Phase-Contrast Magnetic Resonance Imaging Measurements of Cerebral Autoregulation With a Breath-Hold Challenge
A Feasibility Study

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Background and Purpose—Vasomotor reactivity (VMR) testing can identify patients with hemodynamically critical cerebrovascular disease. The use of VMR has been limited by the invasiveness of most of the available methods and of acetazolamide as VMR stimulus. In the present study, we evaluated a completely noninvasive VMR approach by combining quantitative phase-contrast magnetic resonance imaging (MRI) with a breath-hold challenge.

Methods—Volume flow rates in the right and left internal carotid artery (ICA), basilar artery (BA), superior sagittal sinus, and sinus rectus were measured on 2-dimensional phase-contrast MR angiograms (MRAs) with a temporal resolution of 4.3 seconds. In 20 healthy control subjects, the VMR was assessed during 2 consecutive 30-second periods of breath-holding.

Results—A flow increase on breath-holding of 66% was found for the left ICA (240\(\pm\)54 mL/min to 398\(\pm\)120 mL/min; \(P<0.01\)), 59% for the right ICA (253\(\pm\)98 mL/min to 402\(\pm\)159 mL/min; \(P<0.01\)), 71% for the BA (107\(\pm\)48 mL/min to 184\(\pm\)79 mL/min; \(P<0.01\)), 62% for the superior sagittal sinus (232\(\pm\)75 mL/min to 375\(\pm\)130 mL/min; \(P<0.01\)), and 65% for the sinus rectus (77\(\pm\)30 mL/min to 127\(\pm\)38 mL/min; \(P<0.01\)). The coefficient of variation for the total volume flow increase in the brain feeding arteries (ICAs and BA) between the first and the second breath-holds was 18%.

Conclusion—The combination of MRA phase-contrast volume flow measurements and a breath-holding challenge allows for a fast, completely noninvasive, and reproducible assessment of VMR. (Stroke. 2004;35:1350-1354.)

Key Words: cerebral blood flow ■ vasomotor reactivity ■ cerebrovascular circulation ■ magnetic resonance imaging ■ cerebral veins

Vasomotor reactivity (VMR), ie, vasodilatory response of the cerebral resistance vessels, has been demonstrated to be of prognostic importance in cerebrovascular disease.\(^1,2\) Thus far, the use of VMR has been limited by the invasiveness of most of the available methods and of acetazolamide as VMR stimulus. Firstly, the methods to monitor cerebral hemodynamics, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), use (ionizing) radiation or administration of intravenous agents.\(^3,4\) Secondly, the most frequently used VMR stimuli require the intravenous administration of acetazolamide or a carbon dioxide (CO\(_2\)) challenge with a CO\(_2\) mask.\(^5-7\) However, simple breath-holding has also been proposed as a noninvasive alternative.\(^8,9\) Currently, noninvasive methods to monitor cerebral hemodynamics are transcranial doppler (TCD) sonography and phase-contrast magnetic resonance imaging (MRI).

With phase-contrast MRI, absolute volume flow and changes in volume flow can be obtained. Resting phase-contrast volume flow measurements have been used to evaluate cerebral hemodynamic impairment in patients with obstructive disease of the internal carotid artery (ICA) or posterior circulation,\(^10-12\) arteriovenous malformations,\(^13,14\) and the evaluation of vascular interventions, such as bypass surgery,\(^15,16\) or carotid endarterectomy.\(^17\) Recently, in vivo studies have demonstrated the reproducibility of phase-contrast volume flow measurements in rest and volume flow increase on an acetazolamide challenge.\(^18,19\) Thus far, no studies evaluated the amount and reproducibility of the volume flow increase in the arteries in the neck on a breath-hold challenge. Current abdominal and cardiac MRI scan protocols frequently use breath-holding periods of 15 to 30 seconds to decrease respiratory motion artifacts. Therefore, breath-holding combined with MRI volume flow measurements may be added to existing scan protocols to measure VMR noninvasively.

