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Temporary application of Lower Body Positive Pressure improves intracranial velocities in symptomatic acute carotid occlusion or tight stenosis: a pilot study

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Abstract

Background. Patients with isolated cervical carotid artery occlusion not eligible to recanalization therapies but with compromised intracranial hemodynamics may be at risk of further clinical events. Apart from lying flat until spontaneous recanalization or adjustment of the collateral circulation hopefully occurs, no specific treatment is currently implemented. Improving collateral flow is an attractive option in this setting. Lower body positive pressure (LBPP) is known to result in rapid venous blood shift from the lower to the upper body part, in turn improving cardiac preload and output, and is routinely used in acute hemorrhagic shock. We report here cerebral blood flow velocities measured during LBPP in this patient population.

Methods. This is a retrospective analysis of the clinical, physiological and transcranial Doppler (TCD) monitoring data collected during and 15min after LBPP in 21 consecutive patients (10 females, median age: 54yrs) with recently symptomatic isolated carotid occlusion/tight stenosis (unilateral in 18) mostly due to atherosclerosis or dissection. LBPP was applied during 90min at a median 5 days after symptom onset.

Results. At baseline, middle-cerebral artery (MCA) velocities were markedly lower on the symptomatic, as compared to asymptomatic, side. LBPP significantly improved blood flow velocities in both the symptomatic and asymptomatic MCA as well as the basilar artery, which persisted 15 min after discontinuing the procedure. LBPP also resulted in mild but significant increases in mean arterial blood pressure.

Conclusions. LBPP improved intracranial hemodynamics downstream recently symptomatic carotid occlusion/tight stenosis as well as in the contralateral and posterior circulations, which persisted after LBPP deflation. Randomized trials should determine if this easy-to-use, non-invasive, non-pharmacologic approach has long-lasting benefits on the intracranial circulation and improves functional outcome.

Introduction

Acute carotid artery occlusion leads to the recruitment of collateral circulation via the circle of Willis, leptomeningeal anastomoses or both. The degree to which these collateral pathways are recruited influences final infarct size(1). In patients not eligible to recanalization therapy or in whom recanalization has failed, improving collateral flow is an attractive therapeutic strategy (2). To this end, one potential approach is lower body positive pressure (LBPP).

Lower-body positive pressure (LBPP) is obtained by means of medical antishock trousers (MAST) that comprise bladders positioned over both the lower limbs and the abdomen, inflated to venous pressure levels (15 to 20 mmHg). LBPP is known to result in rapid blood shift from the lower body venous compartment towards the upper body part, in turn improving cardiac preload and, subsequently cardiac output(3-7), followed by a sustained reduced venous capacitance. With a slightly delayed effect, LBPP also results in higher plasma volume via increased interstitial pressure in the muscular and visceral masses(8, 9). Accordingly, although at higher pressures, LBPP is currently routinely used in acute conditions such as obstetric hemorrhage and lower-body hemorrhagic injury(10, 11). The above physiological effects likely explain the increase in cerebral blood flow velocities observed after LBPP(12). We previously reported improved cerebrovascular blood flow velocities during LBPP in two patients with recent internal carotid artery occlusion and cerebral hemodynamic compromise, with apparent clinical benefit and no adverse effects(13).

We present here a retrospective analysis of all consecutive patients treated by the authors with LBPP for symptomatic recent carotid artery occlusion/tight stenosis. The effects of the intervention on cerebral blood flow velocities were measured in all patients. We hypothesize

that LBPP will improve intracranial hemodynamics in the affected territory as well as in the contralateral and posterior circulation, via collateral pathways.

