

ABSTRACT

AIM OF THE STUDY: prospective study on 900 consecutive puerperae to assess normal values and range of the blood flow velocity in the middle cerebral artery (MCA) in both hemispheres.

MATERIAL AND METHOD: M1 and M2 segments of both MCAs were assessed in all subjects within 96 hours of delivery. Mean flow velocity (MFV) was recorded after adjusting for insonation angle. Lindegaard index (LI= MCA- Internal Carotid Artery MFV ratio) was calculated whenever MFV exceeded 100 cm/sec. Asymmetry indexes (AIs) were calculated inter hemispherically for M1 and M2 segments separately

RESULTS: MFVs were 74 ± 17 and 72 ± 17 in right and 73 ± 17 and 72 ± 17 cm/sec in left M1 and M2 respectively. One-hundred thirty-six subjects (12.1%) exceeded the threshold of 100 cm/sec, but LI was consistently <3 in all of them. MFV was inversely and independently correlated to haemoglobin levels and to parity. Mean AIs were 0.25 ± 23 in M1 and 0.45 ± 25 in M2.

CONCLUSION: MFV in MCA of healthy subjects in early puerperium is higher than in age matched non puerperal women and may exceed the threshold of 100 cm/sec with no evidence of intracranial spasm, because of blood loss during delivery. MFV is independently correlated with parity. Right-to-left MFV asymmetry may reach 50% as a consequence of a transient imbalance in vascular tone regulation.

Key words: mean flow velocity, puerperium, asymmetry index, middle cerebral artery

INTRODUCTION

In the early days post delivery, brain circulation undergoes a profound adaptation to changing hemodynamic and biochemical conditions, including fluid shift, cardiac output, oestrogens and haemoglobin levels and arterial blood pressure (1,2).

This process of gradual return to non gravidic cerebral hemodynamics may be deranged in pre-eclampsia and eclampsia, in which a severe perturbation in cerebral autoregulation, as yet ill understood, may bring about cerebral oedema, infarction or haemorrhage (3,4,5,6,7).

Transcranial Doppler sonography (TCD), due to its unique capability to assess in real time the fluctuations of the velocity of cerebral blood flow, has been extensively employed to study cerebral hemodynamics during pregnancy and in puerperium, but often with conflicting results (8,9).

One of the main drawbacks in the interpretation of the existing literature is the lack of robust normative data on brain vessel velocimetry, as in the vast majority of reports the numerosity of the control groups with no recognized pathology, taken as reference standard, was less than 30 subjects (10). This has generated a great deal of uncertainty about the range of normal variations in blood flow velocity in intracranial vessels, thus hampering the establishment of sound cut-off values between normal and pathological findings.

To overcome this shortcoming we undertook a prospective study on a large cohort of consecutive women who had given birth after a non complicated pregnancy and labour to assess normal values and range of the blood flow velocity in the middle cerebral artery (MCA) in both hemispheres.

MATERIAL AND METHODS

The study protocol was approved by the S. Orsola Hospital Institutional Review Board (Ethics Committee). All patients provided informed consent before entering the study.

The study period extends from November 2011 to July 2013. We studied all female subjects having given birth after a non complicated pregnancy and labour in the obstetrics department of the S. Orsola Hospital (first 86 cases, then Poliambulanza Hospital, as the former was incorporated in the latter) in Brescia, Italy.

The subjects underwent a basal visit within 96 hr of delivery, in which a chart review was performed and a structured interview was administered in person by one research assistant, with particular emphasis on headache. Information was collected on maternal demographics, labour and delivery details, anaesthesia during labour and delivery and headache characteristics and management. The following data were also collected: age, ethnicity, height, weight gain, arterial blood-pressure, history of primary headache disorders, history of arterial hypertension, smoking habits, alcohol intake, diabetes, dyslipidemia, family history of stroke and detailed characteristics of recent pregnancy and delivery, including medications and drugs taken during pregnancy. We also recorded in all subjects haemoglobin, uric acid and albuminuria levels. Thereafter, arterial blood pressure (ABP) was measured noninvasively. Patients fulfilling the criteria for pre-eclampsia (systolic BP > 140 Hg/mm or diastolic BP > 90 Hg/mm and albuminuria exceeding 0.3 g/l in a 24 hour collection) were excluded from the study.

