ANESTHESIOLOGY

Cerebral Blood Flow Assessed with Phase-contrast Magnetic Resonance Imaging during Blood Pressure Changes with Noradrenaline and Labetalol: A Trial in Healthy Volunteers

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Previous studies have relied on indirect measures of cerebral blood flow, such as flow velocity (transcranial Doppler) or cerebral oxygenation (near infrared spectroscopy)
- These studies have called into question the reliability of using the mean arterial pressure as a proxy for cerebral blood flow
- Phase-contrast magnetic resonance imaging enables fast and accurate quantitative measurements of blood flow

What This Article Tells Us That Is New

- In healthy unanesthetized volunteers, norepinephrine increased arterial pressure but decreased the cerebral blood flow
- Cerebral blood flow was correlated with cardiac output, not arterial blood pressure

ABSTRACT

Background: Adequate cerebral perfusion is central during general anesthesia. However, perfusion is not readily measured bedside. Clinicians currently rely mainly on mean arterial pressure (MAP) as a surrogate, even though the relationship between blood pressure and cerebral blood flow is not well understood. The aim of this study was to apply phase-contrast magnetic resonance imaging to characterize blood flow responses in healthy volunteers to commonly used pharmacologic agents that increase or decrease arterial blood pressure.

Methods: Eighteen healthy volunteers aged 30 to 50 yr were investigated with phase-contrast magnetic resonance imaging. Intra-arterial blood pressure monitoring was used. First, intravenous noradrenaline was administered to a target MAP of 20% above baseline. After a wash-out period, intravenous labetalol was given to a target MAP of 15% below baseline. Cerebral blood flow was measured using phase-contrast magnetic resonance imaging and defined as the sum of flow in the internal carotid arteries and vertebral arteries. Cardiac output (CO) was defined as the flow in the ascending aorta.

Results: Baseline median cerebral blood flow was 772 ml/min (interquartile range, 674 to 871), and CO was 5,874 ml/min (5,199 to 6,355). The median dose of noradrenaline was 0.17 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (0.14 to 0.22). During noradrenaline infusion, cerebral blood flow decreased to 705 ml/min (606 to 748; $P = 0.001$), and CO decreased to 4,995 ml/min (4,705 to 5,635; $P = 0.01$). A median dose of labetalol was 120 mg (118 to 150). After labetalol boluses, cerebral blood flow was unchanged at 769 ml/min (734 to 900; $P = 0.68$). CO increased to 6,413 ml/min (6,056 to 7,464; $P = 0.03$).

Conclusions: In healthy, awake subjects, increasing MAP using intravenous noradrenaline decreased cerebral blood flow and CO. These data do not support inducing hypertension with noradrenaline to increase cerebral blood flow. Cerebral blood flow was unchanged when decreasing MAP using labetalol.

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Although there is consensus that maintaining adequate cerebral blood flow during general anesthesia is imperative, how to achieve it is a long-standing controversy. The issue is complicated by a lack of reliable methods to assess cerebral blood flow at the bedside. Commonly, mean arterial pressure (MAP) is used as a surrogate indicator for cerebral blood flow,[1] even though the relationship between blood pressure and cerebral blood flow is not fully understood. In the current era, potent vasoactive drugs (including α- and β-adrenergic agonist noradrenaline) are widely implemented to maintain a desired MAP,[2] even though it is unclear whether raising MAP corresponds to cerebral blood flow increase. Several recent studies during general anesthesia suggest that there may be no increased perfusion or even possibly decreased perfusion when MAP was raised with vasoconstrictor drugs.[3,4]

Acute hypertension is also common in certain perioperative populations, including for patients with ischemic stroke undergoing mechanical thrombectomy[5] and patients with intracerebral hemorrhages,[6] in whom hypertension can be associated with worse functional outcomes.[5,7,8] First-line perioperative treatment to lower MAP can be the α- and β-adrenergic antagonist labetalol.[6] Notably, however, a recent randomized controlled trial was terminated early because intensive blood pressure control was associated with harm in a cohort undergoing mechanical thrombectomy.[5] The effects of acute blood pressure–lowering therapy on cerebral blood flow are not well studied and are an important aspect of the interaction between blood pressure and outcome.

Previous studies have often estimated cerebral blood flow by indirect measures such as near-infrared spectroscopy or transcranial Doppler, both of which, while practically accessible at the bedside, have distinct weaknesses.[9,10] To understand the specific effects of perioperative pharmacologic circulatory interventions on cerebral blood flow, studies are needed that use direct cerebral blood flow measurements and, first, eliminate other pharmacologic and pathologic interactions including anesthetic drugs. Phase-contrast magnetic resonance imaging enables fast and accurate quantitative measurement of blood flow. It is currently the reference standard for noninvasive intravascular flow measurements[11] and useful in experimental settings.