Patients and Methods

Patients

This is a retrospective analysis of all 21 patients who received LBPP as part of routine care in our institutions (Lariboisière and Bichat University Hospitals, Paris, France) between 2004 and 2014, including the two previously reported patients(13). All patients were recently symptomatic with carotid artery occlusion or near-occlusion and severe hemodynamic compromise based on the occurrence of hemodynamic clinical events (e.g., transient ischemic attack when raising from bed) and/or transcranial Doppler (TCD) assessment, but without extensive brain infarction, and who were judged by the physician-in-charge to be at risk of neurological deterioration and to derive potential benefit from improved cerebral perfusion via LBPP. All patients were kept in a lying flat head position to avoid hemodynamic clinical deterioration.

LBPP procedure

A MAST device was applied for 90min as previously detailed (Berthet et *al.*, 2010). The patient lying in supine position, the garment was applied from the ankle to the costal margin, and the bladder pressures were set at 20 mmHg on the lower limbs and 10 mmHg on the abdominal area, to ensure a positive pressure gradient(5). Given the liability to develop hypovolemia from the prolonged supine position as part of their clinical management (see above), a fluid loading of 500mL of colloid (Plasmion®) was infused over 15min just prior to MAST inflation. As per standard instructions for users, LBPP was not implemented in patients with heart failure, recent (<3 months) myocardial infarction, acute deep vein thrombosis or skin lesions.

Physiological measurements

In order to monitor the effects of LBPP on intracranial hemodynamics, the systolic and diastolic velocities on the symptomatic and asymptomatic MCA (MCA_{sv} and MCA_{dv}, respectively) and the basilar artery (BA_{sv} and BA_{dv}) were measured by means of pulsed Doppler at baseline, immediately after fluid loading, 5min and 90min after the beginning of LBPP procedure, and again 15min after MAST deflation (to be referred to below as Baseline, Fluid, LBPP+5min, LBPP+90min and post-LBPP, respectively), using TCD (DWL Elektronische System GmbH, Singen, Germany). We used a 2 MHz probe positioned at 55mm and 85mm depth for the MCA and the basilar artery, respectively. Velocities were calculated by standard spectral analysis(14) implemented in the proprietary software of the TCD machine and applied onto Doppler spectra averaged over 6 cardiac cycles. The mean arterial blood pressure (MABP) and heart rate (HR) were also monitored.

Clinical evaluation

The neurological status was monitored using the NIHSS scale immediately before and after the LBPP procedure.

The protocol was approved by the Inserm Institutional Review Board (IRB # 00003888). In accordance with French legislation, as this study only implied retrospective analysis of anonymized data collected as part of routine care, each patient was informed by post of his/her participation in this study, and was offered the possibility to withdraw.

Data handling and statistical analysis

Results were expressed as mean (and SD) or median (and first (Q1) and third (Q3) quartiles) while categorical variables were expressed as counts and percentages.

The statistical analysis aimed to assess the changes in physiological values (i.e., MCA and BA diastolic and systolic velocities, HR and MABP) over time (i.e, across the five time-points, from

baseline to post-LBPP), but also, regarding MCA velocities, according to hemispheric side, i.e., symptomatic vs asymptomatic. To this end, we used linear mixed models (LMM), which are better suited to this type of dataset than repeated-measures ANOVAs. Fixed effects were: i) Time (i.e. Baseline, Fluid, LBPP+5min, LBPP+90min and post-LBPP); and ii) only for MCA velocities, Side and Time x Side interaction. The aim of assessing the Time x Side interaction was to investigate whether the effect of LBPP on the time course of MCA velocities differed between sides. Patient ID was the random effect. Note that we a priori excluded from the above analyses all patients with bilateral carotid occlusion/tight stenosis, because it was considered that the asymptomatic side could not be used as control.

As a pre-planned *post-hoc* analysis, we also assessed differences between time-points. For non-lateralized measures (i.e., HR, MABP, BA_{sv} and BA_{dv}), post hoc tests systematically assessed differences in velocity values from one time point to the next, and also between baseline and both LBPP+90min and post-LBPP. For lateralized measures, i.e., MCA velocities, the same comparisons were performed separately for the symptomatic and asymptomatic sides, and for the systolic and diastolic velocities. Correction for multiple tests was performed using the Benjamini-Hochberg method; however, for the sake of physiological interest, the effects of side (MCA velocities) were tested in a systematic, exploratory fashion.