A transcranial ultrasound study was performed in all the remaining patients to detect any early sign of vasospasm. Sequential Transcranial Colour-Coded Sonography (TCCS) was conducted by trained examiners using a Philips IU 21 device. TCCS examinations were performed with a center transmit frequency of 3-3.5MHz in colour mode using established methods (11,12,13). The Doppler gate was set at 5 to 10mm. The proximal (M1) and distal (M2) segments of the MCA were identified on colour representation through bilateral temporal skull windows from depths of 55 to 65mm and 45 to 55 mm, respectively. When the spectral display of velocity reached a steady state mean flow velocity (MFV) was recorded after adjusting for insonation angle (see figures 1 and 2). Asymmetry indexes (AIs) according to the formula proposed by Zanette

$$(MFV_{\text{right}} - MFV_{\text{left}})/((MFV_{\text{right}} + MFV_{\text{left}})/2) \times 100$$

were calculated inter hemispherically for M1 and M2 segments separately and intra hemispherically (by substituting in the formula proximal and distal to right and left velocities respectively) between M1 and M2 segments bilaterally (13, 14). Asymmetry indexes are non

dimensional values that represent the percent difference in velocity between two arterial segments by taking as reference the mean of the velocities of the two segments under study. Submandibular windows were used to measure flow velocity in the distal internal carotid artery (ICA) proximal to its entry into the skull, at the depth of 40 to 60mm. MFV of 100 cm/sec was selected as the normal upper limit in this study, according to threshold criteria derived from the literature; any higher value was considered suggestive of MCA stenosis (15,16,17). In patients with MCA velocity exceeding the threshold, we also calculated Lindegaard Index (LI) by dividing the MFV in MCA by the mean flow velocity of ipsilateral distal extracranial ICA. Published studies have indicated that an LI of 3 to 6 can be considered as mild vasospasm and greater than 6 can be considered moderate-to severe vasospasm (18).

At the end of the enrolment we were thus able to assess normal values of MFV in both MCAs and to correlate the findings with variables potentially able to affect cerebral blood flow velocity. Continuous variables were compared by mean of two-tailed T test if normally distributed or non parametric tests if the distribution was skewed. Frequencies were compared by Chi square test and bivariate correlations with Pearson's correlation coefficient test. Regression analyses were conducted to assess independent predictors of MFV (SPSS version 22).

RESULTS

During the inclusion period of 20 months, 900 women were enrolled in the study: 75.3% of them were of Caucasian ethnicity (the remaining being distributed between Chinese 2.2%, Indo-Pakistani 4.8%, Black 3.6%, Mediterranean African 3.9%, Slavic 4.3%, South American 2.1%, Romanian 3.6%, Unknown 0.2%), mean age was 31 ± 5 (range 16-45), overall 53% at their first or second pregnancy, 32% at the third one, the remaining 15% being distributed to up to six previous pregnancies. They were evaluated at a mean of 1.5 ± 1 days post partum (range 0-11). Relevant demographic, anthropometric and biological variables are reported in Table 1.

On basal TCCS assessment, flow velocities were overall symmetrically and evenly distributed (see Figure 3) and in the upper range of normal values (right M1 and M2 74 ± 17 and 72 ± 17 cm/sec respectively; left M1 and left M2 73 ± 17 and 72 ± 17 cm/sec respectively). Neither right vs. left M1 MFV nor right vs. left M2 MFV were statistically different from each other ($p=0.935$ and $p=0.717$ respectively), as well as M1 vs. M2 MFV on both right and left sides ($p=0.092$ and $p=0.117$ respectively). One-hundred thirty-six subjects (12.1%) exceeded in at least 1 measurement the threshold of 100 cm/sec, but LI was consistently <3 in all of them, thus suggesting that velocity increase was not caused by intracranial vasospasm. As the four velocity values recorded for each patient were not statistically different from each other, we computed a single averaged MFV value for each patient as the mean of right and left M1 and M2. Averaged MFV negatively correlated with age (Pearson's coefficient $= -0.80$, $p=0.020$), parity (Pearson's coefficient $= -0.171$, $p<0.0001$) and with haemoglobin level (Pearson's coefficient $= -0.256$, $p<0.0001$). History of migraine did not influence averaged MFV (74 ± 14 cm/sec in subjects with vs. 72 ± 14 in those without migraine, $p=0.076$), nor did administration of ergometrine during labour (73 ± 14 cm/sec when ergometrine was used vs. 74 ± 14 when it was not used, $p=0.182$).

