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ORIGINAL ARTICLE

Fetal brain hemodynamics in pregnancies at term: correlation with gestational age, birthweight and clinical outcome

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ABSTRACT

Introduction: The primary aim of this study was to ascertain the strength of association between cerebral blood flow assessed in anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries and the following clinical outcomes: small for gestational age (SGA), induction of labor (IOL) for oligohydramnios and caesarean section (CS) for nonreassuring fetal status (NRFS) during labor.

Material and methods: Retrospective analysis of prospectively collected data on consecutive singleton pregnancies from 40 0/7 to 41 6/7 week of gestation. UA, ACA, MCA, PCA pulsatility index (PI) were measured from 40 weeks of gestations. Furthermore, the ratios between cerebral blood flow and UA (CPR, ACA/UA and PCA/UA) were calculated and correlated with the observed outcomes.

Results: Two hundred twenty-four singleton pregnancies were included in the study. Mean PI of either ACA ($p = .04$), MCA ($p = .008$), and PCA ($p = .003$) were lower in the SGA compared to non-SGA group; furthermore, mean PCA PI was significantly lower than MCA PI ($p = .04$). Furthermore, CPR ($p = .016$), ACA/UA ($p = .02$), and PCA/UA ($p = .003$) were significantly lower in the SGA group compared to controls. UA, ACA, MCA, and PCA PI were higher in women undergoing IOL for oligohydramnios compared to controls. Logistic regression analysis showed that CPR and PCA/UA ratio were independently associated with SGA. SGA, ACA PI, and ACA/UA were independently associated with CS for NRFS. Finally, birthweight centile, were independently associated with IOL oligohydramnios. Despite this, the predictive accuracy of Doppler in detecting any of the explored outcome was only poor to moderate.

Conclusion: Redistribution of cerebral blood flow at term is significantly associated with SGA, IOL for oligohydramnios and CS for NRFS in labor. However, the predictive accuracy of Doppler at term is only poor to moderate, thus advising against its use in clinical practice as a stand-alone screening test for adverse perinatal outcome in pregnancies at term.

KEY MESSAGE

Redistribution of cerebral blood flow at term is significantly associated with SGA, IOL for oligohydramnios and CS for NRFS in labor.

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Introduction

Placental insufficiency and fetal growth restriction (FGR) are among the major determinants of perinatal mortality and morbidity in singleton pregnancies [1–3].

Two main clinical phenotypes can be identified within the heterogeneous populations of small fetuses: that related to placental insufficiency and defined as "true" FGR and that in which no signs of placental dysfunction can be detected on prenatal imaging and

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are commonly labeled as small for gestational age (SGA) fetuses [4]. This classification reflects the risk of adverse perinatal outcome, with FGR fetuses showing a higher burden of cardiovascular and neurocognitive impairment compared to SGA [5,6].

Prediction of FGR is another relevant issue; while progressive changes in umbilical artery (UA) Doppler reliably detects a large proportion of FGR before term, commonly before 32 weeks of gestations, it is still debated on how to identify small fetuses close to or at term who are at higher risk of perinatal compromise [7–9]. The main parameter to document this process is the progressive reduction of middle cerebral artery (MCA) pulsatility index (PI) on ultrasound [10,11]. Initially considered a protective mechanism for the fetal brain, a low MCA PI has been recently shown to be independently associated with altered brain metabolism and abnormal neuropsychological performance after birth [12]. Furthermore, redistribution of blood flow during chronic hypoxia has been shown to occur in other brain territories, such as those supplied by the anterior (ACA) and posterior (PCA) cerebral arteries and to correlate with clinical outcome [13,14].

The classical definition of FGR has been recently challenged by new evidences which pose the attention on the role of cerebroplacental ratio (CPR), a ratio between the fetal middle cerebral artery (MCA) and UA pulsatility index (PI), as a surrogate for assessing the growth potential of a fetus *in utero* [15–18].

However, many of these studies come from countries in which third trimester assessment of fetal growth is not routinely undertaken and are affected by a large heterogeneity in inclusion criteria, gestational ages at scan, protocols for antenatal management and clinical outcomes. Furthermore, although the CPR has been shown to be independently associated with clinical outcome irrespective of fetal size, its predictive accuracy has not been consistently reported.