Type II tests were performed, and Cohen's f^2 were calculated, using the marginal R^2 , for each effect to estimate their size. Normality of residuals and random effects as well as heteroskedasticity were verified visually. Influencers and outliers were checked computing hat values and Cook distances. Statistical analyses were performed using R 3.5.0. Package lme4 (version 1.1-17) was used to perform-the linear mixed model.

Results

1. Clinical data

Twenty-one consecutive patients (11 males) were treated with LBPP. **Table 1** summarizes the demographics and main clinical data. Median age was 54 years (Interquartile range – IQR [41-66]). Eighteen patients had a stroke and three had a TIA (i.e., transient symptoms with carotid

occlusion/tight stenosis and negative diffusion-weighted imaging). The NIHSS score immediately before the LBPP procedure ranged from 0 to 22 (median: 9 [IQR 2-16]).

Eighteen patients had ipsilateral internal carotid artery (ICA) occlusion or near-occlusion. The remaining three patients had bilateral ICA occlusion/near-occlusion, but one side only was symptomatic. There was no instance of associated MCA occlusion (i.e., tandem occlusion).

The cause of carotid disease was atherosclerosis (n=9 [43%]), dissection (n=8 [38%]), embolism (n=1 [5%]), dysplasia (n=1 [5%]) unknown (n=2 [10%]). Individual data are presented in **Supplemental Table 1**.

On MR angiography, there was no evidence of 'isolated' ICA, i.e., the symptomatic ICA was always supplied via the contralateral ICA and/or the posterior circulation.

2. LBPP procedure and safety aspects

The LBPP procedure was performed at a median of 5 days (IQR [2-14]) after stroke onset (Supplemental Table 1). There was no instance of NIHSS worsening during LBPP, and the NIHSS improved in 8 patients (Supplemental Table 1). No adverse event was observed, apart from three patients who complained of slight lower-body discomfort related to the pants.

3. Physiological measures

The raw physiological measures at baseline for the 21 patients are shown in Supplemental Table 1.

As per the statistical plan (see Methods), the three patients with bilateral carotid occlusion/tight stenosis were excluded from the Linear Mixed Model, which was therefore applied to the 18 patients with unilateral carotid obstruction.

The results to be presented below will follow the outline of the statistical analysis, namely i) main effect of Time; ii) main effect of Side; iii) interaction between Time and Side; and iv) time-course of MCA velocities for each hemisphere separately. In summary, the results showed significant improvement in all measured intracranial velocities, both during and after the LBPP procedure.

3.1. Main effect of Time

There was a significant Time effect on all variables (p value range: 0.0017 to 0.0199, after correction for multiple tests), except heart rate (**Table 2, Figure 1**). Post-hoc tests on the BA, HR and MABP time-point data disclosed significant differences, in the form of consistent increases in BAsv and BAdv from baseline to fluid load (p=0.0375 and p=0.0427 respectively), and in BAsv, BAdv and MABP from baseline to both LBPP+90min (p=0.0074, p=0.0070 and p=0.0202, respectively) and post-LBPP (p=0.0069, p=0.0003 and p=0.0451, respectively) (**Figure 1 C-D-F**).

3.2. Main effect of Side (MCA velocities)

There was a highly significant effect of hemispheric side, with the asymptomatic side consistently showing higher systolic and diastolic velocities than on the symptomatic side (p <0.0001 for both) (**Table 2**).

3.3. Interaction between Side and Time (MCA velocities).

The Side x Time interaction analysis revealed no significant difference in velocity time course between sides (**Table 2**). This finding indicates that the just-described significant effect of Side applies to all timepoints, including baseline (see **Supplemental Table 1** for individual data).