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The aim of this phase-contrast magnetic resonance imaging study was to quantify the blood flow responses in healthy volunteers to commonly used pharmacologic agents that increase or decrease arterial blood pressure. A secondary aim was to establish a protocol for studying drug effects on cerebral blood flow that could be applied to study participants under general anesthesia and with cerebrovascular disease.

Materials and Methods

Eighteen healthy, awake volunteers were studied. Using phase-contrast magnetic resonance imaging, cerebral blood flow was measured at baseline and after raising and lowering MAP using noradrenaline and labetalol, respectively. A 20% increase and a 15% decrease in MAP were targeted. The study was conducted at Umeå University Hospital (Umeå, Sweden) between May 2021 and January 2022.

Ethical Considerations

All participants provided written informed consent. The study was approved by the Swedish Ethical Review Authority (approval No. 2020-05764) and performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Study Population

Through advertisements in the local hospital and social media, we recruited healthy volunteers aged between 30 and 50 yr. Possible participants were assessed by a physician (J.B.) to confirm health, with medical history, cardiopulmonary, and neurologic examination, as well as electrocardiogram. A screening magnetic resonance imaging examination of the brain was performed to exclude intracranial expansivities or vascular abnormalities. Additional exclusion criteria were any disease or pharmacologic treatment affecting the cardiovascular or nervous systems, Body Mass Index less than 18.5 or greater than 29.9, electrocardiogram abnormalities, or contraindications to any of the study drugs.

Treatment Protocol

Nicotine, caffeine, alcohol, or physical exercise were not permitted 12 h before the study procedure. Direct blood pressure monitoring was performed with a hospital standard radial artery catheter and a fluid-filled system and transducer. Electrocardiogram and pulse oximetry were recorded continuously.

The study procedure was initiated with baseline phase-contrast magnetic resonance imaging blood flow sequences (see "Magnetic Resonance Imaging" section) and MAP measurements (fig. 1). Thereafter, an infusion of noradrenaline was started at 0.04 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Plasmalyte (Baxter, USA) was used as an infusion carrier. The infusion rate was increased every 2 min in increments of 0.01

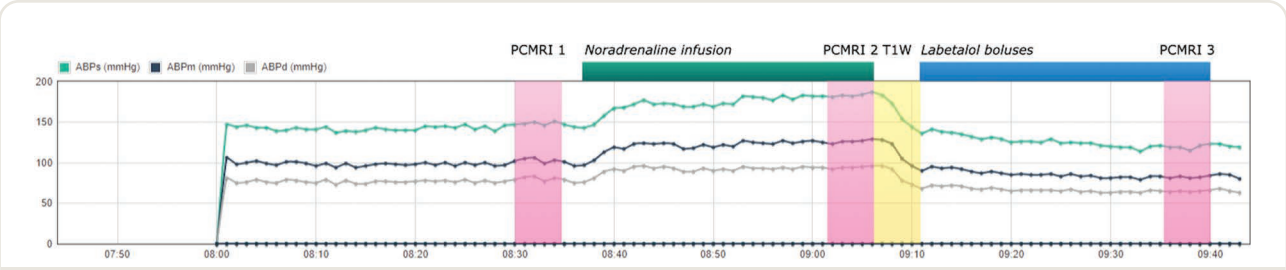

Fig. 1. Study procedure. Example study procedure timeline from one subject including blood pressure curves with timing of drug administration and magnetic resonance imaging (MRI) acquisitions overlaid. ABPs, systolic blood pressure; ABPm, mean arterial pressure; ABPd, diastolic blood pressure; PCMRI, phase contrast MRI; T1W, T1-weighted structural MRI.

to 0.04 μg · kg^{-1} · h^{-1} at the discretion of the supervising anesthesiologist to achieve a target of 20% MAP increase. An upper limit was set at a systolic blood pressure of 200 mmHg. When the target MAP was reached, phase-contrast magnetic resonance imaging was repeated, and the noradrenaline infusion was subsequently stopped. When MAP had returned to baseline and a wash-out period of 5 min had been observed, IV labetalol was administered. The initial dose was 20 mg followed by boluses of 10 to 20 mg every 2 min, depending on blood pressure response, to a target of 15% MAP decrease from baseline or a maximal dose of 150 mg. When target MAP or maximal dose was reached, phase-contrast magnetic resonance imaging was repeated. Total procedure time was approximately 90 min. The procedure was discontinued in case of adverse events or if the subject for some other reason could not reach the prespecified blood pressure change or drug dose. The subjects were observed for a minimum of 120 min after completion of the procedure.

