Classical conditioning of ventilatory responses in humans

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GALLEGO, JORGE, AND PIERRE PERRUCHET. *Classical conditioning of ventilatory responses in humans.* J. Appl. Physiol. 70(2): 676–682, 1991.—A classical conditioning experiment, in which an auditory stimulus was paired with a hypoxic stimulus, was carried out on 34 normal subjects assigned to two groups (experimental and control). Each subject took part in one session divided into two phases, acquisition and test. In the acquisition phase, eight hypoxic and eight auditory stimuli were paired in the experimental group and unpaired in the control group. In the test phase, which was identical for the two groups, the hypoxic stimuli were suppressed and three purely auditory stimuli were presented. Significant differences between the two groups in ventilatory response to these auditory stimuli provided evidence for conditioning. In the control group, no significant changes were elicited by the auditory stimuli, whereas a conditioned increase in total cycle duration was observed in the experimental group. The conditioned response closely resembled the first component of the hypoxic response. Analysis of the pattern of the conditioned response, along with postexperimental interviews, strongly suggests that this response was not mediated by volitional factors.

control of breathing; hypoxia; auditory stimulus

REPORTS in the physiological literature claim that breathing may be influenced by conditioning processes (4, 7). Classical conditioning of breathing refers to the fact that, if a stimulus is paired with another stimulus that evokes a ventilatory response, this first stimulus can reliably elicit a ventilatory response that differs significantly from the one it elicited initially. The stimulus and the response are termed conditioned. Conditioning processes are thought to affect breathing in normal everyday circumstances. For instance, the anticipatory change in breathing pattern before muscular exercise is one of the normal breathing acts that are interpreted as resulting from conditioning (28, 30). Numerous authors have argued that the conditioning hypothesis is not only relevant to normal respiratory functions but also necessary for an understanding of various respiratory dysfunctions (13), such as asthmatic attacks (8, 19, 26, 27) and dyspnea (9). This approach has direct implications for behavioral therapies, such as deconditioning and desensitization.

However, in contemporary research, interest in the widely accepted notion of ventilatory conditioning is disproportionately low with respect to its high theoretical and practical impact. Despite the contribution of early studies in ventilatory conditioning (1, 3, 18, 29), many questions remain unresolved. In these early studies, sensory conditioned stimuli were found to elicit a ventilatory conditioned response after they had been paired with ventilatory unconditioned stimuli such as hypercapnia or hypoxia. However, since then, substantial changes have taken place in conditioning methodology, especially in experimental controls (23). The need for control procedures stems from the fact that the response to the conditioned stimulus does not necessarily result from the pairing of the conditioned and unconditioned stimuli. It may also be merely unconditioned. This is particularly true for breathing, because extensive evidence from later studies shows that a wide variety of sensory stimuli may elicit changes in breathing pattern. This problem is further complicated by the fact that the occurrence of ventilatory stimuli may have a nonspecific influence on the ventilatory response to sensory stimuli, for instance, by acting on arousal or emotional state. As a consequence, the evidence for conditioning must imperatively rely on control procedures incorporating unpaired presentations of sensory and ventilatory stimuli. One further issue, which was not discussed in these early works, is the possibility that the subjects voluntarily respond to the conditioned stimulus (5). Finally, these experiments were conducted on very small samples, and no inference tests were performed to support their conclusions. Thus the question of how breathing is affected by conditioning in humans deserves further experimental research.

The aim of the present study was to investigate ventilatory conditioning in controlled experimental conditions. In this experiment, a hypoxic stimulus was paired with an auditory stimulus to investigate the pairing-specific changes in the ventilatory response to this auditory stimulus. These findings provide evidence for a genuine conditioned involuntary ventilatory response. However, more unexpected, perhaps, than the result that breathing can be conditioned are the speed of the conditioning process and the pattern of the conditioned response, which receive particular attention here.