3.4. Time-course of MCA velocities for each cerebral hemisphere separately

The exploratory analysis for the symptomatic side revealed significant increases in both MCAsv and MCAdv from baseline to LBPP+90min (p=0.0032 and p=0.0004, respectively), and from baseline to post-LBPP (p=0.0247 and p=0.0239, respectively) (**Figure 1 A and B**).

The exploratory analysis of the asymptomatic side showed significant increases in both MCAsv and MCAAdv from baseline to fluid load ($p=0.0426$ and $p=0.0457$, respectively), as well as from baseline to post-LBPP ($p=0.0177$ and $p=0.0403$, respectively). In addition, the MCAAdv also significantly increased from baseline to LBPP+90min ($p=0.0153$) (Figure 1A and 1B).

Discussion

In the present sample of symptomatic patients with recent carotid occlusion/tight stenosis, LBPP inflated at venous pressures with prior fluid load significantly increased blood flow velocity in the ipsilateral as well as the contralateral MCA and the basilar artery. In this sample, the presence of compromised intracranial hemodynamics was documented by the markedly lower baseline MCA velocities on the symptomatic as compared to the asymptomatic side. Remarkably, the hemodynamic effects of LBPP were sustained after MAST deflation, as shown by TCD measurements carried out 15min after the procedure was completed (Fig 1). This was particularly true on the symptomatic side, as shown by the significant increase in MCA velocity from LBPP+90min to post-LBPP (Fig 1 A, B). Of note, fluid load in itself was associated with a significant increase in velocities for all intracranial arteries except the symptomatic MCA. The procedure also resulted in a small but statistically significant increase in MABP.

We applied the LBPP procedure to consecutive patients with persistent carotid occlusion/tight stenosis >24hrs after the clinical event, and who were considered at high risk of clinical deterioration by their clinician-in-charge because of intracranial hemodynamic compromise. The hemodynamic benefits derived from LBPP in our patients likely occurred via increased blood flow in the carotid territory through the circle of Willis and/or the leptomeningeal collaterals. This can be inferred because, in all patients in whom the circle of Willis was assessable by MRA, the carotid territory was supplied by the anterior and/or posterior communicating arteries.

The expected physiologic effects of LBPP include a shift of blood from the subdiaphragmatic veins towards the central compartment, as well as an augmentation of plasma volume, together resulting in an “internal fluid loading effect”. These physiologic effects have been shown to result in increased intracranial blood flow velocities in healthy subjects(12), as also observed in our patients with symptomatic carotid occlusion/tight stenosis. Given that the MCA diameter is not expected to substantially change during physiological challenges(15), this increase in velocities likely reflects a higher bulk flow. Of note, as seen here, LBPP may also induce mild increases in MABP, which might have contributed in part to the enhanced MCA velocities observed here, given the presumably lost downstream autoregulation. Because acute stroke patients may be hypovolemic after long stays in the supine position, we sensitized these hemodynamic responses by adding moderate fluid loading prior to the LBPP procedure.

Regarding the sustained increase in MCA flow velocities observed 15min after end of the LBPP procedure, a likely mechanism may involve a lingering augmentation of plasma volume(16). Another, non-mutually exclusive, mechanism may involve persistence of the functional effects of LBPP on the collateral circulation.

The present work has the limitations inherent to case series, and the findings reported here are hypothesis-generating and will need to be replicated in a randomized controlled trial, assessing not only the intracranial hemodynamics but also tissue perfusion and clinical outcome. It should be noted that, due to the statistical design chosen, the three patients with bilateral carotid occlusion/near-occlusion were excluded from the analysis. Nevertheless, adding these three patients in a post hoc analysis did not substantially affect the results (data not shown). In addition, this retrospective study collected all consecutive patients with cervical internal carotid

occlusion/tight stenosis in whom LBPP was applied in two large stroke centers over the period of observation, which inevitably implies heterogeneity in underlying vascular etiologies with likely different potential for rapid reversibility, notably atheroma and dissection. Studies on more homogeneous samples would be important to consider in future. Finally, LBPP was applied here for 90mins, which is the typical duration for uses of MAST in emergency situations. However, it would be of interest to test other durations in future.

