Pediatric Transcranial Doppler Ultrasound- Part 2

Global Applications in Resource Limited Settings

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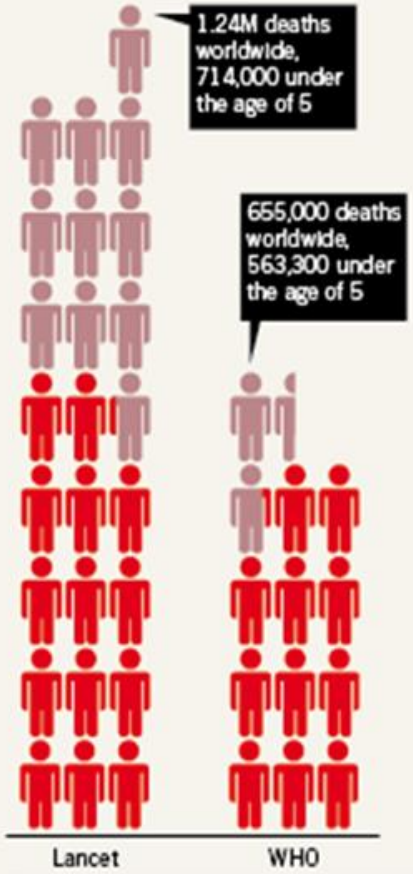
Cerebral Malaria

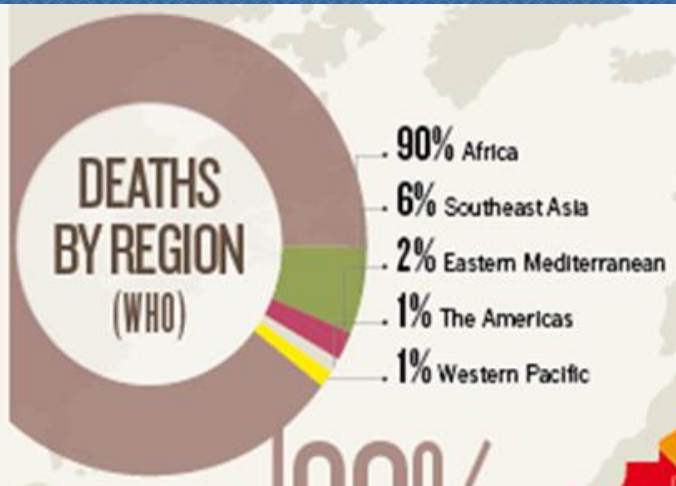
World Health Organization Definition:

- Asexual forms of *P falciparum* parasites on peripheral blood smear
- Coma with inability to localize painful stimuli; BCS <2
- No other causes to explain coma

MALARIA DEATH DISPARITY

The Lancet numbers differ because the authors used verbal autopsy, in which they interview the relatives of a person who has recently died to determine a cause of death. Interviews can identify people who died of malaria but went undiagnosed or treated.



