To advance ischemic stroke care, clinically versatile imaging parameters to identify patients with symptomatic cerebrovascular steno-occlusive disease at highest risk for recurrent stroke are strongly desired. Although increased oxygen extraction fraction from PET and impaired cerebrovascular reactivity (CVR) from xenon-CT and SPECT have been strongly associated with recurrent stroke risk, these imaging modalities are not feasible for routine clinical stroke imaging.

To address this well-known challenge, we have recently validated two emerging imaging parameters derived from existing clinical imaging techniques that have ample availability in routine ischemic stroke management in patients with symptomatic cerebrovascular steno-occlusive disease as follows:

1. Increased ipsilateral systolic flow of the P2 segment of the posterior cerebral artery (PCA-P2) from transcranial Doppler (TCD) ultrasonography.

ABBREVIATIONS  
BOLD = blood oxygenation level–dependent; CVR = cerebrovascular reactivity; ICA = internal carotid artery; MCA = middle cerebral artery; MP-RAGE = magnetization-prepared rapid acquisition gradient echo; PCA-P2 = P2 segment of the posterior cerebral artery; TCD = transcranial Doppler.
trasonography is routinely used in the diagnosis and management of symptomatic steno-occlusive disease.\(^8\)
Increased PCA-\(P_2\) systolic flow velocity is a surrogate marker for the necessity of leptomeningeal collateral activation to compensate a state of hypoperfusion\(^6,9\) and has been linked to increased risk for recurrent ischemia and increased steal volume (i.e., paradoxical CVR).\(^5,10\)

2. CVR measured quantitatively with blood oxygenation level–dependent (BOLD) functional MRI during a standardized hypercapnic–\(\text{CO}_2\)–stimulus (BOLD-CVR) has demonstrated a good agreement with hemodynamic failure derived from acetazolamide-challenged\(^{(15\text{O}-)}\) \(\text{H}_2\text{O}-\text{PET}\).\(^7,11,12\) CVR describes the remaining vasodilatory capacity at the brain tissue level, whereas impaired CVR,\(^12-14\) especially paradoxical BOLD-CVR (i.e., steal volume), has been associated with an increased risk for recurrent ischemic events.\(^1,15,16\)

Recently, we have found a strong agreement between PCA-\(P_2\) systolic flow velocity and BOLD-CVR, with higher PCA-\(P_2\) systolic flow velocity values correlating to impaired BOLD-CVR and steal volume.\(^7,17\) This makes PCA-\(P_2\) flow velocity, which can even be performed at the bedside,\(^8\) eligible as a clinical screening tool for symptomatic steno-occlusive patients prone to ischemic stroke recurrence who are in need of a further hemodynamic work-up to assess brain tissue perfusion, typically obtained with advanced neuroimaging techniques such as PET, SPECT, or BOLD-CVR.

Hemodynamic adaptations, such as collateral flow activation and compensatory autoregulation of the cerebrovascular reserve capacity, however, may follow a different pattern for various stages of ischemic stroke.\(^14,18-20\) Most studies investigating ischemic stroke hemodynamics interchangeably merge patient data from acute stages with chronic stages after ischemic stroke. Therefore, it is unknown whether increased ipsilateral PCA-\(P_2\) flow activation and ipsilateral BOLD-CVR impairment have clinical merit for both the acute and chronic stages of ischemic stroke.\(^7,12,17\)

Hence, our aim was to compare symptomatic patients with steno-occlusive disease who underwent BOLD-CVR and TCD ultrasonography in the acute stage of ischemic stroke (<10 days) with those who underwent imaging in the chronic stage (>3 months) using a matched-pair cohort study design.

**Methods**

**Patient Selection**

The data that support the findings of this study are available on reasonable request from the corresponding author (M.S.). This project is part of an ongoing BOLD-CVR study in patients with symptomatic cerebrovascular steno-occlusive disease that has been approved by the local research ethics board (Kantonale Ethikkommission Zurich). Written informed consent was obtained from each participant before inclusion in the database. The study was conducted in accordance with the ethical standards as defined in the 1964 Declaration of Helsinki and its later amendments.

The inclusion criteria were 1) patient age 18 years or older with symptomatic unilateral steno-occlusive disease and 2) who exhibited focal neurological symptoms that were sudden in onset and referable to the appropriate anterior circulation large-artery distribution (ipsilateral to the significant large-vessel atherosclerotic pathology), including one or more transient ischemic attacks, characterized by focal neurological dysfunction or transient monocular blindness, or one or more minor (nondisabling) ischemic strokes.\(^21\) Unilateral disease was considered as a maximal stenosis of 50% on the contralateral side graded by duplex sonography according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.\(^2,22\)

First, all symptomatic patients with unilateral steno-occlusive disease who underwent a separate clinical TCD ultrasonography investigation were selected from the database. For the acute group (scanning performed <10 days from the stroke event), only patients who underwent both examinations within 1 week were included in this study. For the chronic group (scanning performed >90 days from the stroke event), we allowed for an interval of 8 weeks, and TCD ultrasonography could not have been performed in the acute stroke phase. Patients with an insufficient insonation bone window by TCD examination, a vascular pathology of the posterior circulation, or bilateral anterior circulation steno-occlusive disease (inclusive of moyamoya disease) were excluded from further analysis.

