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CAROTID BARORECEPTOR REFLEX IN MAN, ITS MODULATION OVER THE RESPIRATORY CYCLE

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Abstract. Carotid baroreceptors were stimulated in 40 healthy volunteers by a rapid increase of the carotid transmural pressure due to subatmospheric pressure applied to a tight neck chamber (neck suction). Heart rate, arterial blood pressure and respiratory response were recorded. Reflex vagal inhibition of the sinus node preceded a blood pressure fall. Cardiac response adapted in a few seconds during prolonged baroreceptor stimulation, whereas reflex hypotension was maintained over the whole stimulation period applied up to 30 s. Augmented inspiratory movements were observed during neck suction. Short-lasting baroreceptor stimuli produced much less cardiac inhibition if applied during the early inspiratory than during the expiratory phase. On the peak and on the plateau of the voluntarily sustained deep inspirations, a spontaneous sinus bradycardia and a facilitation of the baroreceptor-cardiac reflex appeared. Voluntarily delayed expiration following deep and sustained inspiration coincided with cardioacceleration and baroreflex inhibition. Thus voluntarily imposed breathing patterns may reverse both respiratory sinus arrhythmia and cyclical modulation of the baroreflex responsiveness over the respiratory cycle.

INTRODUCTION

The discovery of central and reflex interaction between respiratory control systems and sympatho-vagal control of the circulation originates from the classical works of Adrian, Bronk and Phillips (1932) and Anrep

et al. (1936). A growing interest in this problem nowdays reflects the general trend to analyze complex interactions between functional systems of the body and is additionally stimulated by the understanding that central neuronal mechanisms may be common or closely related in both respiratory and circulatory control systems. It seems to be true in regard to common central chemical drive of the respiration and the central origin of spontaneous sympathetic activity (29, 31). New developments in this field have been summarized in a recent international symposium (17).

Inspiratory-expiratory cyclical modulation of the carotid baroreceptor-cardiac reflex (CBCR) was discovered in dogs in 1961 (17). Baroreceptor induced reflex vagal bradycardia is completely inhibited or reduced during inspiration in dogs (8, 23) and in cats (24).

Still, very little is known of the validity of these and other experimental findings in humans. Paucity of non-invasive, dynamic, and reliable methods applicable to man is the main reason.

Recently, a non-invasive method of quantitative and controlled stimulation of the carotid baroreceptors in man has been developed (12). The procedure consists in the technical improvement of an earlier original technique (14) applying the principle of physiological stimulation of the baroreceptors with a rapid, controlled increase of the transmural pressure in the carotid sinuses. Transmural pressure is suddenly elevated by the application of subatmospheric pressure around the neck (4, 20) or around the head and the neck within a tight plastic box (5).

The purpose of the present paper was to check if the respiratory modulation of the carotid baroreflex observed in dogs (8, 18) and in cats (24) also occurs in man. Furthermore, we tried to find out if voluntary changes of breathing patterns could influence CBCR sensitivity. This kind of experiment was impossible to carry out on animals. Our results convinced us that man may in some respects provide us with more information on specific mechanisms of central interaction between respiratory and circulatory control systems than anesthetized experimental animals. Preliminary results of our experiments have been published before (17, 26, 31).

METHODS

Experiments were carried out on 40 healthy volunteers, 35 men and 5 women, 19–25 years old in a resting supine position. We tried to adapt the subjects to the experimental procedure. Therefore in many cases the recordings were repeated on several occasions in order to avoid emotional tension which greatly influences baroreflex sensitivity

(6). Stimulation of the carotid baroreceptors (CB) was produced with a method similiar to that used by Eckberg et al. (12) with the exception of some minor modification in the construction of the neck chamber (Fig. 1). Subatmospheric pressure is transmitted unchanged (9) or with some linear and reproducible reduction (20) through the neck tissues to the external wall of the carotid arteries and sinues. The resulting sudden rise of the transmural carotid pressure and, consequently, carotid sinus