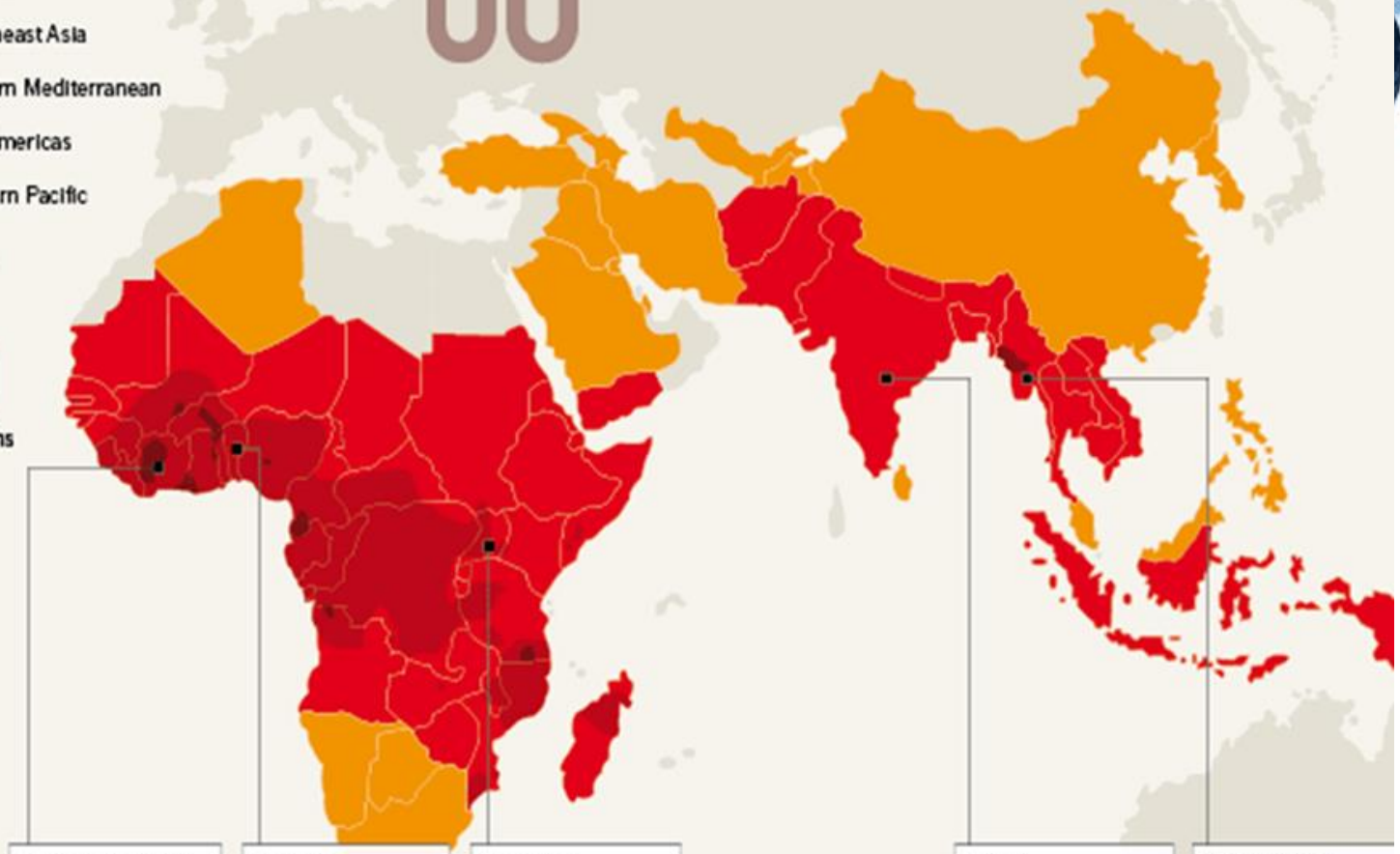


90%

90% of malaria deaths are in Africa

60

Every 60 seconds a child dies of malaria



COTE D'IVOIRE
WHO: 1,023
Lancet: 31,664

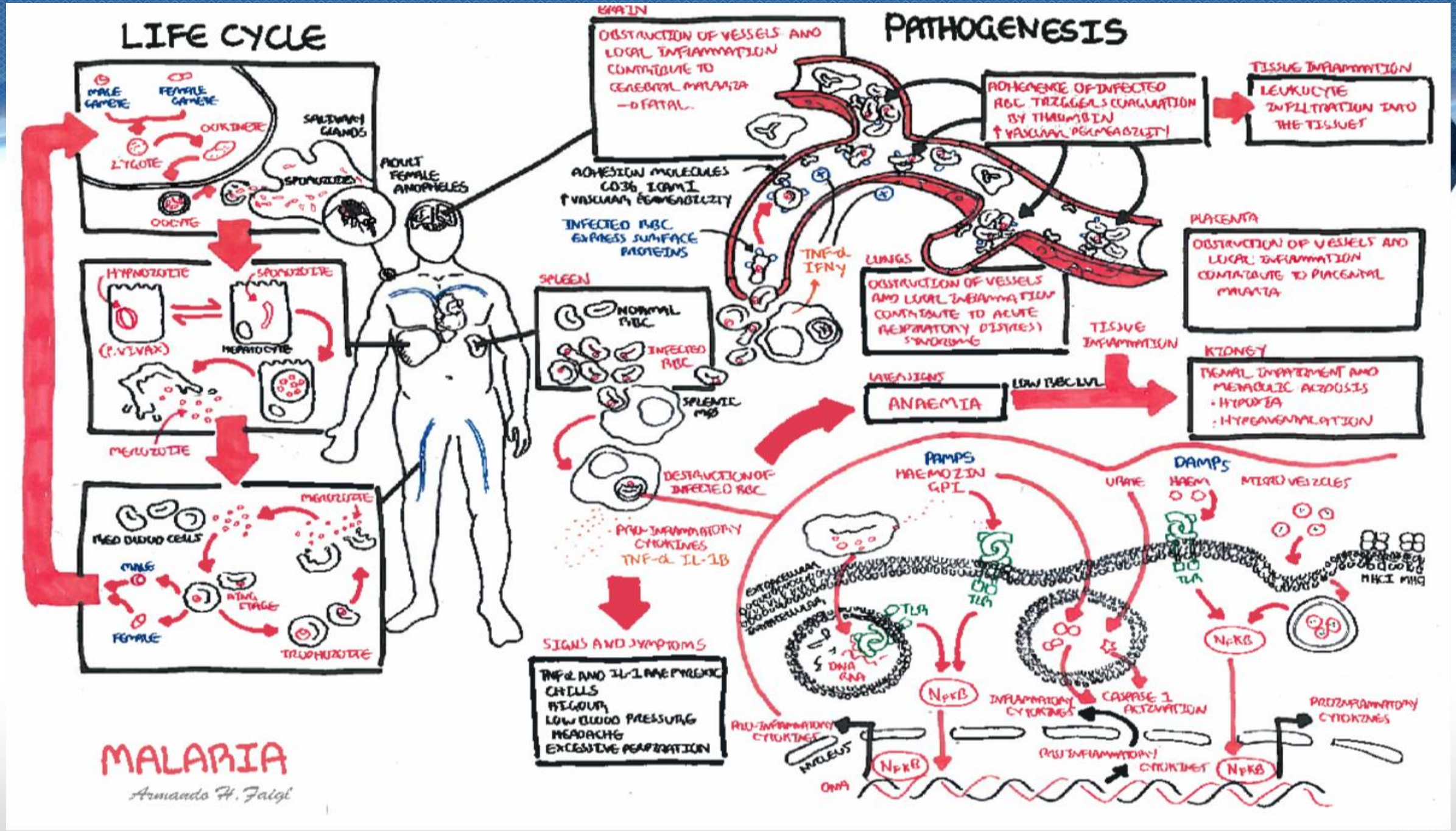
BENIN
WHO: 964
Lancet: 14,415

UGANDA
WHO: 8,431
Lancet: 41,648

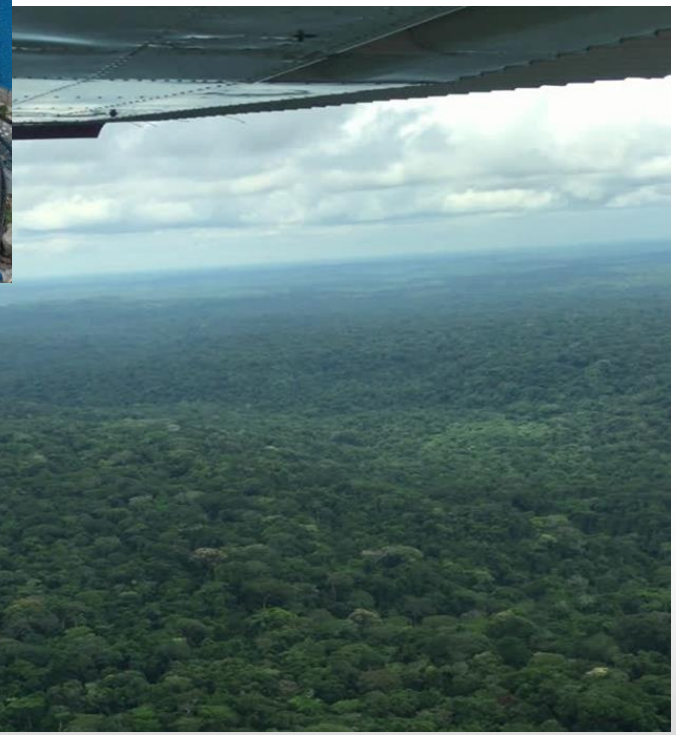
INDIA
WHO: 1,023
Lancet: 46,970

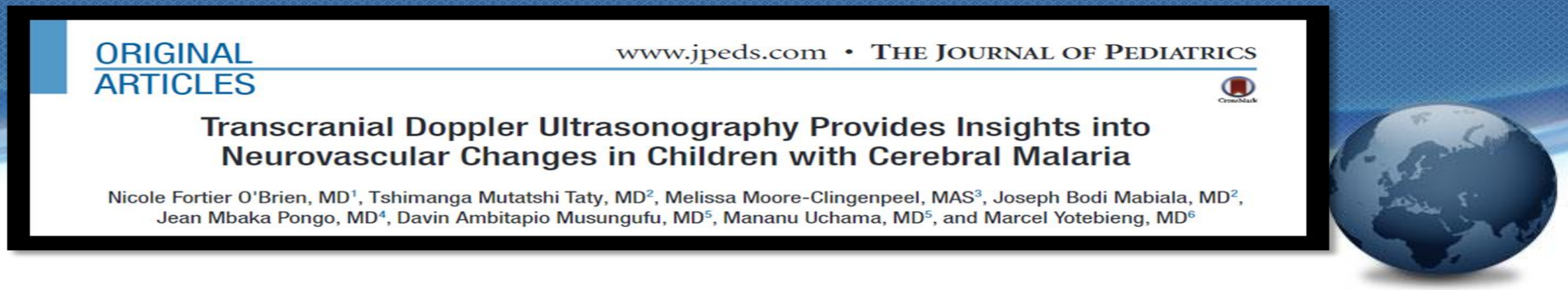
MYANMAR
WHO: 788
Lancet: 21,995

= 50,000 people
Deaths
Deaths under 5yrs


LIFE CYCLE
MALE GAMETE
FEMALE GAMETE
OOKINETE
ZYGOTE
SALIVARY GLANDS
SPOROZOITES
ADULT FEMALE ANOPHELES
OOCYTE
HYPNOZOITE
(P.VIVAX)
SCHIZONTE
MEROCYTE
MEROZOITE
MEROZOITE
RED BLOOD CELLS
MALE
RING STAGE
FEMALE
TROPHOZOITE
MALARIA
Armando H. Faigt
PATHOGENESIS
BRAIN
OBSTRUCTION OF VESSELS AND LOCAL INFLAMMATION CONTRIBUTE TO CEREBRAL MALARIA → FATAL
ADHERENCE OF INFECTED RBC TRIGGERS COAGULATION BY THROMBIN ↑VASCULAR PERMEABILITY
TISSUE INFLAMMATION
LEUKOCYTE INFILTRATION INTO THE TISSUE
ADHESION MOLECULES CD36 ICAM I ↑VASCULAR PERMEABILITY
INFECTED RBC EXPRESS SURFACE PROTEINS
TNF-α IFNγ
PLACENTA
OBSTRUCTION OF VESSELS AND LOCAL INFLAMMATION CONTRIBUTE TO PLACENTAL MALARIA
LUNGS
OBSTRUCTION OF VESSELS AND LOCAL INFLAMMATION CONTRIBUTE TO ACUTE RESPIRATORY DISTRESS SYNDROME
SPLEEN
NORMAL RBC
INFECTED RBC
SPLENIC MΦ
TISSUE INFLAMMATION
KIDNEY
RENAL IMPAIRMENT AND METABOLIC ACIDOSIS
- HYPOXIA
- HYPERVENTILATION
ULCERATIONS
ANAEMIA
LOW RBC LVL
DESTRUCTION OF INFECTED RBC
PAMPS
HAEMOZIN
GPI
DAMPS
UREA
HAEM
MICROVESICLES
PRO-INFLAMMATORY CYTOKINES
TNF-α IL-1β
SIGNS AND SYMPTOMS
TNF-α AND IL-1 ARE PYROGENIC
CHILLS
RIGOUR
LOW BLOOD PRESSURE
HEADACHE
EXCESSIVE PERSPIRATION
EXTRACELLULAR
TLR
DNA
RNA
MHC I MHC II
NFκB
INFLAMMATORY CYTOKINES
CASPASE 1 ACTIVATION
PRO-INFLAMMATORY CYTOKINES
NUCLEUS
DNA
NFκB
PRO-INFLAMMATORY CYTOKINES
NFκB


KAP-FRET
VOYAGE FRETS & AFFRETEMENTS
TOUTES DESTINATIONS
AEROPORT DE NDOLO
DESTINATIONS
- LODJA
- BASANKUS



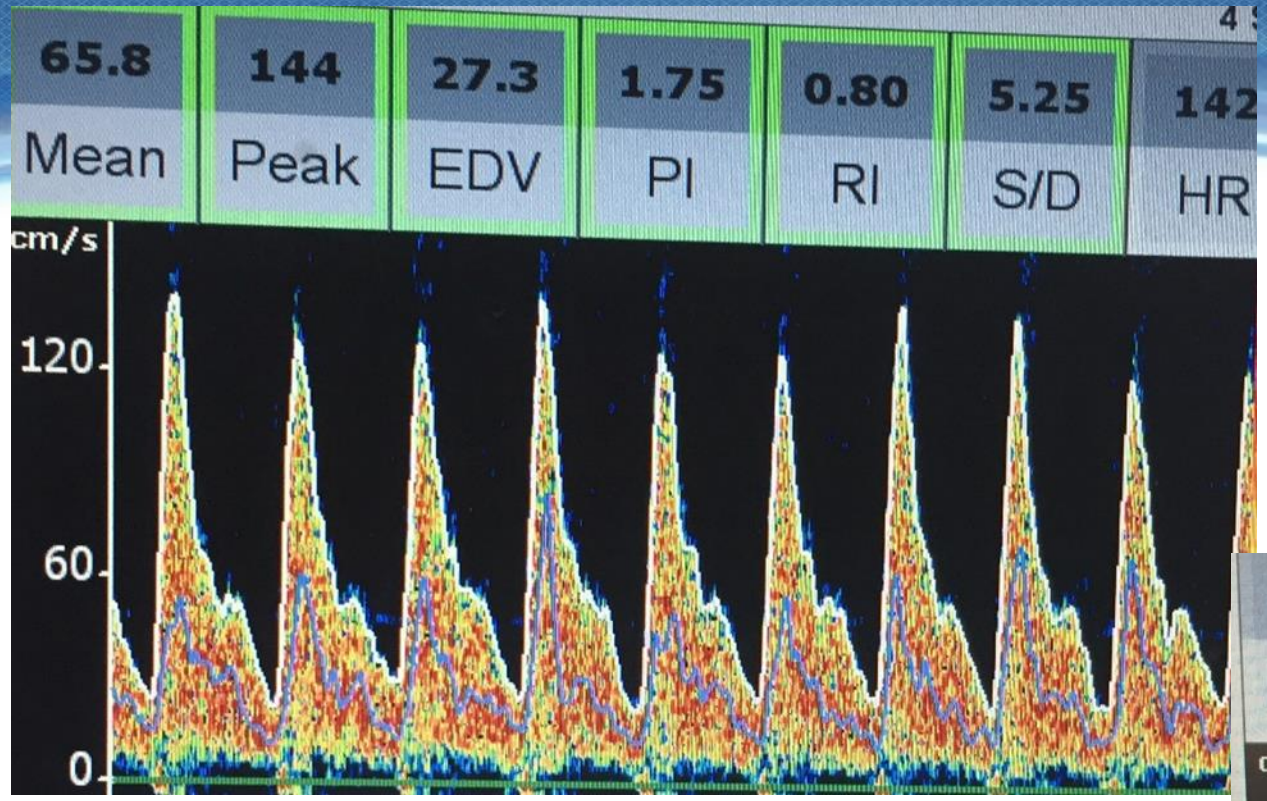


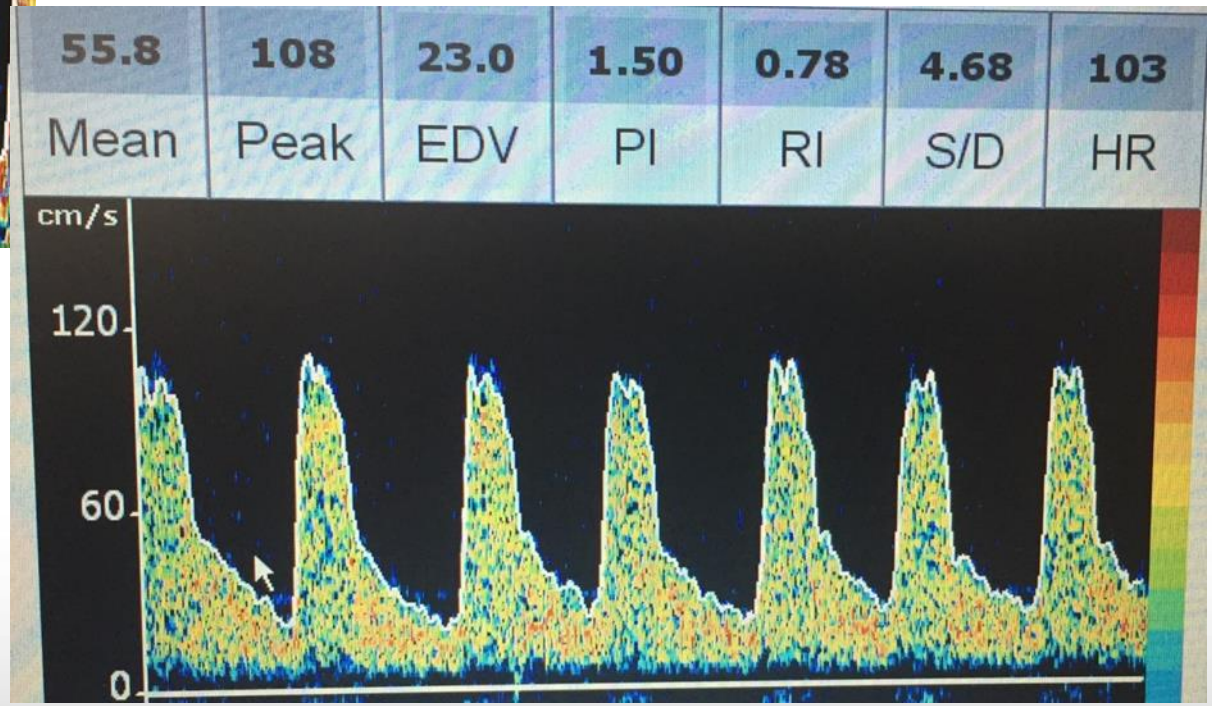
– 3 sites across the Democratic Republic of the Congo
– Inclusion criteria:
  • Children age 3 mo to 16 years with cerebral malaria
– Exclusion criteria:
  • Known or suspected sickle cell disease

– 153 children with CM; 155 “control” children with severe malaria without neurologic symptoms

- Demographics, clinical variables, laboratory results recorded
- Daily TCD evaluations through death, discharge, hospital day 8
  - Vs, Vd, Vm, PI of bilateral MCAs, BA, OA
  - Central veins when able
  - Autoregulation