METHODS

Subjects. Thirty-seven healthy undergraduate students, enrolled for the most part in medical school or psychology curricula, volunteered for this experiment. They were informed about the nature of the stimuli but not the purpose of the experiment. None was familiar with breathing experiments. Two subjects found the experimental conditions excessively unpleasant and did not complete a normal session. One further subject was discarded for a technical failure during the session. The

remaining 34 subjects (10 males and 24 females; mean age 24 ± 5 yr) took part in one experimental session.

Apparatus. The experimental setup was composed of a facial mask attached to a heated Fleisch pneumotachograph (no. 2) with its pressure transducer (Schlumberger CH510510, no. 13, conditioner CA1065), an analog processing device built in the laboratory that detected the transitions between inspiration and expiration and integrated the flow signal for the calculation of tidal volume (V_T), an analog-to-digital converter (Selia PA300), a microcomputer (Olivetti M24), an O_2 analyzer (Taylor Servomex 0A250), and an oscilloscope (Tektronix 5103N). The dead space of the set pneumotachograph mask was <150 ml. The two inputs to the computer were V_T and a signal from a relay that shifted each time the flow crossed zero. The computer used this binary signal to compute inspiratory and expiratory times and total duration of cycles (T_T). The sampling frequency for this signal was ~100 Hz. Volume measurements for both room air and high N_2 concentration were calibrated before each session in ATPS conditions with a sinusoidal pump built in the laboratory. All volume measurements were then converted into BTPS units. The auditory stimuli were generated at a comfortable audible volume (~20 dB) by the computer and delivered binaurally to the subject via soundproof headphones. The hypoxic stimulus was produced by delivering a N_2 flow (25 l/min) into an open cone-shaped tube fixed to the pneumotachograph. This addition of N_2 gradually lowered the inhaled fraction of O_2 to ~3%. The bottle of N_2 was placed in an adjacent room to avoid detection of the switching to N_2 inflow. Computer programs were written in BASIC and compiled by Quick BASIC Compiler (Microsoft).

Procedure and design. Subjects were seated semirecumbent such that they were unable to watch the apparatus or see when the inspired gas was changed. After being randomly assigned to one of the two groups (control and experimental), the subjects received standardized information on the occasional occurrence of a continuous tone and occasional feeling of breathlessness due to the momentary inhalation of a gas with a low concentration of O_2. During the session, subjects wore an airtight facial mask attached to the pneumotachograph that was fastened to the head and suspended at the appropriate height (no leakage was observed). Music was piped in as a distraction. The same recording was used for all experimental and control subjects. A 10-min rest period was allowed for the subjects to adapt to the apparatus. Twenty consecutive baseline values for ventilatory data were first collected after the rest period. Each session was then divided into two phases: acquisition and test. In the acquisition phase, the subjects were exposed to eight auditory and eight hypoxic stimuli. The two stimuli always started at the onset of inspiration and lasted for 12 breathing cycles. The only procedural difference between the two groups concerned the temporal relationship between these stimuli. In the experimental group, the hypoxic and auditory stimuli were delivered simultaneously. The difference in the dynamics of these two stimuli guaranteed the anteriority of the conditioned auditory stimulus to the unconditioned hypoxic stimulus, which is one of the prerequisites of the conditioning paradigm. In the control group, auditory and hypoxic stimuli were unpaired and delivered in a strict alternating pattern beginning with hypoxia. This control procedure has been termed "explicitly impaired" (23) or "sequential" (22). The test phase was identical for both groups: three exclusively auditory stimuli were delivered. The interval between the offset of one stimulus and the onset of the next was 80 s in the experimental group and 120 s in the control group, yielding an approximately equal session duration for both groups (~55 min).

TABLE 1. *Baseline ventilatory data*

	T_I, ms	T_E, ms	T_T, ms	V_T, ml	$\dot{V}$, l/min
Control	1,770±416	2,239±774	4,009±1,036	709±337	10.29±2.77
Experimental	1,619±321	2,216±633	3,836± 863	727±173	11.45±1.50

Values are means ± SD. T_I and T_E, inspiratory and expiratory times, respectively; $\dot{V}$, minute ventilation.