The primary aim of this study was to ascertain the strength of association between cerebral blood flow assessed ACA, MCA, and PCA in pregnancies at term and the following clinical outcomes: small for gestational age (SGA), induction of labor (IOL) for oligohydramnios and caesarean section for abnormal nonreassuring fetal status (NRFS) in labor. The secondary aims were to test the predictive accuracy of cerebral Doppler in detecting any of the observed outcomes and to explore its correlation with gestational age.

Materials and methods

This is a retrospective analysis of prospectively collected data in a dedicated term clinic in a single tertiary referral center (University of Rome, Rome, Italy) over a 2-year period from January 2016 to January 2017.

Inclusion criteria were: singleton pregnancy, 40 0/7 – 41 6/7 week of gestation, absence of fetal structural abnormalities, absence of maternal comorbidities, and/or complications and no drugs intake. Pregnancies complicated by fetal abnormality, aneuploidy, antepartum stillbirth, or maternal complications were excluded. Written informed consent was obtained from the women recruited on the study. The study was approved by the local IRB.

The primary outcome of the study was to explore the strength of association between placental and cerebral Doppler and the following clinical outcomes, SGA at birth, IOL for oligohydramnios, and CS for NRFS. SGA was defined as a birthweight $\leq$10th percentile for the gestational age at birth using the National Chart. NRFS during labor was defined as the presence of a suspicious or pathological CTG tracing according to the FIGO consensus guidelines on CTG interpretation [19] Finally, oligohydramnios was defined as a maximal vertical pocket $<$2 cm [20].

Doppler parameters explored were: UA PI, MCA PI, ACA PI, PCA PI and their ratio with the UA (MCA/UA PI or CPR, ACA/UA and PCA/UA).

Gestational age was defined according to the crown–rump length during the first trimester ultrasound scan. Women included in the study underwent fetal ultrasound Doppler surveillance every 3 days until delivery from 40 weeks of gestation. All the examination was carried out for research purpose and clinicians in delivery suite were blinded to the ultrasound findings, unless frankly pathological, such as abnormal Doppler waveform in the UA. All women underwent IOL at 41 6/7 if spontaneous onset of labor did not occur.

Pulsed Doppler parameters were performed automatically from three or more consecutive waveforms by using Voluson E8 (GE Medical System, Zipf, Austria) ultrasound machine equipped with a 3.5-MHz convex probe, during fetal quiescence, in the absence of fetal tachycardia, and keeping an insonation angle as close as to 0° as possible.

UA PI was performed from a free-floating cord loop. The MCA PI was obtained in a cross-sectional view of the head, at the level of its origin from the circle of Willis. The CPR was calculated as a ratio of the MCA PI divided by UA PI. For ACA PI, the Doppler gate was placed in its first segment, immediately after the origin of the ACA from the internal carotid artery. PCA PI was studied in a transverse plane with a posterior projection and a clear view of the cerebellum, the Doppler gate was placed in its first segment, immediately after its origin from the basilar artery. Every Doppler parameter was assessed three different times same by an experienced operator and intra-observer reliability calculated.

The potential associations between the recorded parameters and the outcomes were first evaluated with standard univariate analyses: chi-squared test for categorical variables; *t*-test and Kruskal-Wallis test for normally distributed and non-normally distributed continuous variables, respectively (distribution assessed with Shapiro-Wilk test).

Second, the potential independent predictors of each outcome were evaluated using multivariate logistic regression, and five separate models were fit (as above reported). In each model, the following criteria for covariates inclusion were adopted: clinical relevance; *p*-value $<.1$ and change in the odds ratio of significant predictors greater than 20%. To reduce potential overfitting, the overall number of covariates was limited to 1/7 of the successes in all phases of model fitting. The goodness-of-fit was evaluated using Hosmer-Lemeshow test, and the predictive power through C-statistics (area under the Receiving Operator Curve). Standard postestimation tests were used to assess final model validity, performing multicollinearity and influential observation analyses (using standardized residuals, change in Pearson and deviance chi-square), and testing for potential statistical interactions between outcomes and included covariates. Less than 10% of influential observations were found for each model using any approach, and when analyses were repeated excluding the outliers, no relevant changes were observed, and no observation was thus excluded. Missing values were less than 1% for all variables, therefore no missing imputation technique was adopted.