In the present study, we evaluated with quantitative phase-contrast MRI the volume flow increase on a 30-second breath-hold challenge. The relative and absolute change in volume flow and reproducibility were assessed for the left and right ICAs, the basilar artery (BA), and dural venous sinus flow (sinus rectus, superior sagittal sinus).
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Figure 1. Sagittal localizer MRA (A) illustrating the positioning of the axial-oblique 2-dimensional phase-contrast MRA phase image (B), with regions of interest drawn around the right ICA (1), basilar artery (2), left ICA (3), sinus rectus (4), and superior sagittal sinus (5). White and black color of the arteries and the sinuses on the phase image indicate opposite flow directions.

**Materials and Methods**

**MRI**

MRI was performed on a 1.5-T whole-body system (Gyroscan ACS-NT; Philips Medical Systems). On the basis of a localizer MR angiography (MRA) slab in the sagittal plane, a 2-dimensional phase-contrast slice was positioned at the level of the skull base to measure the volume flow in the ICAs, the BA, the sinus rectus, and the superior sagittal sinus (Figure 1). The MRA volume flow measurements in the present study are derived from a previously developed and optimized protocol (nontriggered; repetition time [TR], 16 ms; echo time [TE], 9 ms; flip angle, 7.5°; slice thickness, 5 mm; field of view, 250×250 mm; matrix size, 256×256; 8 averages; velocity sensitivity, 150 cm/s). A series of 80 dynamics was acquired with a 4.3-second temporal resolution per dynamic leading to a scan time of 5 minutes 44 seconds. Two periods of breath-holding, each with a 30-second duration (7 dynamics), were performed during the series of dynamics. The interval between the 2 breath-holding periods was 1 minute long. To avoid artificially lowering of the cerebral perfusion after a deep inspiration (Valsalva effect), Adequate breath-holding during the 30-second period was monitored by a pressure sensor under a respiratory band located at the abdomen. To restrain bulk motion, subjects were stabilized using foam pads and a head strap.

**Subjects and Data Analyses**

Twenty healthy young volunteers (age range 22 to 32 years; 10 females, 10 males) were imaged using this protocol. Subjects gave informed written consent before participating. The study protocol was approved by the institutional review board.

On an independent workstation, quantitative flow volumes and maximum flow velocities were calculated in the ICAs, BA, sinus rectus, and superior sagittal sinus by integrating across manually drawn regions of interest that encased the vessel lumen closely (Figure 1). Resting volume flow and maximum flow velocity values were obtained by averaging over 5 dynamics before the first breath-holding period and 5 dynamics between the 2 breath-holding periods. Volume flow and maximum flow velocity during the first and second breath-holding periods were obtained by averaging the flow values of 2 dynamics obtained 25.8 to 34.4 seconds after the beginning of the breath-hold challenges. To determine the average percent increase in flow volume and velocity, the response of the first and the second breath-holding period was averaged before calculating a group response. The breath-holding index (BHI), a quotient of percentage volume flow or flow velocity increase and time of breath holding, was calculated based on the mean time from the start of breath-holding (30.1 seconds) for these 2 dynamics.

**Statistical Analysis**

Quantitative volume flow and flow velocity was expressed as mean±SD. Differences in volume flow between the rest and the breath-holding period and differences in volume flow and reactivity between the first and the second breath-holds were analyzed with the Student t test for 2 related samples. In all tests, P<0.05 was considered statistically significant.

Reproducibility of the increase in volume flow on a breath-hold challenge was analyzed according to the method of Bland and Altman. With the difference between the volume flow increase for the first and the second breath-holding period, the standard deviation of the difference (SDD) was calculated. The SDD is a measure of the repeatability of the method. The 95% limits of agreement were calculated (ie, the mean difference±1.96×SDD). The coefficient of variation was calculated (ie, the SDD given as a percentage of the mean cerebral blood flow).

**Results**

Figure 2 shows the arterial and venous volume flow in rest and during 2 30-second breath-holding periods for an average subject. For the right and left ICAs, BA, sinus rectus, and superior sagittal sinus, an increase in volume flow was found during breath-holding, which returned to baseline flow values soon after the breath-holding period.