Statistical analysis. The raw data were the individual breath-by-breath values of T_T and V_T. Data analysis was the same for these two variables. For each subject and for each stimulus (hypoxic, auditory, or both simultaneously), 36 cycles were taken into account: the 12 cycles immediately preceding the stimulus, the 12 cycles during which the stimulus was delivered, and the 12 cycles following the stimulus. The 12 cycles in each sequence were averaged to obtain a block factor with three levels (pre-, during, and poststimulus). The resulting values were then averaged over all the identical stimuli of the experimental phase (acquisition or test). The effect of a given stimulus was evaluated by comparing the level during stimulus with the averaged pre- and poststimulus levels.

The data analysis had two purposes. The first was to assess conditioning by comparing, in the test phase, the effect of the auditory stimulus in experimental and control subjects. This difference between the two groups is statistically assessed by a significant interaction between the group and block factors. These planned comparisons were carried out by separate mixed analyses of variance for T_T and V_T, with group as the between-subject factor and phase and block as within-subject factors. The second purpose was to compare the pattern of the conditioned and unconditioned responses. This comparison was based on the latency of the response, estimated by the number of breathing cycles between the onset of the stimulus and the peak value of the response.

RESULTS

The baseline data are presented in Table 1. The slightly higher minute ventilation than that observed in comparable conditions [8–10 l/min (14, 15)] apparently reflects the stress caused by the expectation of the hypoxic stimuli that none of the subjects had experienced before. There was no significant difference between groups for the baseline values. Homogeneity of groups was therefore assumed for the remaining analyses.

Evidence for conditioning was unambiguously provided by the comparison between control and experimental groups in the test phase. Figure 1 clearly indicates different patterns of T_T response to the auditory stimulus for the two groups. In the experimental group, T_T values were significantly higher during the stimulus