Looking at the raw data we noticed that averaged MFV showed an abrupt drop in women of >1 parity (see supplementary table 1), therefore we dichotomously regrouped parity in 0-1 and >1 (see supplementary table 2). Averaged MFV was significantly higher in 0-1 than in >1 parity women (76 ± 14 vs. 70 ± 12 cm/sec respectively, $p<0.0001$).

Comparing subjects with averaged MFV ≥ 100 cm/sec with those below for anthropometric (age, height, weight, BMI, ABP) and biological (haemoglobin, albuminuria, uric acid) variables, haemoglobin (Hb) level was significantly lower in patients with MFV ≥ 100 cm/sec (10.1 ± 2 vs. 11.4 ± 1.3 g/l respectively – $p<0.0001$ on t-test).

Age, parity (dichotomously defined) and haemoglobin level were entered as predictors in a logistic regression analysis where averaged MFV > 100 cm/sec was the dependent variable and in a linear

regression analysis where MFV was the dependent variable. In both analyses parity and haemoglobin levels remained significant predictors whereas age did not (Table 2)

Interhemispheric asymmetry indexes were also distributed along a normal curve in both proximal and distal segments of MCA(see figure 4). Mean values were $0.25 \pm .23$ in M1 and $0.45 \pm .25$ in M2 ($p=0.86$). Likewise, on both sides proximal to distal asymmetry indexes were $1.6 \pm .25$ and $1.8 \pm .25$ in right and left MCAs respectively ($p=0.85$).

DISCUSSION

The aim of the present study was to assess normal values and variability of the MFV of middle cerebral arteries in a large cohort of consecutive women in the first post-delivery week. We deliberately chose to limit the assessment to this artery because it carries almost 80% of the entire cerebral blood flow, its straight course allows prompt identification and assessment of the true blood flow velocity and reproducibility of measurements is high (12,13). During pregnancy, MFV in MCA progressively decreases from the first to the third trimester (8,9,10). This change, assuming intact cerebral autoregulation, has been attributed to oestrogen mediated vasodilatation of brain arteries (10). Following delivery, MFV progressively and quickly increases in the first post partum week, to decrease thereafter to pre-gestational levels by the 40th day post partum (10). Therefore it is important to establish the upper limit of normality when MFV peaks at its maximum, as further increases may indicate a pathological vasoconstriction of brain vessels such as that occurring in pre-eclampsia or in the so called post partum angiopathy manifesting as thunderclap headache (19, 20, 21, 22).

So far, studies assessing the variations of hemodynamic parameters in puerperium have relied on normative data derived from very small cohorts of control subjects, which partly explains the conflicting findings when comparing velocities in normal versus pre-eclamptic and eclamptic patients (3,8,9).

To overcome this shortcoming we studied 900 consecutive women at an average of 1.5 days post-partum after rigorously excluding all cases of suspected pre-eclampsia and were thus able to establish the mean and the range of velocity values in both the proximal and the distal segments of middle cerebral arteries of both sides, as well as the side-to-side asymmetry and proximal-to-distal asymmetry in each vessel.

MFV values were normally distributed and mean values symmetrical in both the proximal and distal segments. Absolute values compared well with the findings of the literature. Sanchez-Arjona et al. found a single value of 73.1 ± 14.33 cm/sec and 75.68 ± 15.84 cm/sec in right and left MCAs respectively in a sample of 100 women (aged 30 ± 6 years) assessed within 5 days (75% between 1 and 3) of delivery (23). Serra –Serra et al. reported an averaged value of 74.2 ± 10.5 cm/sec on day 3 post delivery in 21 women aged 28.8 ± 4.5 (10). Normative data in non puerperal age-matched women are available in Liboni et al.: these authors found values of 72.15 ± 6.37 cm/sec in left and 70.68 ± 6.79 cm/sec in right MCA in a sample of 34 subjects aged 20-34 years (24).