Statistical significance was defined as a two-sided *p*-value $<.05$, and all analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013).

Results

Two hundred twenty-four consecutive pregnancies were included in the study. General maternal and ultrasound characteristics of the study populations are reported in Supplementary Table 1. Mean maternal age was 30 ± 7.3 years, while gestational age at birth 40.7 ± 0.4 weeks. Vaginal delivery was accomplished in 73.7% of the cases, while 26.3% had CS, the large majority of cases due NRFS at CTG with no difference between women delivered at or beyond term (Table 1); IOL for oligohydramnios was required in 8.9% of the cases. About 26.8% of women delivered within 24 h from the last scan, while 34.4% and 38.8% within 48 and 72 h respectively. The large majority of newborns in the present cohort had a normal birthweight, while SGA occurred in 7.6% of the cases.

SGA fetuses were more likely to have CS ($p < .001$), especially for NRFS ($p < .001$) and IOL for oligohydramnios than the control group (Table 1). No difference in mean UA PI was observed between SGA and AGA fetuses, while mean PI of either ACA ($p = .04$), MCA ($p = .008$), and PCA ($p = .003$) was lower in the SGA group (Table 1). Finally, CPR ($p = .016$), ACA/UA ($p = .02$), and PCA/UA ($p = .003$) were lower in the SGA group (Table 1).

Thirty-eight pregnancies had CS in labor due to NRFS; the prevalence of SGA fetuses was higher in the

Table 1. Comparison of the selected maternal-fetal characteristics and Doppler parameters in small for gestational age (SGA) versus appropriate for gestational age (AGA) and large for gestational age (LGA) fetuses.

	Outcome		
Doppler parameter	SGA ($n = 17$)	Non-SGA ($n = 207$)	*p*-Value[a]
Mean UA PI (SD)	0.94 (0.15)	0.88 (0.13)	.06
Mean MCA, PI, (SD)	1.28 (0.29)	1.46 (0.27)	.008
Mean CPR (MCA/UA) (SD)	1.42 (0.55)	1.70 (0.44)	.016
Mean ACA, PI, (SD)	1.19 (0.17)	1.27 (0.14)	.04
Mean PCA, PI, (SD)	1.12 (0.12)	1.22 (0.12)	.003
Mean ACA/UA PI ratio (SD)	1.32 (0.39)	1.46 (0.25)	.02
Mean PCA/UA PI ratio (SD)	1.23 (0.31)	1.40 (0.22)	.003
	CD for NRFS ($n = 38$)	Controls ($n = 186$)	
Mean UA PI (SD)	0.96 (0.14)	0.87 (0.13)	<.001
Mean MCA, PI, (SD)	1.26 (0.23)	1.48 (0.27)	<.001
Mean CPR (MCA/UA) (SD)	1.35 (0.37)	1.74 (0.44)	<.001
Mean ACA, PI, (SD)	1.18 (0.15)	1.28 (0.14)	<.001
Mean PCA, PI, (SD)	1.16 (0.14)	1.22 (0.12)	.008
Mean ACA/UA PI ratio (SD)	1.25 (0.22)	1.49 (0.25)	<.001
Mean PCA/UA PI ratio (SD)	1.23 (0.20)	1.42 (0.23)	<.001
	IOL oligohydramnios ($n = 20$)	No IOL ($n = 204$)	
Mean UA PI (SD)	0.99 (0.15)	0.88 (0.13)	.001
Mean MCA, PI, (SD)	1.20 (0.24)	1.47 (0.27)	<.001
Mean CPR (MCA/UA) (SD)	1.26 (0.39)	1.72 (0.44)	<.001
Mean ACA, PI, (SD)	1.15 (0.16)	1.27 (0.14)	<.001
Mean PCA, PI, (SD)	1.14 (0.16)	1.22 (0.12)	.008
Mean ACA/UA PI ratio (SD)	1.19 (0.23)	1.48 (0.25)	<.001
Mean PCA/UA PI ratio (SD)	1.17 (0.18)	1.41 (0.23)	<.001

[a]Chi-squared test for categorical variables; *t*-test for continuous variables with parametric distribution, Kruskal-Wallis test for continuous variables with nonparametric distribution. SD: standard deviation; BMI: body mass index; NRFS: non-reassuring fetal staus; UA: umbilical artery; MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery; PI: pulsatility index; CPR: cerebreoplacental ratio.