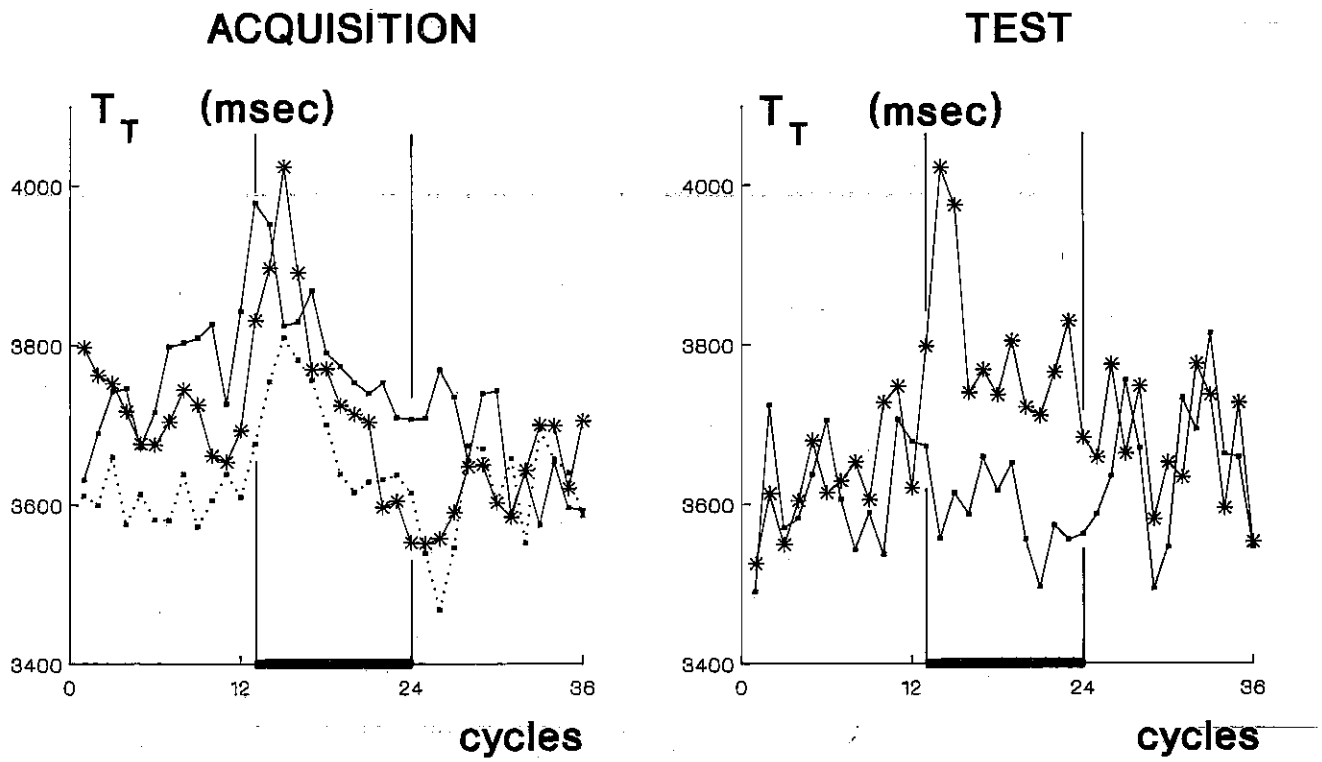

FIG. 1. TT before, during, and after stimulation. Period of stimulation is indicated by heavy line on cycle axis. Values are averaged over all stimuli of corresponding experimental phase. *–*, Experimental group (simultaneous auditory and hypoxic stimuli); ■–■, control group auditory stimuli; ■· · ·■, control group hypoxic stimuli.

[$F(1,16) = 5.82$, $P < 0.03$]. Conversely, in the control group, no significant change was elicited by the same stimuli delivered in identical conditions. This difference in TT between experimental and control groups was demonstrated by a reliable group-by-block interaction [$F(1,32) = 5.69$, $P < 0.03$]. A difference between the two groups also appeared for VT (Fig. 2), but the corresponding interaction did not reach significance [$F(1,32) = 2.55$, $P = 0.12$ (NS)], showing that conditioning affected TT rather than VT. The minute ventilation was not significantly different between the two groups (Fig. 3). No differential effect of conditioning was observed for inspiratory and expiratory durations, which varied in a way similar to TT. The main observation is therefore a

