Cerebral vasomotor reactivity before and after blood pressure reduction in hypertensive patients.

Running head: Hypertension and cerebral vasomotor reactivity

J.A.H.R. Claassena,b, B.D. Levineb, R. Zhangb

a Department of Geriatric Medicine, Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
b Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas and the University of Texas Southwestern Medical Center, 7232 Greenville Ave, Dallas, TX 75231

Correspondence to: Rong Zhang
Institute for Exercise and Environmental Medicine,
Presbyterian Hospital of Dallas
7232 Greenville Ave, Dallas, TX 75231
Telephone: (214) 345-4619
FAX: (214) 345-4618
E-mail: RongZhang@TexasHealth.org

Disclosures: none to declare
ABSTRACT

Background: Hypertension is associated with cerebrovascular remodeling and endothelial dysfunction, which may reduce cerebral vasomotor reactivity to CO₂. Treatment combining blood pressure (BP) reduction with inhibition of vascular effects of angiotensin II may reverse these changes. However, the reduction in BP at the onset of treatment can compromise cerebral perfusion and exhaust vasomotor reserve, leading to impaired CO₂ reactivity.

Methods: 11 patients with newly diagnosed, untreated mild to moderate hypertension, 9 men, 2 women, age (mean (SD)) 52 (9) years, and 8 controls, 7 men, 1 woman, age 46 (10) years were studied. Patients received losartan/hydrochlorothiazide (50/12.5 or 100/25 mg) to reduce BP to < 140 / < 90 mmHg within 1-2 weeks. BP (Finapres), heart rate, CBFV (cerebral blood flow-velocity, transcranial Doppler), cerebrovascular resistance, and CO₂ reactivity were measured at baseline, after the rapid BP reduction, and after long-term treatment (3-4 months).

Results: At baseline, hypertension was not associated with reduced CO₂ reactivity. Treatment effectively lowered BP from 148(12)/ 89(7) to 130(15)/ 80(9) after 1-2 weeks and 125(10)/ 77(7) mmHg after 3-4 months (p = 0.003). CO₂ reactivity was not affected by the reduction in BP within 2 weeks, and long term treatment did not augment reactivity.

Conclusions: In hypertension without diabetes or advanced cerebrovascular disease, CO₂ reactivity is not reduced, and rapid normalization (within 2 weeks) of BP does not exhaust vasomotor reserve. CO₂ reactivity did not change between 2 and 12 weeks of treatment, which argues against a direct vascular effect of angiotensin II inhibition within this period.

Key Words: cerebrovascular circulation; carbon dioxide; Transcranial Doppler ultrasonography; vascular response; hypocapnia; hypercapnia
INTRODUCTION

Hypertension causes remodeling of cerebral arteries with increases in wall thickness/lumen ratio \(^1\) and impaired endothelium-mediated vasodilatation.\(^2\) These changes may reduce cerebrovascular reactivity to CO\(_2\).\(^3\) Cerebral vasomotor responses to changes in arterial CO\(_2\) (CVMR) have been widely used as a clinical test to evaluate vascular function in patients with carotid stenosis.\(^4,5\) Relatively few studies have investigated CVMR in hypertension. Most found that CVMR was reduced in hypertension and could be restored with treatment.\(^6,7,8,9\) Unfortunately, blood pressure (BP) was not recorded during the CVMR tests in all but one\(^9\) of these studies. BP is affected substantially by changes in CO\(_2\), and the influence of BP on cerebral blood flow will confound CVMR.\(^10\) Moreover, whether this BP response to CO\(_2\) is altered by hypertension is unknown. Therefore, further evaluation of CVMR in hypertension is warranted and should include evaluation of the interaction of CO\(_2\), BP and cerebral blood flow.\(^11\)

Although treatment of hypertension has been shown convincingly to reduce stroke risk, and may also beneficially affect onset and progression of dementia,\(^2,12\) considerable uncertainty remains about the possible adverse effects of BP lowering treatment on cerebral perfusion.\(^13\) Structural changes and endothelial dysfunction may reduce the capacity of cerebral vessels to compensate for the reduction BP, creating susceptibility to brain ischemia.\(^13\)