CD group (29.0 versus 3.2%, $p < .001$) and 50% of pregnancies which had CS for NRFS were previously induced because of oligohydramnios.

UA PI ($p < .001$), MCA PI ($p < .001$), ACA PI ($p < .001$), and PCA PI ($p = .008$) were lower in pregnancies delivered for NRFS than controls; mean PCA PI was lower than MCA PI (0.002) while there was no difference between MCA and ACA ($p = .08$) and ACA and PCA PI ($p = .55$). Furthermore, all the ratios between placental and cerebral blood flow were lower in the CS group (Table 1). The differences in Doppler parameters between the two groups tended to persist when analyzing SGA and non-SGA fetuses separately (Supplementary Table 3).

About 8.9% (95% CI 5.9–13.4) of women had IOL for oligohydramnios. Mean birthweight was lower in the oligohydramnios group compared with pregnancies with normal amniotic fluid (3000 versus 3370 g, $p < .001$); likewise, the prevalence of SGA newborns was higher in the oligohydramnios group (45 versus 3.9%, $p < .001$).

UA, ACA, MCA, and PCA PI were higher in the oligohydramnios group compared to controls. Furthermore, all the ratios between placental and cerebral vessels, including either ACA, MCA, or PCA, and those between the cerebral vessels were lower in pregnancies with oligohydramnios (Supplementary Table 2). These differences were observed in the majority of the Doppler parameters explored even when stratifying the analysis according to the SGA status (Supplementary Table 3).

Logistic regression analysis showed that CPR (OR: 0.52, 95% CI 0.3–0.6) and PCA/UA ratio (OR: 0.42, 95% CI 0.22–0.50) were independently associated with SGA. SGA (OR: 3.26, 95% CI 1.9–7.2), CPR (OR: 0.28, 95% CI 0.1–0.6), ACA PI (OR: 0.63, 95% CI 0.4–0.9), and ACA/UA (OR: 0.21, 95% CI 0.01–2.9) were independently associated with CS for NRFS. Finally, birthweight centile (OR: 0.89, 95% CI 0.7–0.9), CPR (OR: 0.05, 95% CI 0.01–0.3) ACA PI (OR: 0.50, 95% CI 0.3–0.7) were independently associated with IOL oligohydramnios (Table 2).

However, when translating this into a predictive model, either placental or cerebral vessels and their ratios had a poor to moderate diagnostic accuracy in identifying each of the observed (Table 2, Figure 1).

Discussion

The findings from this study showed that fetuses with SGA, IOL for oligohydramnios and CS for NRFS and at term had lower impendence to cerebral blood flow in either ACA, MCA, and PCA territories than controls.

Table 2. Multivariate logistic regression and ROC analyses for the Doppler parameters significantly associated with SGA, CD for and NRFS and IOL for oligohydramnios.

Parameter	OR (95% CI)	*p*-Value	AUC (95% CI)
		SGA[a]	
CPR (1-unit increase)	0.49 (0.31–0.52)	.04	0.682 (0.53–0.84)
PCA/UA ratio (1-unit increase)	0.42 (0.22–0.50)	.002	0.532 (0.33–0.74)
		CD fo NRFS[a]	
SGA	3.26 (1.9–7.2)	.04	–[b]
CPR (1-unit increase)	0.28 (0.1–0.6)	.008	0.749 (0.66–0.83)
ACA PI (10-unit increase)	0.63 (0.4–0.9)	.012	0.695 (0.60–0.79)
ACA/UA (1-unit increase)	0.21 (0.01–2.9)	.2	0.720 (0.63–0.81)
		IOL for oligohydramnios[a]	
BW centile (1-unit increase)	0.89 (0.7–0.9)	.003	0.832 (0.74–0.93)
CPR (1-unit increase)	0.05 (0.01–0.3)	.001	0.781 (0.67–0.89)
ACA PI (10-unit increase)	0.50 (0.3–0.7)	.003	0.718 (0.59–0.85)

SGA: small for gestational age; CTG: cardiotocography; CPR: cerebroplacental ratio, ACA: anterior cerebral artery; PI: pulsatility index; UA: umbilical artery; BW: birthweight.
[a]Adjusted for age, parity, smoking status, and mode of delivery.
[b]AUC not computed being SGA a categorical variable.

