

## CARDIORESPIRATORY INTERACTIONS TO EXTERNAL STIMULI

L. BERNARDI, C. PORTA, L. SPICUZZA<sup>1</sup> AND P. SLEIGHT<sup>2</sup>

*Dipartimento di Medicina Interna, IRCCS "S. Matteo" and University of Pavia, Italy; <sup>1</sup>Institute of Respiratory Diseases, University of Catania, Italy; <sup>2</sup>Department of Cardiovascular Medicine, "John Radcliffe" Hospital, Oxford, UK*

### INTRODUCTION

The recently published INTERHEART study (21) has underlined that psychosocial factors are responsible for around 30% of the population attributable risk for myocardial infarction in almost all populations. Distinct effects of stress are apparent even on a small time scale (seconds-minutes).

These effects are mediated mostly by the autonomic nervous system in order to achieve appropriate matching for changes in peripheral demand. It is well recognized that the disparate patterns of increased heart rate, myocardial contractility, cardiac output, arterial pressure and appropriate peripheral blood flow distribution depend upon an autonomic control shifted towards sympathetic predominance in a dynamic interaction with humoral modifications. In addition to cardiovascular changes, respiratory function is also highly sensitive to changes in sympathetic activity and metabolic demands, via both central command and activation of chemoreflex mechanisms, that all are enhanced by increased sympathetic activity (23). All these factors contribute in different ways to the variability of heart rate and blood pressure. However, the task of the blood pressure control system is to maintain the blood-pressure constant between some boundaries; hence the system has to maintain an ability to respond continuously to changes in the cardiovascular state caused by psychological and environmental factors (17).

Nevertheless, extreme and/or prolonged sympathetic activation seems able to impair such control mechanisms, leading to permanent or exaggerated increases in blood pressure, that in turn can be responsible for the increase in cardiovascular accidents well documented in patients with arterial hypertension. Similarly, in heart failure, the exaggerated and prolonged sympathetic stimulation is responsible for an increased workload for the heart, in addition to degenerative responses in the heart and blood vessels, and an exaggerated ventilatory response, that together contribute to a further worsening of pump function and exercise tolerance (11).

The cardiovascular and respiratory responses to external stimuli may be an important means to test individual cardiovascular reactivity, and to identify subjects at risk of hypertension. A better knowledge of these integrated responses could be also used

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Correspondence to: Prof. L. Bernardi, Clinica Medica 2, IRCCS "S. Matteo" and Università di Pavia, 27100 Pavia, Italy; Tel. +39 0382 502979, Fax: +39 0382 529196, E-mail: lbern1ps@unipv.it

to reverse the response to potentially stressful stimuli, and be a potentially clinically useful tool. In this respect, we have tested the cardiovascular and respiratory modifications induced by a number of external stimuli, and have found that appropriate modification of the respiratory pattern can in fact induce changes that appear to have useful clinical application in different diseases.

## RESULTS

### *Interaction between verbalisation, mental stress, breathing pattern and cardiovascular variability*

We investigated whether talking or reading (silently or aloud, which greatly changes the respiratory pattern), could affect cardiovascular variables, and to what extent this voluntary activity could modify sympathetic modulation (7), either by itself, or by the effect of associated mental stress. We measured heart rate variability (HRV), respiration and blood pressure in a group of healthy subjects, during controlled breathing (i.e. absence of verbal respiratory changes and stressful mental activity), reading aloud, reading silently, and mental arithmetic (silently and aloud), in order to ascertain the interaction between changes in respiratory pattern, mental arousal, verbalisation and HRV. We studied controlled breathing in order to eliminate the possibility that occasional slower or faster breaths could superimpose new cardiovascular fluctuations on the spontaneous cardiovascular rhythms. Since reading aloud would clearly impose a different respiratory pattern from normal breathing we compared this with reading silently. Since reading might be regarded as a mild arousal, and since arousal is known to depress the gain of the baroreflex control of the sinus node (12) we also studied the effect of definite stress, by performing mental arithmetic both silently and aloud. During activities such as reading and mental arithmetic, either aloud or silent, the respiratory changes produced by speech markedly alter the cardiovascular rhythms, as a result of the change in respiratory pattern necessarily imposed by speech (7). There is clearly a complex interplay between mental activities with and without speech and various degrees of stress, and the respiratory pattern. These factors in turn alter HRV in two directions:

- a) Mental activity appears invariably associated with some degree of sympathetic activation, whose degree depends upon the amount of stress involved in performing the mental task. In agreement with previous reports (14) we found that these manoeuvres caused different levels of sympathetic activation, as could be seen by the decrease in RR interval, increase in BP, and decrease in heart rate variability. This however was clearly evident only for those conditions which did not interfere with the breathing pattern.
- b) The slowing of breathing observed with verbalisation during mental stress had the invariable effect of amplifying the slow (0.1 Hz) spontaneous fluctuations (LF) in heart rate and blood pressure, regardless of the amount of stress involved in the mental task performed. This was evident by the similarity in RR interval spectra

seen during simple free talking, reading aloud and mental arithmetic, all showing a marked predominance in LF, despite differences in mean heart rate. The slowing of breathing per se thus generated a particular effect on the RR spectrum, by bringing respiratory sinus arrhythmia (a predominantly vagal effect) into the spontaneous non-respiratory LF rhythm of the cardiovascular system.

*Effects of regular slow breathing on cardiovascular autonomic modulation and on respiratory control*

Although the origin of this slow cardiovascular rhythm is not completely established, it is likely that sympathetic activation plays a major role in its generation, particularly in the blood pressure (15). There is also a considerable body of evidence showing that this slow rhythm can be produced, or at least is highly influenced by the activity of the arterial baroreceptors and the consequent "hunting" in the efferent activity as a result of the interaction between the fast (vagal) and slow (sympathetic) responses (3). In addition, the blood pressure signal shows a marked tendency to respond at this particular frequency (2). Thus, slow breaths by interfering with this rhythm may influence also the cardiovascular control by important regulatory mechanisms such as the arterial baroreceptors. In theory, this effect could be enhanced if respiration could be maintained at a regular (rather than episodic) slower rate, and (by consequence) increased tidal volume. We have found that this (or similar) effect can be obtained in several different ways: by recitation of rhythmic formulae, by the practice of yoga, by listening to specific types of music.

Recitation of rhythmic formulae has been used for centuries in different cultures. The rosary prayer has been present in western cultures since the crusades, when it was "imported" from the Arabs, who in turn seem to have taken it from the tradition of the Mantras of Indian and Himalayan Yoga culture. Surprisingly, we have found that recitation of the Ave Maria, the main prayer of the rosary, induces a perfect respiratory rhythm at about 0.1 Hz, which induces similar waves in the entire cardiovascular system. Moreover, this is accompanied by a significant increase in the baroreflex sensitivity, decrease in heart rate and blood pressure, and increase in cerebrovascular modulation, as compared to simple random verbalization (5).

While recitation of a rhythmic formula involves active manipulation of breathing, it is also possible that similar effects could be induced by passive listening to rhythmic sounds. We have studied the effect of passive listening to 6 types of music samples, in a group of professional musicians and an in a control group of non musicians. The samples differed in terms of pace, harmonic structure and style. Preliminary results indicate that in all subjects the faster rhythms increased minute ventilation (mainly by a proportional increase in breathing rate), and increased heart rate and blood pressure, whereas slower rhythms or even the absence of a definite rhythm induced opposite effects. Therefore, it is possible to conclude that perception of rhythmic formulae at a given speed can influence the respiratory frequency, even without active voluntary control. As a consequence, while faster musical rhythms can induce an arousal effect, slower rhythms (regardless of music style), again can induce favorable cardiovascular effects.

There is evidence that slow breathing, either obtained by active practice, as by the effect of yoga, or during rhythmic verbalization, not only modifies that cardiovascular control, but it can even modify the respiratory control during both long and short time practice. We found that slow breathing has the capability to reduce the chemoreflex sensitivity to both hypoxia and hypercapnia. This can be obtained in subjects with no previous training in slow breathing, and typically lasts as long as the slow breathing is maintained (1). However, long term practice in yoga results in a slowing of the spontaneous breathing rate and minute ventilation, higher end-tidal CO<sub>2</sub> and reduced central and peripheral chemoreflex (24).