Magnetic Resonance Imaging

The brain magnetic resonance imaging screening included T1- and T2-weighted, T2-FLAIR, and time-of-flight angiography sequences. During the study procedure, T1-weighted three-dimensional images were acquired for calculating brain volume (magnetization prepared rapid gradient echo imaging with repetition time/echo time/flip angle of 10.3 ms/4.9 ms/8°).

All phase-contrast magnetic resonance imaging scans were performed at a Philips Ingenia 3 tesla system with a 20-channel head–neck coil. A first phase-contrast magnetic resonance imaging plane was placed at the C2–C3 level of the neck, with the following parameters: retrospective gating using peripheral pulse recording, heart phases = 32, acquired voxel size = 1 × 1 mm with 3-mm slice thickness, repetition time/echo time = 9.2 ms/5.5 ms, flip angle = 10°, and velocity encoding = 80 cm/s. A second phase-contrast magnetic resonance imaging plane was placed perpendicular to the ascending aorta, thus also transecting the descending aorta, with the following parameters: retrospective gating using peripheral pulse recording, heart phases = 32, acquired voxel size = 2.5 × 2.5 mm with 8-mm slice thickness, repetition time/echo time = 4.2ms/2.6 ms, flip angle = 10°, velocity encoding = 150 cm/s.

Flow measurements were done using Segment version 3.2 R9074 (https://medviso.com/segment).[12] The images were manually inspected for signs of aliasing or motion artefacts. Aliasing was corrected using a built-in feature in Segment. For C2–C3 planes, a region of interest delineating the boundaries of the artery was manually drawn by a single operator (J.B.) for the internal carotid arteries, external carotid arteries, and vertebral arteries using the phase images. The size of the region of interest was kept constant throughout the cardiac cycle. For aortic planes, the software's semiautomatic vessel segmentation algorithm was used.[11] To assess interrater reliability, a second operator (K.P.) independently measured the first five subjects (90 arteries). The intraclass correlation coefficient was 0.99 (95% CI, 0.98 to 0.99) for C2–C3 planes and 1.00 (95% CI, 0.99 to 1) for aortic planes, which was considered excellent. The brain volumes were automatically segmented using FreeSurfer version 7.2 (https://surfer.nmr.mgh.harvard.edu).[13]

Cerebral blood flow was defined as the sum of flow rates in the internal carotid arteries and vertebral arteries.[14] Cardiac output (CO) was defined as flow rate in the ascending aorta. Stroke volume was calculated as CO/heart rate. Right and left external carotid artery flows were summed and were interpreted as a characterization of peripheral blood flow. Cerebrovascular resistance was calculated as (MAP − intracranial pressure)/(cerebral blood flow/brain weight). Systemic vascular resistance was calculated as ([MAP − central venous pressure]/CO) × 80. Central venous pressure and intracranial pressure were both assumed to be 10 mmHg.[15,16] Brain weight was calculated as brain volume × 1.03.[17]

Power Analysis

A power analysis was performed based on measurements from the first five subjects. From this pilot data, we assumed a 72 ml/min mean difference in cerebral blood flow between baseline and noradrenaline with a SD of the mean difference of 75 ml/min. To achieve a power of 0.9 at an α level of 0.05, we estimated 14 completed subjects would be

needed. As we were unsure of the dropout rate, especially during the COVID-19 pandemic, subjects were screened for inclusion until 25 had been deemed eligible for the study procedure.

Statistical Analysis

Statistical analysis was performed using SPSS 27 (IBM Corp., USA). Variable distributions were checked for normality using Shapiro–Wilk tests and were found to be non-normal in most cases. The values displayed are thus medians (interquartile range) if not otherwise specified. Cerebral blood flow, CO, stroke volume, external carotid artery flow, descending aortic flow, as well as blood pressure, and heart rate (HR) during intravenous noradrenaline and labetalol administration were compared to baseline using Wilcoxon signed rank test. Change in cerebral blood flow and CO were co-primary outcomes, and change in stroke volume, external carotid artery flow and descending aortic flow were considered secondary outcomes. As sensitivity analyses, above comparisons were repeated using paired *t* tests. We also compared observed changes by sex. Relative change in cerebral blood flow after noradrenaline (noradrenaline cerebral blood flow/baseline cerebral blood flow − 1) and labetalol, as well as relative change in CO after noradrenaline and labetalol, respectively, were compared using Mann–Whitney U tests. After the primary and secondary outcomes were known, an exploratory analysis was added to improve our understanding of the results. Noradrenaline and labetalol cerebral blood flow/CO ratios, as well as external carotid artery/CO and descending aorta/CO ratios, were compared to baseline using Wilcoxon signed rank tests. Spearman correlation coefficients between relative changes in internal carotid artery, vertebral artery, and cerebral blood flow were calculated.