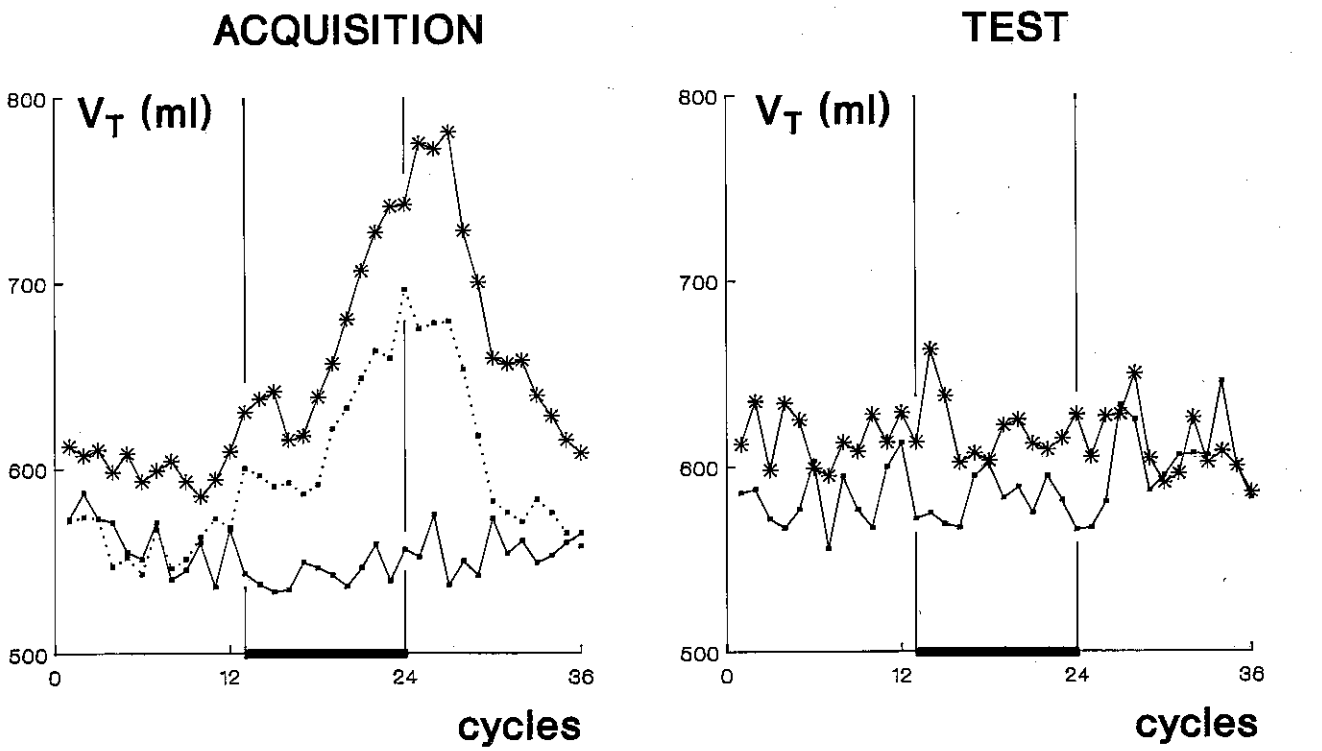

FIG. 2. VT before, during, and after stimulation. See legend of Fig. 1 for details and symbols.