- Neurologic outcomes 6 months from admission

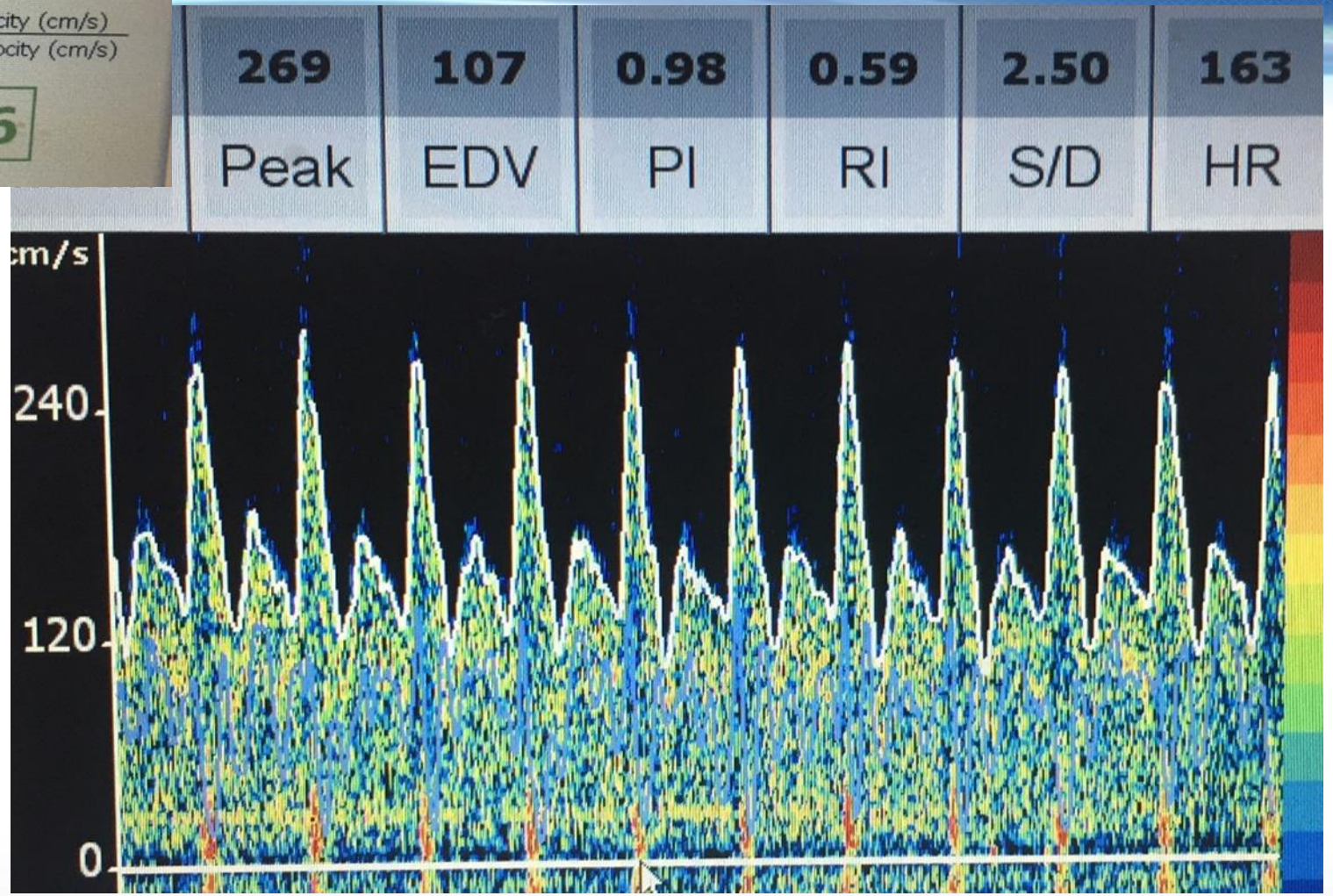

65.8
Mean
144
Peak
27.3
EDV
1.75
PI
0.80
RI
5.25
S/D
142
HR
cm/s
120
60
0

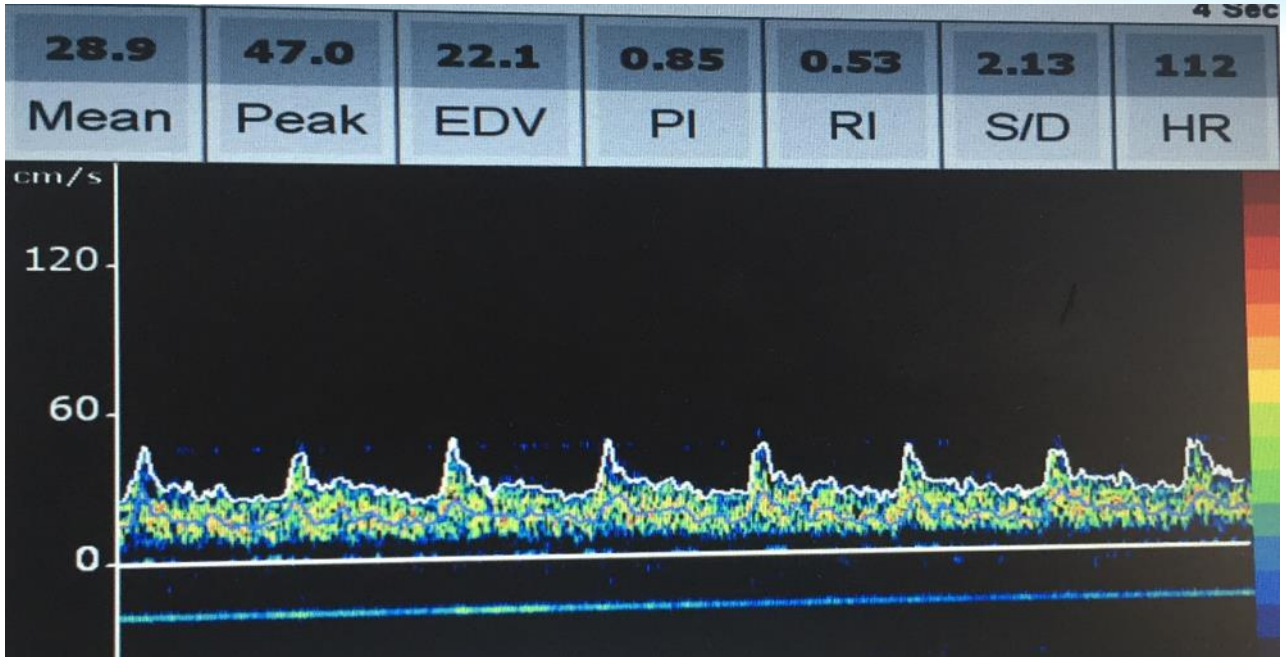

55.8
Mean
108
Peak
23.0
EDV
1.50
PI
0.78
RI
4.68
S/D
103
HR
cm/s
120
60
0

Right Lindegaard Ratio

R-MCA Mean Velocity (cm/s) / R-EX-ICA Mean Velocity (cm/s)