Results

Thirty-nine subjects were screened for inclusion. From these, 21 were excluded (fig. 2). Exclusions included three adverse events causing interruption of the procedure: one instance of ventricular bigeminy during noradrenaline infusion, one instance of claustrophobia, and one vagal reaction to arterial line insertion; two subjects were also excluded for not reaching target blood pressure or drug dose despite not having an adverse event. The final study population thus included 18 subjects. Noradrenaline cerebral blood flow was not calculated in one subject as the cross-section of one internal carotid artery was nonperpendicular. Calculations including noradrenaline cerebral blood flow are thus from 17 subjects. For the same reason, external carotid artery flow was not measurable in three subjects. Calculations including external carotid artery flow therefore use 15 subjects. Aliasing was found in two arteries (0.7%). No significant motion artefacts were found. Among included subjects, the median age was 34 yr (32 to 38), and 9 (50%) were female.

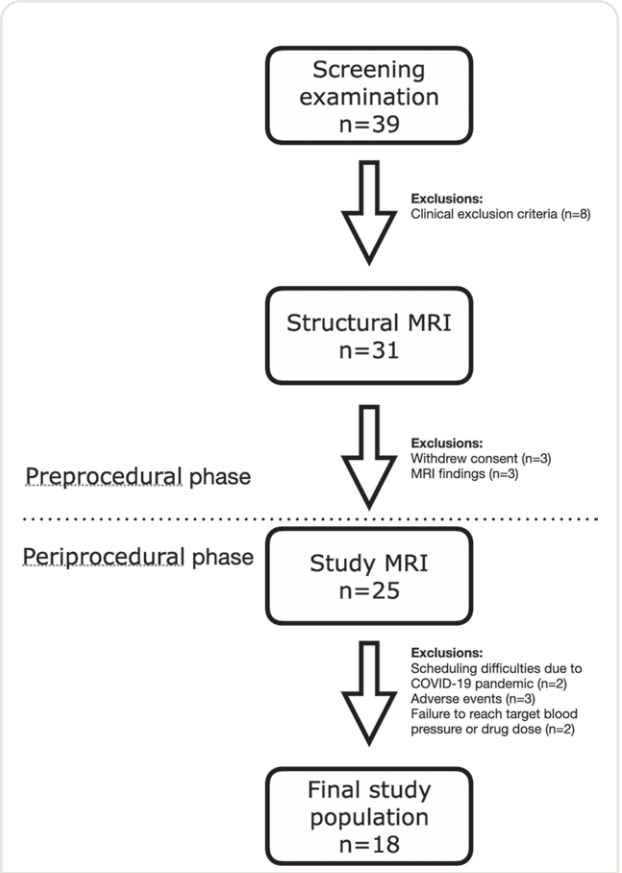

Fig. 2. Study population. Flowchart describing the inclusion of subjects. Magnetic resonance imaging (MRI) findings causing exclusion included arachnoid and pineal gland cysts.

The median weight was 72 kg (64 to 89), and the median height was 174 cm (168 to 182). The systemic hemodynamic values at baseline and the changes after noradrenaline and labetalol are displayed in table 1.

The primary and secondary outcomes are presented in table 2 and figure 3. The baseline median cerebral blood flow was 772 ml/min (interquartile range, 674 to 871), and CO was 5,874 ml/min (5,199 to 6,355). The median dose of noradrenaline was 0.17 μg·kg·h (0.14 to 0.22). During infusion, cerebral blood flow decreased to 705 ml/min (606 to 748; $P = 0.001$; fig. 3), and CO decreased to 4,995 ml/min (4,705 to 5,635; $P = 0.01$). The median dose of labetalol was 120 mg (118 to 150). After labetalol boluses, cerebral blood flow was unchanged at 769 ml/min (734 to 900; $P = 0.68$; fig. 3). CO increased to 6,413 ml/min (6,056 to 7,464; $P = 0.03$). Males had a larger relative reduction of cerebral blood flow in response to noradrenaline than females (−0.18 [−0.13 to −0.19] *vs.* −0.10 [−0.04 to −0.14]; $P = 0.03$), while there was no significant difference for labetalol. No sex differences were found regarding CO.