Angiotensin II is implicated in the structural and functional cerebrovascular changes in hypertension.\(^2\) Treatment blocking the effects of angiotensin II may have beneficial cerebrovascular effects (outside its effects on BP) \(^14,15\) and restore CVMR. However, clinical trials to date have provided conflicting results and this issue remains to be resolved.\(^2,12\)

In this study, we have tested the hypothesis that impaired vasodilatory capacity in hypertensive patients causes a (further) reduction in CVMR when BP is lowered. Moreover, we hypothesized that patients are most susceptible for this impairment at the onset of treatment. We investigated CVMR in patients with untreated hypertension, using a modified CVMR test to account for effects of BP on CVMR and to
address effects of hypertension on the BP response to CO₂. Subsequently, we investigated longitudinal effects of antihypertensive treatment on CVMR by measuring CVMR at onset of treatment ("short term": after rapid normalization of BP within 1-2 weeks) and again after 3-4 months ("long term"). We used hydrochlorothiazide combined with losartan to investigate the short term and long term effects of angiotensine II blockade on CVMR.

MATERIALS AND METHODS

Subjects

This study was conducted in a subgroup of subjects who participated in research on dynamic cerebral autoregulation in hypertension. 11 patients with mild to moderate hypertension (9 men, 2 women) with a mean age of 52 (SD 9) years (range, 39 – 66), and 8 healthy subjects (7 men, 1 woman) with a mean age of 46 (SD 10) years (range, 38 - 66) participated (Table 1). Based on the variance of the CVMR measurements, this study had 90 % power to detect small changes in CVMR (1.5 %/mm Hg).

All patients had recently been diagnosed with hypertension (up to 3 months prior to enrolment) and had not yet started treatment, nor had they received prior antihypertensive treatment. Classification of hypertension (JNC 7 and ESC/ESH 2007; mild to moderate, stage 1-2) was based on the average of cuff BP measurements during at least two office visits. 17 Participants underwent a thorough medical history and physical examination, as well as blood chemistry evaluation and echocardiography, to exclude angina pectoris, myocardial infarction, heart failure, diabetes, renal disease, lung disease, or history of stroke. None were current smokers, and none received treatment for any disease. Patients with systolic pressure > 180 and/or diastolic pressure > 110 mmHg) were excluded. The study was conducted in accordance with the guidelines set by the Declaration of Helsinki, and the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas approved the study. All participants provided informed consent in writing.
Instrumentation

Finger photoplethysmography (Finapres, Ohmeda, Madison, WI) was used to measure beat-to-beat changes in BP. Intermittent cuff BP was measured at the upper arm using electrosphygmomanometry (SunTech Medical, Inc., Morrisville, NC). CBF-velocity (CBFV) was recorded in the middle cerebral artery (MCA) using transcranial Doppler (TCD, Multiflow, DWL Germany). The Doppler probe was placed over the subject’s temporal window and fixed at a constant angle with a probe holder that was custom made to fit each subject’s facial bone structure. This technique allowed CBFV to be measured precisely at the same acoustic window and at the same angle for repeated studies.10 Heart rate was monitored using ECG. End-tidal CO2 (ETCO2) was monitored via a nasal cannula using a capnograph (Criticare Systems, Inc., Waukesha, WI).

Protocol

Experiments were performed in the morning at least two hours after a light breakfast. The subjects refrained from heavy exercise and caffeinated or alcoholic beverages at least 24 hours before the tests. Baseline measurements of six min of beat-to-beat BP and CBFV during spontaneous breathing were recorded after at least 30 min of supine rest.

We estimated CVMR using breath-by-breath changes in ETCO2, CBFV and BP.10 Subjects were studied in the supine position to allow comparison with other imaging technology such as MRI or PET.18,19 To obtain a wide range of CO2 changes (from ~ 20 to 60 mmHg ETCO2), a modified rebreathing protocol was used with a period of voluntary hyperventilation preceding rebreathing. Rebreathing was continued for 5 min, before returning to room air for recovery (4 min). A small amount of oxygen was bled into the rebreathing bag at the subject’s basal metabolic rate (estimated using the Harris-Benedict formula) to maintain arterial oxygen saturation (SaO2) constant.10