1.96



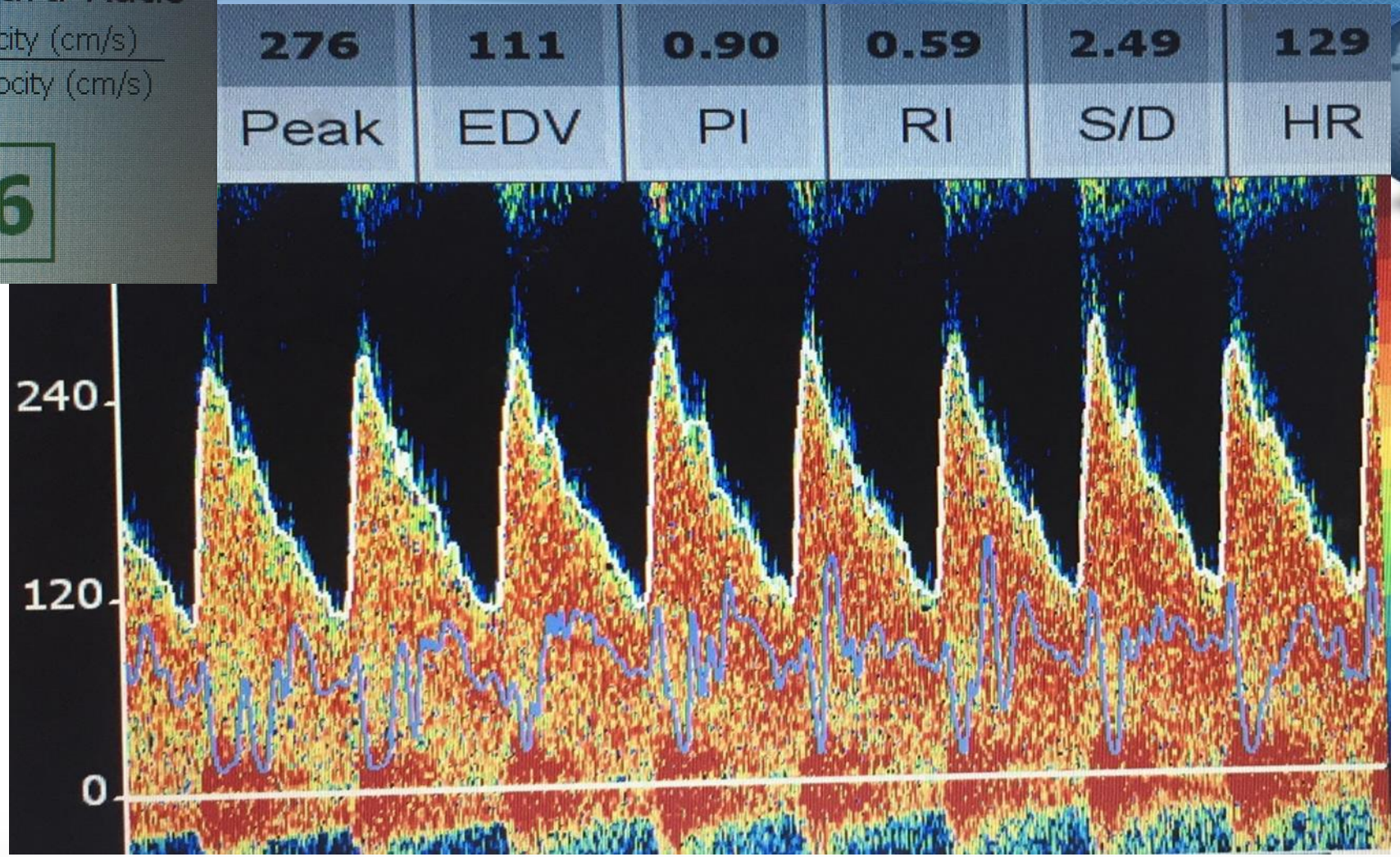

4 Sec
28.9
Mean
47.0
Peak
22.1
EDV
0.85
PI
0.53
RI
2.13
S/D
112
HR
cm/s
120
60
0

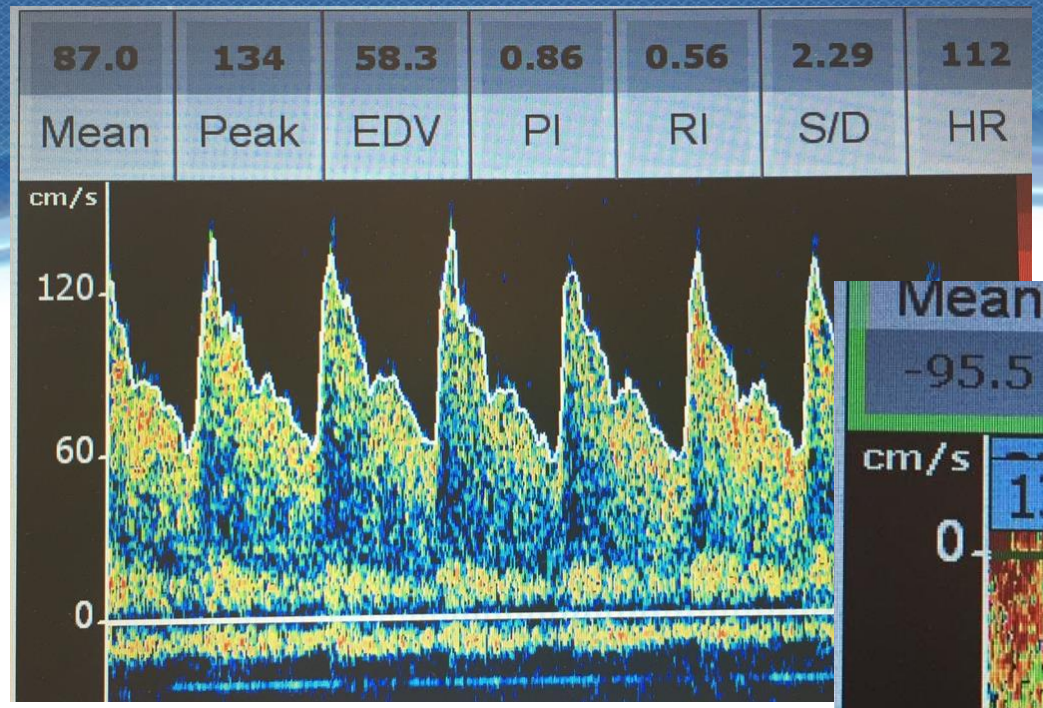
Right Lindegaard Ratio

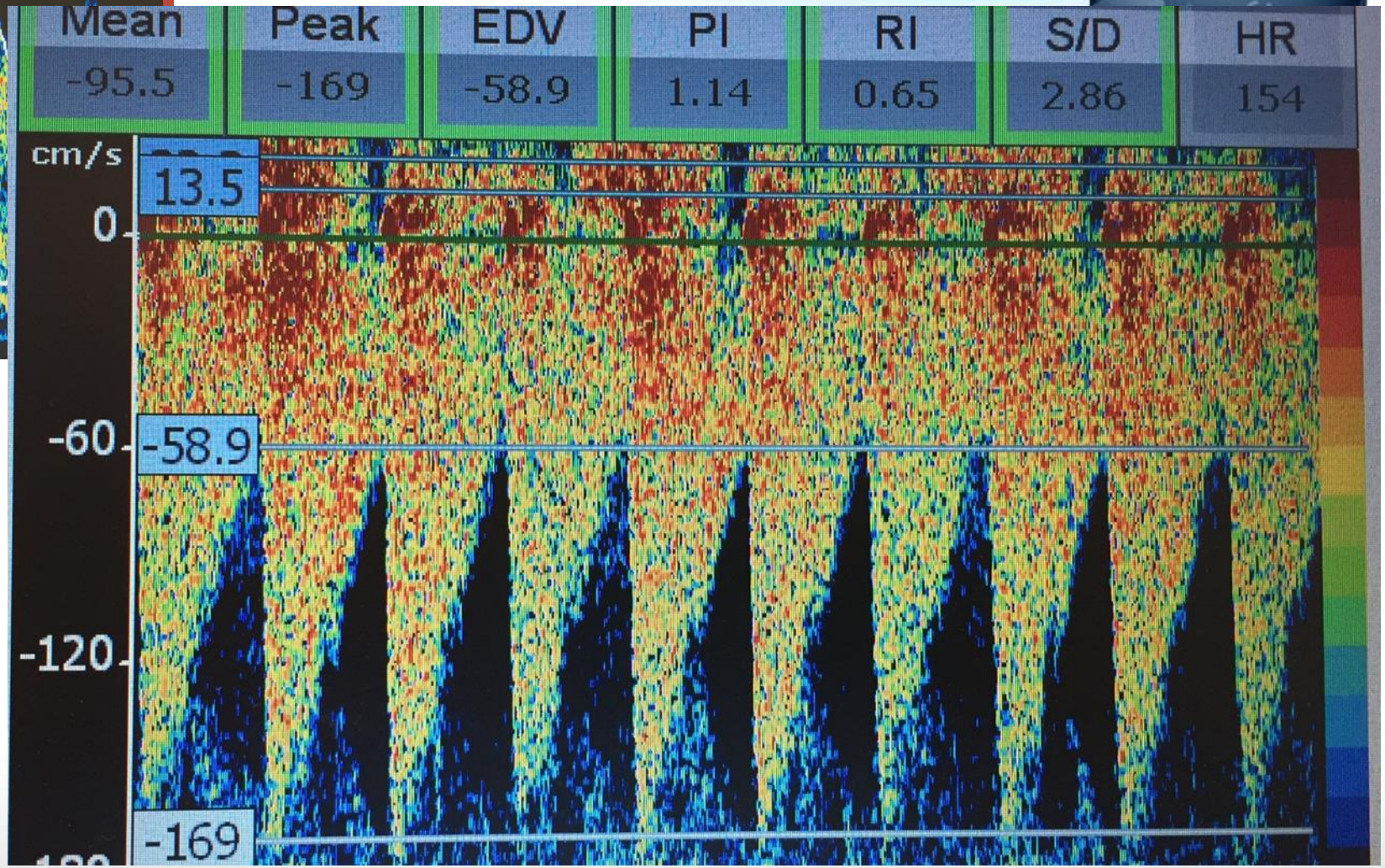
R-MCA Mean Velocity (cm/s)

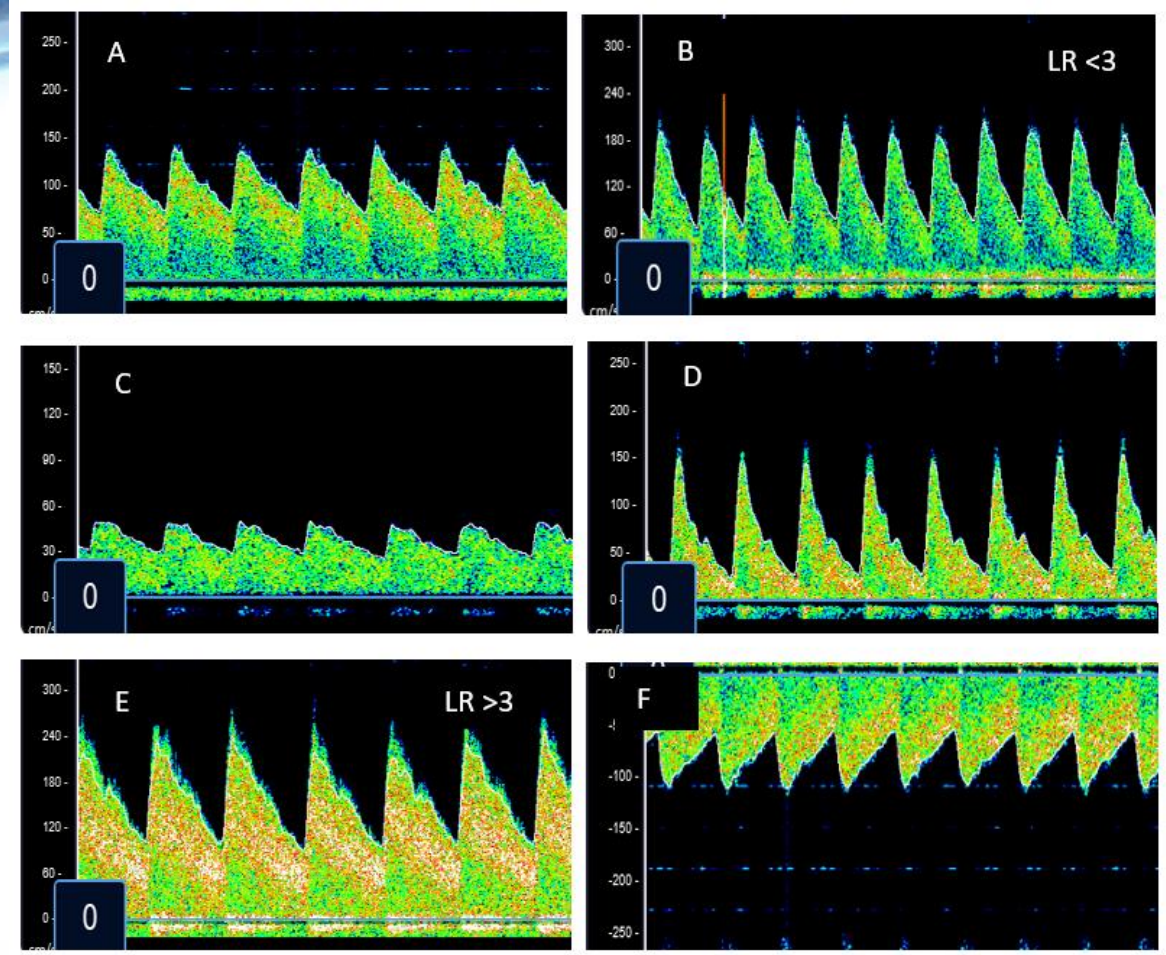
R-EX-ICA Mean Velocity (cm/s)

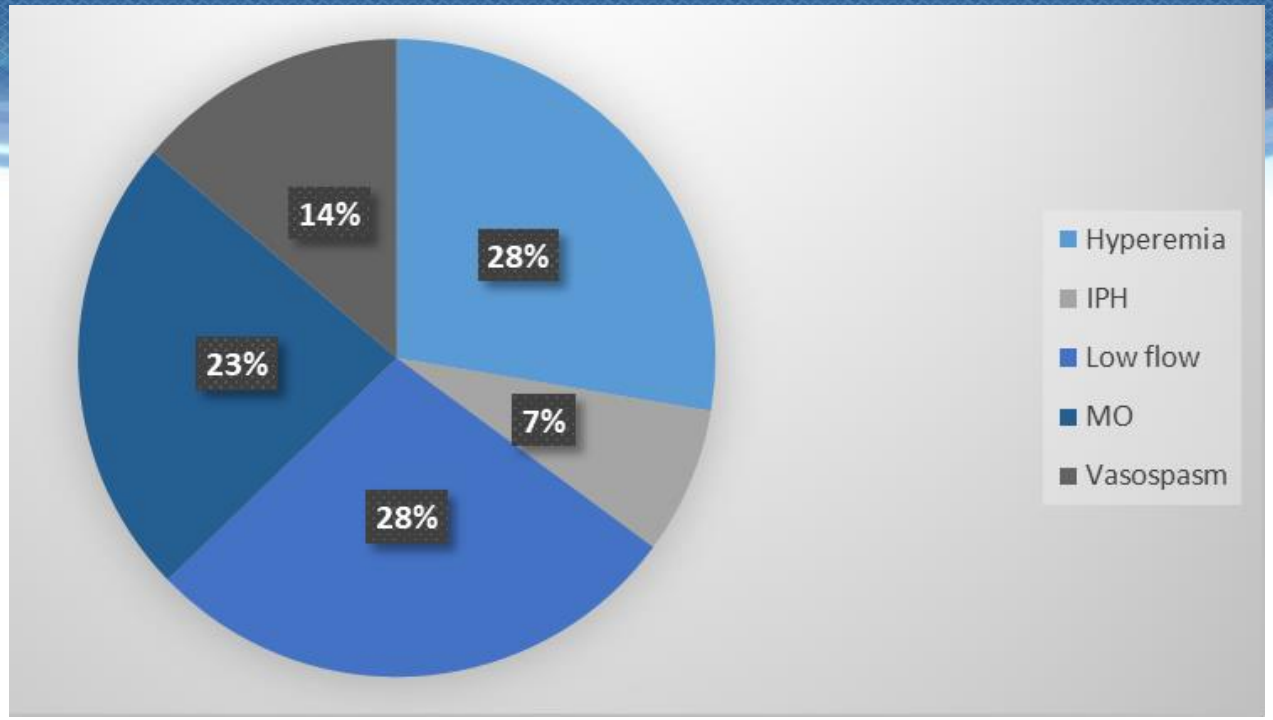
7.16




87.0
134
58.3
0.86
0.56
2.29
112
Mean
Peak
EDV
PI
RI
S/D
HR
cm/s
120
60
0


Mean
-95.5
Peak
-169
EDV
-58.9
PI
1.14
RI
0.65
S/D
2.86
HR
154
cm/s
13.5
0
-60
-58.9
-120
-169





A. Normal MCA TCD flow velocities and waveform for a 3-year-old child.
B. TCD with increased systolic flow velocity, increased diastolic flow velocity. Lindegaard ratio (LR) <3. These findings represent a child categorized as having hyperemia.
C. TCD with decreased systolic flow velocity, decreased diastolic flow velocity, decreased mean flow velocity. These findings represent a child categorized as having low flow.
D. TCD with normal systolic flow velocity, reduced diastolic flow velocity, increased pulsatility index. These findings represent a child categorized as having microvascular obstruction. Opening pressure at the time this TCD was performed was 11 cm H2O.
E. TCD with increased systolic flow velocity, increased diastolic flow velocity. LR >3. These findings represent a child categorized as having cerebral vasospasm.
F. TCD with increased systolic flow velocity, increased diastolic flow velocity, increased mean flow velocity in the basilar artery. At the same time, all measurements in the MCAs were normal. These findings represent a child categorized as having isolated posterior hyperemia.

Table II. Clinical and laboratory findings of children with retinopathy-positive cerebral malaria and comparison patients with severe malaria without neurologic involvement

Characteristics	Retinopathy-positive cerebral malaria (n = 160)	Comparison patients (n = 155)	*P* value*
Age, mo, mean ± SD	56 ± 3	49 ± 3	.14
Male sex, n (%)	84 (53%)	83 (54%)	.74
Variable before admission, mean ± SD			
Duration of illness, d	5.3 ± 2.7	4.8 ± 2.1	.81
Duration of coma, d	2 ± 1	—	—
Seizures, n (%)			
Before arrival	140 (88%)	35 (23%)	<.001
At presentation			
Requiring benzodiazepine	98 (61%)	22 (14%)	<.001
Requiring phenobarbital	56 (35%)	0 (0%)	<.001
Beyond initial presentation	33 (21%)	0 (0%)	<.001
Temperature, °C, mean ± SD	37.9 ± 0.06	38.1 ± 0.07	.07
Pulse rate, beats/min, mean ± SD	135 ± 2	136 ± 3	.97
Respiratory rate, breaths/min, mean ± SD	35 ± 4	33 ± 2	.99
Oxygen saturation, %, mean ± SD	94 ± 1	95 ± 2	.82
BCS, n (%)			
0	61 (38%)	—	—
1	79 (49%)	—	—
2	20 (13%)	—	—
3	—	—	—
4	—	—	—
5	—	155 (100%)	—
Parasites/mm^3, median (IQR)	28 700 (15 200, 180 00)	25 515 (14 800, 187 000)	.98
Hemoglobin, g/dL, mean ± SD	8.2 ± 0.2	6.5 ± 0.17	<.001
White cells, $\times 10^{-9}$/L, mean ± SD	13 604 ± 725	12 698 ± 591	.34
Lactate, mmol/L, median (IQR)	2 (1.4, 3)	1.9 (1, 2.3)	.04
Blood glucose, mg/dL, mean ± SD	117 ± 37	118 ± 29	.80
CSF opening pressure, cm/H_2O, median (IQR)	12 (6, 49)	—	—
TCD diagnostic category, n (%)†			
Microvascular obstruction	35 (22%)	21 (13%)	.05
Hyperemia	42 (26%)	6 (4%)	<.001
Vasospasm	21 (13%)	0 (0%)	<.001
Low flow	46 (28%)	10 (7%)	<.001
IPH	7 (4%)	0 (0%)	.03
Normal flow	5 (3%)	118 (76%)	<.001

CSF, cerebrospinal fluid; *IPH*, isolated posterior hyperemia.
**P* values were estimated with the use of Student *t* tests for means, Wilcoxon rank-sum tests for medians, and Pearson χ^2 tests for proportions.
†Four patients had evidence of terminal ICH on initial TCD examination and were not categorized.