In conclusion, although prospective studies are needed, our findings suggest that LBPP improves the intracranial hemodynamics in patients with subacute symptomatic carotid occlusion/tight stenosis. More widely, this simple-to-administer, non-invasive technique might eventually play a role as temporizing measure leading to stenting or recanalization therapies.

Conflict of Interest: KB is CEO, KBV and A-CL are co-founders, and J-CB has received consultancy fees from, the Neuraltide start-up company.

Data availability: The data reported in this study are available from the corresponding author upon reasonable request.

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Figure Legend

Figure 1: Time-course of MCA velocities (A: systolic; B: diastolic) for the symptomatic and asymptomatic sides separately, and for basilar artery velocity (C: systolic; D: diastolic), heart rate (E) and mean arterial blood pressure (MABP; F) at baseline, during LBPP and 15 min after end of the procedure for the subset of 18 patients with unilateral carotid occlusion/tight stenosis. Shown are estimated marginal means obtained by the linear mixed models. Post hoc tests compared neighbouring time points and also baseline data to both LBPP+90min and post-LBPP values (see Methods). Statistically significant post-hoc comparisons, shown as asterisks, involved only comparisons to Baseline (see Results for the p values).

Table 1: Demographics and main clinical data. Counts, percentages and medians [IQR] are shown.

	Patients n=21
Age	54 [41-66]
Sex	
<i>Women</i>	10 (47.6%)
<i>Men</i>	11 (52.3%)
Vascular Risk Factors	
<i>Hypertension</i>	7
<i>Hypercholesterolemia</i>	4
<i>NIDM</i>	2
<i>Smoking</i>	4
Stroke/TIA	18/3
Territory	
<i>left MCA</i>	9 (42.8%)
<i>right MCA</i>	12 (57.1%)
Carotid occlusion/stenosis	
<i>ICA occlusion</i>	14 (66.6%)
<i>ICA tight stenosis</i>	3 (14.2%)
<i>left CCA occlusion</i>	1 (4.7%)
<i>left ICA occlusion/right ICA occlusion</i>	2 (9.5%)
<i>left ICA occlusion/right ICA stenosis</i>	1 (4.7%)
Cause of carotid occlusion/stenosis	
<i>Atherosclerosis</i>	9 (42.8%)
<i>Dissection</i>	8 (38.1%)
<i>cardioembolism</i>	1 (4.7%)
<i>fibromuscular dysplasia</i>	1 (4.7%)
<i>Unknown</i>	2 (9.5%)
NIHSS	
<i>before LBPP</i>	9.00 [2, 16]
<i>after LBPP</i>	7.50 [1, 15]
LBPP procedure delay (days)	5.00 [2, 14]

Abbreviations: NIDM: non-insulin-dependent diabetes mellitus; TIA: transient ischemic attack; MCA: middle cerebral artery; ICA: internal carotid artery; CCA: common carotid artery; LBPP: lower body positive pressure.

Table 2. Results of the linear mixed model to model trajectories on the 6 variables. Statistically significant results are shown in bold face.

	Time			Hemispheric side			Time x Side		
	Cohen'f2	P value	P value*	Cohen'f2	P value	P value*	Cohen'f2	P value	P value*
MCAsv	0.0454	0.0002	0.0007	1.3572	<0.0001	<0.0001	0.0029	0.8097	0.8097
MCAdv	0.0489	0.0001	0.0007	0.2823	<0.0001	<0.0001	0.0139	0.1387	0.2774
BAsv	0.0256	0.0130	0.0195						
BAdv	0.0555	0.0008	0.0017						
MABP	0.0484	0.0166	0.0199						
HR	0.0041	0.5739	0.5739						

* Corrected for multiple tests

Figure 1

