Autonomic dysfunction affects dynamic cerebral autoregulation during Valsalva maneuver: comparison between healthy and autonomic dysfunction subjects

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Autonomic dysfunction affects dynamic cerebral autoregulation during Valsalva maneuver: comparison between healthy and autonomic dysfunction subjects. J Appl Physiol 117: 205–213, 2014. First published June 12, 2014; doi:10.1152/japplphysiol.00893.2013.—The role of autonomic nervous system (ANS) in the regulation of cerebral blood flow (CBF) to arterial blood pressure (ABP) fluctuations [cerebral autoregulation (CA)] is still controversial. We aimed to study the repercussion of autonomic failure (AF) on dynamic CA during the Valsalva maneuver (VM). Eight AF subjects with familial amyloidotic polyneuropathy (FAP) were compared with eight healthy controls. ABP and CBF velocity (CBFV) were measured continuously with Finapres and transcranial Doppler, respectively. Cerebrovascular response was evaluated by cerebrovascular resistance index (CVRi), constant closing pressure (CrCP), and resistance-area product (RAP) changes. Dynamic CA was derived from continuous estimates of autoregulatory index (ARI) [ARI(t)]. During phase II of VM, FAP subjects showed a more pronounced decrease in normalized CBFV (78 ± 19 and 111 ± 16%; P = 0.002), ABP (78 ± 19 and 124 ± 12%; P = 0.0003), and RAP (67 ± 17 and 89 ± 17%; P = 0.019) compared with controls. CrCP and CVRi increased similarly in both groups during strain. ARI(t) showed a biphasic variation in controls with initial increase followed by a decrease during phase II but in FAP this response was blunted (5.4 ± 3.0 and 2.0 ± 2.9; P = 0.033). Our data suggest that dynamic cerebral autoregulatory response is a time-varying phenomena during VM and that it is disturbed by autonomic dysfunction. This study also emphasizes the fact that RAP + GCP model allowed additional insights into understanding of cerebral hemodynamics, showing a higher vasodilatory response expressed by RAP in AF and an equal CrCP response in both groups during the increased intracranial and intrathoracic pressure, while classical CVRi paradoxically suggests a cerebral vasoconstriction.

cerebral autoregulation; cerebral vasoreactivity; autonomic nervous system; Valsalva maneuver; transcranial Doppler

THE ROLE OF AUTONOMIC NERVOUS SYSTEM (ANS) in the adaptation of the cerebral vasculature to arterial blood pressure (ABP) fluctuations, commonly referred to as dynamic cerebral autoregulation (CA), has been the subject of ongoing debate (5, 15, 22, 33, 50, 51, 53). Besides considerable physiological interest, it can have profound clinical impact since ANS dysfunction is related to cerebrovascular disease (10) and the cerebrovascular consequences of widely used parasympathetic and sympathetic modulating drugs are largely ignored.

Contrary to earlier static methods of studying CA (41), dynamic CA reflects regulation of CBF in response to rapid changes of ABP (2, 16, 33, 48, 49, 57).

The Valsalva maneuver (VM) is particularly well suited for studying both dynamic CA (49, 55) and the involvement of ANS in the regulation of CBF because it challenges the cerebrovascular bed by inducing predictable changes in ABP and is extensively characterized in terms of autonomic contribution (19, 49). However, most indexes of dynamic CA assume steady-state physiological conditions (2, 15, 33, 48, 57), which are not strictly met during VM. Therefore, commonly used linear approaches, such as transfer function analysis (57), cannot be applied (17, 20, 25, 28, 32, 44, 55). Facing these problems, recent developments in modeling dynamic CA have led to nonstationary indexes of dynamic CA (17, 20, 25, 28, 32, 44). Particularly, continuous estimation of autoregulatory index (ARI) has been validated during transient changes induced by respiratory maneuvers (17, 35, 36, 40), but this approach has never been tested in VM. In addition to nonstationary indexes of CA, models of the instantaneous relationship between ABP and CBFV can also help to elucidate cerebral hemodynamics during the VM and the ANS influences thereupon. The CBFV response during VM was shown to be largely explained by changes in critical closing pressure (CrCP) (13), possibly reflecting the rise in central venous pressure and intracranial pressure previously reported (21, 42) while resistance-area product (RAP) seemed to reflect the vasodilation effort during the VM (13). The capability of this two-parameter model to separate metabolic and myogenic cerebrovascular mechanisms has been proposed during changes in posture and sensorimotor stimulation (5, 7, 27, 34, 37).