The baseline median cerebral blood flow/CO ratio was 0.13 (0.11 to 0.15; fig. 4), the external carotid artery/CO ratio was 0.03 (0.02 to 0.04) and descending aorta/CO was

Table 1. Hemodynamic Characteristics

		Noradrenaline			Labetalol		
Parameter	**Baseline**	**Level**	**Δ**	***P* Value**	**Level**	**Δ**	***P* Value**
Systolic blood pressure, mmHg	130 (123 to 138)	156 (144 to 163)	22 (19 to 27)	< 0.001	118 (110 to 126)	−11 (−17 to −6)	< 0.001
Diastolic blood pressure, mmHg	65 (60 to 69)	81 (73 to 83)	14 (12 to 16)	< 0.001	57 (53 to 64)	−8 (−11 to −4)	< 0.001
Mean arterial pressure, mmHg	86 (80 to 90)	107 (98 to 110)	20 (18 to 22)	< 0.001	78 (70 to 83)	−10 (−14 to −5)	< 0.001
Pulse pressure, mmHg	68 (60 to 71)	78 (71 to 81)	8 (4 to 14)	< 0.001	63 (55 to 66)	−5 (−6 to −2)	0.002
Heart rate, beats/min	66 (57 to 73)	53 (46 to 62)	−12 (−20 to −5)	< 0.001	71 (66 to 79)	8 (1 to 14)	0.02

The values are given as the median (interquartile range).

Table 2. Effects of Noradrenaline and Labetalol on Cerebral and Peripheral Blood Flow

		Noradrenaline			Labetalol		
Characteristic	**Baseline**	**Level**	**Δ**	***P* Value**	**Level**	**Δ**	***P* Value**
Cerebral blood flow, ml/min	772 (674 to 871)	705 (606 to 748)	−112 (−166 to −61)	0.001	769 (734 to 900)	3 (−29 to 53)	0.68
Cerebral blood flow, ml min^{-1} 100 g^{-1}	66 (59 to 72)	58 (52 to 61)	−10 (−13 to −6)	< 0.001	67 (63 to 70)	1 (−3 to 4)	0.73
External carotid arteries, ml/min	188 (150 to 273)	166 (137 to 222)	−26 (−65 to 5)	0.02	254 (215 to 334)	69 (33 to 158)	0.001
Cardiac output, ml/min	5,874 (5,199 to 6,355)	4,995 (4,705 to 5,635)	−910 (−1,433 to −123)	0.01	6,413 (6,056 to 7,464)	627 (−63 to 1,418)	0.03
Stroke volume, ml	93 (81 to 100)	100 (88 to 112)	8 (−13 to 23)	0.002	92 (80 to 102)	−2 (−15 to 11)	0.53
Descending aorta, ml/min	3,873 (3,291 to 4,402)	3,021 (2,720 to 3,654)	−838 (−1,203 to −96)	0.03	4,144 (3,852 to 4,590)	190 (−455 to 881)	0.35
Systemic vascular resistance, dyn s^{-1} cm^{-5}	1,068 (848 to 1,173)	1,500 (1,288 to 1,690)	469 (312 to 599)	< 0.001	800 (723 to 904)	−233 (−309 to −102)	< 0.001
Cerebrovascular resistance, mmHg ml^{-1} min^{-1} 100 g^{-1}	1.11 (0.96 to 1.35)	1.67 (1.42 to 1.93)	0.53 (0.42 to 0.61)	< 0.001	0.97 (0.84 to 1.16)	−0.16 (−0.27 to −0.06)	< 0.001

The values are given as the median (interquartile range).

0.67 (0.65 to 0.73). There was no change in cerebral blood flow/CO or external carotid artery/CO ratios during noradrenaline infusion, while the descending aorta/CO ratio decreased to 0.60 (0.58 to 0.63; $P < 0.001$). After labetalol boluses, the cerebral blood flow/CO ratio decreased to 0.12 (0.11 to 0.13; $P = 0.02$), while the external carotid artery/CO ratio increased to 0.04 (0.03 to 0.05); $P < 0.001$). There was no difference in descending aorta/CO ratio after labetalol.

The relative change in cerebral blood flow during noradrenaline infusion was strongly correlated to relative change in both internal carotid artery and vertebral artery flows (correlation coefficients 0.88 and 0.82; both $P < 0.001$). The correlation between the relative change in internal carotid artery and vertebral artery was 0.5 ($P = 0.03$). After labetalol, the corresponding correlation coefficients were 0.74 for relative change in internal carotid artery flow *versus* cerebral blood flow ($P < 0.001$) and 0.82 for vertebral artery flow *versus* cerebral blood flow ($P < 0.001$). There was no significant correlation between relative change in internal carotid artery *versus* vertebral artery flow after labetalol.