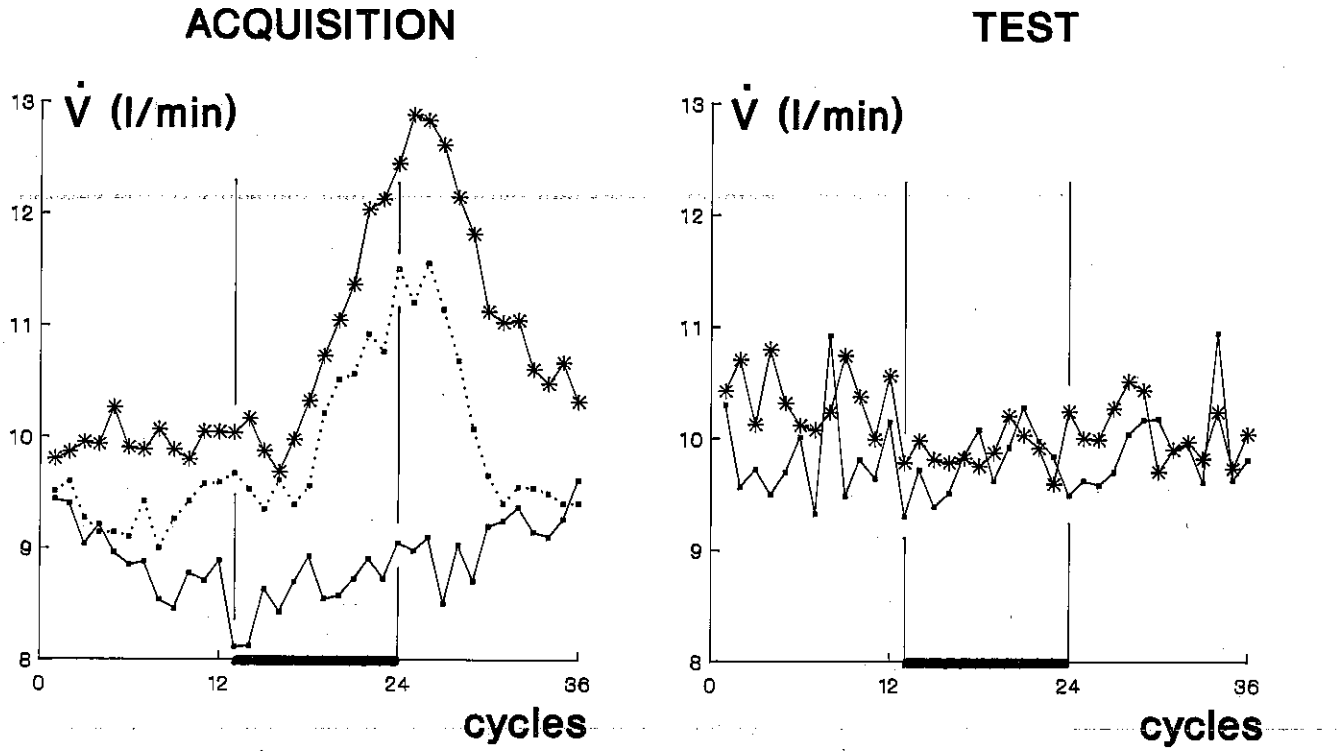

FIG. 3. Minute ventilation ($\dot{V}$) before, during, and after stimulation. See legend of Fig. 1 for details and symbols.

conditioned response, characterized principally by a significant increase in TT.

A finer description of the conditioned response called for preliminary analysis of the unconditioned responses to auditory and hypoxic stimuli. These responses were available in the control group in the acquisition phase, where both stimuli were presented separately. As shown in Fig. 1, the pattern of hypoxic and auditory responses displayed by the control group in the acquisition phase was markedly different: the peak TT of the auditory response (3,978 ± 751 ms) was immediate and corresponded to a significant increase compared with the prestimulus level [$F(1,16) = 11.82$, $P < 0.003$]. Conversely, the hypoxic response presented a delay, and its peak value, although marginally significant (3,825 ± 667 ms, $P < 0.061$), was only reached in the third stimulated cycle. In the experimental subjects, who were exposed in the acquisition phase to simultaneous auditory and hypoxic stimuli, the two effects were combined. The increase in TT appeared immediately, but the increase persisted until the third stimulated cycle [4,018 ± 1,040 ms, $F(1,16) = 13.09$, $P < 0.003$].

The first component of the conditioned TT response in the experimental group (Fig. 1, test phase) presented a similar feature for the unconditioned response in that this response did not immediately follow the stimulus. The peak value in TT appeared from the second stimulated cycle [4,023 ± 1,019 ms, $F(1,16) = 9.78$, $P < 0.006$], but no significant increase was observed in the first stimulated cycle [$F(1,16) = 4.07$, NS]. A comparable pattern between unconditioned and conditioned responses appeared for VT (Fig. 2), but the corresponding changes did not reach significance. On the other hand, the conditioned response did not display any decrease of TT below the baseline level (which might have corresponded to the increase of breathing frequency during hypoxia) or an increase in VT. This indicates that conditioning mainly concerned the first component of the hypoxic response, i.e., the initial increase in TT, rather than the second and main component, i.e., the decrease in TT associated with the increase in minute ventilation.

In the control group, the absence of any major effect of auditory stimuli in the test phase contrasted with the transient increase in TT elicited by this stimulus in the acquisition phase (Fig. 1). Complementary analyses of variance with trials as a within-subject factor did not show any significant decrease in the TT response in the acquisition phase, suggesting that the repeated exposure to auditory stimuli did not induce any habituation effects. However, the hypothesis of a gradual decay in amplitude of the ventilatory response to auditory stimuli could not be entirely ruled out on the basis of this negative result.

DISCUSSION

The present results provide evidence that an auditory stimulus that has been paired repeatedly with a hypoxic stimulus may acquire the ability to elicit a ventilatory response as a consequence of this pairing. This suggests that the ventilatory effects of auditory and presumably many other sensory stimuli may, at least partially, be the result of prior conditioning. Given the generality of conditioning processes, especially in the cardiac field (11), this might not seem surprising; however, to our knowledge, clear experimental proof was lacking. However, conditioning mainly concerned the first component of the hypoxic TT response, i.e., the initial increase of this variable after one or two cycles. The conditioned response did not exhibit variations similar to the second

and main component of the hypoxic response, i.e., the increase of the minute ventilation. The finding that the different components of the hypoxic response were affected differently by conditioning is consistent with the hypothesis that their neurological control is also different. The present data suggest that the first component of the ventilatory response is conditioned first. Arguably, longer conditioning could induce a conditioned response resulting in a decrease in TT and a concomitant increase of minute ventilation. Further experiments are necessary to clarify this point.