From the limited evidence available it thus seems that the values in early post partum are slightly higher than in age matched non puerperal subjects. The reasons for this difference are probably

multiple. A mild vasoconstriction caused by the abrupt drop in the oestrogen level as well as variations in haemodilution have been advocated as putative mechanisms (10,23). However, our findings indicate that the most important factor underlying the increased average MFV is haemoglobin level. In patients with at least one MFV value > 100 cm/sec, as well as in those with averaged MFV > 100 cm/sec, haemoglobin levels were significantly lower than in subject with MFV ≤ 100 cm/sec, and overall averaged MFV velocity was highly correlated with Hb. Since MFV as measured by transcranial Doppler is known to be negatively correlated with haematocrit (25) the most obvious explanation for the raised velocities is the blood loss related to delivery. It is important to have this finding in mind when using absolute values to classify normal vs. abnormal values, as the threshold of 100 cm/sec is commonly held as the cut-off value for intracranial stenosis (15, 16, 17). In our cohort, 12.1% of patients exceeded that threshold in at least one measurement, and a similar proportion (10%) has been reported by Sanchez-Arjona et al. (23), but in our subjects Lindegaard Index, which compares mean flow velocities in ipsilateral MCA and ICA was consistently < 3 in all cases with MF > 100 cm/sec hereby excluding intracranial vasospasm as the underlying mechanism.

Age was the second variable which correlated with MFV in the univariate analysis. This relationship has been repeatedly reported but on a wider age range (24, 26, 27). In our cohort the age range was quite narrow (16-45 years) with the 5th percentile at 23 and the 95th at 39, and age was no longer significant as independent predictor in the regression analysis. On the other hand, parity was strongly correlated with MFV (see supplementary figure 1) and remained a significant predictor of lower velocities in the regression analysis. Since parity was strongly correlated with age, the higher the parity the higher the age (see supplementary table 3 and supplementary figure 2), it appears that the rise in MFV following delivery is somehow related to previous gestational burden, being progressively dampened as the number of previous pregnancies increases. Whether this occurs because of a reduced sensitivity of brain vessels to hormonal changes or because of a reduced adrenergic discharge following delivery or for other reasons cannot be settled at present and could be matter for future studies.

One finding which is not available in the literature, to the best of our knowledge, is the degree of side-to-side and proximal-to-distal asymmetry in the examined vessels.

MFV showed a trend to decrease non significantly from M1 to M2 on both sides as would be expected after the takeoff of penetrating arterioles between the proximal and distal portion of the main trunk. Our data show that up to about 50% reduced MFV in distal as compared to proximal segment may be normal, probably depending on the variable amount of blood flow diverted to basal penetrators.

Side-to-side asymmetry is currently being used to diagnose distal branch occlusion, following the seminal observations of Zanette et al. who established a cutoff threshold of 21%, based on the maximum asymmetry detected in a sample of 60 healthy people (14).

Our findings in a much larger cohort of women indicate that this threshold has to be elevated to $\pm 48\%$ for M1 and $\pm 50\%$ for M2 segments (2 SD from the mean), as is shown in figure 4, the plus or minus sign depending on whether MFV is higher in the right or left MCA respectively. This, of course, applies only to the specific condition of early post delivery state. The reason why in this particular condition interhemispheric asymmetries are so much expanded is unknown at the moment. One can only speculate that the sensitivity of brain vessels to the regulatory mechanism of vascular tone may become asymmetrical in some individuals in the early post delivery period and hence a functional asymmetry in vessel diameter takes place. This effect is expected to progressively fade away and interhemispheric asymmetry return within narrower limits in the following weeks.