Antihypertensive treatment

After the baseline test, patients received low dose losartan/hydrochlorothiazide (50/12.5 mg once daily) for one week. If BP was not below a systolic pressure < 140 mmHg and diastolic pressure < 90 mmHg the dose was increased to 100/25 mg. The
short-term test (one to two weeks after start of treatment) was performed when this goal of BP control was reached. The long-term test was scheduled after three to four months of continued treatment. In patients, 24-h ambulatory BP (ABPM, Accutrack II, SunTech, Inc.) was measured before treatment and repeated on the days before the short and long-term tests and at mid-term. In controls, 24-h ABPM was measured once at baseline and once before the long-term test. Patients took losartan/hydrochlorothiazide in the morning 2-3 h before the study to ensure its optimal BP lowering effects. Throughout the study, BP was monitored at weekly intervals. In addition serum electrolytes and plasma renin activity and aldosterone were measured before and during treatment. Sample tubes were not chilled prior to or following blood collection. Serum separation tubes were used for aldosterone and EDTA for plasma renin activity. The samples were spun within 30-45 min after collection at 3560 RPM for 20 min and frozen immediately at –80°C, until processing by National Reference Laboratory.

Data analysis

Off-line data analysis was performed using Acknowledge software (BIOPAC Systems, Inc, Goleta, CA). Baseline BP, HR and CBFV were obtained from the average of beat-to-beat data; ETCO₂ was derived from the breath-to-breath data. Cerebrovascular conductance index (CVCI) was calculated as mean CBFV divided by mean BP for all beat-to-beat data. Since CBFV may be affected directly by changes in BP, estimations of CVMR based on CVCI may reveal intrinsic vascular responses to changes in CO₂. During hyperventilation and rebreathing, breath-to-breath values of mean CBFV, BP, CVCI, HR and ETCO₂ were obtained. Towards the end of rebreathing, CBFV reached a plateau-phase; a similar plateau was observed for hypoventilation, indicating a steady-state. To compare with studies that measured steady-state conditions, the first part of data analysis was performed using these plateau values. Thus, maximum hypocapnic (~20 mmHg below baseline ETCO₂) reduction in CBFV and CVCI (in %), maximum hypercapnic (~20 mmHg above baseline) increase in CBFV and CVCI (in %), and total range of change in CBFV and CVCI (hypocapnic + hypercapnic, in %) were derived. Next, CVMR was expressed as the ratio of % change
in CBFV or CVCI over the whole range of changes in ETCO$_2$ (hypocapnic + hypercapnic).

The second part of data-analysis focused on the dynamic responses of CBFV to the transient changes in ETCO$_2$. CVMR was estimated nonlinearly for breath-to-breath changes in CBFV and CVCI. A 4 parameter logistic function was used for sigmoidal curve fitting, where model parameter $a$ represents the total range of change in CBFV or CVCI; $y_0$ is the maximum value of CBFV or CVCI during hypercapnia; $x_0$ is the level of ETCO$_2$ where vascular reactivity to changes in CO$_2$ is maximal; and $b$ is a constant that determines the sigmoidal shape of the curve (Fig. 1). Finally, linear regression of changes in CBFV and CVCI in the range of ETCO$_2$ between 40-50 mmHg was performed. The slope of this regression is a robust method to estimate maximum vascular reactivity, expected to be very sensitive to altered myogenic and structural cerebrovascular properties, associated with hypertension.$^{1,22,23}$

**Statistics**

T-tests, and analysis of variance with Bonferroni correction for multiple comparisons, were used to compare the differences and interactions between the subject groups and the effects of antihypertensive treatment on baseline hemodynamics and CVMR (SigmaStat, version 3.11 Systat Software Inc.) All data were normally distributed (Q-Q plots). However, because PRA and aldosterone often are not normally distributed, analysis was repeated after log transformation, and with the non-parametric Friedman’s test. Data are presented as mean (SD), with their associated P values.

**RESULTS**

**Effects of Treatment**

Significant reductions in BP were achieved within 1-2 weeks of treatment. This reduction was well maintained over the period of 3-4 months with the same dose of drugs (Table 1). The rapid dose adjustment within the first 1-2 weeks did not prompt subsequent dose reduction due to excess BP reduction or electrolyte disorders. All
participants were “normal dippers” (10-20% nocturnal BP decline), and treatment affected nocturnal BP similarly as awake BP.