The results of the sensitivity analysis are presented in supplementary tables 1 and 2 (https://links.lww.com/ALN/D312). The results were generally unchanged from the main analysis. Peak velocities for each measured artery are displayed in supplementary figure 1 (https://links.lww.com/ALN/D312).

Discussion

We found that increasing blood pressure using the α- and β-adrenergic agonist noradrenaline produced a reduction in both cerebral blood flow and CO in healthy, awake volunteers. Lowering blood pressure using the α- and β-adrenergic antagonist labetalol generated an increase in CO and peripheral flow, while cerebral blood flow remained unchanged.

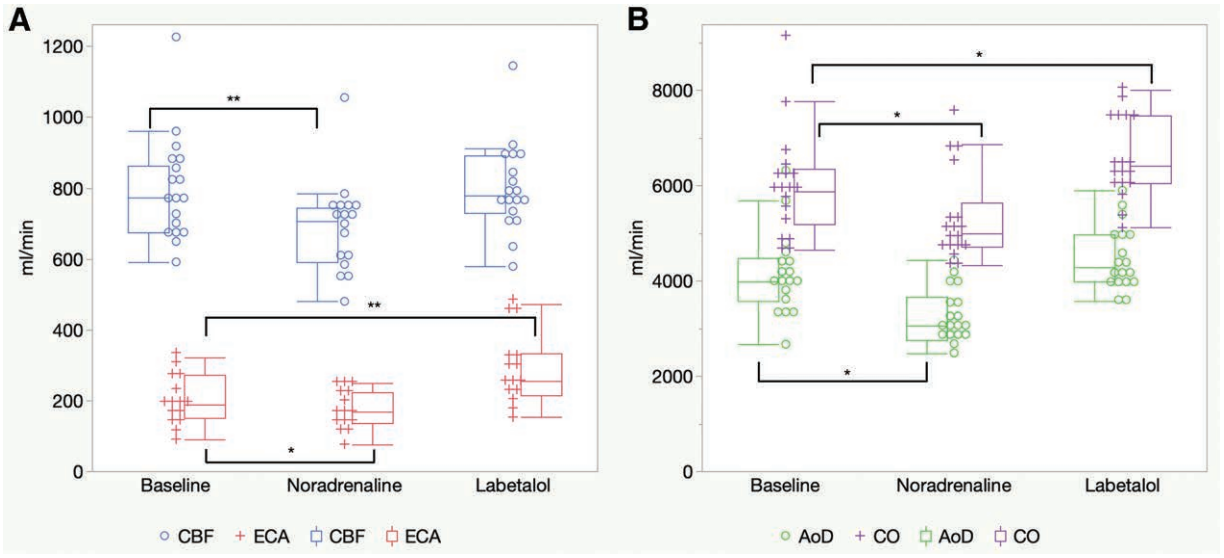

Fig. 3. Changes in blood flow. The box-and-whisker and scatter plots describe changes in cerebral blood flow (CBF) and external carotid artery (ECA) flow (*A*) or cardiac output (CO) and descending aorta flow (*B*). *Lines in boxes*, median; *bounds of boxes*, 25th and 75th percentiles; *whiskers*, 10th and 90th percentiles; *dots* and *crosses*, individual cases; *bars*, significant differences; $*P < 0.05$; $**P < 0.01$. AoD, descending aorta.