According to the protocol of the present study a follow up TCCS assessment was not routinely performed unless indicated on clinical grounds. Therefore we were able to monitor the evolution of early interhemispheric asymmetry in only 12 subjects. In these patients M1 asymmetry index was 0.8 ± 28 on the first assessment and 1.1 ± 5 on the follow-up assessment performed one month later (data not shown). These findings need to be taken very cautiously given the small sample size, but are consistent with the idea that early post delivery asymmetry may represent a functional transient imbalance in the brain vessel sensitivity to regulatory stimuli.

Merits of the present study are the prospective nature, the large cohort size and the systematic investigation of all included subjects.

The main limit of the study was that it was based on a single centre experience.

In conclusion our study indicates that in the early post partum state MFV in MCA of healthy subjects may exceed the threshold of 100 cm/sec with no evidence of intracranial spasm, most probably as the result of the blood loss during delivery. Furthermore, MFV tends to be independently correlated with parity. Right-to-left MFV asymmetry may reach 50% as a consequence of a transient imbalance in vascular tone regulation.

REFERENCES

1. Akhter T, Larsson A, Larsson M, Wikström AK, Naessen T. Artery wall layer dimensions during normal pregnancy: a longitudinal study using noninvasive high-frequency ultrasound. *Am J Physiol Heart Circ Physiol* 2013; 304: H229–H234.
2. Skeik N, Porten BR, Kadkhodayan Y, McDonald W, Lahham F. Postpartum reversible cerebral vasoconstriction syndrome: Review and analysis of the current data. *Vasc Med.* 2015 ;20: 256-265.
3. Demarin V, Rundek T, Hodek B. Maternal cerebral circulation in normal and abnormal pregnancies. *Acta Obstet Gynecol Scand* 1997; 76: 619-24
4. Williams K, Wilson S. Persistence of cerebral hemodynamic changes in patients with eclampsia: a report of three cases. *Am J Obstet Gynecol* 1999; 181: 1162-1165.
5. Del Zotto E, Giossi A, Volonghi I, Costa P, Padovani A, Pezzini A. Ischemic Stroke during Pregnancy and Puerperium. *Stroke Res Treat* 2011 jan 27;2011:6060780. doi: 10.4061/2011/606780.
6. Cantu-Brito C, Arauz A, Aburto Y, Barinagarrementeria F, Ruiz-sandoval JL, Baizabal-carvallo JF. Cerebrovascular complications during pregnancy and postpartum: clinical and prognosis observations in 240 Hispanic women. *European Journal of Neurology* 2011; 18: 819-825.
7. Block HS. Neurological Complications of Pregnancy. *Curr Neurol Neurosci Rep.* 2016;16:67. doi: 10.1007/s11910-016-0665-2.
8. Sherman RW, Bowie RA, Henfrey MME, Mahajan RP, Bogod D. Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography. *British Journal of Anaesthesia* 2002; 89 : 687-692.
9. Williams K, Galerneau F. Maternal transcranial Doppler in pre-eclampsia and eclampsia. *Ultrasound Obstet Gynecol* 2003; 21: 507–513 .
10. Serra-Serra V, Kyle P M, Chandran R, Redman CWG. Maternal middle cerebral artery velocimetry in normal pregnancy and postpartum. *British Journal of Obstetrics and Gynaecology* 1997;104: 904-909.