## CLINICAL APPLICATION

### *Essential Hypertension*

Sympathetic hyperactivity and parasympathetic underactivity have a major role in the etiology of hypertension (9). Such imbalance is present not only in early and borderline hypertension but also contributes to the maintenance of sustained hypertension. One of the mechanisms that influence this autonomic imbalance, which is characteristic of hypertension, is the reduced baroreflex sensitivity (8). An impairment of the baroreflex has a direct relation to increased 24-h blood pressure variability, which in turn correlates with the increase in target-organ damage (16). At the same time, there are reports indicating a chemoreflex activation in essential hypertension, which in turn can increase sympathetic activity (22).

In a preliminary study on a group of hypertensives (10), we tested whether slow breathing at 6 breaths/min could modify baroreflex sensitivity in hypertensive patients and in normal controls. During slow breathing, the hypertensive subjects showed significant decreases in systolic and diastolic pressures, and significant increase in the baroreflex sensitivity. Therefore, at least during a short-term observation, clinical results confirm that modification of the respiratory pattern can induce rapid favourable results, although the long term effect of this practice still need to be evaluated (10).

### *Heart failure*

Increased sympathetic activation, reduction in parasympathetic tone, reduction in baroreflex sensitivity, and enhanced chemoreflex sensitivity, are now widely recognized indices of poor prognosis in heart failure, and strongly contribute to the reduced exercise tolerance of these patients, additional to, or even independently from pump failure drive (11). Respiratory disorders in heart failure patients include reduced diffusion capacity and impaired ventilation/perfusion ratio. Abnormalities in the ventilatory pattern are also frequent and lead to frank Cheyne Stokes respiration, which has adverse prognostic significance (19). Unstable ventilatory patterns cause low and unstable oxygen saturation, with consequent increase in sympathetic activity and further increase in oxygen demand. Physical deconditioning enhances sympathetic activity and stimulates ventilation further, and also affects lung musculature, thus decreasing the ability to maintain adequate ventilation during exercise, and possibly contributing to the symptom of dyspnea (13).

In patients with heart failure reducing the breathing rate can increase resting oxygen saturation due to an improvement of ventilation/perfusion inequality (6). In heart failure slow breathing increases baroreflex and reduces chemoreflex sensitivity, which are frequently depressed or exaggerated, respectively (4). Both these abnormalities are associated with a poor prognosis (18, 20). Simple training (performed 1 hour a day for one month), and aimed at a permanently slow breathing rate reduces dyspnea and improves exercise performance (6).

### CONCLUSIONS

The responses of the cardiovascular and respiratory systems to external stimuli show a tight interaction that can be modulated through selection of different rhythmic patterns. These interfere with the spontaneous rhythms that regulate the cardiovascular and respiratory functions. The breathing rate (and depth) is a simple variable that can be modified by volitional control, but, with continuous practice, volitional training appears to modify even the spontaneous rhythm. In addition, the respiratory pattern can also be easily influenced by external stimuli like listening to special types of music or by rhythmic verbal formulae. In turn, the breathing pattern can modify cardiovascular and even respiratory control. In particular, a slow (0.1 Hz) breathing rate can induce a reduction in the excitatory and an enhancement in the inhibitory branches of the autonomic nervous system. This modification can be of considerable clinical value in conditions associated with depressed inhibitory and enhanced excitatory reflexes, such as hypertension and heart failure. Increasing clinical evidence supports this hypothesis.

### SUMMARY

Respiration is a powerful modulator of heart rate variability, and of baro- or chemo-reflex sensitivity. This occurs via a mechanical effect of breathing that synchronizes all cardiovascular variables at the respiratory rhythm, particularly when this occurs at a particular slow rate coincident with the Mayer waves in arterial pressure (approximately 6 cycles/min). Recitation of the rosary prayer (or of most mantras), induces a marked enhancement of these slow rhythms, whereas random verbalization or random breathing does not. This phenomenon in turn increases baroreflex sensitivity and reduces chemoreflex sensitivity, leading to increases in parasympathetic and reductions in sympathetic activity. The opposite can be seen during either verbalization or mental stress tests. Qualitatively similar effects can be obtained even by passive listening to more or less rhythmic auditory stimuli, such as music, and the speed of the rhythm (rather than the style) appears to be one of the main determinants of the cardiovascular and respiratory responses. These findings have clinical relevance. Appropriate modulation of breathing, can improve/restore autonomic control of cardiovascular and respi-

ratory systems in relevant diseases such as hypertension and heart failure, and might therefore help improving exercise tolerance, quality of life, and ultimately, survival.

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