Our AF model consists of a population with familial amyloidotic polyneuropathy (FAP) type I (4). It is a hereditary autosomal dominant disease resulting from mutation of the transthyretin (TTR) gene, leading to deposition of abnormal protein in many organs, typically in the peripheral nerves (4). This causes early dysfunction of autonomic fibers being orthostatic hypotension the hallmark of the disease. The fact that central nervous system is usually spared (24) and the usual absence of classic vascular risk factors makes FAP a well-suited model to study the impact of AF on cerebrovascular regulation.

To understand the behavior of CA during VM and the role of ANS in cerebrovascular regulation, we aimed to compare dynamic CA changes between healthy and FAP patients during VM, testing two related hypotheses: 1) dynamic CA does not
remain constant during VM in either controls or FAP subjects, and 2) AF affects the dynamic CA response.

MATERIALS AND METHODS

This study was performed in São João Hospital Center, a university hospital in Porto, Portugal. The local institutional ethical committee approved the study. Each participant gave written and signed informed consent.

Population Studied

Eight FAP patients (7 male) with TTR Val30Met mutation and mean age of 31.4 ± 6.5 (range 23–43) yr were included in AF group. Only patients with severe (parasympathetic and sympathetic) AF were selected, as determined by a composite scoring system previously described (8) and detailed below. The control group consisted in eight healthy volunteers (5 male) from our hospital and faculty staff, with a mean age of 28.3 ± 5.9 yr (range 27–36). All participants performed a carotid and transcranial duplex scan, with a HDI 5000 device (Philips). Normal findings of extra- and intracranial vessels, and a good temporal acoustic bone window, were required as inclusion criteria. Classical risk factors including smoking, hypertension, diabetes mellitus, and dyslipidemia were exclusion criteria for all participants.

Experimental Protocol

Participants were asked to refrain from any medication, alcohol-, nicotine-, or caffeine-containing products for a minimum of 12 h. Evaluations were carried out in a quiet room with a constant temperature around 22°C. ABP and heart rate (HR) were continuously monitored in the left hand with a noninvasive finger cuff Finapres device (model 2300; Ohmeda, Englewood, CO) with its pressure height correction unit placed at heart level. CBFV was recorded in M1 segment of both middle cerebral arteries (MCA) at a depth of 50–55 mm with 2-MHz pulsed wave Doppler monitoring probes of a Multidop X4 Doppler device (DWL, Sipplingen, Germany) mounted on an individually fitted headband. Data were continuously stored in a computer (model 2300; Ohmeda, Englewood, CO) with a uniform time base. To correct for differences at baseline values, all beat-to-beat estimates were interpolated with a third-order polynomial and resampled at 0.2-s intervals to generate a time series with a uniform time base. To correct for differences at baseline values and, in the case of CBFV, to become independent from the transcranial Doppler insonation angle, data were also normalized by their mean baseline values (period of 10 s before beginning of VM) and expressed in percentages.

Characteristics of VM were manually marked in individual ABP curves and were used to calculate the values of parameters in each phase. To assure that groups could be compared at similar time marks, the values for these phases in FAP subjects were obtained at points that represented the mean time of the fiducial marks from the control group. A recovery phase at 35 s from the beginning of phase I of VM was also added to analysis. To estimate representative group mean and SD of the temporal changes in parameters, the beginning of phase I was used to synchronize the calculations, since it is not affected by AF (19, 55). To further explore the cerebrovascular hemodynamic response to VM, we performed a subcomponent analysis of CBFV temporal changes and evaluated CA through calculation of continuous ARI, as explained below.