11. von Reutern GM, Budingen HJ. Ultrasound Diagnosis in Cerebrovascular Disease. Georg Thieme. Stuttgart 1993.
12. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982; 57: 769–774.
13. Bartels E. Color-Coded Duplex Ultrasonography of the cerebral vessels- Atlas and manual. Schattauer . Stuttgart 1999.
14. Zanette EM, Fieschi C, Bozzao L, Roberti C, Toni D, Argentino C, Lenzi GL
Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. Stroke 1989;20:899-903.
15. Felberg RA, Christou I, Demchuk AM, Malkoff M, Alexandrov AV. Screening for Intracranial Stenosis With Transcranial Doppler: The Accuracy of Mean Flow Velocity Thresholds. Journal of Neuroimaging 2002; 12: 1-6.
16. Navarro JC, Lao AY, Sharma VK, Tsivgoulis G, Alexandrov AV. The Accuracy of Transcranial Doppler in the Diagnosis of Middle Cerebral Artery Stenosis. Cerebrovasc Dis 2007;23:325–330.
17. Zhao L, Barlinn K, Sharma VK, Tsivgoulis G, Cava LF, Vasdekis SN, Teoh H L, Triantafyllou N, Chan BPL, Sharma A, Voumvourakis K, Stamboulis E, Saqqur M, Harrigan MR, Albright KC, Alexandrov AV. Velocity Criteria for Intracranial Stenosis Revisited An International Multicenter Study of Transcranial Doppler and Digital Subtraction Angiography. Stroke. 2011;42:3429-3434.
18. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. Acta Neurochirurgica 1989; 100: 12-24.
19. Headache classification subcommittee of the International Headache Society. The international classification of headache disorders. Cephalalgia 2004; 24: 1–160.
20. Calabrese LH, Dodick DW, Schwedt TJ, Singhal A. Narrative Review: Reversible Cerebral Vasoconstriction Syndromes. Ann Intern Med 2007; 146: 34-44.
21. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol. 2012 ;11 :906-917.

22. Fugate JE, Amerisio SF, Ortiz G et al. Variable presentations of postpartum angiopathy. *Stroke* 2012; 43: 670-676.
23. Sánchez-Arjona MB, Franco-Macías E, Casado-Chacón JL, Díaz-Espejo C, Gil-Peralta A, Cayuela-Domínguez A. Velocimetría Doppler transcraneal en puérperas normotensas. *REV NEUROL* 2003; 36: 101-104.
24. Liboni W, Allais G, Mana O, Molinari F, Grippi G, Negri E, Benedetto C. Transcranial doppler for monitoring the cerebral blood flow dynamics: normal ranges in the Italian female population. *Panminerva Med* 2006;48: 187-191.
25. Brass L M, Pavlakis S G, DeVivo D, Piomelli S, Mohr J P. Transcranial Doppler measurements of the middle cerebral artery. Effect of hematocrit. *Stroke* 1988; 19: 1466-1469.
26. Grolimund P, Seiler RW. Age dependence of the flow velocity in the basal cerebral arteries—a transcranial Doppler ultrasound study. *Ultrasound in Medicine & Biology* 1988;14:191-198.
27. Tegeler CH, Crutchfield K, Katsnelson M, Kim J, Tang R, Passmore Griffin L, Rundek T, Evans G. Transcranial Doppler velocities in a large, healthy population. *J Neuroimaging*. 2013;23:466-72.

TABLES

VARIABLE	N./AVAILABLE COHORT	%	MEAN	SD
History of migraine	292/850	34.4		
History of hypertension	35/863	4.1		
History of diabetes	39/869	4.5		
Hystory of dyslipidaemia	30/850	3.5		
Active smoking	145/900	16.1		
Alcohol (≥ 2 drinks)	9/900	1.0		
Ergot during delivery	500/900	55.6		
BMI	892/900	98.8	22	4
Gestational age (weeks)	892/900	98.8	39	2
Systolic BP Hg/mm	829/900	92.1	110	12
Diastolic BP Hg/mm	829/900	92.1	68	9
Albuminuria (mg/dl)	769/900	85.4	7.8	19.6
Hb (g/l)	758/900	85.4	11.3	1.3

Table 1: basal demographic, anthropometric and biological variables

	Logistic regression analysis. Averaged MFV >100 cm/sec as dependent variable				Linear regression analysis. Averaged MFV as dependent variable			
	O.R.	95% C.I. for O.R.		Sign.	O.R.	95% C.I. for O.R.		Sign.
		LOWER	UPPER			LOWER	UPPER	
AGE	1.011	0.968	1.055	0.622	-0.025	-0.264	0.129	0.498
HAEMOGLOBIN	0.728	0.627	0.845	0.0001	-0.243	-3.153	-1.740	0.0001
PARITY	0.443	0.279	0.705	0.001	-0.178	-6.913	-2.892	0.0001

Table 2. Regression analysis. (O.R: odds ratio; C.I: confidence interval; Sign: level of significance)