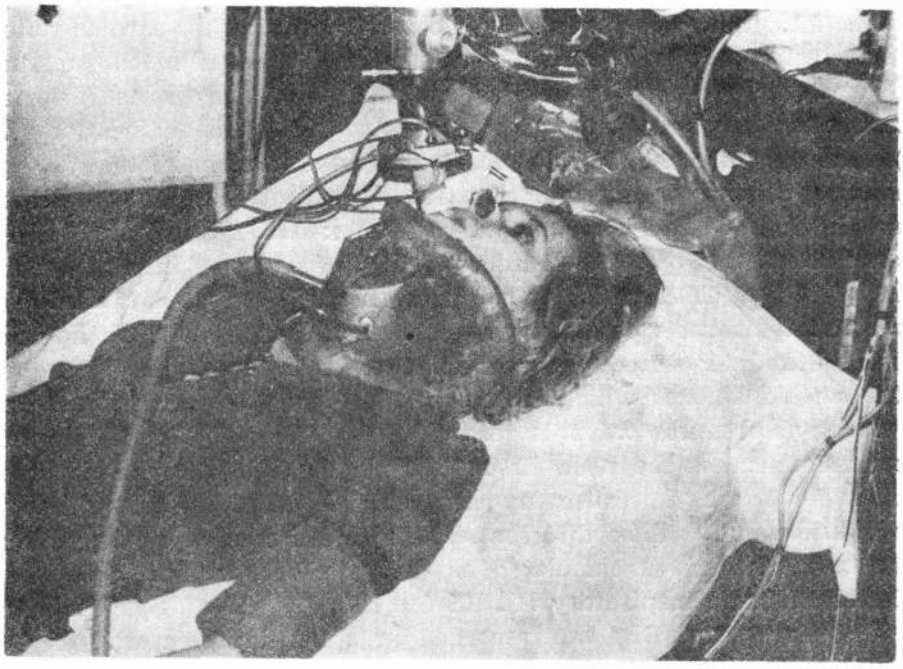

Fig. 1. Experimental step-up for the study of the carotid baroreceptor reflex. Tight neck chamber connected with vacuum source. Mouthpiece for end-tidal CO_2 and tidal volume registrations used also for sudden closing of air inflow before anticipated inspiration.

distension is the most natural stimulus for the carotid baroreceptors. Sudden neck suction was begun when rotation of a solenoid valve established continuity between the neck chamber and the vacuum source. Stimuli were initiated automatically by electronic triggering of the rotation of the valve with a constant 0.7 s delay prior to the anticipated *P* wave of the ECG which is the moment of the cardiac cycle when the responsiveness of the carotid baroreceptor-cardiac reflex (CBCR) is highest (9). Neck suction could also be initiated automatically with a controlled delay after the onset of inspiration which was recorded, as chest expansion, by a strain-gauge attached to a belt fixed

around the chest (Fig. 1). Thus the onset of baroreceptor stimulation was timed and adjusted to the desired phase of the respiratory cycle. Intensity of the stimulation varied in the range between 20 and 40 mmHg subatmospheric pressure in different experiments and depended on individual responsiveness to carotid baroreceptor stimulation. Various intensities of stimulation were tested at the beginning of the experiment and the selected one was of suprathreshold intensity producing clear cut and reproducible heart rate and blood pressure response. Brief, 1–2 s neck suction stimuli were applied for carotid baroreceptor-cardiac reflex (CBCR) testing. Longer, 10–30 s stimuli were used if blood pressure and respiratory responses were also examined. ECG and the heart period were continuously recorded as instantaneous, beat-by-beat, R-R interval (HI). The time corresponding to successive HI was converted to a voltage signal proportional to interval duration. Sensitivity of the CBCR was measured as the open loop gain of the reflex $\Delta HI/\Delta P_n$, where ΔHI — reflex prolongation of the R-R interval, ΔP_n — subatmospheric pressure applied to the neck chamber. It has been assumed that the transmission of the subatmospheric pressure wave across the soft tissues of the neck is ideal (9) and ΔP_n is equal to the increase of the transmural pressure in the carotid sinuses which is equal to the baroreceptor stimulus. If the negative pressure wave is reduced in a linear fashion during its transmission across the neck tissues (20), it signifies a systemic error which however will not cause any change of the calculated gain although its absolute value will be different. Magnitude of the respiratory sinus arrhythmia (RSA) was calculated as the maximal difference between expiratory HI and inspiratory HI. $RSA = HI_{exp} - HI_{insp}$. Systolic arterial blood pressure (BP) was recorded in a non-invasive way as the pressure in the arm cuff automatically adjusted to the level set by the first Korotkoff sound by an electronic feed-back system operated through a microphone built into the arm cuff. The transformed microphone signal triggered the opening of a valve which connected a pressure reservoir with the arm cuff. A Statham pressure transducer and a "Farum" electromanometer were used for all pressure measurements. In some experiments tidal volume was measured by a spirograph and endtidal CO_2 content by an infrared Beckman gas analyzer. All data were recorded by six channel polygraph (Warsaw Technical University).