After evaluation, 165 patients (96 with acute stroke and 69 with chronic stroke) qualified for inclusion. Based on the average BOLD-CVR values of the ipsilateral hemisphere, we were able to match 80 patients (40 per group) and include them for further analysis. Patients who underwent both BOLD-CVR and TCD ultrasonography studies in the acute stage of ischemic stroke (<10 days) composed the acute hemodynamic cohort, whereas patients who underwent both examinations in the chronic stroke stage (>3 months) made up the chronic hemodynamic cohort. Some patient data from this cohort have been reported previously.\(^7,17\)

**Image Acquisition and Analysis**

BOLD functional MRI images were obtained using a 3-T Skyra VDI3 (Siemens Healthcare) scanner with \(\text{CO}_2\) as the vasoactive stimulus modulated by a computer-controlled gas blender with prospective gas-targeting algorithms (RespirAct, Thornhill Research Institute). This allowed for a short 80-second duration of iso-oxic hypercapnia to induce a vascular response. A high-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) image was obtained for anatomical overlay of the BOLD-CVR images. All BOLD-CVR images were obtained using a previously published method,\(^23\) which has been used in multiple studies,\(^14,17,20\) BOLD-CVR, defined as the percentage of the BOLD signal change/mm Hg \(\text{CO}_2\), was calculated from the slope of a linear least-square fit of the BOLD signal time course to the \(\text{CO}_2\) time course during the BOLD scan.\(^23\)

From the T1-weighted MP-RAGE scan, a probability map for the gray matter, white matter, and CSF was obtained. Each T1-weighted MP-RAGE image was then manually masked for the affected hemisphere, and in combination with a gray-white matter probability map (>80%...
probability), CVR of the affected hemisphere was calculated.

**Steal Volume Analysis**

Steal volume, describing the number of voxels with paradoxical (i.e., negative) BOLD-CVR and measured in milliliters, was determined by measuring the number of voxels in the whole brain as well as in the ipsilateral and contralateral hemispheres, with < 0% BOLD signal change/mm Hg CO₂ after exclusion of voxels around the frontal sinus in order to exclude artifacts.

**Analysis of the MCA Territory**

Quantitative BOLD-CVR values of the middle cerebral artery (MCA) territory of the ipsilateral and contralateral hemispheres were determined by applying a vascular atlas to the normalized CVR maps. This vascular atlas was derived from the predefined brain regions listed in the standard N30R83 atlas by Hammers et al.²⁴ and Kuhn et al.²⁵

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics version 26 (IBM Corp.). All normally distributed continuous variables are reported as mean ± SD. Categorical ordinal variables are presented as median (IQR), whereas dichotomous variables are shown as frequency (%). To evaluate the comparability of both groups, the chi-square test and the Student t-test were used. A 2-sided p value < 0.05 was considered significant. A linear regression analysis for both groups was performed between the ipsilateral PCA-P₂ systolic flow velocity and BOLD-CVR of the ipsilateral hemisphere, and BOLD-CVR of the ipsilateral MCA territory and the ipsilateral steal volume. The resulting slopes and intercepts were statistically compared to evaluate differences between groups.

**Results**

**Study Population Characteristics**

A flowchart illustrating patient screening and inclusion is shown in Fig. 1. In the acute hemodynamic cohort, which included patients in an acute ischemic stroke stage, 20 patients with internal carotid artery (ICA) occlusion, 1 patient with MCA occlusion, 4 patients with tandem (ICA and MCA) occlusion, 13 patients with ICA stenosis, and 2 patients with MCA stenosis were included. The chronic hemodynamic cohort consisted of 23 patients with ICA occlusion, 1 patient with MCA occlusion, 15 patients with ICA stenosis, and 1 patient with MCA stenosis.
Table 1 shows the relevant clinical and baseline characteristics of the enrolled patients. As shown in Table 2, no significant differences were found in relevant BOLD-CVR values of the whole brain, hemispheres, MCA territories, steal volumes, or PCA-P2 systolic flow velocities.