Before treatment, no differences in CBFV were observed between control subjects and patients with hypertension. CBFV did not change after short and long-term reductions in BP.

Plasma renin activity, but not aldosterone, was slightly higher at baseline in patients, and increased following treatment. LDL-cholesterol did not differ between patients and controls (117 (35) vs. 111 (32) mg/dL. Treatment did not importantly alter electrolytes, cholesterol or renal function (Table 1).

Estimation of CVMR

Maximum (plateau) changes in CBFV and CVCI with hyperventilation and rebreathing were similar in patients and controls, and neither short-term nor long-term treatment affected these values (Table 2). Examples of sigmoidal curve fitting of changes in CBFV and CVCI vs. ETCO2 are presented in Fig 1 and 2. The results of non-linear parameter identification are summarized in Table 2. No differences in the model parameters were observed between patients and controls before or after treatment. The steep portion of changes in CBFV or CVCI to ETCO2 was identified in the range between 40-50 mmHg (Fig 1, 2). Estimation of CVMRmax in this range of ETCO2 also did not differ between patients and controls nor was it influenced by treatment (Table 2). Group-averaged curves were similar for patients and controls, and are not shown.

Effects of CO2 on BP and HR

Patients and controls had similar changes in ETCO2 during hyperventilation and rebreathing (Fig 1, 2). In controls, hyperventilation decreased BP by 16 (SD 3) mmHg and increased HR by 17 (SD 11) bpm. Rebreathing increased BP by 27 (SD 14) mmHg without a change in HR. In patients, hyperventilation lowered BP by 21 (SD 12) mmHg and increased HR by 14 (SD 10) bpm. During rebreathing, BP increased by 25 (SD 8) mmHg, without a change in HR. Neither short-term nor long-term treatment altered the BP and HR response to CO2.
DISCUSSION

This study assessed cerebral vasomotor reactivity to CO\textsubscript{2}, using a recently developed modified rebreathing method \cite{10}, in patients with untreated mild to moderate hypertension. There are four major findings. In contrast with existing reports, there was no difference in CVMR between patients and controls. With treatment, lowering of BP within 1-2 weeks with losartan/hydrochlorothiazide did not reduce CVMR, despite evidence for compensatory cerebral vasodilatation. Moreover, long-term BP control with this regimen, which results in inhibition of angiotensin II, had no effect on CVMR or cerebrovascular conductance. Finally, there was no difference in the BP and HR responses to CO\textsubscript{2} stimuli between patients and controls, and these responses were not influenced by antihypertensive treatment.

Normal CVMR in hypertension

Troisi et al., using a breath hold index with TCD, found reduced CVMR in hypertensive subjects (aged 34 (SD 7) y), which was partially restored with atenolol.\textsuperscript{8} The breath hold index describes vascular reactivity in a small hypercapnic range and provides no information on changes in ETCO\textsubscript{2} or BP. Serrador et al. reported reduced CVMR (TCD) in controlled and uncontrolled hypertension without co-morbidity.\textsuperscript{9} Their data were corrected for a hypothetical effect of cerebral autoregulation. Without this correction the difference between patients and controls was lost.\textsuperscript{9} Hypertensive subjects with reduced CVMR (TCD) in the study by Maeda et al. all had advanced cerebrovascular disease.\textsuperscript{7} Finally, the reported reduction in CVMR (perfusion MRI) by Kario et al.\textsuperscript{6} was limited to patients with both hypertension and diabetes.

Two studies found normal CVMR in hypertension. Tominaga et al. studied 9 patients without cerebrovascular disease.\textsuperscript{24} The Xenon- method used to measure CBF allowed for only 3-5 measurements in the hypocapnic-hypercapnic range (20-55 mm Hg). Oku et al. studied 8 hypertensive patients with minimal or no cerebrovascular disease.\textsuperscript{18} Only 2 measurements of CBF using PET were performed, before and after acetazolam ide injection to induce hypercapnia). Our study adds by exploring a much
wider range of changes in CO$_2$, by strongly increasing the number of CBF measurements, and by investigating transient changes in CO$_2$, CBFV and CVCI together, to account for alterations in BP during CO$_2$ stimuli.