RESULTS

Heart rate, blood pressure and respiratory responses to carotid baroreceptor (CB) stimulation. After a short latency a prolongation of the R-R interval appears, beginning with the next cardiac cycle following

the onset of neck suction (Fig. 2). Reflex prolongation of the heart period is entirely due to sinus node inhibition as no P-Q interval prolongation, atrioventricular block or extrasystoles were observed. Thus the R–R interval is a reliable index of the heart period during CB stimulation. A fast adaptation of the cardiac response was observed with prolonged neck suction (Fig. 2), yet the heart rate never reached control

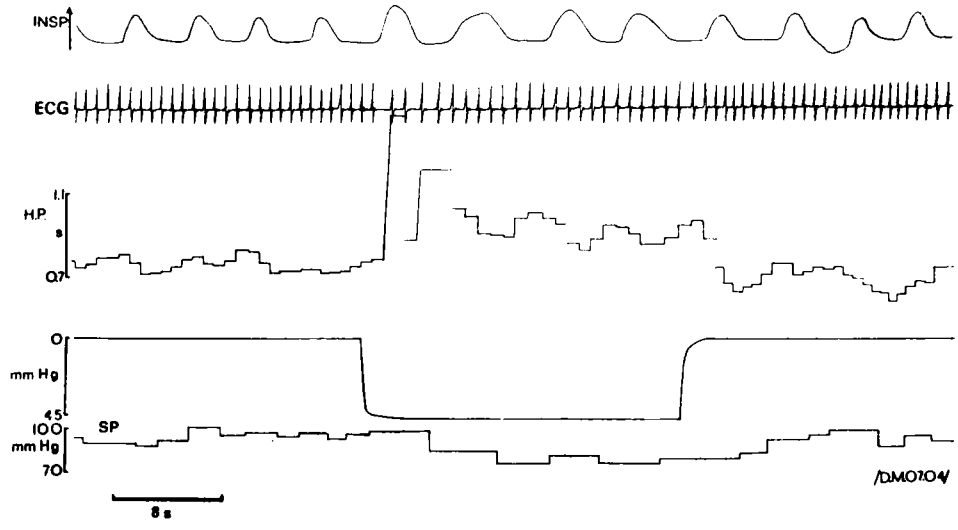

Fig. 2. Carotid baroreflex in man. Traces from the top downwards: inspiratory increase of the chest dimension recorded by a strain gauge, ECG, instantaneous, beat-by-beat heart period (R-R interval), pressure in the neck chamber, systolic arterial blood pressure recorded in the armcuff. Onset of the rapid subatmospheric pressure applied to the neck chamber is followed by a prompt sinus bardycardia and by a delayed drop of the arterial blood pressure. Augmented amplitude of the inspiratory chest movements and enhanced respiratory sinus arrhythmia occur over the period of the carotid baroreceptor stimulation.

values, even during CB stimulation lasting 30 s, provided the intensity of the stimulus was high enough to produce a significant sinus node inhibition.

The onset of the blood pressure fall is delayed for 4–6 s after cardiac response (Fig. 2). Unlike the quick adaptation of the CBCR, reduced BP was maintained for the whole period of CB stimulation, up to 30 s on some occasions.