In Figure 3a, the average (n=20 subjects) baseline volume flow and volume flow during breath-holding are shown in mL/min (mean, SD) for the right ICA, left ICA, BA, sinus rectus, and superior sagittal sinus. The flow increase on breath-holding was 59% for the right ICA (253±98 mL/min to 402±159 mL/min; P<0.01), 66% for the left ICA (240±54 mL/min to 398±120 mL/min; P<0.01), 71% for the BA (107±48 mL/min to 184±79 mL/min; P<0.01), 65% for the sinus rectus (77±30 mL/min to 127±38 mL/min; P<0.01), and 62% for the superior sagittal sinus (232±75 mL/min to 375±130 mL/min; P<0.01). The BHI for the volume flow increase was 1.96 for the right ICA, 2.19 for the left ICA, 2.35 for the right BA, 2.16 for the sinus rectus, and 2.06 for the superior sagittal sinus.

In Figure 3b, the maximum flow velocity and maximum flow velocity during breath-holding are shown in centimeters per second (mean, SD) for the right and left ICAs, BA, sinus rectus, and superior sagittal sinus. The flow velocity increase on breath-holding was 48% for the right ICA (28±10 cm/sec to 42±14 cm/sec; P<0.001), 53% for the left ICA (28±11 cm/sec to 43±21 cm/sec; P<0.01), 47% for the BA (24±13 cm/sec to 35±20 cm/sec; P<0.01), 41% for the sinus rectus (19±7 cm/sec to 26±9 cm/sec; P<0.01), and 75% (19±9 cm/sec to 33±15 cm/sec; P<0.01) for the superior sagittal sinus. The BHI for the flow velocity increase was 1.59 for the right ICA, 1.76 for the left ICA, 1.56 for the BA, 1.36 for the sinus rectus, and 2.49 for the superior sagittal sinus.

No significant difference in baseline volume flow between the first and the second breath-hold was found for the right ICA (248 mL/min versus 231 mL/min), the left ICA (254 mL/min versus 252 mL/min), the BA (109 mL/min versus 105 mL/min), the sinus rectus (73 mL/min versus 80 mL/min), and the superior sagittal sinus (234 mL/min versus 229 mL/min). Furthermore, no significant difference in volume flow increase between the first and the second breath-holding period was found. The coefficient of variation of the volume flow increase between the first and the second breath-hold
was 33% for the right ICA, 30% for the left ICA, 25% for the BA, 34% for the sinus rectus, and 30% for the superior sagittal sinus. The coefficient of variation for the total volume flow increase in the brain feeding arteries (ICAs and BA) was 18%.

**Discussion**

In the present study, we show the absolute volume flow increase, relative volume flow increase, and reproducibility of noninvasive VMR measurements with phase-contrast MRI in combination with a breath-hold challenge. Optimal angulation of the 2-dimensional phase-contrast MRI scan allowed simultaneous assessment of the change in volume flow of the right and left ICAs, BA, sinus rectus, and superior sagittal sinus.

A 384 mL/min (64%) increase in total volume flow was found of the brain feeding arteries on breath-holding. In previous phase-contrast MRA studies, an acetazolamide challenge resulted in 278 mL/min (46%) and 300 mL/min increase in total volume flow. Furthermore, in a color Doppler study, a volume flow increase of 215 mL/min (50%) was found for an acetazolamide challenge and 163 mL/min (47%) for a CO2 challenge. We found a significant volume flow increase for the sinus rectus and the superior sagittal sinus. These findings are in agreement with the tight coupling between arterial and venous flow to prevent elevation of intracranial pressure.