It is worth noting that only eight trials were sufficient to obtain the conditioned response. Given that ventilatory stimuli are frequently associated with numerous sensory stimuli in everyday life, the findings provide some insights into the potential impact of conditioning in breathing and strengthen the assumptions made by several authors on this point. They also provide some support for the hypothesis implicit to many breathing therapies that breathing pattern can be changed through learning. The present results should also be borne in mind whenever ventilatory stimuli are used in experimental designs. Because these stimuli are inevitably associated with various uncontrolled ones, such as noise of apparatus, odor of inhaled mixtures, and many other visual and auditory cues related to the experimental environment, ventilatory response is likely to be conditioned over the time course of the experiment as the result of a process that is difficult if not impossible to control. In experimental research, there is a tendency to select subjects from among seasoned participants in control-of-breathing studies for practical reasons, to ensure rapid familiarization to the laboratory environment, and to limit the behavioral bias. Although this procedure may be justifiable in some cases, ventilatory behavior of these familiarized subjects could very well be affected by previous conditioning because of their past experience with laboratory conditions and manipulations. There may be a distinct advantage in conducting breathing experiments on subjects with no past experience of this kind.

One potential objection to this overall interpretation in terms of conditioning is that the experimental group response to auditory stimuli was no more than voluntary behavior. This concern is common to all conditioning experiments dealing with motor activities in conscious subjects, and as a general rule the volitional factor can never be completely ruled out. In general, subjects aware of the contingency between a conditioned and an unpleasant unconditioned stimulus might produce voluntary behavior to limit the negative effects of the unconditioned stimulus. In the present context, there are four separate sources of evidence to support the claim that volition was not an important factor. The first reason is that a voluntary response to the conditioned stimulus is necessarily based on the awareness of the contingency between the unconditioned and conditioned stimuli. Although it is almost impossible to cancel out all the causes of detection of a change in any inspired mixture, the present experiment was especially designed to limit the awareness of the onset of the ventilatory stimulus, and apparently this was partially successful. For this first experiment, hypoxia was preferred to hypercapnia because the taste of CO_2 is a strong marker of the presence of the unconditional stimulus; its use would require additional experimental precautions. Furthermore, the subjects wore soundproof headphones and were distracted with music. Informal interviews carried out after the session showed that all subjects had felt some dyspnea and had increased their ventilation at certain moments of the session, in accordance with the information they received at the beginning of the session, but most were unable to specify the timing of the hypoxic stimulus. Although introspective reports must be interpreted with caution in any kind of experiment, it is reasonable to assume here that the subjects were not in a position to detect the exact time of onset of the stimulus and hence its contiguity with the auditory signal. The second reason is related to the direction of the conditioned change in TT. As seen above, the conditioned response was mainly an increase in TT, with no significant change in minute ventilation. Had the subjects attempted to voluntarily anticipate the stimulus to limit the unpleasant effects of hypoxia, they would have increased the minute ventilation at the onset of the auditory stimulus by decreasing TT, increasing VT, or both. If subjects were acting voluntarily, the purpose of increasing TT would be hard to understand. The third reason is based on the timing of the conditioned response. It is logical to expect a voluntary response to occur immediately after the onset of the stimulus and not after the subjects had counted two cycles or waited a set period of time. Actually, the conditioned response presented a delay of one or two cycles, very similar to the delay of the unconditioned response to hypoxia. The fourth and last reason is related to the order of magnitude of the conditioned increase in TT (a fraction of a second for most subjects), a feat of which few untrained subjects are capable (14, 15). All these reasons argue strongly for the assumption that responses were genuine involuntary conditioned behaviors.

