients studied, total lung capacity was normal (97.69 ± 2.61% predicted, mean ± SEM) residual volume was markedly elevated, (171.14 ± 11.61% predicted), functional residual capacity was 122.63 ± 6.17% predicted, and vital capacity was 81.67 ± 1.88% predicted. These changes of lung volume paralleled maximum static mouth pressures, with inspiratory muscles being less affected than expiratory muscles; mean static inspiratory pressure was 61.58 ± 6.15% predicted versus mean static expiratory pressure 36.88 ± 3.05% predicted (P < 0.001). Transdiaphragmatic pressure during a maximal static inspiratory maneuver at total lung capacity was normal (28 cm H2O), while at residual volume during the same maneuver it was less than 50% normal (69 cm H2O).

Two characteristic flow volume curves were observed. In 12 patients (group 1) the curves were normal. In 15 patients (group 2) the curve was distinctly abnormal: peak flow was reduced and flow fell with a concavity to the volume axis giving the impression that flow had dropped off the flow-limiting envelope near residual volume. Flow rates at 70, 60 and 50% of the TLC were not significantly different between the 2 groups, although the weaker group 2 patients had lower peak flows (P < 0.05). Group 2 patients had a significantly higher residual volume (P < 0.01) and a lower vital capacity (P < 0.001) than group 1 patients. Further, a significant inverse relationship existed in group 2 patients between residual volume and maximum static expiratory pressure (r = 0.66, P < 0.01). There was no difference in TLC and transdiaphragmatic pressure between the groups. No abnormalities of pulmonary mechanics were observed in either group.

To examine whether flow-limitation was achieved during forced expiration, maximum expiratory flow-volume curves were measured in 6 group 1 and 6 group 2 patients breathing through a small, added external resis-

*From the Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston. Supported by NIH grants HL10463 and HL07010.
Discussion

Dr. Kryger: Dr. Kreitzer, were there any differences in inspiratory flow volume loops between your 2 groups of patients?

Dr. Kreitzer: There were no differences in either the shape of the maximum inspiratory flow volume curves or in peak inspiratory flow.

Dr. Edelman: Were there differences in hypercapnic drives to breathe and Pco2 in your two groups of patients?

Dr. Kreitzer: There were no differences between the groups in arterial blood gases. Carbon dioxide response curves have not yet been measured.

Dr. Souhrada: Was there evidence of obstruction in your patients, and if so, was there a bronchodilator response?

Dr. Kreitzer: There was no evidence of obstruction. Therefore, we did not examine bronchodilator effects.

Dr. Motoyama: Was there any difference in TLC in your two groups of patients?

Dr. Kreitzer: There was no significant difference.

Dr. Motoyama: Was there dynamic compression? One group appeared to have a higher V max.

Dr. Kreitzer: Although peak flows were different, there was no difference in flows at 75, 50 and 25% of vital capacity.

Dr. Weil: Depression of drive in these patients seems to be a function of the type of disease, not necessarily the degree of weakness. In myotonic dystrophy, for example, there is depression of chemical drives to breathe, but not in other types of muscular disease with similar weakness.

Dr. Neff: Was the degree of dyspnea quantified?

Dr. Kreitzer: There were no respiratory symptoms, but we quantified muscular strength and group 2 patients were weaker than group 1 patients as tested by physical therapists.

Dr. Evanich: Do you know the neurophysiology of the respiratory muscles in these patients? Were the abdominal muscles and intercostal muscles paralyzed?

Dr. Kreitzer: I can’t answer that question at this point since no EMG’s were performed.

Dr. Grassino: Was there any difference in expiratory or inspiratory muscle weakness?

Dr. Kreitzer: In our patients, diaphragmatic function was apparently spared.

Dr. Grassino: How can you explain this?

Dr. Saunders: This may reflect the distribution of the disease.

The Hyperpnea of Exercise and Chemical Disequilibria

G. F. Filley, M.D.; R. C. Hale, B.S.; J. Kratochvil, Ph.D.; and D. E. Olson, M.D.

The CO2 output (VCO2) is always proportional to ΔPco2, the gradient between pulmonary capillary Pco2 and alveolar Pco2. Since exercise ventilation (Ve) is proportional to VCO2, it must be linked to ΔPco2, but the nature of the linkage is not known. We theorize that an intrapulmonary receptor sensitive to ΔPco2 via the rate of change of plasma pH is the link.

Infusing CO2-rich blood into the pulmonary artery increases ΔPco2 and Ve, whereas one breath of 5-10% CO2 lowers ΔPco2, the inspiratory volume Vi of that breath, and the rate Vi/Ti of inspiration during exercise. The disequilibrium pH rise normally found in blood after it leaves air-breathing lungs can be calculated to rise more with normal exercise (and in the CO2 infusion experiment) and to fall with the abnormal, even negative ΔPco2 caused by CO2 breathing.

To test the theory noninvasively in exercising man, we have increased ΔPco2 without the psychologic and other disturbances caused by intravenous infusions or forced breathing. We have done this by suddenly lowering Pco2 in the lungs of exercising subjects previously breathing a hypercapnic background mixture. In the same subjects whose ventilation was depressed by lowering their ΔPco2, raising it by this method increased their ventilation, thus supporting the theory.

Method

After walking for 4 minutes at 3% mph on a 4% grade breathing 100% O2 or a background mixture of 4% CO2, 15% O2 balance N2, 13 subjects were suddenly and silently switched for one breath to a test mixture of CO2 in N2 or of 100% O2. Before and during the one test breath the subjects were either connected to a closed low resistance (1-2 cm H2O 1-sec) spirometer system or to a pneumotachograph by a 3-way valve in such a way that the inspiration of the test breath could be faithfully recorded either via a bag in box connected to the spirometer or by an integrator and Electronics for Medicine recorder for comparison with the inspirations during background breathing. Pco2 at the mouth was also recorded. The subjects watched and listened to TV as they walked, and except for the taste of the gas when CO2 was breathed, they could not tell when they were being switched to the test mixtures. In two subjects, CO2 test