Direct comparisons between studies is complicated because different populations were studied. We studied newly diagnosed, relatively healthy patients, whereas others included patients known to have hypertension as well as patients with co-morbidities, indicating that there may be important differences in the duration of hypertensive disease between studies. Nonetheless, CVMR was normal in these different groups, and impaired CVMR in these studies was limited to patients with co-existing diabetes and/or evidence for cerebrovascular disease. The presence of cerebrovascular disease may reflect a longer disease duration or it may point towards increased susceptibility for cerebrovascular disease in certain hypertensive patients. Consistent with this, CVMR remains normal in spontaneously hypertensive rats, whereas CVMR is impaired in the stroke-prone genetic variant, at advanced age when cerebrovascular disease has developed.

**Effects of treatment on CVMR**

We did not observe a reduction in CVMR following BP reduction with treatment. Given that the study was powered to detect a small reduction in CVMR, this suggests one of the following: the amount of BP reduction was too small to affect CVMR, or losartan had beneficial effects on remodeling or cerebral autoregulation.

**BP reduction and CVMR**

CVMR is reduced in patients with carotid artery stenosis, who have reduced perfusion pressure and compensatory cerebral vasodilatation. Reduction in CVMR was also observed after acute reduction in BP in animals and human subjects. The reduction in BP in our study was smaller and more gradual than that in the acute hypotension experiments, where BP was rapidly reduced below the normal autoregulation range. The reduction in BP is also not likely to approximate the reduction in perfusion pressure caused by a severe carotid artery stenosis. Moreover, the magnitude of vasodilatation to compensate the BP reduction may be too small to
influence the much stronger CO$_2$-induced vasodilatation. For example, for a 20% reduction in perfusion pressure, CBF can be maintained constant by an increase in cerebral blood vessel diameter of $\approx$ 6%. However, maximum hypercapnia, associated with a 100% increase in flow, brings about a 20% increase in diameter. Finally, vasodilatation in response to BP reduction may be mediated through different cerebral vessels than CO$_2$-induced vasodilatation. The latter is largely determined by smaller (intraparenchymal) cerebral arteries, arterioles and capillaries$^{32}$ whereas the former is more determined by larger (extraparenchymal) vessels: under normal conditions, larger arteries (diameter $>200$ $\mu$m) account for $\approx$ 40% of total cerebral vascular resistance, but their relative contribution increases in chronic hypertension$^{33}$. In hypertensive rats with BP $\approx$ 160 mmHg (controls: 98 mmHg), pial arteriolar pressure was only $\approx$ 80 mmHg (controls: 60 mmHg)$^{34}$ Thus, microvessels may retain normal vascular reactivity to CO$_2$ as they are protected by the resistance changes in larger arteries$^{33}$ alternatively, the adaptations that take place in larger arteries as a result of either hypertension or BP lowering are not reflected in CVMR.

Effects of angiotensine II blockade

We have studied the effects of losartan on CVMR after 1-2 weeks and again after 12 weeks of treatment. Should losartan have a beneficial effect on cerebral remodeling and endothelial function, an improvement of CVMR with treatment would have been expected and CVMR would have increased between 2 and 12 weeks. One other study (the study by Oku et al. cited above) has investigated the effects of losartan on CVMR, and found no change in CVMR in 8 hypertensive patients after 8-23 weeks of treatment$^{18}$. Only two measurements of CBF were performed and only in the hypercapnic range, using acetazolamide. A second study investigated the effect of 12-16 weeks of candesartan, and observed reduced CVMR using MRI in hypertensives with diabetes (n=20) with improvement following treatment$^6$. Patients with hypertension alone (n=20) had no reduction or change in CVMR. Cerebrovascular disease (multiple infarcts on MRI) was present in resp. 50 and 25% of these patients. Losartan beneficially affected cerebral autoregulation in animal studies$^{15}$. There was however no difference in autoregulation in patients with hypertension before and after treatment with losartan$^{16}$. 
CBFV was maintained stable with reductions in BP following treatment, meaning that compensatory vasodilatation took place as shown by the increase in CVCI (Table 2). This however did not reduce CVMR. This study was not designed to disentangle interactions between cerebral autoregulation and vasomotor reactivity, which are two different systems. The stable cerebral perfusion and CVRM following BP lowering treatment with losartan/hydrochlorothiazide neither proofs nor refutes beneficial effects of losartan on the cerebral circulation, however, the absence of a difference in these parameters between short term and long term treatment does not indicate such beneficial effects.