Table IV. Clinical and laboratory findings in children meeting each diagnostic group

Flow groups	Microvascular obstruction (n = 35)	Hyperemia (n = 42)	Vasospasm (n = 21)	Low flow (n = 46)	IPH (n = 7)	*P* value*
Age, mo, median (IQR)	39 (24, 72)	60 (24, 122)	48 (19, 96)	38 (28, 60)	27 (18, 60)	.17
Male sex, n (%)	21 (60%)	21 (50%)	9 (42%)	27 (66%)	4 (57%)	.21
No. days to present, median (IQR)	4 (3, 8)	4 (2, 5)	6 (3, 8)	4 (3, 6)	5 (4, 6)	.23
Seizures, n (%)	31 (89%)	36 (86%)	19 (90%)	40 (98%)	7 (100%)	.25
Temperature, °C, mean ± SD	38.1 ± 0.96	38.3 ± 0.72	38.1 ± 0.94	38.4 ± 1	38.4 ± 0.7	.43
Pulse, beats/min, mean ± SD	134 ± 20	136 ± 29	139 ± 34	137 ± 25	145 ± 14	.80
Respiratory rate, breaths/min, mean ± SD	28 ± 8	35 ± 13	37 ± 11	37 ± 11	37 ± 14	.05
Oxygen saturation, %, median (IQR)	96 (93, 98)	96 (93, 98)	98 (94, 99)	95 (92, 98)	95 (94, 96)	.30
Hemoglobin, g/dL, mean ± SD	7.5 ± 1.2	8.2 ± 2.5	9 ± 3.4	8.1 ± 2.3	7.6 ± 1.9	.11
White cells, $\times 10^{-9}$/L, median (IQR)	6800 (5600, 11 800)	14 550 (9990, 17 400)	15 324 (7300, 23 400)	12 000 (8600, 16 800)	9900 (8500, 13 300)	.001
Lactate, mmol/L, median (IQR)	1.25 (1.2, 5.5)	2.2 (1.6, 2.8)	2.7 (1.6, 3.1)	2 (1.6, 3.4)	2.2 (2, 2.4)	.20
Glucose, mg/dL, mean ± SD	118 ± 17	113 ± 37	116 ± 29	123 ± 38	113 ± 33	.57
CSF opening pressure, cm/H_2O, median (IQR)	12 (9, 23)	11 (9, 39)	9 (6, 19)	16 (11, 21)	10 (8, 22)	.84

**P* values were estimated with the use of one-way ANOVA or Kruskal–Wallis tests.

Table V. Predicted probabilities (with 95% CIs) of neurologic sequelae or death in children with cerebral malaria in each TCD diagnostic group

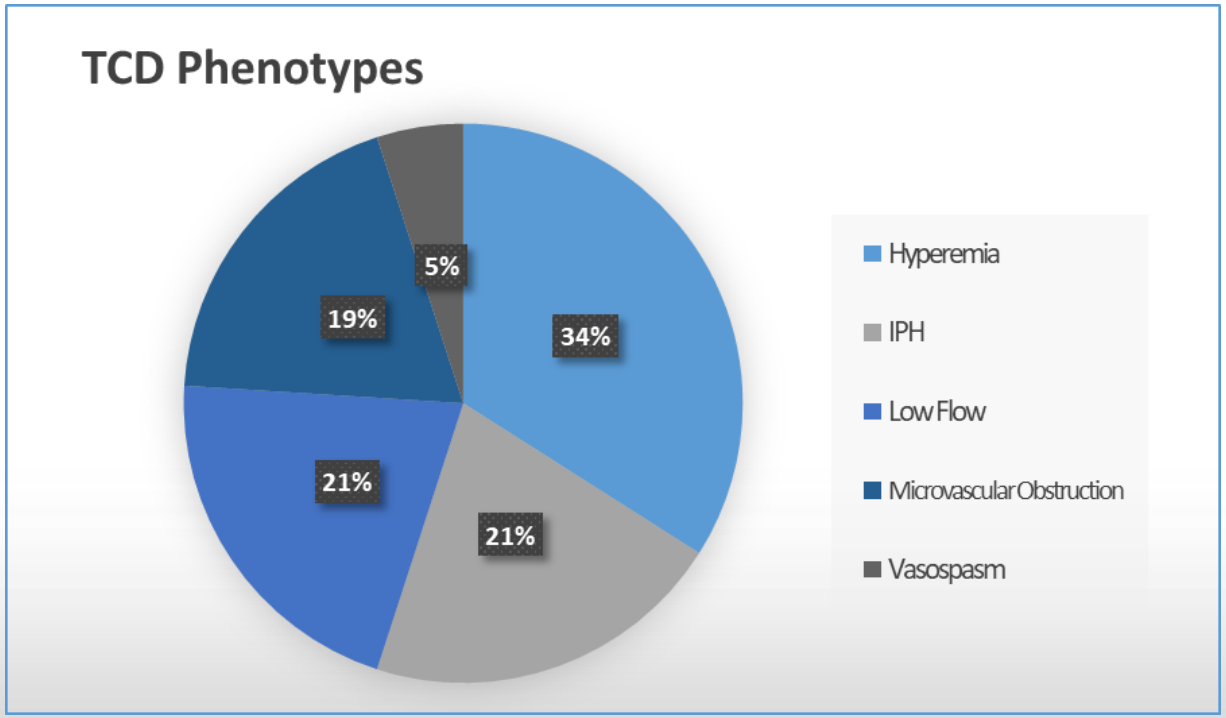
	Probability of neurologic sequelae		Probability of death	
Microvascular obstruction	15.56	(4.97-26.14)	22.22	(10.08-34.37)
Hyperemia	17.5	(5.73-29.28)	27.5	(13.66-41.34)
Vasospasm	45.45	(24.65-66.26)	18.18	(2.07-34.3)
Low	24.62	(14.14-35.09)	32.31	(20.94-43.68)
IPH	20	(0-44.79)	20	(0-44.79)

- “An investigative study into the pathophysiologic mechanisms of CM using TCD” (U01AI126610)

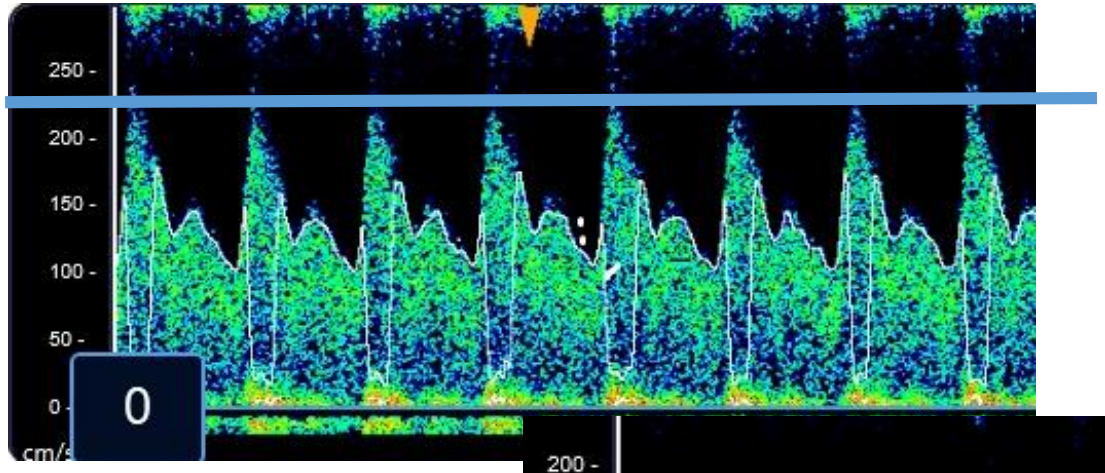
BLANTYRE MALARIA PROJECT

- Using extensive infrastructure to evaluate relationships between typical pathophysiologic contributors to each TCD phenotype
  - Blood gas analysis
  - Cardiac ultrasound
  - Electrolytes
  - EEG
  - MRI
  - Optic nerve sheath diameter

- 128 CM patients to date
  - Similar frequency of each TCD phenotype compared to the Congolese cohort

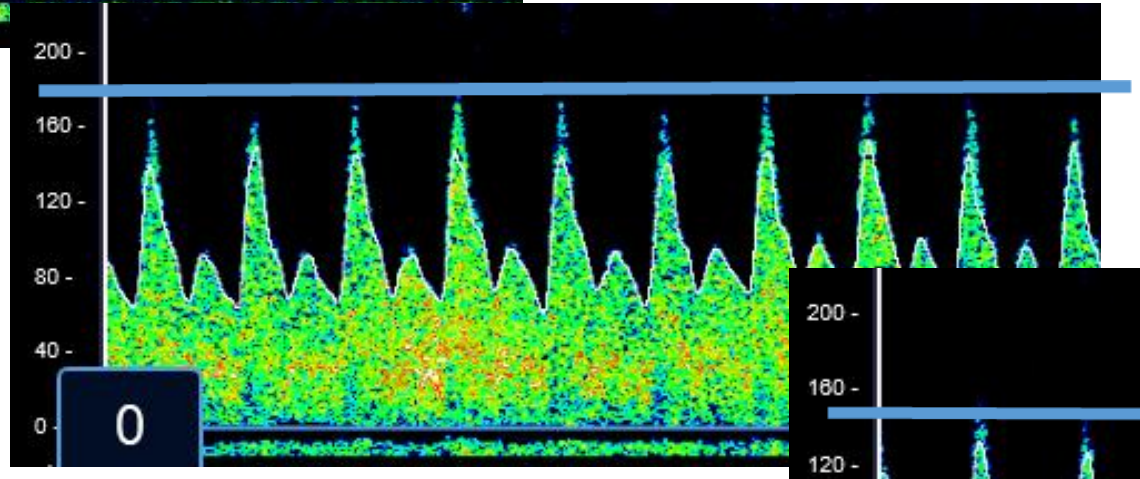


Hyperemia- 5 yo female, 3 days of fever and 2 episodes of seizures

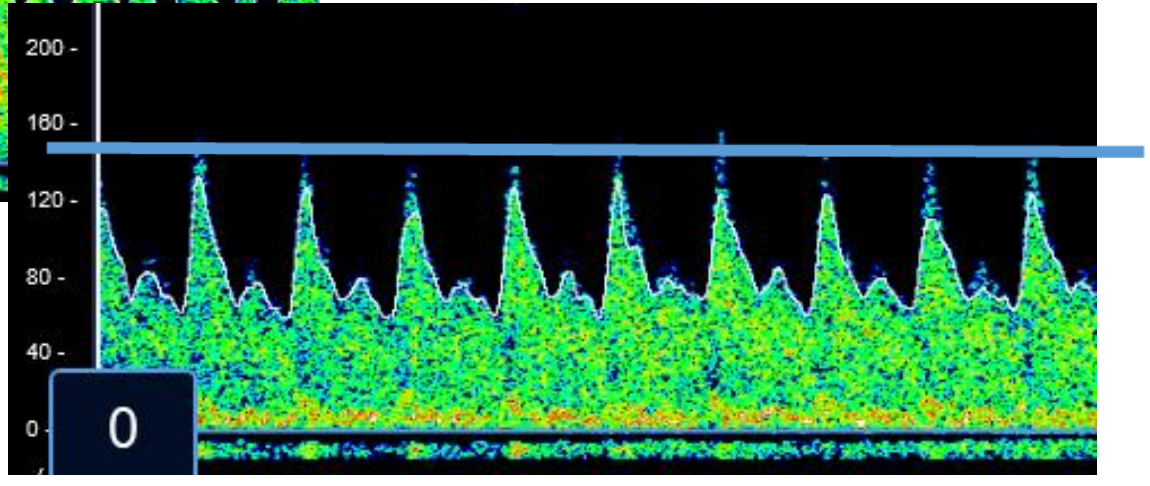


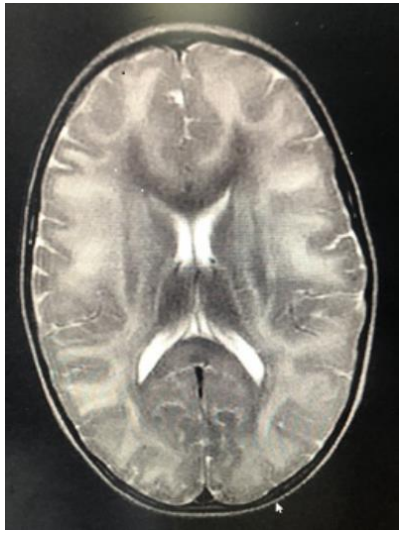
Day 1- Peak flows 240s (>5SD above age normal)
Temp 37.6, HR 142, BP 99/55, MP +++, PCV 24,
Gas 7.42/33/2, BCS 1
EEG without epileptiform discharges