Components of CBFV during VM. To weight the separate contributions of ABP, CrCP, RAP, and CVRi to the CBFV responses
induced by VM, we performed a subcomponent analysis as described previously (38). In summary, the two-parameter model, \( \text{CBFV} = (\text{ABP} - \text{CrCP})/\text{RAP} \), can be linearized given the small changes in RAP and further normalized (38) to represent any changes in CBFV as the sum of three subcomponents corresponding to the respective changes in ABP, CrCP, and RAP:

\[
\Delta V = \Delta V_{\text{ABP}} + \Delta V_{\text{CrCP}} + \Delta V_{\text{RAP}}
\]

With the use of a similar procedure for the single parameter model, \( \text{CBFV} = \text{ABP}/\text{CVRi} \) leads to:

\[
\Delta V = \Delta V_{\text{ABP}} + \Delta V_{\text{CVRI}}
\]

where the different terms represent the concomitant changes in ABP (\( \Delta V_{\text{ABP}} \), CrCP (\( \Delta V_{\text{CrCP}} \)), RAP (\( \Delta V_{\text{RAP}} \)), and CVRi (\( \Delta V_{\text{CVRI}} \)), all in units of CBFV. The reference values were chosen as the mean value of the 10-s interval preceding VM and units are expressed in percentage after normalization. The main advantage of this approach is that at any given time changes in CBFV can be explained by corresponding changes in ABP and the model parameters. Of relevance, reductions in RAP, CVRi, or CrCP will all lead to increases in CBFV and for this reason the respective subcomponents will be represented by positive values. Previous work (38) suggested that \( \Delta V_{\text{RAP}} \) expresses predominantly the myogenic response to blood pressure changes, but this association has not been firmly established.

**Continuous dynamic ARI.** Time-varying estimates of dynamic autoregulation were based on the ARI (35) introduced by Tiecks et al. (48). In their original communication, a second-order differential equation model was used to generate template mean CBFV step responses to changes in mean ABP. Ten combinations of the gain, time constant, and damping coefficients of the differential equations define the ARI ranging from zero (absence of CA) to nine (best CA) (48). Noteworthy, classical calculation of a single ARI index for recordings lasting several minutes is not acceptable during maneuvers like VM that induce nonstationary time series. For this propose, a time-varying ARI \( ARI(t) \) was derived from autoregressive moving average (ARMA) models with time-varying parameters after implementation of Tiecks’ model as an ARMA structure and use of the Walsh set of orthogonal basis functions to obtain ARMA models with time-varying parameters as previously described (35). Once those parameters are obtained, it is possible to calculate a corresponding CBFV step response for each instant of time, with each one leading to an estimate of \( ARI(t) \). A maximum of 19 orthogonal functions were adopted, and \( ARI(t) \) was calculated at 0.2-s intervals. Using this model, Panerai et al. (35) showed that \( ARI(t) \) presented characteristic time-varying patterns during respiratory maneuvers of apnea and hyperventilation, providing a physiological validation of this method.

**Statistical Analysis**

Normality of the variables was determined by Shapiro–Wilk test. Student’s \( t \)-test was used to compare baseline resting values between groups and paired \( t \)-test to compare right and left MCA within each group. In the absence of statistically significant differences between parameters derived from the right and left MCA, these were averaged for all subsequent analyses. Two-way repeated measures ANOVA was used to find differences between groups and different phases of VM: within each group differences between phases were calculated using simple contrast with baseline resting values as reference; Bonferroni’s post hoc test for multiple comparisons was used to detect differences between groups at each phase when interaction between group and phase factor was significant. Statistical significance was inferred at a \( P < 0.05 \) level.