Conditioned changes in ventilatory response to auditory stimuli, as for all conditioned responses, can be interpreted in a variety of ways (20, 24). On the one hand, the auditory stimulus may have become a substitute for the hypoxic stimulus as a result of their prior pairing. If so, the new response elicited by the auditory stimuli would resemble the hypoxic response in some way. On the other hand, a conditioned response could reflect pairing-specific increments in a preexisting response to the auditory stimuli. This process, often depicted as pairing-specific sensitization (21), may lead to a conditioned response similar to the initial response to auditory stimuli. The analysis below of hypoxic and auditory responses and their subsequent comparison with the conditioned response examines the explanatory power of each of these alternatives.

As recently pointed out (6), upward and downward steps of hypoxia have been used for several decades to detect the contribution of arterial chemoreceptors in exercise, but it is only fairly recently that this stimulus has been used in comprehensive studies of the dynamics of the hypoxic response (2, 10). Comparison between studies is hindered by the diversity of the stimuli employed and by differences in observational foci. The stimulus used here, which is not a standard one, is not adapted to a

quantitative stimulus-response analysis. However, it made it possible to obtain some observations that are consistent with previous studies more specifically oriented toward this type of analysis. The hypoxic response observed here was twofold: first, a brief lengthening of TT and, second, a decrease in TT with a concomitant increase in VT leading to the increase in minute ventilation characterizing most of the response. Inspiratory and expiratory variations paralleled those of TT. A similar dynamic pattern has been observed in another situation using a hypoxic stimulus (17), where it was suggested that the initial increase of the duration of inspiration might be a dynamic feature of the control system whatever the nature and the site of action of the stimulus. Nevertheless, individual differences appeared in the pattern of hypoxic response, and the characteristics of the average dynamic response to hypoxia depicted here may not correspond to all the individual patterns.

Our data provide suggestive evidence that the ventilatory response to auditory stimuli is highly context dependent. Besides the fact discussed throughout this paper that these stimuli may acquire a significance and elicit a conditioned response, subjects' responsiveness may depend to a greater extent on the occurrence of prior different stimuli. This is suggested by the finding that the control group responded differently to the auditory stimuli in the two phases of the experiment. When auditory stimuli alternated with hypoxia (in the acquisition phase), they elicited an immediate increase in TT and a concomitant but nonsignificant increase in VT. Conversely, no change was observed when auditory stimuli were presented alone (in the test phase). A habituation process gradually leading to the complete extinction of the ventilatory response might explain the observed data, but this was not statistically supported (no decreasing trend across successive stimulations was observed). A plausible assumption is that the temporal proximity between the hypoxic and auditory stimuli potentiated the ventilatory response to the latter. This effect logically disappeared when the hypoxic stimuli were no longer presented in the test phase. It is likely that the tones of the kind used here did not elicit any response by themselves, as a recent study has suggested (25). These observations point to the major influence of situational factors and past experience in ventilatory responses to sensory stimuli and make it difficult to define the ventilatory response to a given sensory stimulus in general terms. That is possibly one of the causes of the conflicting results in this area of research (16).

The comparison between the conditioned and the unconditioned responses led to interesting observations. The conditioned response displayed by the experimental group was a partial replication of the hypoxic response, because only the first component of the response, the initial increase of TT and seemingly of VT, was actually elicited by the conditioned stimulus. However, the latency and the amplitude of this first component were similar to the first component of the hypoxic response. This strengthens the hypothesis for substitution of the hypoxic stimulus by the auditory stimulus. Conversely, the latency of the conditioned response differed clearly from that of the response to the auditory stimulus. This finding reduces the explanatory power of the pairing-specific sensitization hypothesis in the present context. However, this issue must be confirmed by further investigations, in particular by carrying out experiments using various ventilatory and conditioned stimuli.

The present findings provide further evidence that breathing is not only a reactive system governed by feedback mechanisms but also a feedforward control system self-organized on the basis of available information. Breathing pattern is not only adjusted to fulfill metabolic needs but also varies in accordance with impending changes in metabolic needs through cortical and other forebrain structures about which we know little (12). The changes in breathing observed here after a short period of conditioning provide a limited picture of the ventilatory conditioned changes that might occur in natural conditions and, more generally, the multiple conditioned vegetative responses that considerably enhance the adaptability of organisms to varying environmental conditions.

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