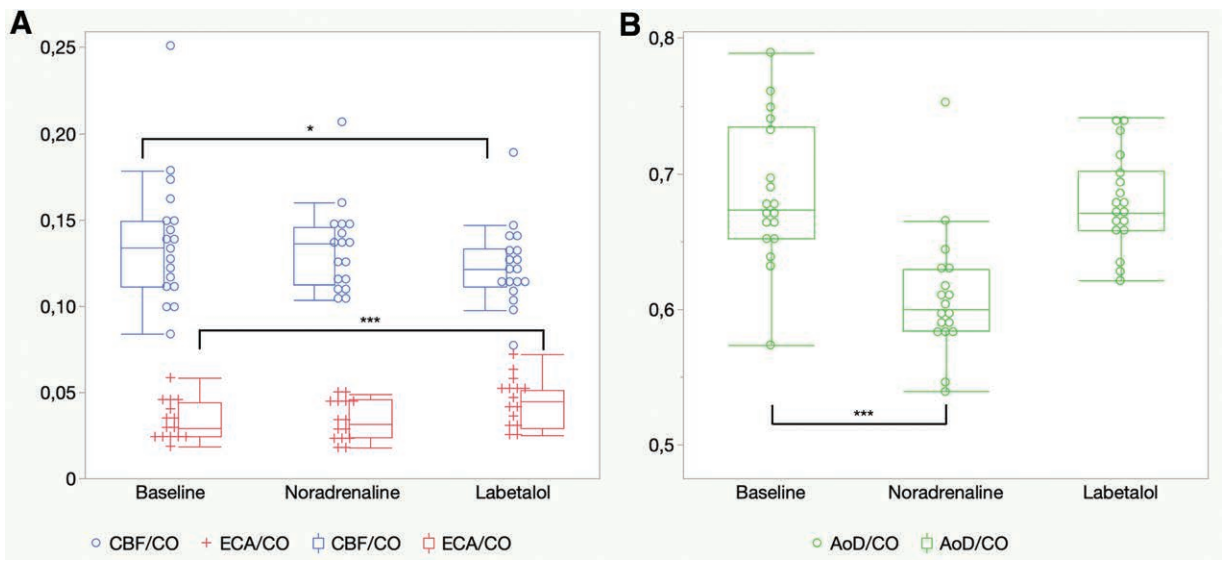

Fig. 4. Changes in blood flow ratios. The box-and-whisker and scatter plots describe changes in cerebral blood flow (CBF) and external carotid artery (ECA) flow to cardiac output (CO) ratios (*A*) and descending aorta to CO ratio (*B*). *Lines in boxes*, median; *bounds of boxes*, 25th and 75th percentiles; *whiskers*, 10th and 90th percentiles; *bars*, significant differences; *dots* and *crosses*, individual cases; $*P < 0.05$; $***P < 0.001$. AoD, descending aorta.

Regarding noradrenaline, our findings confirm those of several early studies with a reduction in cerebral blood flow accompanied by increased cerebrovascular resistance and lower HR.[18,19] Others found no significant change in cerebral blood flow but numerically pointed in the same direction.[20–22] More contemporary data suggest that middle cerebral artery flow velocity is either constant or reduced[23,24] with increasing doses. In addition, cerebral oxygenation may be reduced.[24] We also found a reduction in CO as opposed to unchanged in a previous study of healthy, awake subjects.[24] Likely, the data from this current study are highly reliable, as direct measurements with

phase-contrast magnetic resonance imaging were used in contrast to stroke volume estimation from the arterial pressure waveform, in which there are many possible sources of error. In addition, this study targeted a MAP increase of 20% instead of fixed doses, leading to slightly higher doses overall. We observed a larger decrease in cerebral blood flow in men compared to women. However, the groups are small, and the sex-based results should be interpreted cautiously. Further studies are needed to determine whether this difference persists.

The noradrenaline cerebral blood flow/CO ratio was unchanged compared to baseline, suggesting that the decrease of cerebral blood flow is proportional to the decrease in CO. Similar findings were presented in a study of phenylephrine as treatment for intraoperative hypotension in which CO was identified to have the strongest association with cerebral oxygenation out of a number of physiologic variables including MAP.[3] In the same study, after adjusting for CO, MAP was no longer associated with cerebral oxygenation at all. The noradrenaline external carotid artery/CO ratio was also unchanged, and cerebrovascular resistance increased proportionally to systemic vascular resistance. This could be interpreted as cerebral circulation not being prioritized over peripheral flow when facing decreased CO. It could also theoretically represent a cerebral vasoconstriction of the same magnitude as the peripheral vasoconstriction. In either case, the data suggest that cerebral autoregulation does not maintain cerebral blood flow with decreasing CO despite MAP being well above what is commonly considered the lower limit of autoregulation.

Our findings confirm previous reports of unchanged cerebral blood flow during treatment with labetalol[25,26] in healthy subjects. Similar results have also been found in untreated hypertensives[27] and more recently in patients with subacute ischemic stroke.[28] We also noted an increase in HR, which together with preserved stroke volume resulted in increased CO. Systemic vascular resistance was reduced along with an increase in the external carotid artery/CO ratio, consistent with the expected peripheral vasodilation. Cerebrovascular resistance was also lowered, which was interpreted as an autoregulatory response to reduced MAP. Studies in patients with uncontrolled chronic hypertension,[27] postoperative hypertension,[29] and ischemic heart disease[30–33] have all reported reduced or unchanged HR, CO, and, when measured, cardiac contractility.[29] This stark difference is likely explained by differing autonomic states in healthy subjects *versus* hypertensives. Hypertension may be associated with increased sympathetic activity,[34] decreased cardiac parasympathetic tone,[35] and baroreflex dysfunction.[36] Acute administration of sympathetic blocking agents such as labetalol has been shown to generate a reflex increase in adrenergic tone, presumably due to the reduction in blood pressure unloading baroreceptors.[34] This would lead to reflex tachycardia and increased cardiac output as displayed in this material. Hypertensive subjects, already in a state of increased sympathetic tone, may not compensate this way so readily, and their HR and CO are thus reduced.