Linear Regression Analysis for the Acute and Chronic Hemodynamic Cohorts
PCA-P2 Systolic Flow Velocity and Ipsilateral Hemisphere BOLD-CVR
The linear regression curve between the quantitative ipsilateral PCA-P2 systolic flow velocity values and the mean ipsilateral hemisphere BOLD-CVR values showed a moderate association between PCA-P2 flow velocity and BOLD-CVR for the acute phase ($R = -0.53, R^2 = 0.28, p < 0.001$) and a good correlation for the chronic phase ($R = -0.60, R^2 = 0.36, p < 0.001$). Regression analysis (Fig. 2A) showed no significant difference for either the intercept ($p = 0.84$) or the slope ($p = 0.85$), indicating that a difference in the poststroke phase does not change the relationship between PCA-P2 flow velocity and BOLD-CVR as measured for the ipsilateral (affected) hemisphere.

PCA-P2 Systolic Flow Velocity and Ipsilateral MCA Territory BOLD-CVR
Similarly, the linear regression curve between the quantitative ipsilateral PCA-P2 systolic flow velocity values and the mean ipsilateral (affected) MCA territory BOLD-CVR values showed a strong association in the acute ($R = -0.61, R^2 = 0.36, p < 0.001$) and chronic ($R = -0.54, R^2 = 0.29, p < 0.001$) stroke phases. Regression analysis showed that the stroke phase had no influence on this relationship (intercept, $p = 0.72$; slope, $p = 0.36$) (Fig. 2B).

PCA-P2 Systolic Flow Velocity and Affected Hemisphere Steal Volume
Lastly, we tested the relationship between the quantitative ipsilateral PCA-P2 systolic flow velocity values and the mean ipsilateral (affected) MCA territory BOLD-CVR values showed a strong association in the acute ($R = -0.61, R^2 = 0.36, p < 0.001$) and chronic ($R = -0.54, R^2 = 0.29, p < 0.001$) stroke phases. Regression analysis showed that the stroke phase had no influence on this relationship (intercept, $p = 0.72$; slope, $p = 0.36$) (Fig. 2C).

Discussion
The current matched-pair cohort study shows that the relationship between ipsilateral PCA-P2 systolic flow velocity and BOLD-CVR does not change for the acute and chronic stages of ischemic stroke. This may have clinical merit for a wide stroke population in order to identify symptomatic steno-occlusive patients at risk for recurrent ischemic events. Increased ipsilateral systolic PCA-P2 flow velocity, in particular, has been shown to independently correlate with impaired BOLD-CVR and steal volume.
FIG. 2. Regression analysis of PCA-P2 systolic flow velocity and different BOLD-CVR parameters. A: Regression analysis showing no significant difference for both the intercept (p = 0.84) and slope (p = 0.85), indicating that the difference in the poststroke phase does not change the relationship between ipsilateral PCA-P2 systolic flow velocity and BOLD-CVR of the ipsilateral hemisphere.
and is increased in patients with recurrent stroke. This association describes the necessity of leptomeningeal activation to compensate for a state of hypoperfusion, and makes PCA-P2 systolic flow velocity an ideal screening method for stroke patients requiring further hemodynamic workup. BOLD-CVR, the measurement of intracranial hemodynamic status at the brain tissue level, is a quantitative and highly reproducible imaging method and has shown a good agreement with CVR as measured using the clinical gold-standard (15O-)H2O-PET examination. To allow for an optimal investigation of the relationship between PCA-P2 flow velocities and BOLD-CVR during different stroke stages, patients were matched based on the mean BOLD-CVR of the ipsilateral hemisphere. We found that the systolic PCA-P2 flow velocity of the ipsilateral hemisphere did correlate during both the acute and chronic stroke stages with different BOLD-CVR measurements (ipsilateral hemisphere BOLD-CVR, BOLD-CVR of the ipsilateral MCA territory, and volume of the region with the steal phenomenon [i.e., paradoxical BOLD-CVR]). Moreover, no differences in the intercept and slope between each of the correlations were found, meaning that the influence of the stroke phase (acute vs chronic) on this relationship has been indiscernible. This indicates that systolic PCA-P2 flow velocity can be used as an independent hemodynamic parameter in both acute and chronic hemodynamic stages in patients with symptomatic unilateral anterior circulation steno-occlusive disease.

Hemodynamic Features of Anterior Circulation Steno-Occlusive Disease

Atherosclerotic steno-occlusive disease describes a vascular state in which the extracranial or intracranial arteries supplying the brain show either a stenosis (abnormal narrowing of a blood vessel) or an occlusion (complete blockage of a blood vessel). A stenosis or occlusion of the appropriate anterior circulation large artery is an important cause of anterior circulation ischemic stroke and stroke recurrence and has been linked to chronic deficiencies in regional cerebral blood flow. Acute ischemia results in irreversible loss of brain tissue and function, whereas the presence of a chronic cerebrovascular steno-occlusive disease can alter cerebral hemodynamics up to a point where brain tissue perfusion becomes insufficient (chronic hypoperfusion). The consequences of chronic intermittent hypoperfusion are still not completely understood. It is supposed that the perfusion of brain tissue may be just sufficient enough to prevent gross ischemia but may fail to respond adequately to increases in demand such as those normally seen during neuronal activation. If hemodynamic impairment is present, it is hypothesized to alter brain structure and function. Between acute and chronic stages of stroke, an evolution in collateral flow occurs either parallel to or as a response to these changes; therefore, the efficacy of hemodynamic parameters should be tested for both the acute and chronic stages of stroke. Such studies are lacking, as advanced hemodynamic imaging studies with PET or SPECT are usually difficult and expensive to obtain in a large cohort of stroke patients with varying stroke stages.

