Quebec Cooperative Study
of Friedreich's Ataxia

Regulation of Respiration in Friedreich's Ataxia

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SUMMARY: *Friedreich's Ataxia (F.A.) is a degenerative disease which commonly leads to premature death of cardio-respiratory origin. To explain the early death of these patients, previous investigations have established the existence of 1) a cardiomyopathy in nearly 100% of cases, 2) a restrictive pulmonary syndrome of scoliotic origin and 3) a mild hypoxemia associated with slight respiratory alkalosis and a normal oxyhemoglobin dissociation curve. To further assess the cause of early death in patients with such neuromyopathy, we evaluated, in eleven F.A. patients, the sensitivity of the respiratory centers to hypercapnia, hypoxia, and hyperoxia.*

Ventilatory (V_E, V_T, F, V_T / T_i) and occlusion pressure ($P_{0.1}$) responses were taken as indices of the respiratory centers output during progressive hypercapnia (Read's method) and isocarbic hypoxia (Weil's method). We studied 11 Friedreich's Ataxia patients and 11 age, sex, and arm-span matched controls. The responses of patients to hypercapnia were significantly greater than controls but their responses to hypoxia were similar to controls.

Our study establishes that the respiratory centers are functioning adequately in early Friedreich's Ataxia and do not contribute to cardio-respiratory insufficiency in such neuromyopathy.

RÉSUMÉ: *Le décès dans l'ataxie de Friedreich survient souvent à la suite de troubles cardio-respiratoires. Afin d'expliquer la mort hâtive de ces patients les études antérieures avaient établi l'existence 1) d'une cardiomyopathie chez près de 100% des cas 2) d'un syndrome pulmonaire restrictif d'origine scoliotique et 3) d'une hypoxémie légère associée à une légère alcalose respiratoire avec courbe de dissociation de l'oxyhémoglobine normale. Afin d'étudier plus en détail la cause de ces morts hâtives, nous avons évalué chez onze patients avec ataxie de Friedreich et 11 sujets témoins la sensibilité des centres respiratoires à l'hypercapnée (méthode de Read), l'hypoxie isocarbe (méthode de Weil) et l'hyperoxie. La réponse des patients à l'hypercapnée était significativement augmentée, mais leurs réponses à l'hypoxie sont semblables.*

Notre étude démontre donc que les centres respiratoires fonctionnent adéquatement dans l'ataxie de Friedreich de début, et ne semblent pas contribuer à l'insuffisance cardio-respiratoire dans cette maladie.

INTRODUCTION

Respiratory failure is a common complication and a major cause of death of neuromuscular diseases (Hall, 1977). Chest wall deformities, repeated aspiration, and chronic pulmonary infection have been recognized as major contributing factors. However, occasional reports in the literature have presented cases of respiratory failure due to altered control of breathing in neuromuscular diseases (Paul et al, 1962; Miller et al, 1957; Bokinsky et al, 1973). More recently, two genetically transmitted neuromuscular diseases, Steinert's disease and the Kearns-Sayre syndrome, have been shown to involve the respiratory centers leading to inadequate response to hypoxia and hypercapnia (Carroll et al, 1976; Carroll et al, 1977).

In the Quebec cooperative study of Friedreich's Ataxia (F.A.), we have previously investigated the pulmonary function of F.A. patients (Bureau et al, 1976; 1978). These studies have shown that F.A. leads to chest wall deformities, a restrictive disease and a mild hypoxemia without, however, alterations of the oxyhemoglobin dissociation curve. The present study evaluates the control of breathing in F.A. and it was designed to evaluate the sensitivity of the respiratory centers to hypercapnia, hypoxia, and hyperoxia in patients with clinically well-established Friedreich's Ataxia, but without major restriction of their respiratory mechanics.

MATERIAL AND METHODS

Subjects:

Eleven patients with typical mild Friedreich's Ataxia were voluntarily enrolled in this study. Their mean age was 16.2 with a standard error (SE) of 1.6 and a range of 9 to 27. They were age, sex, and arm-span matched with eleven normal volunteers selected from a pool of 30 normal subjects concomitantly tested. The mean age of controls was 16.2 ± 1.5 (SE). Each subject and his parents were informed of the nature of the study, the potential risks and benefits of the study and appropriate consent forms were signed. The investigation was approved by the committee on the use of human subjects in research of our university.