The increase in ICA flow velocity of 50% is in agreement with the 40% to 45% increase in arterial flow velocity found with breath-holding techniques and the 50% to 60% increase in flow velocity found with TCD and CO2 challenges. A 47% flow velocity increase was found in the BA in our study compared with a 54% increase previously found for

![Graphs of volume flow (mL/min) in rest and during 2 30-second breath-holding periods for the right ICA, left ICA, BA, sinus rectus, and superior sagittal sinus.](http://stroke.ahajournals.org/)
activation were in agreement with literature values.28

velocities of the superior sagittal sinus in rest and during
the sinus rectus in our study. Furthermore, the absolute flow
with a VMR of 75% of the superior sagittal sinus and 41% for
our study. Therefore, the minimal effect of physiological flow
variations may have caused the higher reproducibility of our
study compared with a 1-minute interval in between the first and the second measurement was 15 days in
the brain feeding arteries between the first and the second
breath-hold was 18% compared with a coefficient of variation
of 28% found in a previous phase-contrast study with an
intravenous acetazolamide injection.18 The average time
between the first and the second measurement was 15 days in
the study of Spilt et al compared with a 1-minute interval in
our study. Therefore, the minimal effect of physiological flow
variations may have caused the higher reproducibility of our
VMR study. Furthermore, the reactivity after acetazolamide
was assessed with a single phase-contrast MRA scan of 36
seconds,18 instead of continuous monitoring of the volume
flow. Although previous TCD studies reported a better
reproducibility compared with MRI-based methods, the pre-
presented method has several potential advantages for clinical
studies. Firstly, phase-contrast flow measurements combined
with a breath-hold challenge can be added to existing MRI
protocols. Secondly, in addition to reactivity measurements
absolute values of the total volume flow (mL/min) are
obtained. Total volume flow may be useful as a general
measure of cerebral hemodynamic status in patients with
generalized cerebrovascular diseases31 or potentially in pa-
patients with (vascular) dementia.

Our results show a higher increase in flow velocity in the
superior sagittal sinus (75%) compared with the flow velocity
increase of the ICAs (50%) and BA (47%). This finding is in
agreement with a previous study, in which a higher increase
in velocity of the sphenoparietal sinus was found compared
with the velocity increase in the middle cerebral artery.28 In
the present study, no significant difference was found in
volume flow increase in the superior sagittal sinus compared
with the ICAs and BA. This difference in response between
the flow velocity and volume flow of the arteries and veins
can be explained by a diameter increase of the major brain
feeding arteries and a not extensible venous caliber of the
superior sagittal sinus.25,28 An arterial vasodilatation results in
relatively lower increase in flow velocity. The advantage of
MRA phase-contrast volume flow (mL/min) measurements
above flow velocity-based (cm/sec) techniques is the integra-
tion of flow velocity over the cross-sectional vessel area,
which will reflect more closely the change in cerebral blood
flow at the tissue level.24 The difference in total volume flow
between the arteries and veins in the present study can be
explained by the veins in which no flow measurements were
performed, such as the veins draining directly in the left and
right transverse sinuses.

In the present study, the phase-contrast MRI and breath-
holding protocol were evaluated in healthy control subjects.
Several TCD studies used the same 30-second duration of
breath-holding in stroke patients.29,30 Furthermore, cardiac
MRI studies in acutely ill patients, with expiratory breath-
holding for artifact reduction, indicate that breath-holding can
be performed in clinical settings.31 In stroke patients, the
breath-holding index can be used instead of the percentage
flow/velocity increase to account for a submaximal chal-
genation of flow velocity over the cross-sectional vessel area,
which will reflect more closely the change in cerebral blood
flow at the tissue level.24 The difference in total volume flow
between the arteries and veins in the present study can be
explained by the veins in which no flow measurements were
performed, such as the veins draining directly in the left and
right transverse sinuses.

In conclusion, MRA phase-contrast volume flow measure-
ments with a breath-hold challenge allow for complete
noninvasive and reproducible assessment of cerebrovascular
reactivity. The breath-hold challenge is already used for other
purposes (artifact reduction) in daily MRI scan protocols.
Furthermore, volume flow phase-contrast MRA scans reflect
the change in cerebral blood flow independent of arterial
vasodilatation. When added to existing MRI scan protocols,
phase-contrast MRI may increase the availability of the
valuable prognostic information provided by VMR in patients
with hemodynamically critical cerebrovascular disease.

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Stroke. 2004;35:1350-1354; originally published online May 6, 2004;
doi: 10.1161/01.STR.0000128530.75424.63
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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