Such differences in Doppler findings were observed in either SGA and non-SGA fetuses. Mean PI values were lower in PCA than MCA and ACA, suggesting a preferential blood flow redistribution towards the posterior part of the brain however, when translating these findings into a predictive model, the diagnostic accuracy of any placental or cerebral vessels in detecting any of the explored outcome was low, thus advising against their use in clinical practice as a standalone screening test for adverse perinatal outcome in pregnancies at term.

Antenatal prediction of small fetuses at higher risk for adverse perinatal outcome is challenging.

FGR is not a unique condition but encompasses a wide spectrum of anomalies characterized by a progressive impairment in placental function which does not always translate in a reduced fetal weight. While sequential changes in UA has been shown to reliably detect small fetuses affected by early placental insufficiency and to correlate with clinical outcome, it has still to be ascertained how to identify, among small fetuses at term, those at higher risk of perinatal compromise. UA Doppler in late FGR is usually normal, thus explaining the overall poor detection rate for FGR when approaching to term. A reduced impedance to blood flow in the MCA has been reported to be associated with late FGR and adverse neuropsychological performance after birth; however, it has still to be determined whether delivering these pregnancies would improve their short- and long-term outcomes. Furthermore, despite its association, the predictive accuracy of MCA to detect adverse perinatal outcome has not been consistently reported and it has still to be ascertained whether other factors such as severity

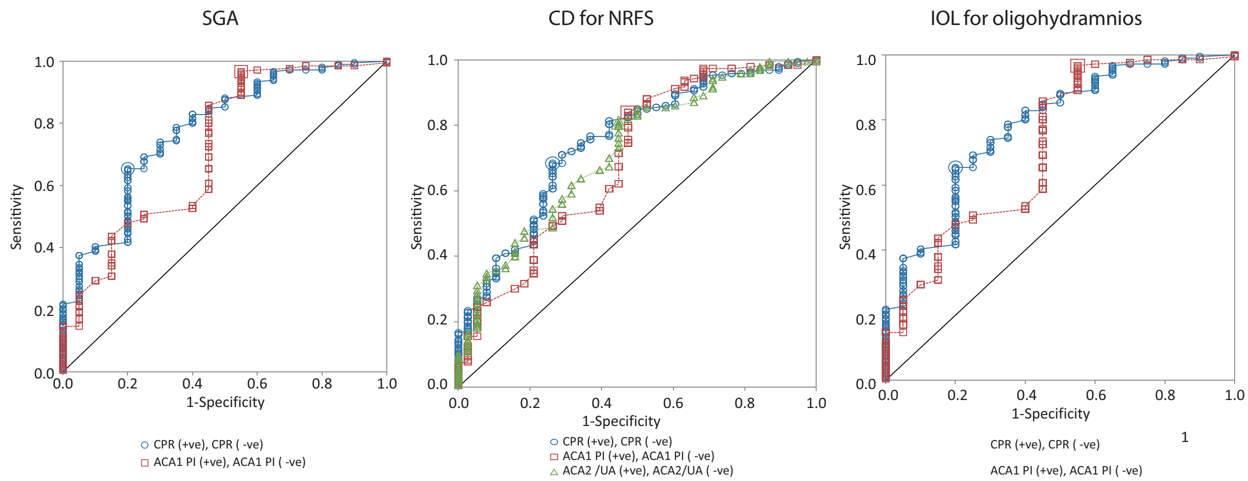

Figure 1. ROC curve analysis of the Doppler parameters significantly associated with SGA; CD for NRFS and IOL for oligohydramnios.

of FGR and gestational age at scan may affect the strength of association and the diagnostic performance of Doppler in predicting antenatal compromise in late FGR. Several diagnostic algorithms to detect perinatal compromise in SGA fetuses have been reported; however, despite the overall good sensitivity, they are still affected by a low specificity [21].