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Procedures:

Each patient underwent, within a month, routine pulmonary function tests as part of their yearly evaluation and the evaluation of their chemical drive of breathing. The entire respiratory centers study lasted on average two hours for each subject. Prior to commencement of the study, each subject underwent a brief orientation period during which he became acquainted with the apparatus and methods and participated in trial runs. Thereafter, each subject had a control study while room air breathing followed by, at random, the hypercapnia, hypoxia, and the hyperoxia tests. Between each test, a 15-minute rest period was allowed, at the end of which additional control studies were obtained. During the entire respiratory centers study period, each subject was in the supine position, a position which is preferred for the measurement of the occlusion pressure ($P_{0.1}$) (Milic-Emili et al, 1975).

Routine Pulmonary Function Tests:

Lung volumes (total lung capacity, functional residual capacity, vital capacity, and residual volume), expiratory flow rates (vital capacity expired in 1 second, maximal mid-expiratory flow rate, maximal voluntary ventilation), diffusion (D_LC0), and blood gas studies were done according to methods previously described (Bureau et al, 1976). In addition, P_{Max}, the mean of maximal inspiratory and expiratory mouth pressures generated by an occlusion at functional residual capacity (end of a normal expiration) was measured in all subjects; P_{Max} being a more sensitive test of alteration of the respiratory mechanics in generalised neuromuscular disease (Black and Hyatt, 1971). These routine pulmonary function tests were performed in the seated position as is usual in clinical pulmonary laboratories.

Control of Breathing Apparatus:

To assess the response of the respiratory centers to hypercapnia, hypoxia, and hyperoxia, we designed the apparatus schematically presented in figure 1. The subject breathed with a mouth-piece through a Fleisch #3 pneumotachograph attached to a Hewlett-Packard flow meter (H.-P. #47304A) and integrator system (H.-P. #8815), the signals of which were displayed on two of the four channels of our H.-P. #7754A recorder. Between the mouth-piece and the pneumotachograph, a pressure line was connected to a pressure transducer H.-P. #270 and its signal displayed on a channel displayed on a recorder. The gas sampling line was connected to a Beckman Lb-1 infra-red analyser and an AEI-S3A oxygen analyser, and their outputs were displayed continuously on frontal readouts of the analysers and recorded on the H.-P. recorder when needed. The combined flow rate of these analysers was 5 ml per second. Calibrations and routine checks for accuracy were done according to methods previously detailed (Bégin et al, 1975; Bureau et al, 1976 and 1978). Above the pneumotachograph, a low resistance Koegel valve separated inspiratory and expiratory lines. On the inspiratory line, a Collins 5-way valve (#P-314) was inserted with selections for either occlusion, room air breathing or breathing gas mixtures of the hypercapnia, hypoxia, or hyperoxia tests. Above that valve, the

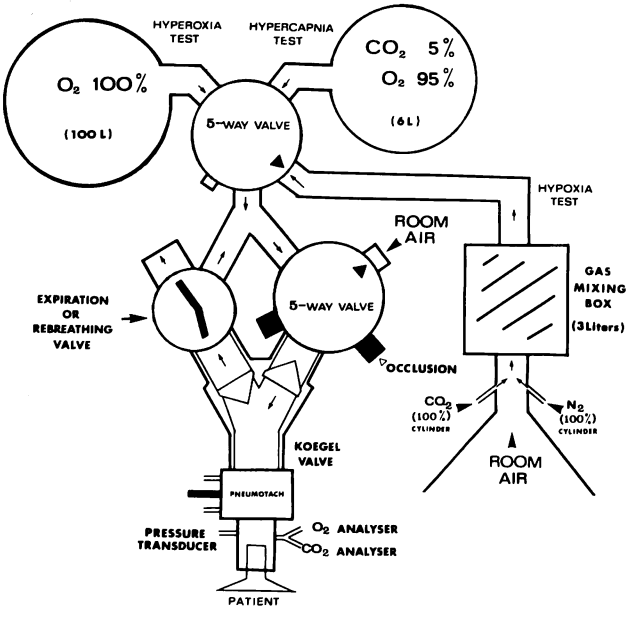

Figure 1 — Schematic outline of the methods used to assess the respiratory response to hypercapnia, isocapnic hypoxia, and hyperoxia. Details of the methods and equipment are presented in the text under *Control of Breathing Apparatus.*