The magnitude of RSA is significantly increased during CB stimulation (Fig. 2). This effect is due to the prolongation of the heart period in the expiratory phase (HI_{exp}) rather than to the shortening of HI_{insp} (Fig. 2).

In 12 subjects an increase of the amplitude of the respiratory chest movements was recorded during neck suction (Fig. 2). This effect disappeared immediately at the cessation of suction. Emotional factors apparently do not account for this effect, as the subjects were well adapted to the experimental procedure, some of them were staff members of the Department. CB stimulations repeated on different occasions in the same subjects always produced the same kind of respiratory response.

Rhythmical variations of the carotid baroreceptor-cardiac reflex (CBCR) sensitivity during spontaneous breathing. Brief, 1–2 s neck suction produces significantly less cardiac inhibition if applied at the beginning of inspiration than during the expiratory phase (Fig. 3).

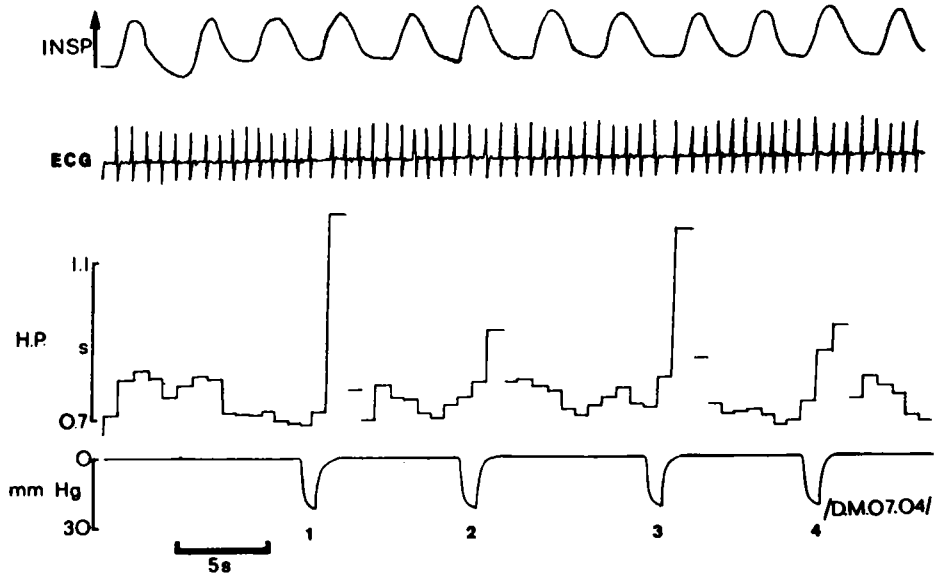

Fig. 3. Respiratory modulation of the carotid baroreceptor-cardiac reflex in man. Brief neck suction applied alternatively in the expiratory phase (1 and 3) and during inspiration (2 and 4). Much less reflex cardiac inhibition during inspiration than in the expiratory phase. Records as in Fig. 2.

The effect cannot be simply explained by spontaneous cardioacceleration occurring usually during inspiration (RSA), because the calculated gain of the reflex $\Delta HI/\Delta P_n$ is also significantly reduced if the baroreceptor stimulus is applied during inspiration.

Very strong, near maximal, over –40 mmHg stimuli tend to minimize the inspiratory-expiratory difference in the CBCR sensitivity. In order to demonstrate the inspiratory-expiratory cycling of CBCR small or

moderate stimuli, in the range of –20 mmHg, are the most suitable. By a proper adjustment of intensity, no CBCR may be provoked during inspiration, whereas during the expiratory phase a marked reflex response appears. Thus weak CBCR may be entirely inhibited by inspiration and manifests itself only during the expiratory phase.

Inhibition of the CBCR by inspiration performed against infinite airway resistance. It has been demonstrated in acute experiments on dogs that lung inflation inhibits CBCR (15) and produces a cardioacceleratory response (2, 3). Therefore, separate experiments were performed in order to check if lung inflation is responsible for the observed inspiratory inhibition of CBCR in man.