Recent studies suggest that the brain sparing in fetuses with an impaired growth could be detected earlier evaluating the PI in the ACA or PCA compared to MCA [13–17]. Differences in the response to hypoxia of different fetal cerebral vascular territories are also supported by experimental research in which the brain of lambs showed an internal redistribution of the blood flow in relation to the degree of the hypoxic insult [22]. Similar findings have been shown in the human fetus by the use of Doppler velocimetry [17]. Increased cerebral diastolic blood velocity in the fetus represents reduced vascular resistance, a characteristic fetal sign of brain sparing in chronic hypoxia [23]. Since each part of the human brain has its defined function, the cerebral circulation might change during hypoxia in a kind of hierarchic way depending on the relative importance of the brain areas for long term survival. Most studies have shown that MCA could represent the whole brain circulation since it is easy to locate in an axial view of the fetal head [20].

In the present study, mean values of ACA, MCA, and PCA were lower in pregnancies with SGA, CD for NRFS or IOL for oligohydramnios than controls, suggesting that in all those conditions potentially associated with impaired placental function, blood flow redistribution occurs in all brain territories; furthermore, we found a preferential perfusion of those areas of the brain the areas supplied by PCA. This low impedance to the blood flow in the PCA was also present in normal pregnancies, although it was further reduced in pregnancies affected by SGA, IOL for oligohydramnios and CS for NRFS. These findings are in accordance to those reported in the study by Morales-Rosello et al. [18], which reported a low impedance to blood flow in the vertebral artery compared to MCA in FGR after 34 weeks of gestation. The lower impendence to blood flow in the posterior part of the brain may be explained on the basis that the cerebral areas supplied by PCA requires a higher blood perfusion to preserve the highest brain functions such as tone and motor control in case of placental insufficiency and may partially explain the higher resistance to chronic hypoxemia shown by the fetal cerebellum and brain stem reported in animal models [24].

CPR has been recently shown to be independently associated with adverse fetal outcome irrespective of fetal weight, thus questioning whether all normally weight fetuses should be considered at low risk of placental insufficiency [18–26]. However, many of these studies come from countries in which third trimester assessment of fetal growth is not routinely undertaken and are affected by a large heterogeneity in inclusion criteria, gestational ages at scan, protocols for antenatal management, and clinical outcomes. Furthermore, such studies did not report the actual diagnostic accuracy of CPR in detecting perinatal compromise at term. This is fundamental, because an increased risk does not automatically translate in an optimal diagnostic performance.

In the present study, we found that, despite associated, CPR was not predictive of any of the observed outcomes; our findings agree with those of Sirico et al. who reported a poor diagnostic accuracy of CPR in identifying adverse perinatal outcome, thus advising against its use a screening test for adverse perinatal outcome [26].

The major limitation of the present study is the lack of assessment of acid–base status at birth, which did not allow correlating the different explored variables and the clinical outcomes. Small sample size, lack of assessment of acid–base status at birth, Bishop score before induction a nonstandardized policy for IOL represent other limitations of this study. Inclusion of consecutive cases, assessment of all cerebral and placental Doppler parameters and their association with objective clinical outcomes are the main strengths of the study. Furthermore, we aimed at ascertaining not only the association between Doppler and clinical outcome but also its usefulness as a screening test to detect perinatal compromise at term.

In summary, term pregnancies with impaired placental function have lower impendence to cerebral blood flow in either ACA, MCA, or PCA territories than controls. Redistribution of blood flow was higher in the cerebral areas supplied by the PCA. Cerebral Doppler at term is independently associated with clinical outcome. Despite this, the predictive accuracy is only low to moderate, thus advising against its use in clinical practice as a standalone screening test for adverse perinatal outcome. Further studies aiming at constructing predictive models incorporating maternal, fetal and ultrasound characteristics are needed in order to assess the role of cerebral Doppler at term in predicting adverse perinatal outcome at term.

Disclosure statement

No potential conflict of interest was reported by the authors.

Financial disclosure

Redistribution of cerebral blood flow at term is significantly associated with SGA, IOL for oligohydramnios and CS for NRFS in labor. The degree of blood flow redistribution is higher in the PCA compared to ACA and MCA.

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