**BP response to CO₂**

Hypercapnia, through central chemoreceptors, causes sympathetic activation which in turn results in elevated BP due to the combined effects of an increase in cardiac output and peripheral vascular resistance. Hypertension is associated with increased baseline sympathetic activity, however whether this leads to an enhanced effect of hypercapnia on BP has not been addressed. We found no difference in BP and HR response between untreated patients with hypertension and controls, and antihypertensive treatment did not alter the BP and HR responses to CO₂. Possibly, despite the difference in baseline activity, sympathetic responses are similar in hypertension and controls. Alternatively, the magnitude of CO₂ induced sympathetic activation obscures the much smaller difference in baseline activity.

**Limitations of this study**

The limitations imposed by the measurement of CBF using TCD, as well as the limitations specific to the method used to estimate CVMR have been discussed. The flow-velocity in the MCA measured by TCD is determined by CBF and by the diameter of the MCA. Therefore, changes in CBFV reflect changes in CBF only if the MCA diameter is constant. During hypotension, hypocapnia and hypercapnia in healthy subjects and neurosurgical patients, MCA diameter was unchanged or showed less than 4 % change. Studies in hypertensive patients are lacking. Measurements of isolated MCA from spontaneously hypertensive rats indicate a 10 % change in diameter with
large changes in mean BP from 40 to 140 mmHg, suggesting that in our study, small changes in MCA diameter cannot be excluded. Such changes would have led to a finding of reduced CBFV after treatment. The relatively narrower MCA lumen in hypertensive patients might increase CBFV, overestimating CBF, and subsequent lumen increase following normalization of BP would then lower CBFV, underestimating CBF.

Nevertheless, our results are concordant with results obtained with other modalities (such as MRI and PET) to measure CBF during hypo- and hypercapnia, which suggests that possible confounding effects of changes in MCA diameter in our study had minimal effect on outcome or interpretation.

As with most other studies that have investigated CVMR in hypertension, this is a study in a small number of subjects. Our method has good reproducibility, in line with other methods to estimate CVMR. A clinically significant reduction in CVMR can be identified even with this small number of subjects. Indeed, this study was adequately powered to detect small differences in CVMR.

In summary, we have studied untreated patients with mild to moderate hypertension in the absence of diabetes or cerebrovascular disease, and have shown that CVMR was not affected. Previous reports of impaired CVMR with hypertension may be explained by co-morbid severe cerebrovascular disease and/or diabetes. We have also shown that despite significant hemodynamic alterations induced by the initiation of antihypertensive treatment, CVMR remained unaffected. We have recently observed that cerebral autoregulation was not altered after short-term and long-term antihypertensive treatment, indicating that cerebral vasodilatory responses to reductions in perfusion pressure were maintained. Together these observations suggest that the cerebrovascular adaptations to a reduction in perfusion pressure are not associated with exhaustion of cerebrovascular reserve. Further studies may elucidate whether the finding of impaired CVMR in a patient with hypertension may herald an increased risk for cerebrovascular disease.

Disclosure: none to declare for all authors.
Acknowledgments: we thank all the subjects for their willingness to participate in this study. This study was supported in part by a grant from the American Heart Association Texas Affiliate 0060024Y.

References


Figure legends

Figure 1. Example of the analysis of vasomotor reactivity in a healthy subject.

Results of the modified rebreathing test and sigmoidal curve-fitting, displaying the changes in cerebral blood flow velocity (CBFV, left) and cerebrovascular conductance index (CVCI, right) in response to end-tidal CO$_2$ (ETCO$_2$) in a healthy control subject. The black dots represent data averaged over the period of one breath, during hyperventilation (data points below 100 %) and CO$_2$-rebreathing (data points above 100%). The sigmoid line is the result of 4-parameter exponential curve fitting of these data points (see text and $^{10}$ for more details). The left graph offers a graphic representation of these 4 identified parameters. “a” is the total range of changes in CVCI or CBFV, “$Y_0$” is the maximum value, “$X_0$” is the level of ETCO$_2$ that exhibits highest CO$_2$ sensitivity, and “b” is a factor that determines the shape of the regression curve.

