Respiratory countermaneuvers in autonomic failure

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Chapter 8
Abstract

**Background:** Selective increase of inspiratory impedance augments blood pressure in healthy subjects through activation of the respiratory pump. We studied the efficacy of respiratory maneuvers to reduce orthostatic hypotension in autonomic failure.

**Methods:** Mean arterial pressure (MAP) after standing up was recorded in 10 patients in five conditions: normal standing, leg muscle tensing, inspiratory pursed lips breathing, inspiratory sniffing, and a device causing inspiratory obstruction.

**Results:** The maneuvers caused significant differences in standing MAP. Inspiratory obstruction and leg muscle tensing increased MAP to a comparable degree. The effect of inspiratory pursed lips breathing and inspiratory sniffing depended on concomitant hyperventilation.

**Conclusion:** Respiratory maneuvers reduce orthostatic hypotension in autonomic failure through activation of the respiratory pump, provided hyperventilation is avoided.
Introduction

Physical countermaneuvers are helpful in reducing hypotension in autonomic failure (AF). Various maneuvers have been used to this end, including leg crossing, muscle tensing, and squatting. Unfortunately these maneuvers are often impractical for patients with autonomic failure secondary to Parkinson's disease or multiple system atrophy owing to impairment of motor skills and balance control.

To our knowledge respiratory countermaneuvers have not been studied yet in AF. The “respiratory pump” affects blood pressure (BP) in several ways, e.g. may augment venous return and thus BP, if the intrathoracic pressure becomes more negative during inspiration. Building on this concept, selective increase of inspiratory impedance by means of an impedance threshold device (ITD) has been found to increase both supine and standing BP in healthy controls. However, increasing the respiratory pump must not lead to hyperventilation in AF, as hypocapnia can induce hypotension in AF. Therefore, hyperventilation should be avoided during respiratory maneuvers in patients with AF.

We investigated the potential of respiratory countermaneuvers to reduce hypotension in AF, using three ways to increase negative inspiratory intrathoracic pressure: an external device causing selective inspiratory obstruction, inspiration through pursed lips and inspiratory sniffing.

Subjects and methods

Subjects

Ten patients with AF (nine men; 66 ± 9 years, mean ± SD) were recruited from the outpatient clinics of two participating tertiary referral centers. Patients were included if they had a diagnosis of AF and symptomatic orthostatic hypotension. Patients were excluded if they had cardiac disease or used antihypertensive medication. Causes of autonomic failure included pure autonomic failure (n=4), multiple system atrophy (n=3), amyloidosis (n=1), anti-Hu neuropathy (n=1), and Parkinson's disease (n=1). Two patients used medication for AF including midodrine (40mg daily, n=1) and fludrocortisone 0.2-0.3 mg (n=2).

Ten healthy controls (seven men; 48 ± 8 years) without orthostatic hypotension, cardiac disease or the use of antihypertensive medication were recruited through an advertisement.
Chapter 8

Controls were included to illustrate the physiological BP response to the maneuvers and orthostasis. The protocol was approved by the Leiden University Medical Centre Ethics committee. Informed consent was obtained.

Measurements

BP was measured by finger volume-clamp method (Finometer, Finapres Medical Systems, the Netherlands), providing continuous, noninvasive pressure measurements. Mean arterial pressure (MAP) was defined as the sum of systolic BP and twice diastolic BP divided by three.

A 2-MHz pulsed Doppler ultrasound system was used to measure peak cerebral blood flow velocity (CBFV) in the proximal segment of the right middle cerebral artery. The probe was secured with a headband to provide a fixed angle of insonation. Mean CBFV (mCBFV) was calculated by dividing the sum of systolic CBFV and twice diastolic CBFV by three. Subjects breathed through a cushion-sealed facemask fitted with elastic bands around the head. A two-way nonrebreathing valve was connected to the mask. Inspiratory pressure was derived from the recordings of a heated pneumotachograph that was connected to the facemask. The change of inspiratory pressure was calculated by subtracting the average standing pressure from the resting supine value. An infrared gas analyser was used to measure the end-tidal CO₂ tension through sampling of the expired air.

Study protocol

Five tests were performed in random order: normal standing (NS), muscle tensing of the legs without leg crossing (MT), and three maneuvers aimed to selectively increase inspiratory impedance: breathing through pursed lips during inspiration (PLB), inspiratory sniffing (IS), and inspiratory obstruction through narrowing of the inspiratory tube of the two-way nonrebreathing valve (IO). Each experiment consisted of a 5-minute measurement in supine rest, after which patients had to stand for 2 minutes. The maneuvers were commenced directly upon standing. Patients who were unsteady were allowed to keep their balance by holding the examiner with one hand. Prior to PLB and IS participants were instructed to inspire with pursed lips or to sniff during inspiration and to expire freely through the mouth, and to avoid overbreathing. In addition, during NS and the respiratory maneuvers subjects were asked to stand without muscle tensing of the legs. After each maneuver the subject marked the severity
Respiratory countermaneuvers in autonomic failure

of orthostatic symptoms on a visual analog scale range from 0 (no symptoms) to 10 (severe lightheadedness or fainting).

Statistics

The primary outcome measure was the MAP of the last 30 seconds of standing. The nonparametric Friedman test for repeated measures was used. A post-hoc analysis was conducted to assess the relation between MAP and CO₂ changes during the maneuver causing the greatest fall of CO₂, using Spearman rank correlation. Statistical significance was set at p<0.05. Data are presented as median and interquartile range (25th to 75th percentile) relative to NS. mCBFV is expressed as the percentage change compared with NS.