The volunteers were breathing through a mouthpiece with the nose occluded by clips. Just before the anticipated inspiration the air inflow was suddenly blocked for one inspiration in such a way that the subject was not aware of the start of the procedure. Simultaneously a brief neck suction was applied at the beginning of the inspiration. Inspiratory CBCR inhibition still occurred although inspiration was performed without any significant lung inflation and chest volume expansion (Fig. 4).

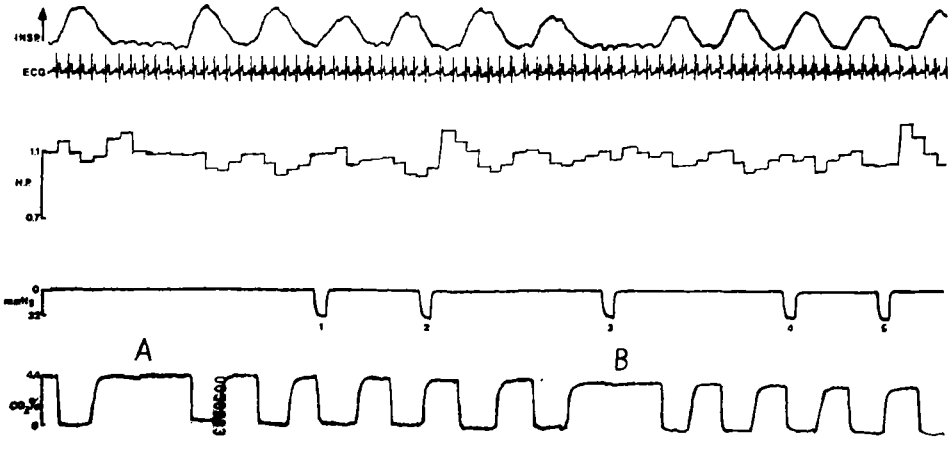

Fig. 4. Inspiratory inhibition of the carotid baroreceptor-cardiac reflex in the absence of any significant lung inflation and chest distension. Traces from the top downwards: inspiratory chest movements, ECG, beat-by-beat R-R interval, pressure in the neck chamber, end-tidal CO_2 content. In *A* air inflow was rapidly blocked just before inspiration. Marked reduction of the amplitude of respiratory sinus arrhythmia appears consequently to decreased inspiratory cardioacceleration. In *B* brief baroreceptor stimulus (3) was applied during inspiration performed against occluded airways. Baroreceptor cardiac reflex is inhibited as it is during free inspiration (1 and 4). 2 and 5 — neck suction applied during expiratory phase followed by clear reflex cardiac inhibition.

Amplitude of a single RSA wave was reduced, although RSA was not entirely abolished by inspiration against an occluded air inflow (Fig. 4).

Modulation of the CBCR sensitivity by voluntarily imposed breathing patterns. The subjects were trained to reduce voluntarily the rate of rise of their inspiratory movements while maintaining an unchanged expiratory phase. In another procedure they were requested to sustain a deep inspiration and to delay expiration for several seconds. During these procedures they markedly exceeded their resting tidal volume.

CB stimulation applied during the slow rise of voluntary inspiration produces much more sinus node inhibition than the same stimulus applied during faster, voluntary inspiration (Fig. 5). There is a striking increase