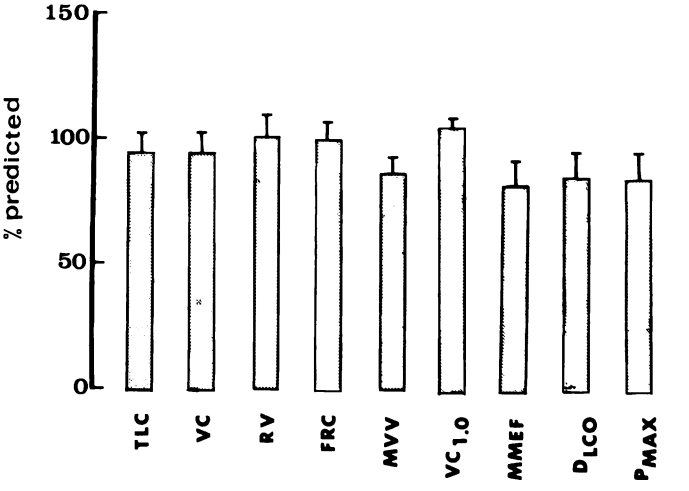

Figure 2 — The routine pulmonary function studies of these patients included total lung capacity (TLC), vital capacity (VC), residual capacity by the helium method (FRC), maximum voluntary ventilation (MVV), vital capacity expired in 1 second ($VC_{1.0}$), maximal mid-expiratory flow rate (MMEF), diffusion for carbon monoxide by the steady state or single breath methods (DL_{CO}) and the maximal pressure generated at the mouth against a closed airway at FRC (P_{Max}). Results are presented as mean ± SE. Predictions for these data analyses were obtained from Beaudry et al, 1967, and Zepletal et al, 1969. P_{Max} predictions were obtained from the controls of this study.

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inspiratory and expiratory valve lines fused in one to a second 5-way valve (Collins P-314) with selection of either the hypercapnia rebreathing, hypoxia, or 0_2 100% breathing tests. On the expiratory line above the Koegel valve, a Collins P-531 valve permitted either rebreathing or non-rebreathing of either gas mixture.

Hypercapnia Test:

For this test, we used the carbon dioxide ($C0_2$) rebreathing method of Read (1967). A six-liter bag filled with a 5% $C0_2$ in oxygen (0_2) was connected to the breathing valve and each subject rebreathed in the bag until his end-tidal $C0_2$ (P_AC0_2) reached 60 millimeters of mercury (mmHg). At that point he was returned to room air breathing.

Hypoxia Test:

The hypoxia non-rebreathing method of Weil was used (Weil et al, 1977). The subject breathed a gas mixture of room air to which was added an increasing volume of pure nitrogen (N_2) until the end-tidal 0_2 (P_A0_2) reached 45 mmHg over a 15-20 minute period. P_A0_2 was maintained at 45 torr for a 2 to 3 minute period. During the test, $C0_2$ was added to the inspiratory line to maintain the P_AC0_2 at 40 ± 1 mmHg. Each subject was continuously monitored during the hypoxia test by one of the physicians (R.B. or M.A.B.) using a continuous electrocardiogram. This terminal P_A0_2 of 45 was selected to avoid serious complications in the patients known to have a cardiomyopathy (Côté et al, 1976).

Hyperoxia Tests:

The transient 0_2 test described by Dejours (1962) was used. Each subject breathed 0_2 100% and V_E was obtained from the five first breaths following the start of 0_2 100% breathing. Thereafter, the subject breathed 0_2 100% for an additional 15 minute period at the end of which a similar measurement of V_E was calculated. During the tests of hyperoxia, end-tidal 0_2 and $C0_2$ were continuously monitored.