Results

Figure 1 shows the changes of MAP over time after standing up for all maneuvers. Values of control subjects are plotted for comparison. Patients with AF are characterized by a high supine MAP and a progressive fall of MAP upon standing. In contrast, controls have a normal supine MAP, a small transient fall of MAP directly upon standing and eventually a net increase of orthostatic MAP.

Over the five conditions significant differences were found for MAP, mCBFV and end-tidal CO₂. IO increased MAP by 8 mmHg (-1 to 13 mmHg), mCBFV by 8% (2 to 23%), and end-tidal CO₂ by 1 mmHg (-1 to 2 mmHg). During IO, inspiratory pressure decreased by 8 cmH₂O (2 to 12 cmH₂O). MT caused an increase of MAP (9 mmHg; 1 to 10 mmHg) and mCBFV (9%; -7 to 18%) with a small decrease of end-tidal CO₂ (-1 mmHg; -2 to 1 mmHg). PLB caused minimal changes of MAP (1 mmHg; -7 to 8 mmHg), mCBFV (2%; -11 to 9%) and end-tidal CO₂ (-2 mmHg; -9 to 0 mmHg). IS decreased MAP (-12 mmHg; -16 to 6 mmHg), mCBFV (-7%; -18 to 14%) and end-tidal CO₂ (-4 mmHg; -10 to -2 mmHg).

Figure 2 shows the relationship between changes of MAP and end-tidal CO₂ tension, for all maneuvers compared to NS. A significant correlation was found between end-tidal CO₂ and MAP changes during IS (r=0.8; Figure 3).
Figure 1  Time course of the mean arterial pressure (MAP) upon standing in patients with autonomic failure (Panel a) and control subjects (Panel b) during normal standing, muscle tensing of the legs (MT) and three respiratory maneuvers: inspiratory sniffing (IS), breathing through pursed lips during inspiration (PLB) and inspiratory obstruction through narrowing of an inspiratory valve (IO).

In 7 patients the highest MAP was recorded during respiratory maneuvers (IO n=5; IS n=1; PLB n=1), during MT (n=2) and during NS (n=1).

No significant differences were found in symptom scores between maneuvers. Only five patients reported symptoms, even though all had marked orthostatic hypotension. For those patients reporting symptoms the average VAS score was 1 for IO, MT, NS, PLB and 2 for IS.
Figure 2  Change of mean arterial pressure (ΔMAP) and end-tidal CO₂ tension (ΔCO₂) observed with four maneuvers: inspiratory sniffing (IS), breathing through pursed lips during inspiration (PLB), muscle tensing of the legs (MT), and inspiratory obstruction through narrowing of an inspiratory valve (IO) in 10 patients with autonomic failure. Data are shown as differences from normal standing. The dots represent the median value and the bars represent the range between the 25th and the 75th percentile. The high variability in the blood pressure response to each maneuver (as indicated by the bars) is best explained by a variable tendency to hyperventilate. Maneuvers tending to cause a decrease of end-tidal CO₂ tension (IS or PLB) were likely to result in a lower MAP, whereas maneuvers with little change of end-tidal CO₂ tension (MT or IO) where likely to cause an increase of MAP.

Discussion

The device causing an increase of inspiratory impedance reduced orthostatic hypotension in AF to a degree comparable with that of MT. Individual responses to PLB and IS varied considerably. In two patients the highest standing MAP was found during PLB or IS, but in others MAP could decrease during these maneuvers. This high variability in efficacy is best explained by a variable tendency to hyperventilate: as shown in Figure 3, more hypocapnia was related to a lower standing MAP. As said, hypocapnia is known to cause vasodepression in patients with AF and thus counteracts the pressor effect of increased inspiratory impe-
Figure 3  Significant correlation ($r=0.8$) between changes in end-tidal CO$_2$ tension ($\Delta$CO$_2$) and changes in mean arterial pressure ($\Delta$MAP) observed with inspiratory sniffing (IS) compared with normal standing.

The median increase of inspiratory impedance during IO was similar to that in published ITD studies.$^{55,57}$ However, our method differed slightly as the ITD resulted in a fixed minimum inspiratory pressure of 7 cmH$_2$O and in our study no threshold was set. The increases of MAP and mCBFV observed during IO were similar to the increase seen in healthy controls during a squat-to-stand test with an ITD.$^{55,58}$ In healthy controls the increase of standing MAP with an ITD resulted from an increase of stroke volume and cardiac output without affecting total peripheral resistance, suggesting augmentation of venous return through activation of the respiratory pump.$^{55}$ In addition, the small increase of CO$_2$ may have added to the pressor
Respiratory countermaneuvers in autonomic failure

effect of IO in AF. Finally, despite our instructions to avoid MT respiratory maneuvers may have caused some tensing of the leg muscles and hereby MT could have contributed to the vasopressive effect of resistive breathing.

A potential limitation of our study is that the instructions of the maneuvers were given without elaborate training, while patients had extensive experience with MT. Training with BP biofeedback has been shown to improve the effectiveness of complex countermaneuvers. It is therefore possible that training improves the efficacy of the respiratory maneuvers, e.g. by preventing hyperventilation.

The magnitude of the rise in MAP during our maneuvers is quite similar to previous studies on other types of countermaneuvers in AF. It should be understood that even small increases of standing MAP can dramatically improve orthostatic tolerance in AF if BP is critically low. Most of our patients did not experience orthostatic symptoms during the study, so we cannot address the effects of the maneuvers on orthostatic complaints. Prospective studies are needed to investigate the benefits of respiratory countermaneuvers in daily life.

External devices increasing inspiratory impedance provide new therapeutic opportunities for patients with AF, which requires the development of small hand-held versions, which is currently underway. The individual responses to PLB and IS varied considerably owing to a variable tendency to hyperventilate. It may therefore be wise teach patients a variety of maneuvers and to select the individually most advantageous ones.

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