Figure 2. Example of vasomotor reactivity analysis in a hypertensive patient.

Results of the modified rebreathing test and sigmoidal curve-fitting in a hypertensive patient. Representation of black dots and sigmoid curve as in figure 1. Top: Changes in cerebral blood flow velocity (CBFV) in response to end-tidal CO$_2$ (ETCO$_2$) at baseline (A), and after 1-2 weeks (B) and 3 months (C) of treatment with losartan/hydrochlorothiazide. Bottom: Changes in cerebrovascular conductance index (CVCI) in response to ETCO$_2$ at baseline (D), and after 1-2 weeks (E) and 3 months (F) of treatment.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline Control</th>
<th>Hypertension</th>
<th>1-2 weeks Control</th>
<th>Hypertension</th>
<th>3-4 months Control</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46 (10)</td>
<td>52 (9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>180 (9)</td>
<td>178 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>87 (16)</td>
<td>88 (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (3)</td>
<td>27 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.02 (0.10)</td>
<td>1.01 (0.19)</td>
<td>0.97 (0.16)</td>
<td>0.96 (0.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.2 (0.21)</td>
<td>4.5 (0.51)</td>
<td>4.5 (0.81)</td>
<td>4.1 (0.27)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA, ng/L</td>
<td>0.67 (0.44)</td>
<td>0.99 (1.04)</td>
<td>3.06 (3.09)</td>
<td>0.78 (0.71)</td>
<td>2.37 (2.40)</td>
<td></td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>4.45 (2.30)</td>
<td>6.27 (3.40)</td>
<td>6.14 (2.76)</td>
<td>4.23 (1.70)</td>
<td>6.07 (4.42)</td>
<td></td>
</tr>
<tr>
<td>24 h ABPM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>awake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>122 (7)</td>
<td>148 (12)*</td>
<td>--</td>
<td>130 (15)†</td>
<td>124 (7)</td>
<td>125 (10)†</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>75 (7)</td>
<td>89 (7)*</td>
<td>--</td>
<td>80 (9)†</td>
<td>76 (7)</td>
<td>77 (7)†</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69 (8)</td>
<td>77 (8)*</td>
<td>--</td>
<td>78 (7)</td>
<td>72 (8)</td>
<td>77 (10)</td>
</tr>
<tr>
<td></td>
<td>nighttime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>110 (10)</td>
<td>129 (17)*</td>
<td>--</td>
<td>113 (9)†</td>
<td>117 (12)</td>
<td>109 (12)†</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>68 (10)</td>
<td>77 (7)</td>
<td>--</td>
<td>70 (6)</td>
<td>70 (9)†</td>
<td>69 (7)†</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>64 (8)</td>
<td>68 (10)</td>
<td>--</td>
<td>70 (9)</td>
<td>67 (9)</td>
<td>66 (10)</td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>49 (11)</td>
<td>49 (12)</td>
<td>--</td>
<td>51 (14)</td>
<td>51 (13)</td>
<td>51 (14)</td>
</tr>
<tr>
<td>CVCI, cm/s/mmHg</td>
<td>0.51 (0.11)</td>
<td>0.45 (0.11)</td>
<td>--</td>
<td>0.53 (0.13)†</td>
<td>0.52 (0.10)</td>
<td>0.55 (0.15)†</td>
</tr>
</tbody>
</table>
Data are mean (SD), n = 8 for control, n = 11 for hypertension. BMI, body mass index. PRA, plasma renin activity. SBP, systolic blood pressure, DBP, diastolic blood pressure, HR, heart rate. These measurements were obtained from 24 h ambulatory BP measurements (ABPM, presented as awake and nighttime averages). Nighttime BP was significantly lower than awake BP in patients and controls (p < 0.01). Mid-term BP (at 6 weeks) was measured in patients only and was 127 (8)/80 (4) mmHg. CBFV, cerebral blood flow velocity, CVCI, cerebrovascular conductance, ETCO$_2$, end-tidal CO$_2$. These measurements were obtained under supine resting conditions. * P < 0.05 for comparison between control subjects and patients with hypertension. † P < 0.01 for comparisons between baseline and treatment for patients with hypertension.
Table 2. Estimates of CVMR in controls and patients with hypertension before and during treatment