Respiratory Centers Output Indices:

During each of the tests of control of breathing, ventilation (V_E), tidal volume (V_T), and respiratory frequency (F) were measured. In addition, for the hypercapnia and hypoxia tests, two newer indices were measured: 1) the mean inspiratory flow rate (V_T/T_i) where T_i is the mean inspiratory time. This is an index of inspiratory neural drive transformed into flow (Milic-Emili and Gunstein, 1976); 2) the occlusion pressure ($P_{0.1}$), the mouth pressure generated at 0.1 second by the inspiratory muscles at functional residual capacity (Whitelaw et al, 1975), a parameter of respiratory centers output that is not influenced by the flow resistance or compliance of the respiratory system (Milic-Emili et al, 1975). In the present study, the occlusion was performed as shown in figure 1, according to the method of Lopata (1977). With the subject's eyes covered during the test, transient silent closure of the inspiratory circuit was performed randomly every 5 to 10 breaths during the hypercapnia and hyopxia tests. The occlusion lasted for between 0.2 and 0.3 second and the negative mouth pressure was measured at 0.1 second after the start of the inspiratory effort, at which time the subject had not realized that the inspiratory line was blocked (Whitelaw et al, 1975). The $P_{0.1}$ was not influenced significantly by the gas analysers. The occlusion pressure is another variable related to inspiratory neural drive which should be thought of as the pressure potentially available for inspiration and therefore, per se, is not influenced by the next step in mechanical transformation of inspiratory neural drive into flow (V_T/T_i), volume (V_T) and ventilation (V_E).

During the hypercania and hypoxia tests, each index measurement was a mean of 3 to 5 individual values obtained for V_T, F, V_T/T_i, $P_{0.1}$ and the mean value of 3 to 5 breaths determined V_E at each arbitrarily selected point. During the hyperoxia test, only V_E was measured as described above.

Statistical Analysis:

In the presentation of the data, mean values are followed by the standard error (SE) as an index of dispersion. Each subject's response to hypercapnia and hypoxia was transformed into a linear regression equation, the classic fit for responses to hypercapnia and the best fit for our hypoxia data, where P_A0_2 did not fall below 45 mmHg, for the reason mentioned earlier. Statistical analysis of the mean slope of the response of patients versus controls was analysed by a student t-test for paired and unpaired values or, when appropriate, by two-factor analysis of variance for experiments having repeated measurements on the same subjects (Snedecor et al, 1967). Differences with $P<.05$ were considered significant.

RESULTS

Routine Pulmonary Function Tests:

The results of lung volumes, expiratory flow rates, diffusion, and P_{Max} of our patients are presented in figure 2 as a percent of their predicted values. All these values fell within normal limits, although slightly below their average predicted. The patients also had an arterial blood sampling while resting, room air breathing and their mean arterial $P0_2$ was 87.5 ± 2.9 mmHg and $PC0_2$ 31.7 ± 1.0 mm Hg.

Respiratory Centers Output to Hypercapnia:

Figure 3 presents the responses of our patients and controls to progressive hypercapnia. The indices of respiratory centers output presented in A to E are minute ventilation, V_E (liter pre minute BTPS), tidal volume V_T (liter), respiratory frequency, F (breath per minute), mean inspiratory flow rate V_T/T_i (liter per second), and occlusion pressure, $P_{0.1}$ (cm H_20). As can be seen in that figure, with progressive hypercapnia there is a significant increase of each parameter for both the normal volunteers (controls) and Friedreich's Ataxia patients ($P<.01$). Furthermore, for each parameter except respiratory frequency, the slope of the response was significantly higher for patients than controls ($P<.001$ for V_E, $P<.01$ for V_T, $P>.05$ for F, $P<.001$ for V_T/T_i and $P<.02$ for $P_{0.1}$).

Respiratory Centers Output to Hypoxia:

The responses of our patients and controls to progressive isocarbic hypoxia is presented in figure 4, the neural drive parameters being similar