Day 2- Peak flows 180's (>3SD above normal), BCS 3



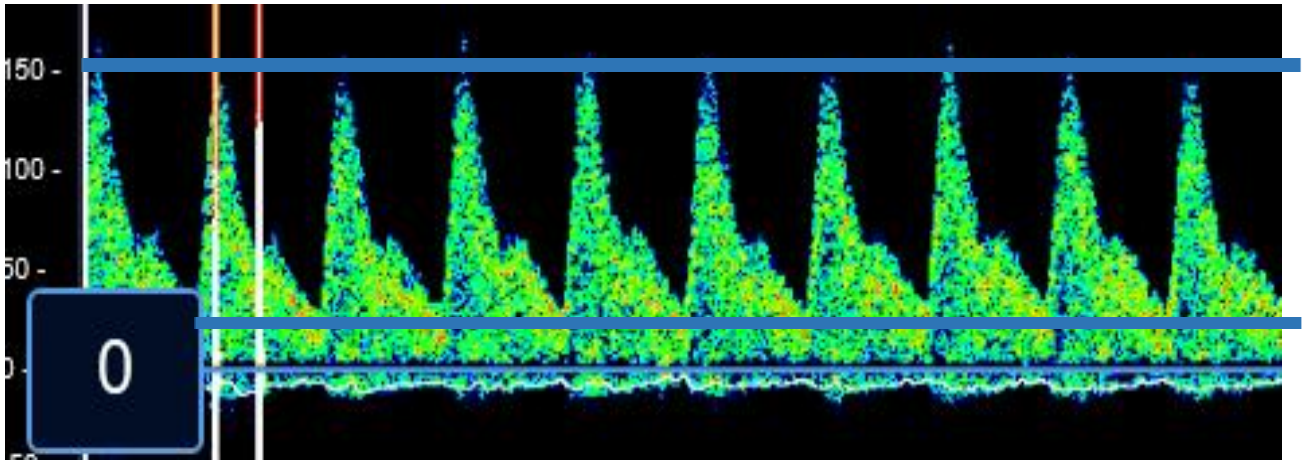
Day 3- Peak flows 140's (normal)
BCS 5, Normal Neurologic Outcome





MRI day 1 with bilateral frontotemporal edema , brain volume score (BVS) 6

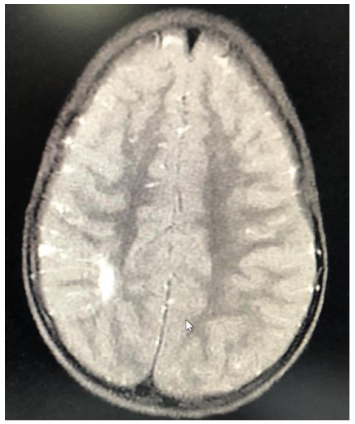
Microvascular Obstruction- 3yo male, 2 days of fever and 4 episodes of seizures



Day 1- MCA systolic flows normal for age;
diastolic flows <3SD below normal; PI 1.52

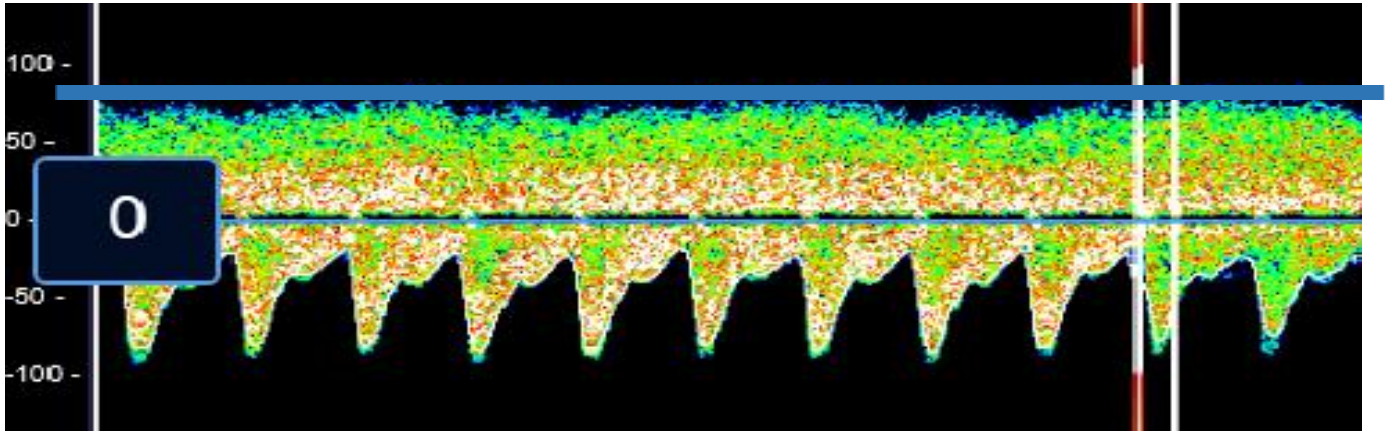
Temp 37.5, HR 148, BP 93/42, MP +, PCV 21,
Lactate 5.1, Gas 7.3/36/-5, BCS 1
OP 14, ONSD 0.49

Venous obstruction with Inferior
Petrosal Sinus flow velocity 77 cm/sec
(normal --20cm/sec)

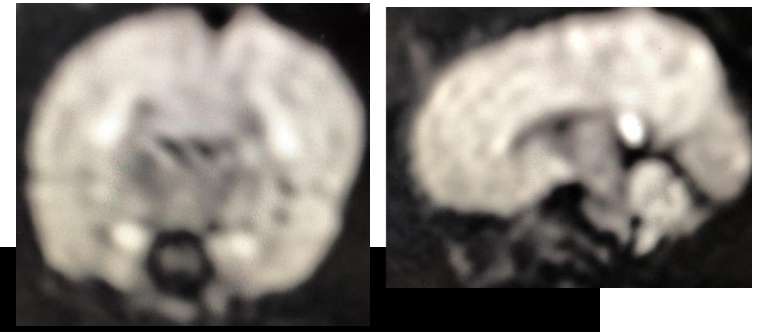


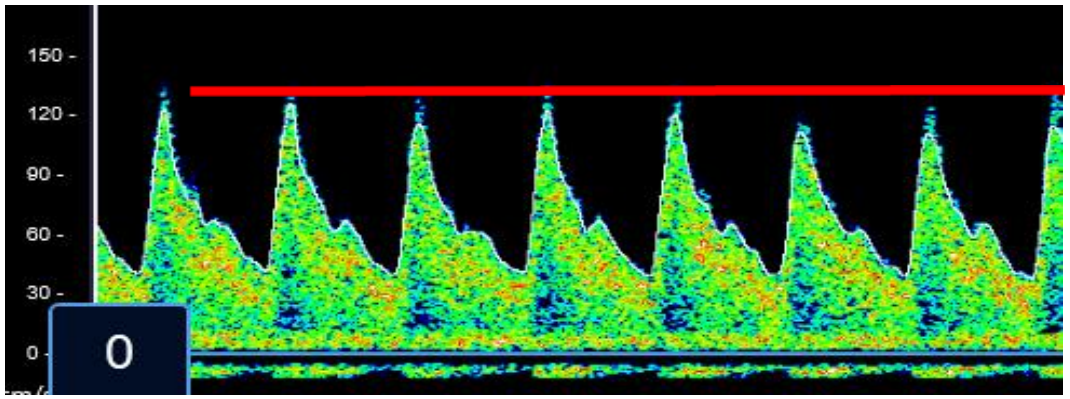
MRI with scattered
hyperintensities
on T2 with DWI changes sub-
cortical region, corpus callosum,
hippocampi, brain volume score 6

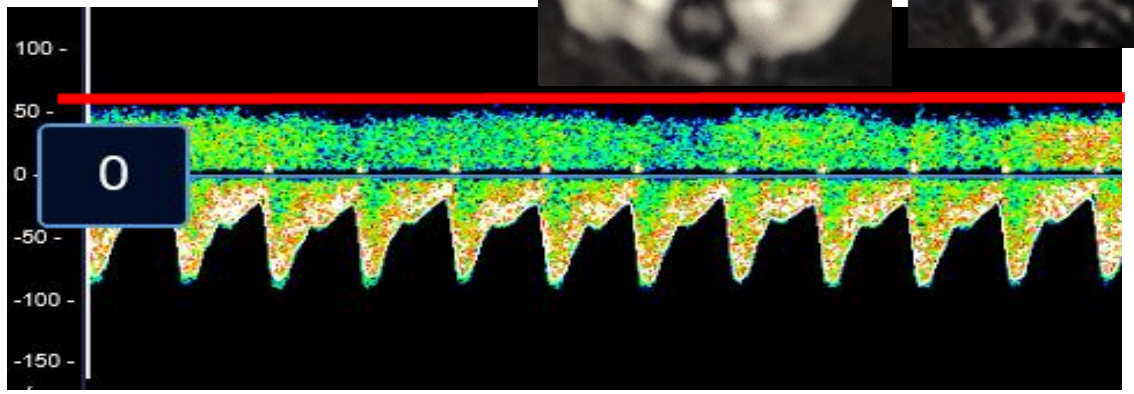
Survived with severe sequelae



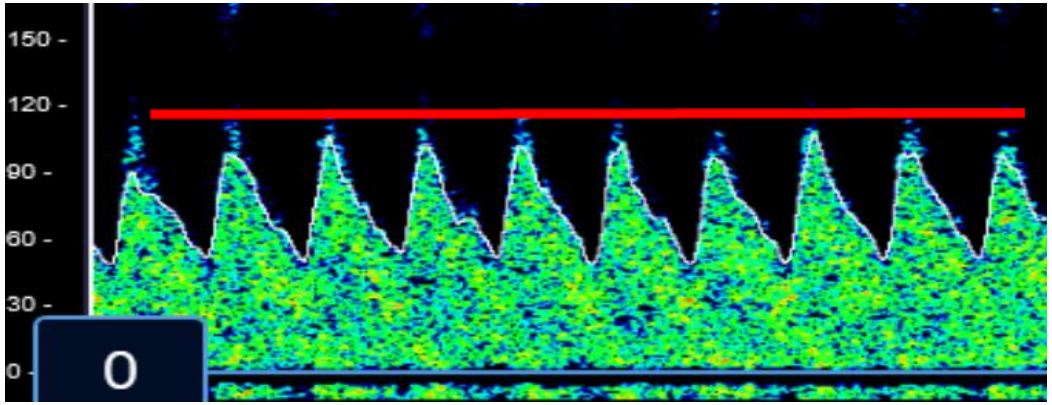
Microvascular Obstruction- Day 2 and Day 4

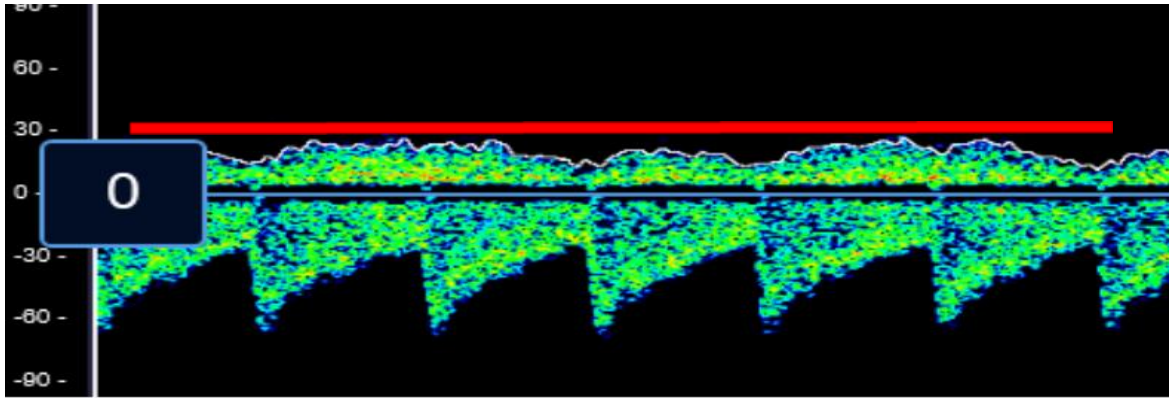






MCA systolic flows normal; diastolic flows improving to <2SD and PI to 1.2; IPS flow down to 55cm/sec