Hemodynamic Impairment and Its Correlation With PCA-P2 Flow Velocity

Previous studies highlighted the importance of systolic PCA-P2 flow velocity, as measured by TCD, as an independent marker of intracranial hemodynamic status in patients with steno-occlusive disease. Since TCD is a noninvasive bedside method, it can be repeatedly used to evaluate the flow velocity of intra- and extracranial vessels, as well as the presence of primary and secondary collaterals, without the need for an exogenous contrast agent. A recent study showed that in patients with symptomatic unilateral steno-occlusive disease, increased ipsilateral TCD PCA-P2 systolic flow velocity is a strong independent predictor of hemodynamic impairment in the ipsilateral hemisphere and MCA territory. A flow increase > 30% in the ipsilateral PCA-P2 segment compared with the contralateral PCA-P2 segment indicates leptomeningeal collateral flow, known as a secondary collateral pathway. Such pathways are recruited once primary collaterals have failed to sufficiently compensate, indicating a more severe impairment. Therefore, a necessary activation of secondary collaterals (e.g., leptomeningeal pial branches over the posterior circulation) has been associated with an increased risk of recurrent stroke.

Using the systolic PCA-P2 flow velocity of the ipsilateral hemisphere, we have found a significant correlation between different quantitative BOLD-CVR measurements on the brain tissue level without an influence of the hemodynamic stage (acute vs chronic) on this correlation. The positive correlation between PCA-P2 flow velocity and steal volume is especially interesting. Steal volume (i.e., a paradoxical, negative BOLD-CVR response to hypercapnia) is a prime hemodynamic parameter or hemodynamic failure type and describes the classic state of hypoperfusion (i.e., tissue at risk for recurrent ischemic stroke). This indicates that despite hemodynamic changes over time, PCA-P2 flow velocity remains linked to the present hemodynamic state of patients with anterior circulation steno-occlusive disease.

Clinical Implications and Future Direction

The good agreement found between increased ipsilateral P2 TCD flow velocity and impaired BOLD-CVR for the acute and chronic stages of ischemic stroke has a potentially important clinical application for a wide stroke population, since both novel parameters have individually been associated with hemodynamic failure (i.e., the imaging parameter correlated with recurrent ischemic stroke).

Furthermore, this study has underlined the value of...
TCD ultrasonography in combination with a quantifiable hemodynamic parameter (i.e., increased ipsilateral $P_f$, flow velocity) as a screening tool for a wide stroke population in order to identify patients with potential hemodynamic failure\(^7\) that will need further imaging workup with either BOLD-CVR, acetazolamide-challenged H\(_2\)O-PET, SPECT, MR perfusion, or whichever modality is considered the institutional clinical standard to assess brain tissue perfusion.

Finally, although randomized controlled clinical trials\(^8\)\(^9\) have failed to show a benefit of cerebral bypass revascularization for stroke prevention, routine clinical experience has indicated that a subset of patients with both acute and chronic ischemic stroke exhibiting impaired or even exhausted cerebral hemodynamic status could benefit from surgical or endovascular recanalization procedures.\(^40\)\(^42\) To detect at-risk patients requiring further and more complex hemodynamic investigations, a noninvasive and bedside-available TCD ultrasonography–derived systolic PCA-$P_f$ flow velocity can be widely implemented as an additional triage investigation.\(^8\)

**Limitations**

The inclusion of patients with different unilateral symptomatic anterior circulation ischemic stroke pathology may have influenced our findings. Specifically, our study enrolled a mixed cohort of symptomatic patients with steno-occlusive disease; that is, patients with occlusion as well as stenosis were included. Cerebral autoregulation was reported to worsen between the acute and subacute stroke phase; therefore, this may have influenced our results, as BOLD-CVR and TCD ultrasonography investigations were not always done on the same day.\(^3\)\(^4\)

**Conclusions**

Our study indicates that the relationship between ipsilateral PCA-$P_f$, systolic flow velocity and BOLD-CVR does not change for the acute and chronic stages of ischemic stroke. This provides further support that these novel hemodynamic imaging parameters may have merit to assess the risk for recurrent ischemic events for a wide ischemic stroke population. PCA-$P_f$ systolic flow velocity, in particular, may be a highly practical screening tool, independent of ischemic stroke stage.

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**References**


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