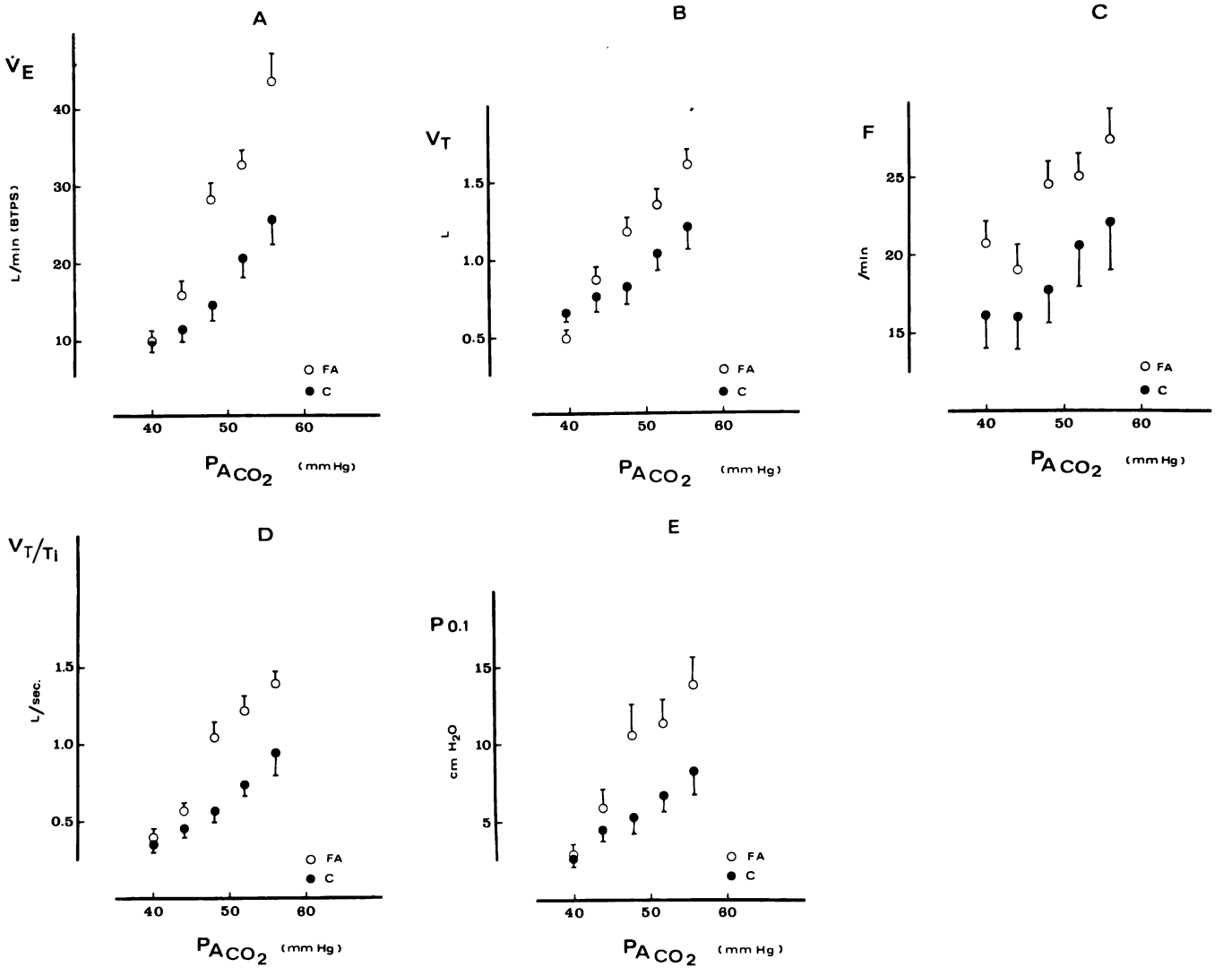

Figure 3—The respiratory centers output to progressive hypercapnia was assessed by looking at the minute ventilation (V_E) in A, tidal volume (V_T) in B, respiratory frequency (F) in C, mean inspiratory flow rate (V_T/T_i) in D and occlusion pressure ($P_{0.1}$) in E. For each parameter, there was a significant increase as P_ACO_2 increased in both normal controls (c) and Friedreich's Ataxia patients (F.A.). Furthermore, the slope of the response was also significantly greater for all parameters except F ($P<.001$ for V_E, $P<.01$ for V_T, $P>.05$ for F, $P<.001$ for V_T/T_i and $P<.02$ for $P_{0.1}$).

to those of hypercapnia presented above. Again, with progressive hypoxia there is a significant increase of each parameter ($P<.05$) except respiratory frequency which has a very small increase for controls and patients ($P>.05$). However, the response to hypoxia did not differentiate patients and controls ($P>.05$).

Ventilatory Responses to Hyperoxia:

The ventilatory responses (V_E) to hyperoxia is presented in figure 5. For both patients and controls, similar changes in V_E were observed. The transient 0_2 inhalation (Dejours' test) caused a slight decrease in V_E. After 15 minutes of 0_2 100% breathing, V_E increased significantly above pre-study levels in both groups ($P<.05$).