**RESULTS**

All FAP subjects had severe grades (III and IV) of AF with the following group-averaged results: HR difference to deep breathing: 3.4 ± 2.7 beats/min; Valsalva HR ratio: 1.1 ± 0.1; 4 subjects with delayed and 4 with absent ABP overshoot in phase IV of VM; fall in systolic ABP during head-up tilt: 35.6 ± 27.2 mmHg; basal plasma norepinephrine: 78.6 ± 64.0 pg/ml; autonomic score: 7.6 ± 1.1. Baseline values for systemic and cerebral hemodynamic parameters were not different between FAP and controls (Table 1). In controls, VM showed ABP and CBFV patterns in agreement with previous studies (Fig. 2). Phase I, a purely mechanical hemodynamic challenge, showed similar responses in healthy and FAP groups, being characterized by a rapidly rising ABP, CVRi, and CrCP and almost unchanged CBFV, RAP, and HR (Fig. 2 and Table 2). There were marked differences between groups in all subsequent phases (Table 2). Systemic hemodynamic response of FAP group revealed known characteristics of AF: there was a decrease in the mean CBFV pulse pressure (systolic–diastolic) also showed marked differences between the two groups (Fig. 3), which reached significance in phases I, IIb, and IV (Table 2).

Mean CBFV dropped in both groups (Fig. 2) but deeper in FAP group and showed a blunted overshoot at phase IV compared with controls (\( P = 0.001 \)). The two models of cerebrovascular resistance studied, CVRi and RAP + CrCP, were substantially different. At the beginning of phase II, there was a decrease in vascular resistance in both groups as expressed by RAP but this cerebral vasodilation response turned out to be more pronounced in FAP group and was still present at phase IV (\( P = 0.001 \)). Nevertheless, this greater drop in RAP was not sufficient to restore CBFV to its baseline values in FAP compared with controls (Fig. 2A). CrCP increased similarly (\( P = 0.235 \)) between phases I to III of VM in both groups (Fig. 2D and Table 2). At phase III, both groups showed rapid restoration of CrCP to baseline values immediately before CBFV overshoot, which was absent in FAP subjects (Fig. 2A). CVRi increased not differently (\( P = 0.390 \)) between groups during phases I through III (Fig. 2F and Table 2).

**Subcomponent Analysis**

Further differences between FAP and controls and between the two different models of cerebrovascular resistance were
revealed by subcomponent analysis (Fig. 4). $\Delta V_{\text{CVRi}}$ showed a biphasic contribution to CBFV variation in both groups without significant differences (Table 3). On the other hand, $\Delta V_{\text{RAP}}$ and $\Delta V_{\text{CrCP}}$ had different temporal patterns with $\Delta V_{\text{RAP}}$ showing marked differences ($P < 0.025$) for phases IIb, III, and IV while $\Delta V_{\text{CrCP}}$ showed similar contribution ($P = 0.162$) to CBFV changes (Table 3).

**Dynamic CA Response**

Temporal changes of $\text{ARI}(t)$ differed significantly between groups ($P = 0.020$; Fig. 5 and Table 3). A biphasic response was observed in controls, characterized by an initial increase in phases I-IIa, followed by a continuous drop until phase IV. In contrast, FAP response was practically unchanged despite a tendency to increase values towards the end of the maneuver. These mean temporal patterns were representative of individual $\text{ARI}(t)$ curves with 8/8 and 5/8 individuals showing similar patterns to the mean of controls and FAP patients, respectively.

**DISCUSSION**

**Main Findings**

In this study we have shown that dynamic CA behaves as a time-varying phenomena during VM and that it is significantly affected by autonomic dysfunction. Our first hypothesis was substantiated by inspection of $\text{ARI}(t)$ patterns in individual subjects, showing excellent agreement with the mean temporal patterns represented in Fig. 5, thus confirming their robustness. For the second hypothesis, the significant effect of autonomic dysfunction was confirmed by two very distinct approaches. In the first of these, the total variation in CBFV was broken down in its subcomponents thus reflecting the relative contribution of concomitant changes in ABP, CrCP, and RAP, showing marked differences between controls and FAP subjects. In particular, despite the larger drop in RAP in FAP, Fig. 2A indicates that these were not enough to restore CBFV to its baseline values as observed for controls. The second approach, involving the use of ARMA modeling to obtain estimates of $\text{ARI}(t)$, again showed marked differences between the two groups as discussed below.