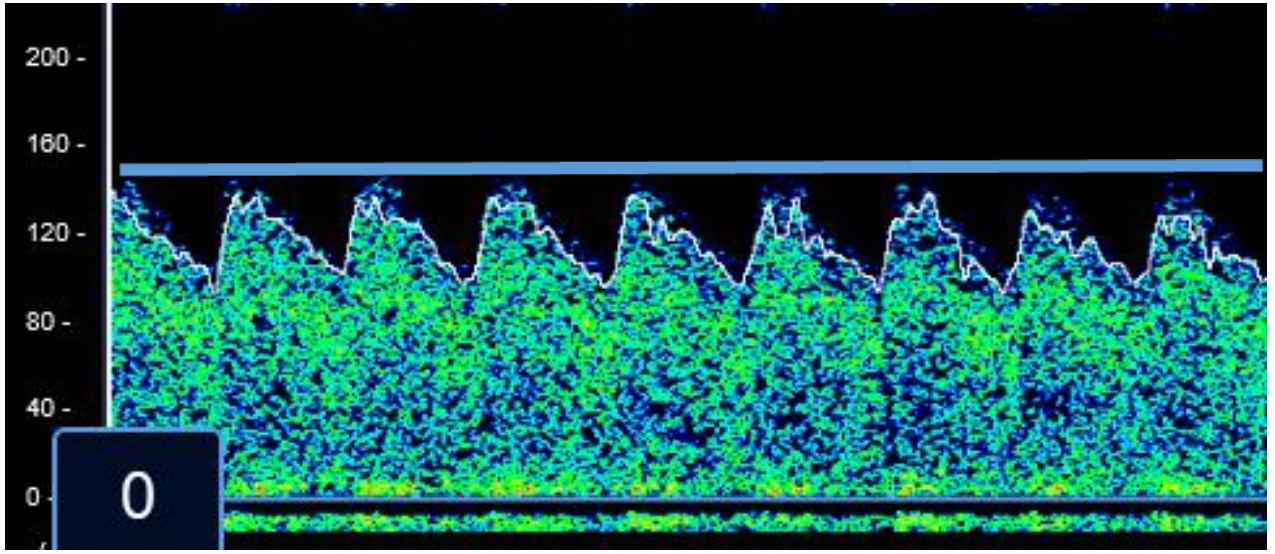




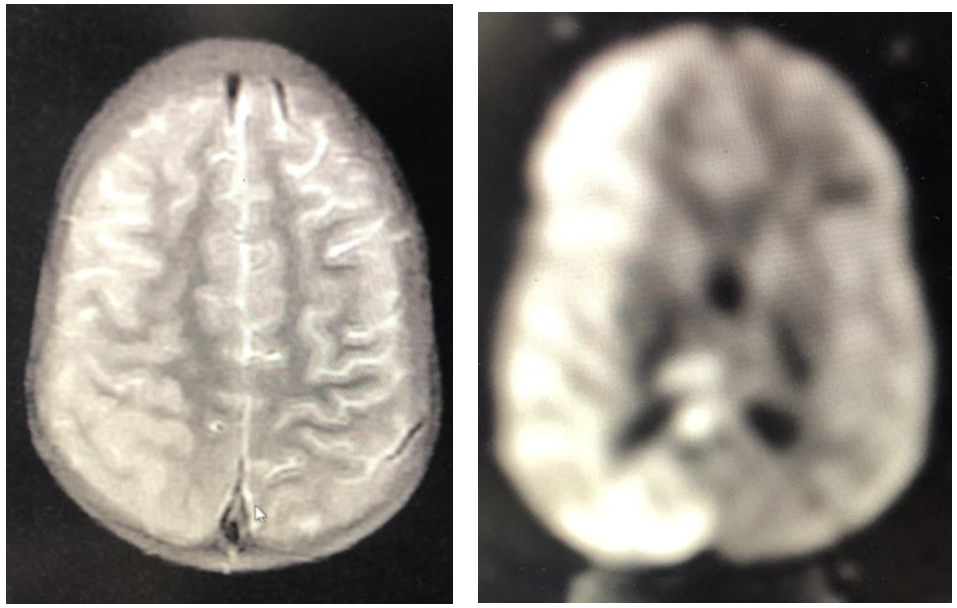
MCA systolic flows normal; diastolic flows normal and PI 0.91; IPS flows down to 25 cm/sec

Vasospasm- 9 mo female, 4 days of fever and no seizures

Day 1- Right MCA peak flows 180's (>5SD from normal), normal carotid flow
PI of 0.28



Temp 37.9, HR 138, BP 83/45, MP ++, PCV 19, Lactate 5.4, Gas 7.36/38/-6, BCS 2

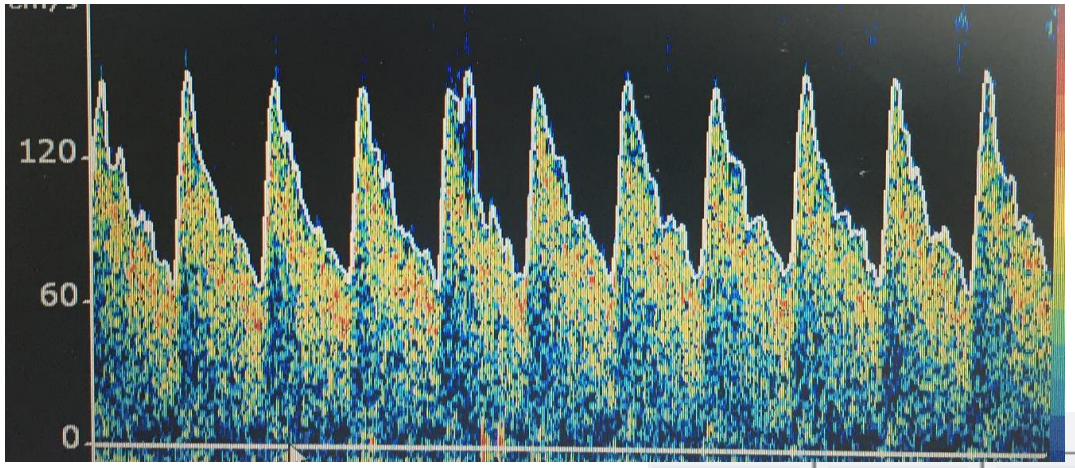


MRI with right sided edema and evidence of ischemic injury in the R MCA distribution, brain volume score 5

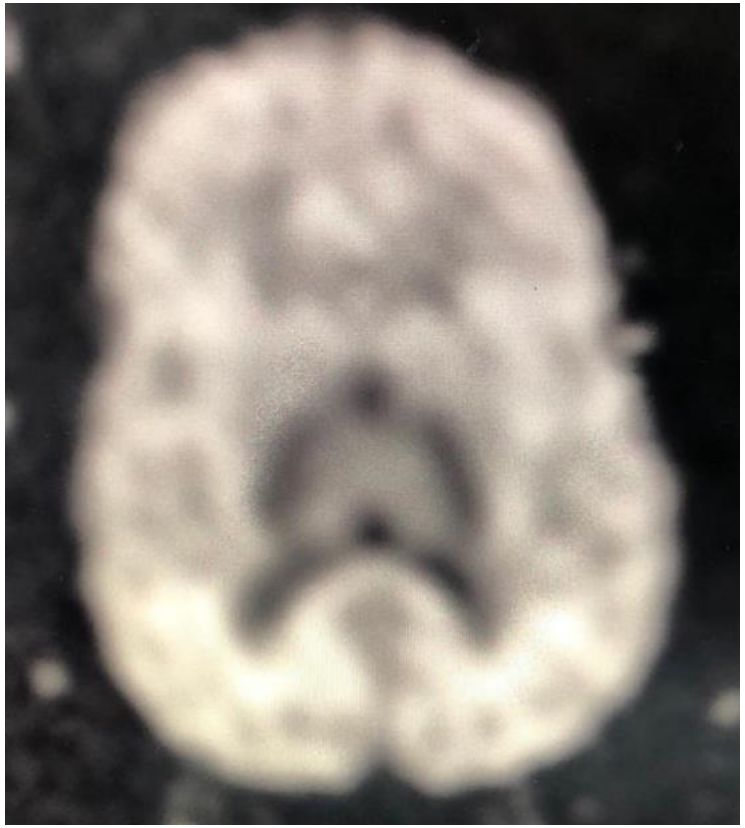
EEG: Right hemisphere suppression and spindle asymmetry with the absence of spindles on the right as well. These findings are indicative of diffuse focal neuronal dysfunction in the right hemisphere.

Survived with left hemiparesis

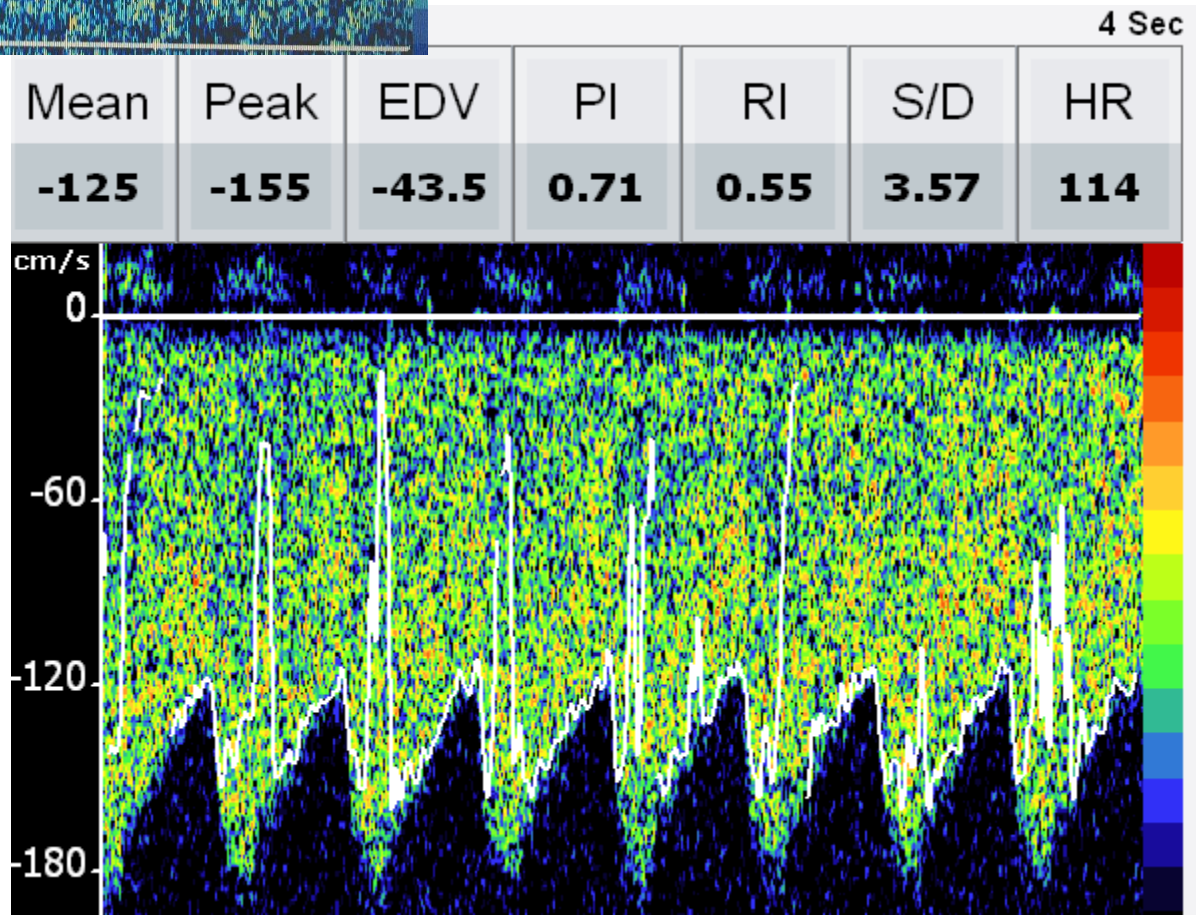
IPH- 4yo 3 days fevers, 2 seizures



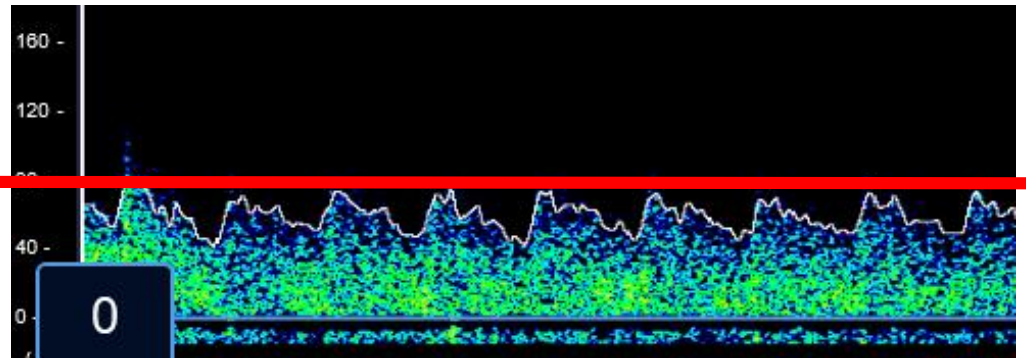
Normal bilateral MCA flows



BA flow >4SD above age normal

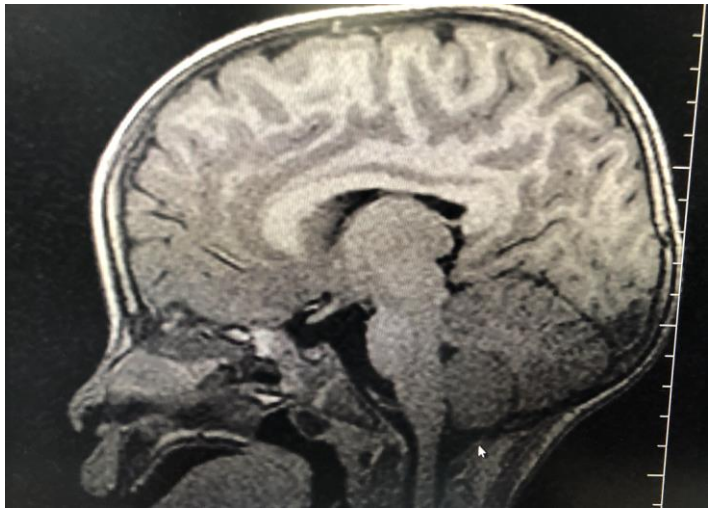


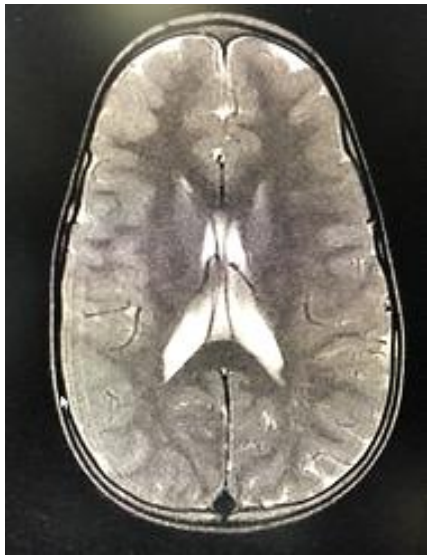
Low Flow- Case 1, Day 1; 6yo 2 days of fevers