DISCUSSION

In recent years, there has been a surge of interest in the evaluation of the regulation of respiration. This has been generated in part by the more frequent clinical observation of patients with normal mechanics presenting in respiratory failure, their incidence in intensive care units having been estimated at 5 to 10% of all respiratory failure admissions (Hall, 1977). In addition, the recent introduction of effective modes of therapy for such patients (Lyons and Huang, 1968; Sutton et al, 1975; Beneker and Roloff, 1976) has contributed to the increasing interest for the investigation of the control of breathing.

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During the last few years, major advances in the evaluation of the respiratory centers have also been realized. Read (1967) developed a carbon dioxide rebreathing technique to evaluate the respiratory centers output to hypercapnia which is quicker and simpler to use than the previously classic steady state method. Weil and his co-workers (1970) standardized another non-steady state method to generate a progressive isocarbic hypoxia which is also quicker and simpler than the previous methods. These two procedures, which in the past would have lasted close to 8 hours, can now be performed in most laboratories within 2 hours.

Along with the introduction of these newer rapid methods of inducing hypercapnia and hypoxia, an increased awareness of the limitations of the response indices in diseases has lead to the use of newer parameters: the occlusion pressure, $P_{0.1}$, and the mean inspiratory flow rate, V_T/T_i. The occlusion pressure is said to be relatively unaffected by respiratory mechanic abnormalities (occurring at zero flow) and has the additional advantage of being a fast and easy parameter to measure (Milic-Emili et al, 1975). The mean inspiratory flow rate is thought of as a measure of the mean flow resulting from the inspiratory neural drive (Milic-Emili