Finally, we also confirmed previous studies (7, 13, 38) showing that a two-parameter model ($\text{RAP} + \text{CrCP}$) provides clearer discrimination of changes in cerebral hemodynamics than the classical, single CVRi parameter.

**Dynamic CA control during VM**

In healthy subjects, dynamic CA as assessed by continuous estimates of $\text{ARI}(t)$ showed a biphasic response to VM, with an initial increase followed by a continuous drop until strain was released. To our knowledge, this is first time that continuous

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Fig. 2. Group-averaged normalized changes in mean CBFV (A), mean ABP (B), heart rate (HR; C), CrCP (D), resistance-area product (RAP; E), and cerebrovascular resistance index (CVRi; F) during the VM in controls (continuous line) and severe familial amyloidotic polineuropahty (FAP) patients (dashed line). Averaging was synchronized at ABP peak in phase I, and the beginning is marked by a vertical arrow. Characteristic phases of VM are shown in roman numerals. For clarity, only the largest ± SD bar is represented at the point of occurrence (wider horizontal top and bottom delimiters for FAP group).
estimates of dynamic CA changes were described in VM. The initial increase of ARl(t) could represent the cerebrovascular autoregulatory effort to bring CBFV levels back to baseline in response to sudden increase of CrCP and effective reduction of perfusion pressure (ABP − CrCP), taking into account that the autoregulatory response normally takes from 2–5 s to be manifested (Fig. 4). However, FAP patients showed no changes in ARl(t) at the same phases despite similar variations of ABP and CrCP. Thus cerebral perfusion pressure changes probably do not explain dynamic CA augmentation at this point. Interestingly, pulse pressure seemed to be the only factor probably do not explain dynamic CA augmentation at this point. However, cerebrovascular and autonomic responses during VM were described as unrelated to Pco2 changes (13, 54, 55). Finally, intracranial pressure elevation is associated with deterioration of dynamic CA as measured by Mx in traumatic