Considering the previous findings mentioned above, our data illustrate the pitfalls of using blood pressure alone as a surrogate for blood flow. A frequently occurring equation is MAP = CO × SVR, where in turn CO = HR × stroke volume. Because HR, cardiac contractility, and vascular tone all are under the influence of various autonomic reflexes, their response to drugs and other alterations of the equilibrium may be difficult to predict and vary across different populations and clinical situations. MAP can thus not be interpreted as end organ flow. Our results suggest that CO is closely tied to cerebral blood flow and may warrant more attention during routine general anesthesia.

The clinical implication of these results is not entirely clear as study participants were awake, healthy, normotensive at baseline and with intact cerebral autoregulation. Two previous studies have found increasing cerebral blood flow and internal carotid artery flow, respectively, in hypotensive subjects when raising MAP using noradrenaline.[21,37] In both studies, hypotension was induced by potent vasodilators (intravenous hexamethonium in one case and epidural bupivacaine and morphine in the other). Increasing MAP was correlated to increasing stroke volume, while HR remained unchanged[37] in that case, supporting that benefit may have been obtained through increasing venous return. In hypotensive patients anesthetized with propofol and remifentanil, raising MAP using phenylephrine produced reduced cerebral oxygenation and CO as described above.[3] A possible clinical interpretation of our findings and the general population awake context may be that vasoconstrictor drugs such as noradrenaline can have their effect as venoconstrictors, which increase venous return and CO, leading to increased cerebral blood flow. If CO is normal at baseline, additional vasoconstriction may not be clinically beneficial, causing bradycardia and reduced CO. The issue of vascular tone, blood volume, cardiac output, and regional vital organ flow is complex, making vasoactive intervention effects challenging to predict. This issue is relevant in the clinical setting, where treatment to target blood pressure levels to try to improve cerebral blood flow in patients with subarachnoid hemorrhage and vasospasm is indicated and where our group at the time of this report has an active trial. A clinically relevant aspect is whether noradrenaline dosing to maintain cerebral blood flow in hypotensive patients can be guided by monitoring CO.

We have in this study successfully implemented a phase-contrast magnetic resonance imaging–based protocol to study changes in cerebral blood flow at controlled changes in blood pressure level with pharmacologic interventions. Strengths include comprehensive measurement of cerebral blood flow, CO, and peripheral flow, which have been rare historically. Particularly, peripheral measures have highlighted the lack of cerebral autoregulatory response to decreased CO. Another important strength is the reliable, accurate, and quantitative blood flow measurement provided by phase-contrast magnetic resonance imaging.[11]

There are limitations to address: our study was designed with healthy, awake participants, and the results cannot be reliably generalized to all clinical and relevant settings (*e.g.*, hypotension or hypertension relating to disease or to effects of other drugs). The order of the study drugs was not randomized, as the half-life of labetalol in plasma is approximately 4 h. Thus, administering noradrenaline after labetalol would have been associated with significant carry-over effects. Another limitation is that we did not measure arterial blood gases to minimize disturbances that might affect blood pressure, although awake and healthy participants would not be expected to have acid–base disturbances. This means we cannot compare serial arterial $Paco_2$ measurements to previous studies. While caffeine was prohibited 12 h before the study procedure to mitigate its vasoactive effects, there is evidence to suggest that users of high amounts of caffeine may have an increased cerebral blood flow in the abstinence state.[38] However, this should not affect the relative changes in cerebral blood flow seen in the current study, because all measurements were done within a relatively short time span and within the same caffeine state. Finally, the exploratory calculations of flows relative to CO were added after knowledge of the primary endpoints and should be interpreted as hypothesis generating.

Conclusions

In healthy, awake subjects, a 20% increase in MAP using intravenous noradrenaline reduced cerebral blood flow and CO. A 15% decrease in MAP using intravenous labetalol did not affect cerebral blood flow but increased CO. These data do not support the general idea of using noradrenaline to induce hypertension with the goal of increasing cerebral blood flow when cerebrovascular autoregulation is thought to be intact. Further studies of cerebral blood flow including interactions with general anesthetics and treatment of hypotension are warranted.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Supplementary tables and figures, https://links.lww.com/ALN/D312

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