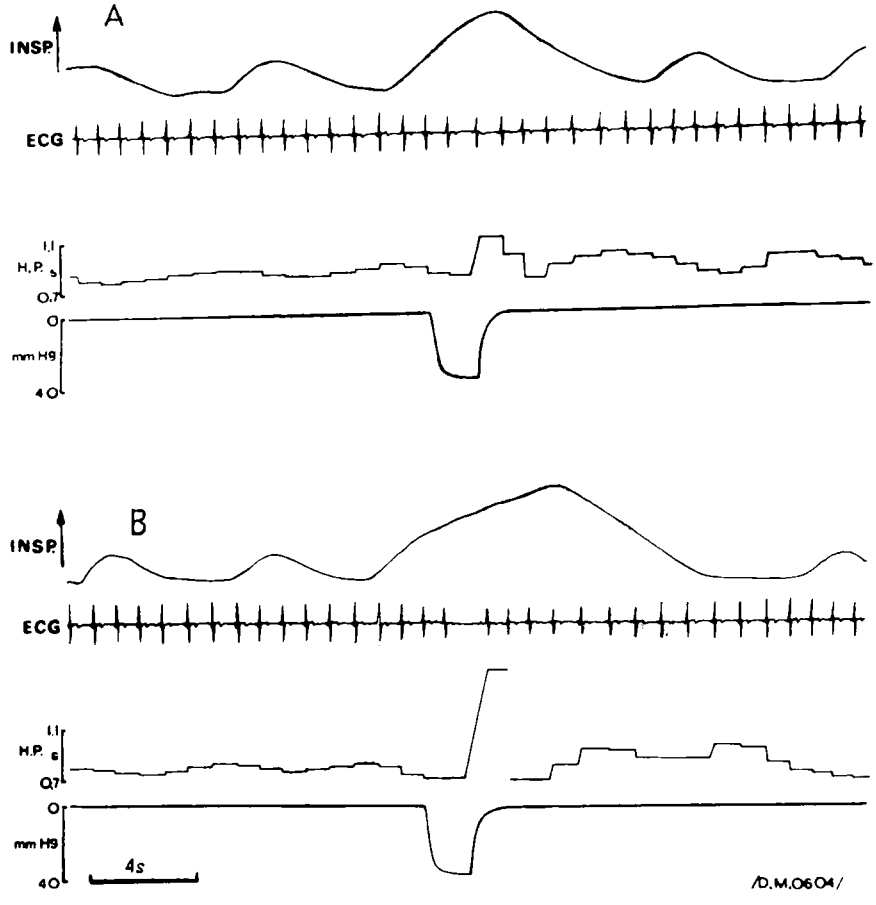

Fig. 5. Increased sensitivity of the carotid baroreceptor-cardiac reflex provoked by neck suction applied during voluntary, slow rising ramplike inspiration (B) as compared to the reflex provoked during voluntary fast rising inspiration (A). Recordings as in Fig. 2.

of the CBCR sensitivity at the peak and on the plateau of voluntarily sustained inspiration (Fig. 6). Increased CBCR responsiveness coincides with a merked sinus bradycardia observed at the top of sustained inspiration. CBCR provoked during sustained deep inspiration does not differ from the response to CB stimuli applied during spontaneous, natural expiration. Conversely, voluntarily delayed expiration produces marked cardioacceleration (Fig. 6) and CBCR inhibition. Thus volunta-

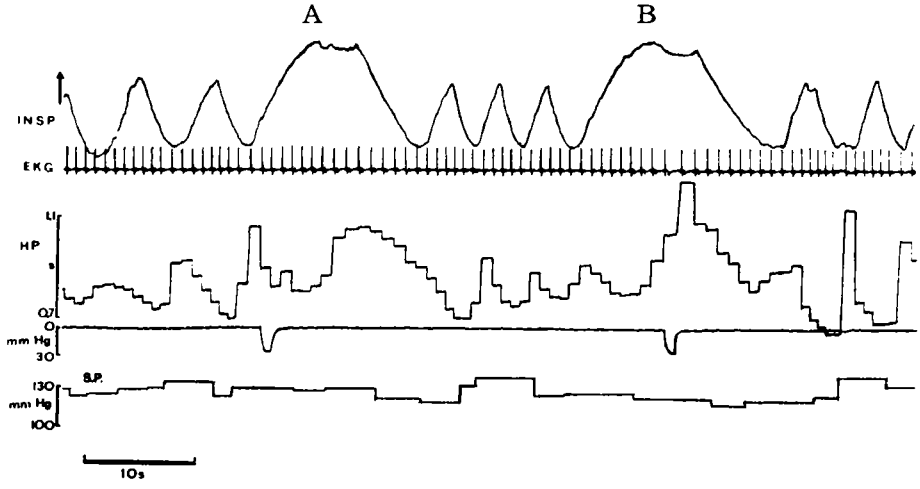

Fig. 6. Effect of the sustained voluntary inspiration *A* and *B* on the responsiveness to carotid baroreceptor stimulation. 1, neck suction applied during the dynamic, rising phase of the voluntary inspiration A produces no response; 2, the same stimulus applied on the plateau of the voluntary inspiration *B* produces strong cardiac inhibition. Parodoxical cardioacceleration occurs during delayed expiratory phase in *A* and *B*. Records as in Fig. 2.