Table 2. Normalized values of variation of cerebral and systemic hemodynamic parameters during each phase of the Valsalva maneuver for controls and FAP patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
<th>Phase IV</th>
<th>Recovery</th>
<th>ANOVA P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, %</td>
<td>105 ± 9</td>
<td>116 ± 12*</td>
<td>101 ± 14</td>
<td>109 ± 17</td>
<td>113 ± 20</td>
<td>83 ± 7*</td>
<td>0.023</td>
</tr>
<tr>
<td>Control</td>
<td>101 ± 2</td>
<td>100 ± 2†</td>
<td>108 ± 9</td>
<td>109 ± 8*</td>
<td>109 ± 8</td>
<td>105 ± 5†</td>
<td></td>
</tr>
<tr>
<td>Mean ABP, %</td>
<td>128 ± 13*</td>
<td>105 ± 4</td>
<td>124 ± 12*</td>
<td>106 ± 14</td>
<td>123 ± 12*</td>
<td>99 ± 8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FAP</td>
<td>122 ± 11*</td>
<td>90 ± 14**</td>
<td>78 ± 19**</td>
<td>78 ± 15**</td>
<td>84 ± 16†</td>
<td>101 ± 19</td>
<td></td>
</tr>
<tr>
<td>Pulse Pressure, %</td>
<td>114 ± 15*</td>
<td>90 ± 14</td>
<td>124 ± 28*</td>
<td>94 ± 26</td>
<td>137 ± 37*</td>
<td>120 ± 21*</td>
<td>0.001</td>
</tr>
<tr>
<td>Control</td>
<td>102 ± 3†</td>
<td>83 ± 19*</td>
<td>72 ± 12†</td>
<td>78 ± 10*</td>
<td>83 ± 15†</td>
<td>105 ± 26</td>
<td></td>
</tr>
<tr>
<td>Mean CBFV, %</td>
<td>107 ± 8</td>
<td>93 ± 10*</td>
<td>111 ± 16</td>
<td>118 ± 15*</td>
<td>150 ± 24*</td>
<td>92 ± 16</td>
<td>0.001</td>
</tr>
<tr>
<td>Control</td>
<td>107 ± 10</td>
<td>69 ± 11†</td>
<td>78 ± 19†</td>
<td>91 ± 19†</td>
<td>101 ± 23†</td>
<td>105 ± 17*</td>
<td></td>
</tr>
<tr>
<td>Mean HR, %</td>
<td>268 ± 178*</td>
<td>244 ± 132*</td>
<td>212 ± 142*</td>
<td>109 ± 54</td>
<td>57 ± 58</td>
<td>121 ± 49</td>
<td>0.235</td>
</tr>
<tr>
<td>Control</td>
<td>196 ± 61*</td>
<td>177 ± 44*</td>
<td>130 ± 67*</td>
<td>121 ± 37</td>
<td>116 ± 27</td>
<td>93 ± 13</td>
<td></td>
</tr>
<tr>
<td>CrCP, %</td>
<td>98 ± 15</td>
<td>77 ± 8*</td>
<td>89 ± 17</td>
<td>90 ± 14</td>
<td>96 ± 10</td>
<td>105 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>RAP, %</td>
<td>87 ± 13</td>
<td>76 ± 29*</td>
<td>67 ± 17†</td>
<td>64 ± 13†</td>
<td>66 ± 14†</td>
<td>100 ± 17</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>127 ± 22*</td>
<td>115 ± 11*</td>
<td>118 ± 17*</td>
<td>92 ± 13</td>
<td>87 ± 14</td>
<td>111 ± 19</td>
<td>0.390</td>
</tr>
<tr>
<td>FAP</td>
<td>120 ± 16*</td>
<td>113 ± 41</td>
<td>97 ± 35</td>
<td>83 ± 20</td>
<td>81 ± 17*</td>
<td>97 ± 17</td>
<td></td>
</tr>
</tbody>
</table>

All values are given in percentage (normalized). *P < 0.05, level of significance for differences between baseline values and each of the Valsalva maneuver phases obtained by repeated-measures ANOVA. †P < 0.05, level of significance for differences between familial amyloidotic polyneuropathy (FAP) and control groups obtained by repeated-measures ANOVA. ‡P value for interaction between phase and group by two-way repeated-measures ANOVA.

Fig. 3. Group-averaged normalized arterial pulse pressure (PP; systolic − diastolic) for controls (solid line) and FAP patients (dashed line). Averaging was synchronized at ABP rise in phase I indicated by the vertical arrow. For clarity, only the largest ± SD bar is represented at the point of occurrence.
brain injury (11). However, during VM, intracranial pressure increases a maximum of 23.5 mmHg (21), and at this range Mx remained normal (11).

The short-term modulation of CA during VM raises important questions for further studies of CA (and other physiological control systems): at some stages enhanced CA is observed, while at other times CA seems to be absent, even in healthy controls. For example, at phase III, where CBFV is high and the drop in ABP helps to restore CBFV to baseline. Active autoregulation at this stage might keep CBFV artificially high, undoing the effect of the restoration of ABP in returning the flow to baseline.