<table>
<thead>
<tr>
<th>Vasomotor reactivity</th>
<th>Control</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3-4 months</td>
</tr>
<tr>
<td><strong>Hypocapnia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>minimum flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBFV, %</td>
<td>60 (9)</td>
<td>65 (9)</td>
</tr>
<tr>
<td>minimum conductance</td>
<td>65 (10)</td>
<td>67 (10)</td>
</tr>
<tr>
<td><strong>Hypercapnia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>maximum flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBFV, %</td>
<td>216 (26)</td>
<td>218 (29)</td>
</tr>
<tr>
<td>maximum conductance</td>
<td>172 (26)</td>
<td>176 (16)</td>
</tr>
<tr>
<td><strong>Logistic model parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-CBFV, %</td>
<td>178 (26)</td>
<td>160 (31)</td>
</tr>
<tr>
<td>a-CVCI, %</td>
<td>114 (22)</td>
<td>106 (15)</td>
</tr>
<tr>
<td>Y0-CBFV, %</td>
<td>227 (24)</td>
<td>213 (35)</td>
</tr>
<tr>
<td>Y0-CVCI, %</td>
<td>180 (25)</td>
<td>177 (19)</td>
</tr>
<tr>
<td>X0-CBFV, mmHg</td>
<td>48 (3)</td>
<td>45 (6)</td>
</tr>
<tr>
<td>X0-CVCI, mmHg</td>
<td>47 (3)</td>
<td>46 (2)</td>
</tr>
<tr>
<td>b-CBFV, constant</td>
<td>0.17 (0.0)</td>
<td>0.22 (0.0)</td>
</tr>
<tr>
<td>b-CVCI, constant</td>
<td>0.25 (0.1)</td>
<td>0.30 (0.1)</td>
</tr>
<tr>
<td><strong>Estimations of CVMR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic regression</td>
<td>CVMRmax-</td>
<td>7.5 (0.8)</td>
</tr>
<tr>
<td></td>
<td>CBFV, %/mmHg</td>
<td>CVMRmax-CBFV, %/mmHg</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Linear regression 40-50 Mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBFV, %/mmHg</td>
<td>7.0 (1.5)</td>
<td>7.8 (0.9)</td>
</tr>
<tr>
<td>CVCI, %/mmHg</td>
<td>8.0 (1.8)</td>
<td>7.9 (1.6)</td>
</tr>
<tr>
<td>CVMRmax-CBFV, %/mmHg</td>
<td>7.3 (1.7)</td>
<td>7.9 (1.5)</td>
</tr>
<tr>
<td>CVMR-CBFV, %/mmHg</td>
<td>7.9 (2.5)</td>
<td>7.6 (1.5)</td>
</tr>
<tr>
<td>CVMRmax-CVCI, %/mmHg</td>
<td>7.4 (1.4)</td>
<td>8.3 (1.4)</td>
</tr>
<tr>
<td>CVMR-CVCI, %/mmHg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (SD). N=7 for control, n=11 for hypertension. CBFV, cerebral blood flow velocity, CVCI, cerebrovascular conductance index. Minimum and maximum values during hypocapnia and hypercapnia represent observed values for CBFV and CVCI. Logistic model parameters represent values for CBFV and CVCI predicted from logistic regression. a-CBFV, total change in CBFV from maximum hypocapnia to maximum hypercapnia in % of baseline. Note that a-CBFV compares to the difference between maximum flow and minimum flow. a-CVCI, similar for CVCI. Y0-CBFV, maximum value for CBFV during hypercapnia, relative to baseline. Note that Y0-CBFV compares to maximum flow. Y0-CVCI, similar for CVCI. X0, value for end-tidal CO2 where CVMRmax, from logistic regression, occurs. CVMRmax, maximum vasomotor reactivity identified with either logistic regression or linear regression in the ETCO2 range between 40-50 mm Hg (see text). CVMR, index of vasomotor reactivity representing the ratio of change in CBFV or CVCI over ETCO2 in the total hypocapnic and hypercapnic range. There were no significant differences between controls and patients or between baseline and follow-up (P > 0.1).
Fig 1
Fig 2

A

B

C

D

E

F

ETCO₂ (mm Hg)