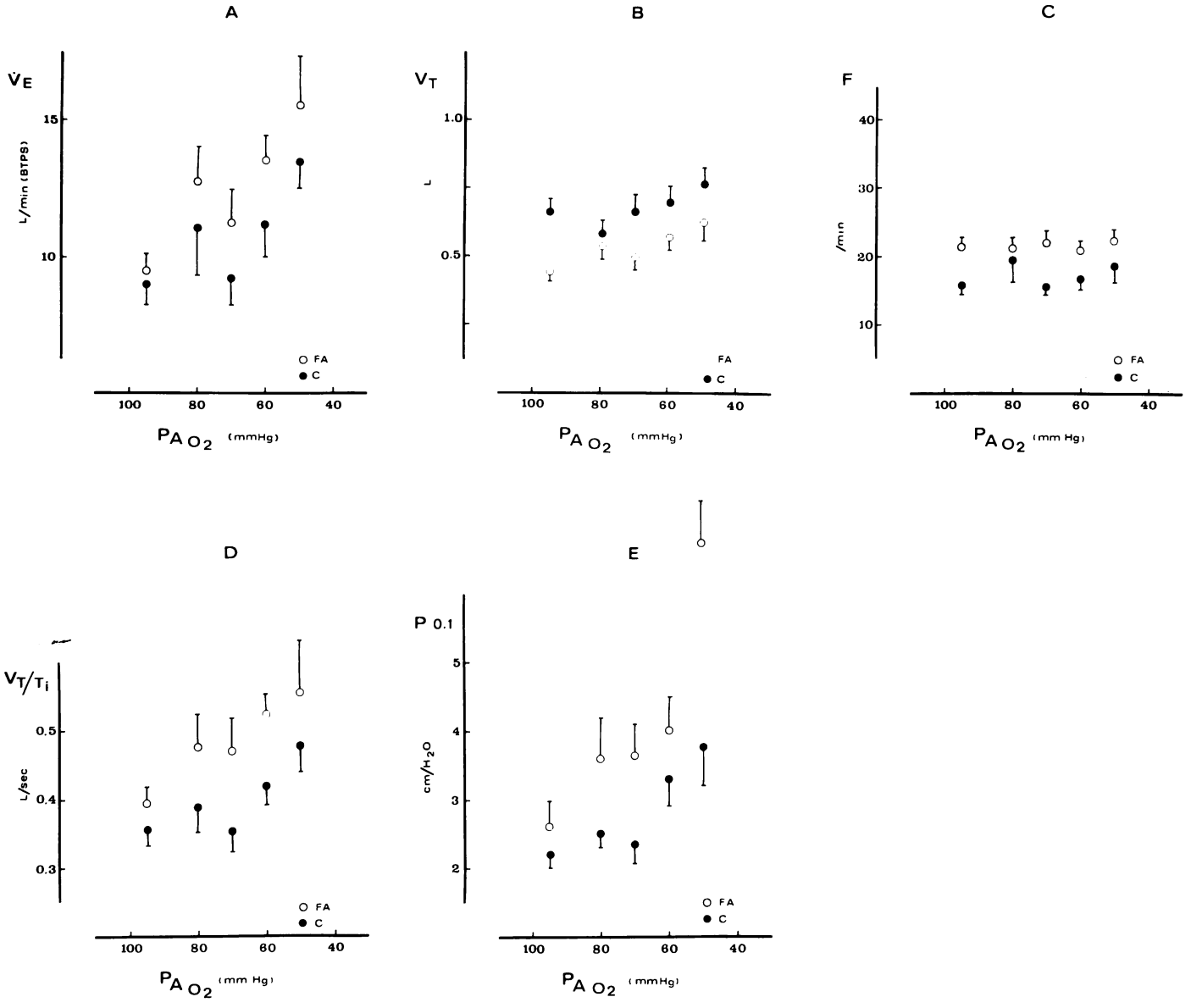

Figure 4—The respiratory centers output to isocarbic progressive hypoxia was assessed by looking at the same parameters as in figure 2. For each parameter except F, there was a significant increase as P_A0_2 decreased in both controls (c) and Friedreich's Ataxia patients (F.A.). However, the slope of the response did not differ significantly between F.A. and c for all parameters.

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and Gunstein, 1976) and therefore is not influenced by the expiratory phase of respiration.

Thus, the assessment of respiratory chemosensitivity is increasingly becoming part of the armamentarium of the clinical pulmonary laboratory and, as such, has lead to better characterization of previously described abnormalities as well as to the discoveries of previously unsuspected dysfunction of the control of breathing in diseases (Bokinsky et al, 1973; Carroll et al, 1976 and 1977).

Such dysfunction of the regulation of respiration has been recently documented in two genetically transmitted neuromuscular diseases, myotonic dystrophy and the oculocraniosomatic neuromuscular disease (Carroll et al, 1976 and 1977). We therefore investigated the functional status of the respiratory centers in a group of Friedreich's Ataxia patients. As a group, their ventilatory pattern (minute ventilation, respiratory frequency and tidal volume) and routine pulmonary function tests (figure 2), were normal except for mild hypocapnia. All of them increased their respiratory centers output to both hypercapnia (figure 3) and hypoxia (figure 4) and their responses to hyperoxia had the same characteristics as normals (figure 5). Therefore, our study demonstrates that in mild to moderate Friedreich's Ataxia, the control of breathing is not primarily defective.

The slightly greater response of the respiratory centers to hypercapnia may be at first glance surprising, but this phenomenon can, at least in part, be explained by the following: first, the $C0_2$ response curve of patients with F.A. is shifted to the left as compared to controls (figure 4A) which is explained in part by their chronic compensated hypocapnia of a mean $PaC0_2$ of 31.7 mmHg associated with a lower bicarbonate level in the blood and CSF (Kellogg, 1963; Heinemann and Goldring, 1975). Secondly, the increased sensitivity suggested by the steeper slope of response to $C0_2$ in all four parameters of neutral output (V_E, V_T, V_T/T_i and $\dot{P}_{0.1}$) may also in part be explained by the relatively sedentary life of our F.A. patients.