rily imposed breathing patterns reverse a spontaneous pattern of respiratory sinus arrhythmia and respiratory CBCR modulation: the usual inspiratory cardioacceleration and CBCR inhibition with following expiratory bradycardia and CBCR facilitation is changed into the pattern of peak inspiratory bradycardia with CBCR facilitation followed by expiratory tachycardia and CBCR inhibition.

DISCUSSION

Inhibitory cardiac response to CB stimulation in man is purely vagal (11), which may explain its short latency. Latency and the time constant of the cardiac response to efferent vagal stimulation is several times shorter than the opposite response to sympathetic stimulation (25). It should be considered that reflex blood pressure fall is delayed for a few seconds after cardiac inhibitory response (see also 4). This obser-

vation suggests that the depressor reflex following CB stimulation is possibly due to sympathetic inhibition and to a decrease of the peripheral vascular resistance rather than to the reduced cardiac output which may result from vagal bradycardia.

Differences of time sequence of the cardiac and blood pressure responses provide a useful technical advantage for the measurement of the gain of CBCR. Increased transmural pressure in the carotid arteries, produced by neck suction, is not reduced by a fall of systemic blood pressure for a few seconds following the onset of CB stimulus. Therefore for the first few seconds CBCR may be analyzed as an open-loop system. Subsequently a reflex fall of the arterial blood pressure will decrease carotid transmural pressure, thus reducing CB stimulus despite an unchanged subatmospheric pressure in the neck chamber. Consequently, after a few seconds the open-loop system is transformed into a closed-loop system with other aortic and cardiac baroreceptor reflexes counteracting the original reflex response. The secondary decrease of the CB stimulus with prolonged neck suction may be one of the causes of the rapid reduction of CBCR during a prolonged neck suction of unchanged intensity (Fig. 1). However, actual adaptation of the human CBCR (10) seems to be the main factor. High dynamic sensitivity of the baroreceptors to the rate of change of the stimulus and their low sensitivity to prolonged static stimuli is a well known phenomenon, also in man (10).

The increase of ventilation observed in some subjects during neck suction deserves particular attention. The effect cannot be explained by an increased baroreceptor input, as there is convincing experimental evidence that arterial baroreceptor stimulation inhibits inspiration and extends the expiratory phase (27). Therefore this unexpected respiratory response has to be related to some other receptors stimulated by the experimental procedure. All volunteers report a subjective feeling of "swelling of the neck". Perhaps distension and distorsion of neck tissues excites skin mechanoreceptors or even laryngeal or tracheal mechanoreceptors. Further investigation is needed to solve this problem. Whatever the reason, our finding casts some doubt on the specifity of the neck suction procedure as an exclusive stimulation technique for the carotid baroreceptors.

Augmentation of the respiratory movements may also be an explanation for the more marked RSA observed during neck suction. However, this is not the most important cause because an increased magnitude of RSA also occurs in subjects who do not demonstrate any clear hyperpnoe during neck suction. There is a linear relation of the RSA magnitude to the existing cardio-vagal tone in man (16). Thus barore-

ceptor stimulation and consequently a reflex rise of the vagal tone may facilitate RSA.

Inhibition of the CBCR in man during spontaneous inspiration and facilitation during the expiratory phase is in complete agreement with experimental data gathered from anesthetized animals (8, 18, 23). Similiar findings in man, parallel to our preliminary earlier reports (26, 30), were made by Eckberg and Orshan (13). Our present results go beyond these original observations and provide some indirect experimental evidence that inspiratory inhibition of CBCR is, at least in part, of central origin. This conclusion is supported by our finding that CBCR inhibition still occurs during inspiration performed without any significant lung inflation and chest volume expansion. However, before a definitive conclusion is made a further research still has to be done on the possible contribution of intrathoracic low pressure cardiopulmonary baroreceptors, which have been known to influence cardiovagal tone and RSA in man (22).