**Effect of Autonomic Dysfunction on Normal Cerebrovascular Control**

In FAP patients, ARI(t) was practically unchanged during strain but increased towards the end of the maneuver, which confers a completely different pattern from control group. Overall, the clear-cut distinct pattern of ARI(t) during VM,
Mechanisms of Cerebrovascular Control During VM and Physiological Correlates

Previous studies (21, 42) have characterized changes in cerebral hemodynamics during VM using invasive measurements (electromagnetic flowmeter), confirming that between phases I to III there is an increase in cerebrospinal fluid pressure (CSFP) of 7.5 mmHg and a decrease in internal carotid blood flow by 21%. Cerebrovascular resistance, calculated as (mean ABP - CSFP)/blood flow, decreased during strain, meaning cerebral vasodilation, and increased during phase IV. Dawson et al. (13), using transcranial Doppler, showed the same temporal profile by using the RAP + CrCP model. Particularly, RAP seemed to change in accordance with the cerebrovascular effort of vasodilation during VM, and CrCP very closely accompanied the changes in intrathoracic and intracranial pressures (13). Our results not only match those of Dawson et al. (13) in the healthy group but also reinforce the value of the CrCP + RAP model over CVRi by showing that the same physiological correlates could be interpreted in a different response caused by autonomic dysfunction. During the normal response to VM, RAP varies as expected, reflecting the cerebral vasodilation effort during phase II (21). AF caused a larger CBFV reduction during phase II compared with controls, consistent with previous studies with ganglionic blockade (55). This is accompanied by a substantial drop in ABP, which is related to adrenergic dysfunction (19). This cerebral vasodilation seems to be better explained by the longer and deeper RAP reduction, while CVRi suggests a paradoxical cerebral vasocostriction (21, 49). We speculate that RAP is more sensitive to ABP variations and, therefore, behaves as a myogenic component of cerebrovascular regulation. Previous studies support this as-

Compared with controls, strongly suggests a major role for ANS involvement in dynamic CA, as proposed by other groups (9, 29, 58). The suggestion of an increase in ARİ(t) during late phase II and III might represent the attempt of cerebrovascular control to restore CBF in the face of a higher drop of ABP (34, 38). This response pattern may not simply imply impaired CA, as patients can achieve very high ARİ and values during baseline (Table 1) and recovery seem similar (Fig. 5). They are also able to modulate ARİ and RAP, but they do so differently than controls. This altered response could be explained solely by the different ABP patterns. However, in phase I the initial increase ABP was similar between groups (Fig. 2 and Table 1) but increased ARİ(t) was shown only by controls. Future studies are needed to address these additional questions generated from our results.

All values are given in percentage (normalized) except for ARİ(t), which are means ± SD. Δv, changes in CBFV. *P < 0.05, level of significance for differences between baseline values and each of the Valsalva maneuver phases obtained by repeated-measures ANOVA. †P < 0.05, level of significance for differences between FAP and control groups obtained by repeated-measures ANOVA. ‡P value for interaction between phase and group by two-way repeated-measures ANOVA.