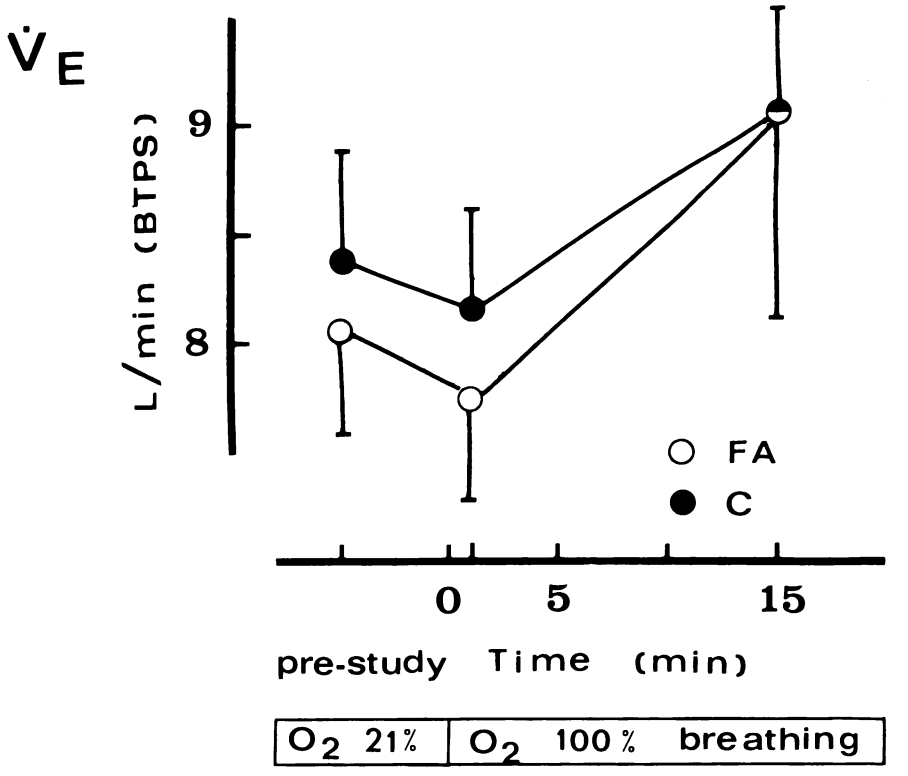

Figure 5 — The ventilatory response to hyperoxia was measured as minute ventilation (V_E) at a pre-study point while subjects were breathing room air. Thereafter, the five first breaths immediately after the start of 0_2 100% breathing were compiled as the second point and the last point was obtained fifteen minutes later over five breaths. In this figure, controls (c) and Friedreich's Ataxia (F.A.) did not differ significantly; however, at fifteen minutes after the start of 0_2 100% breathing, V_E was significantly higher than at pre-study and at the beginning of 0_2 100% breathing for both c and F.A. ($P<.05$).

Most of them are wheel chair bound while controls are normal adolescents. Indeed, a previous study of the effects of physical conditioning (Leitch et al, 1975), has clearly shown that physical training leads to a lesser response of the respiratory centers output to hypercapnia. Although, to our knowledge, the effects of deconditioning on the regulation of respiration has not been assessed, it is possible that deconditioning in our patients has lead to increased respiratory centers output to inhalation of $C0_2$. The responses of Friedreich's Ataxia patients and controls to 0_2 100% do not statistically differ ($P>.05$). For the transient 0_2 inhalation, a measure of the peripheral chemoreceptors sensitivity, the similar responses of patients and controls are in agreement with those previously reported in normals (Dejours, 1962). The initial 5-10% fall of V_E has been used in the past by Dejours to support the concept of the 0_2 drive contribution to ventilation at room air breathing (Dejours et al, 1959; 1963). The ventilatory responses obtained after prolonged hyperoxia are also similar in patients and controls and this data is also consistent with previous reports in man. The increased ventilation observed after 15 minutes of 0_2 100% breathing can be explained by 1) a slight acidification of the arterial blood caused by increased amount of oxyhemoglobin, 2) a greater acidification of venous blood where oxyhemoglobin quantity will be much higher (Gesell effect), 3) reduced cerebral blood flow induced by 0_2 100% breathing, and other metabolic alterations (Dejours et al, 1959). The scope of Dejours' transient hyperoxia test is specific for the peripheral chemoreceptor evaluation while the

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test of sustained hyperoxia is multifactorial. Nevertheless, these are easy tests and they examine aspects of the control of breathing not measured by the more classic hypercapnia and hypoxia tests. In the present study, results of the hyperoxia tests allow us to establish the integrity of the 0_2 sensitivity in patients with Friedreich's Ataxia.

In conclusion, our data establishes that our early, well characterized Friedreich's Ataxia patients had respiratory centers that were adequately responsive to hypercapnia, hypoxia, and hyperoxia. Therefore, these patients should not develop respiratory failure of the central type, at least not early in their disease. The present study, however, does not exclude a later primary defect of the control of respiration nor does it exclude a defect secondary to chronic hypoxia in the later stage of the disease. Further studies involving only severely affected patients are needed to elucidate these points.

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