Central postsynaptic inhibition of the cardio-vagal motoneurons in the nucleus ambiguus of the cat during an inspiratory burst has been described recently (21). We have found that under conditions of rebreathing and increased chemical drive of respiration in conscious man, RSA is markedly increased despite the lack of any increase of tidal volume which was voluntarily kept constant (28). Our present results suggest that even in normoxic and normocapnic conditions, prevention of lung inflation for a period of a single breath significantly reduces, but does not entirely abolish RSA. However, the procedure adopted by us provokes a prolonged and stronger inspiratory drive as the airway resistance becomes infinitely high. One can assume, therefore, that central inspiratory inhibition of the cardio-vagal tone and of CBCR will be enhanced. On the other hand, such an experimental situation seems to have some advantage for research aimed at the analysis of central interaction between respiratory and circulatory control systems in man, as it exaggerates the existing central inspiratory inhibition of the CBCR.

By considering the effects of voluntarily imposed breathing patterns on CBCR sensitivity and on RSA one should recognize that the two main mechanisms which influence cardio-vagal tone — CBCR pulmonary mechanoreceptor reflex (15) and direct central interaction (21) — may be dissociated one from another by voluntary control of chest movements.

Moderate lung inflation produces a reflex cardioacceleration (2, 3), a decrease of the efferent cardio-motor vagal activity (15) and CBCR inhibition (15). The inhibitory effect is greater the faster the lung inflates (15). This may be an explanation of our observation that during slow, ramplike voluntary inspirations, baroreceptor stimuli provoke

more sinus node slowing than during the fast rising inspiration. Lung stretch receptors are apparently responsible for the reflex inhibition of the CBCR in dogs (15). Inspiratory Rβ neurons may possibly mediate in the mechanism of inhibition of the cardio-motor vagal neurons by lung inflation (19). However, a contribution of irritant receptors cannot be excluded (15). Excessive lung inflation produces an opposite response, a bradycardia, in acute experiments in dogs (2, 3). Recruitment of other, perhaps irritant, receptors could be an explanation for the observed decreased heart rate and facilitation of CBCR on the peak and on the plateau of voluntarily sustained deep inspiration in man (Fig. 6). Interaction between upper airway irritant receptor reflexes and the baroreceptor reflex has not been systematically studied so far. However, it has been demonstrated recently that there exists a strong positive interaction between upper airway irritant receptor reflexes and the arterial chemoreceptor cardio-vagal reflex, up to the point of cardiac arrest (7).

During vigorous deep expiration an activation of the irritant or deflation receptors could be expected. This hypothesis, however, does not hold because a tachycardia instead of the expected bradycardia was observed during strong, delayed expiration following deep, sustained inspiration (Fig. 6).

Discrepancies between our observations and expected effects of lung mechanoreceptor stimulation may be overcome by the assumption that during voluntarily imposed arbitrary breathing patterns two different and opposite, out-of-phase inputs converge and compete on the same cardiomotor vagal preganglionic neurons. One of them is the reflex input from the pulmonary mechanoreceptors (with a possible input from the cardio-pulmonary baroreceptors) and another — a central input from the brain stem oscillator. We assume that voluntarily sustained inspiration in man does not mean that brain stem inspiratory neurons are firing for the whole period and continously inhibiting cardio-motor vagal neurons. If the respiratory brain stem oscillator switches over to expiration despite voluntarily sustained inspiratory breath-holding, this effect will result in spontaneous bradycardia and in facilitation of CBCR. This is just what we have observed on the peak and plateau of voluntarily sustained inspiration. Our explanation implies that voluntary control of breathing in man somehow bypasses the brain stem respiratory oscillator. Consequently, the two systems, voluntary and automatic, may function independently and out-of phase. In order to test this hypothesis a separate set of experiments has to be carried out.

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