Table 3. Normalized CBFV changes and its components (ABP, CrCP, and RAP, and CVRi) and ARİ(t) absolute values changes during all phases of the Valsalva maneuver for controls and FAP patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
<th>Phase IV</th>
<th>Recovery</th>
<th>ANOVA P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δv, %</td>
<td>Control</td>
<td>5 ± 9</td>
<td>-12 ± 8*</td>
<td>13 ± 17</td>
<td>20 ± 15*</td>
<td>49 ± 23*</td>
<td>-6 ± 14</td>
</tr>
<tr>
<td></td>
<td>FAP</td>
<td>5 ± 11</td>
<td>-28 ± 10†</td>
<td>-23 ± 18*</td>
<td>-8 ± 19†</td>
<td>2 ± 23†</td>
<td>8 ± 18</td>
</tr>
<tr>
<td>ΔvABP, %</td>
<td>Control</td>
<td>42 ± 19*</td>
<td>8 ± 12</td>
<td>34 ± 17*</td>
<td>6 ± 20</td>
<td>34 ± 17*</td>
<td>7 ± 14</td>
</tr>
<tr>
<td></td>
<td>FAP</td>
<td>35 ± 19*</td>
<td>-4 ± 24</td>
<td>-33 ± 27†</td>
<td>-31 ± 18*</td>
<td>-22 ± 23†</td>
<td>-4 ± 33</td>
</tr>
<tr>
<td>ΔvCVRi, %</td>
<td>Control</td>
<td>-24 ± 20*</td>
<td>-23 ± 13*</td>
<td>-12 ± 15*</td>
<td>-11 ± 12*</td>
<td>16 ± 12*</td>
<td>-13 ± 21</td>
</tr>
<tr>
<td></td>
<td>FAP</td>
<td>-18 ± 14*</td>
<td>-32 ± 14*</td>
<td>-6 ± 29</td>
<td>12 ± 19</td>
<td>15 ± 16*</td>
<td>9 ± 17</td>
</tr>
<tr>
<td>ΔvRAP, %</td>
<td>Control</td>
<td>-40 ± 27*</td>
<td>-37 ± 10*</td>
<td>-32 ± 19*</td>
<td>7 ± 25</td>
<td>7 ± 19</td>
<td>-7 ± 8*</td>
</tr>
<tr>
<td></td>
<td>FAP</td>
<td>-44 ± 25*</td>
<td>-44 ± 20*</td>
<td>-19 ± 24</td>
<td>-10 ± 19</td>
<td>-9 ± 14</td>
<td>3 ± 11</td>
</tr>
<tr>
<td>ΔvRAP + ΔvABP, %</td>
<td>Control</td>
<td>44 ± 21*</td>
<td>26 ± 9*</td>
<td>37 ± 8*</td>
<td>14 ± 17*</td>
<td>30 ± 8*</td>
<td>1 ± 14</td>
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<tr>
<td></td>
<td>FAP</td>
<td>44 ± 28*</td>
<td>22 ± 11*</td>
<td>3 ± 16†</td>
<td>3 ± 15</td>
<td>-5 ± 19†</td>
<td>3 ± 10</td>
</tr>
<tr>
<td>ARİ(t), AU</td>
<td>Control</td>
<td>7.8 ± 0.9*</td>
<td>5.4 ± 2.2</td>
<td>3.7 ± 3.7</td>
<td>1.2 ± 3.2*</td>
<td>0.6 ± 0.9*</td>
<td>5.5 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>FAP</td>
<td>3.3 ± 3.5†</td>
<td>2.2 ± 3.0†</td>
<td>5.4 ± 3.2</td>
<td>4.0 ± 3.5</td>
<td>5.8 ± 3.5†</td>
<td>7.2 ± 3.2</td>
</tr>
</tbody>
</table>

Fig. 5. Group-averaged normalized autoregulatory index changes [ARİ(t)] during the VM for controls (continuous line) and FAP (dotted line) groups. Averaging was synchronized at ABP rise in phase I and the beginning is marked by a vertical arrow. For clarity, only the largest ± SD bar is represented at the point of occurrence (wider horizontal top and bottom delimiters for FAP group).
This population is very homogeneous in its disease process and lacks vascular risks factors, like diabetes, that would make it difficult to discern the effects of autonomic dysfunction among other vascular aggressors.

Conclusions

In summary, by applying a recently designed continuous estimation of ARI, we could measure, for the first time, the dynamic CA performance during VM. Our data suggest that dynamic CA undergoes temporal changes during the VM and that it is significantly altered in subjects with severe autonomic failure. Moreover, a two-parameter model, including CrCP and RAP, allowed a clearer insight into cerebral hemodynamics than the CVRi alone. Further physiological studies are needed to describe the multiple interactions between ABP changes and cerebrovascular parameters in response to different maneuvers in patient populations with ANS dysfunction.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: P.M.C., R.S., J.F., R.B.P., and E.A. conception and design of research; P.M.C. and R.B.P. analyzed data; P.M.C., R.B.P., and E.A. interpreted results of experiments; P.M.C. prepared figures; P.M.C. drafted manuscript; P.M.C., J.F., R.B.P., and E.A. edited and revised manuscript; P.M.C., R.S., J.F., R.B.P., and E.A. approved final version of manuscript; R.S. performed experiments.

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