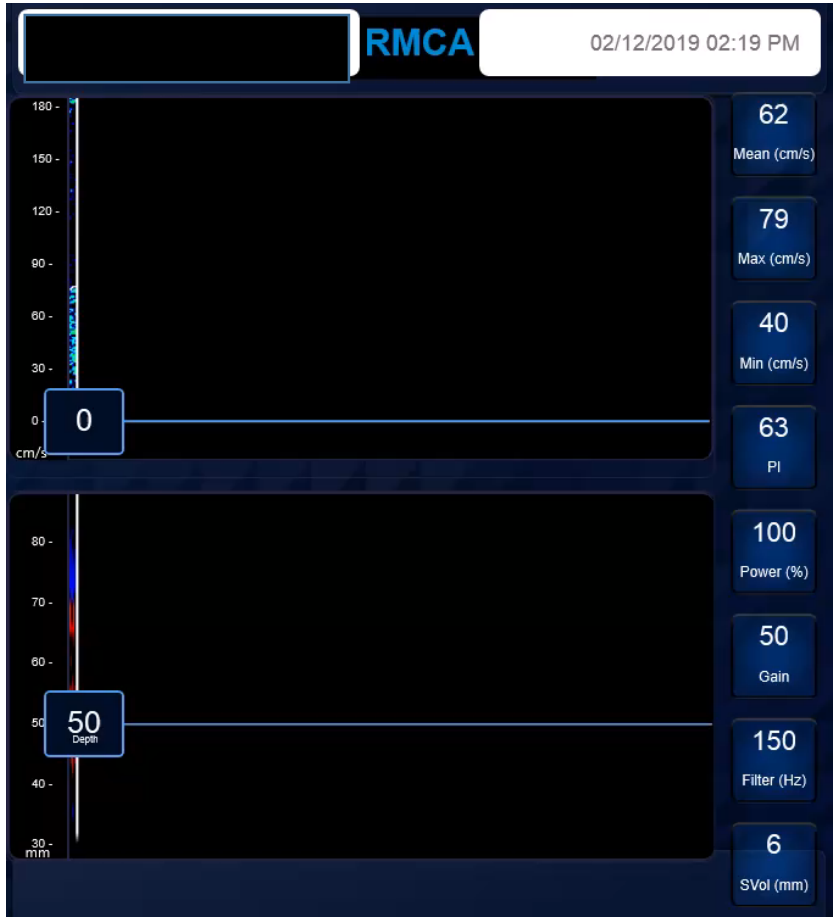


MCA peak flows in the 80's (<5SD from age normal);
PI 0.35

HR 144, BP 114/75, MAP 88, PCV 22, BCS 1

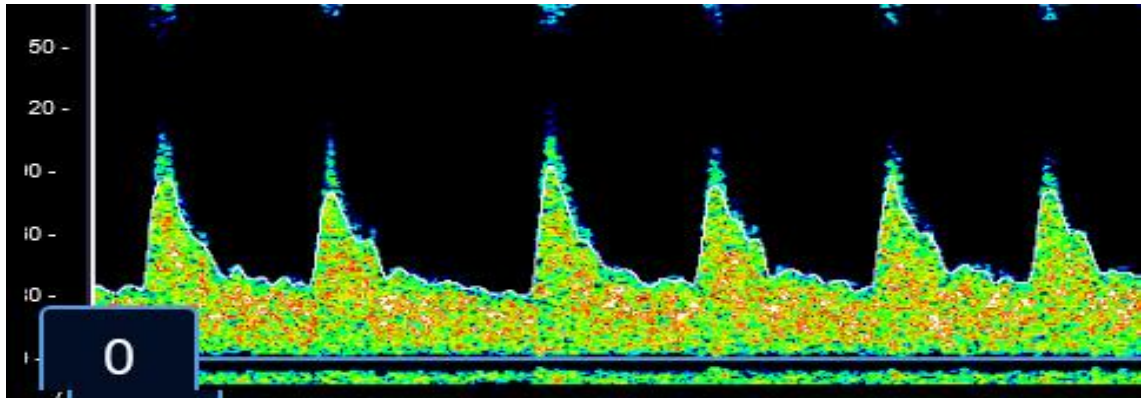


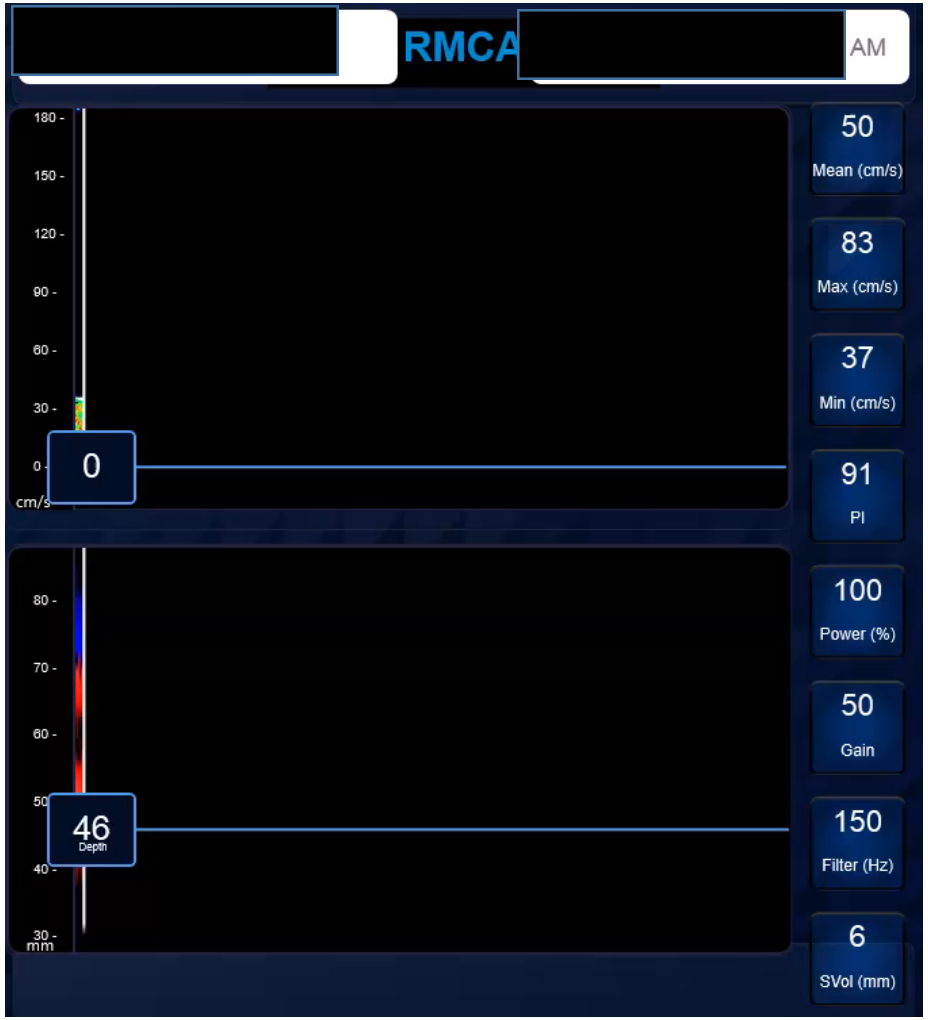




Brain volume score 4, OP on LP 20, ONSD 0.46

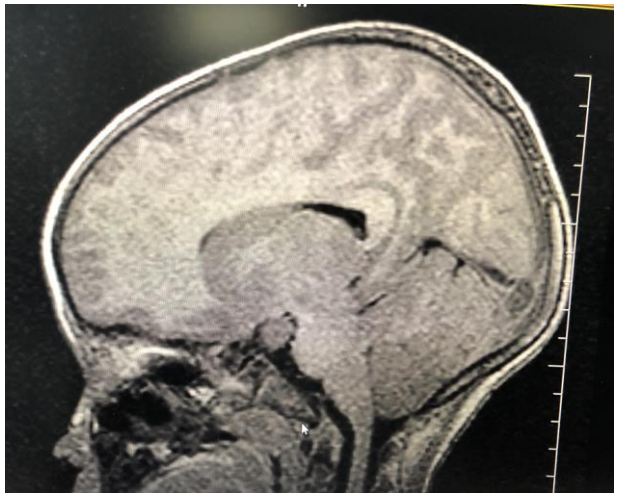
Low Flow- Day 2





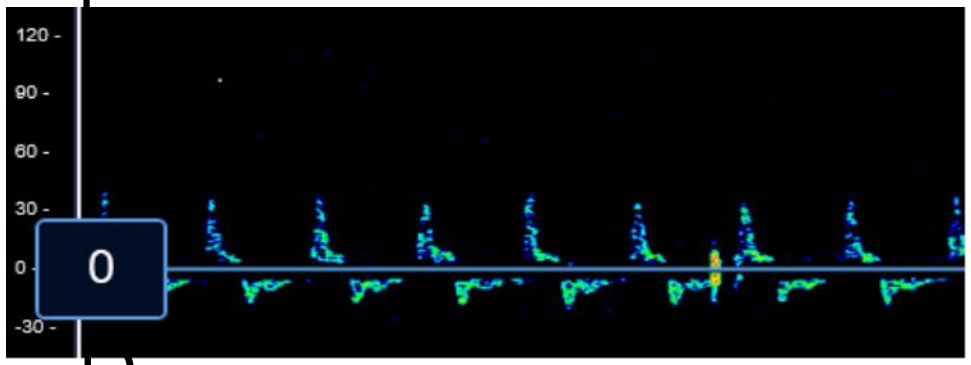
Ongoing insufficient perfusion within MCAs;
Flattening of diastolic flow suggests increasing ICP

Neurologic exam unchanged, BCS remains 1



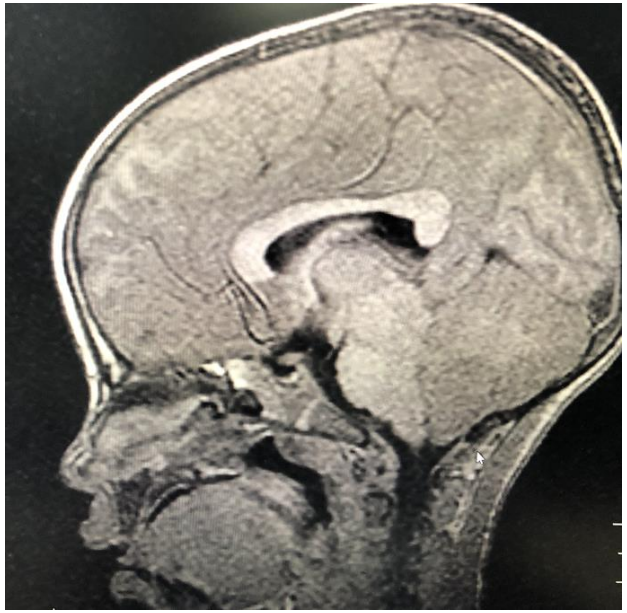
Brain volume score 8, ONSD 0.52

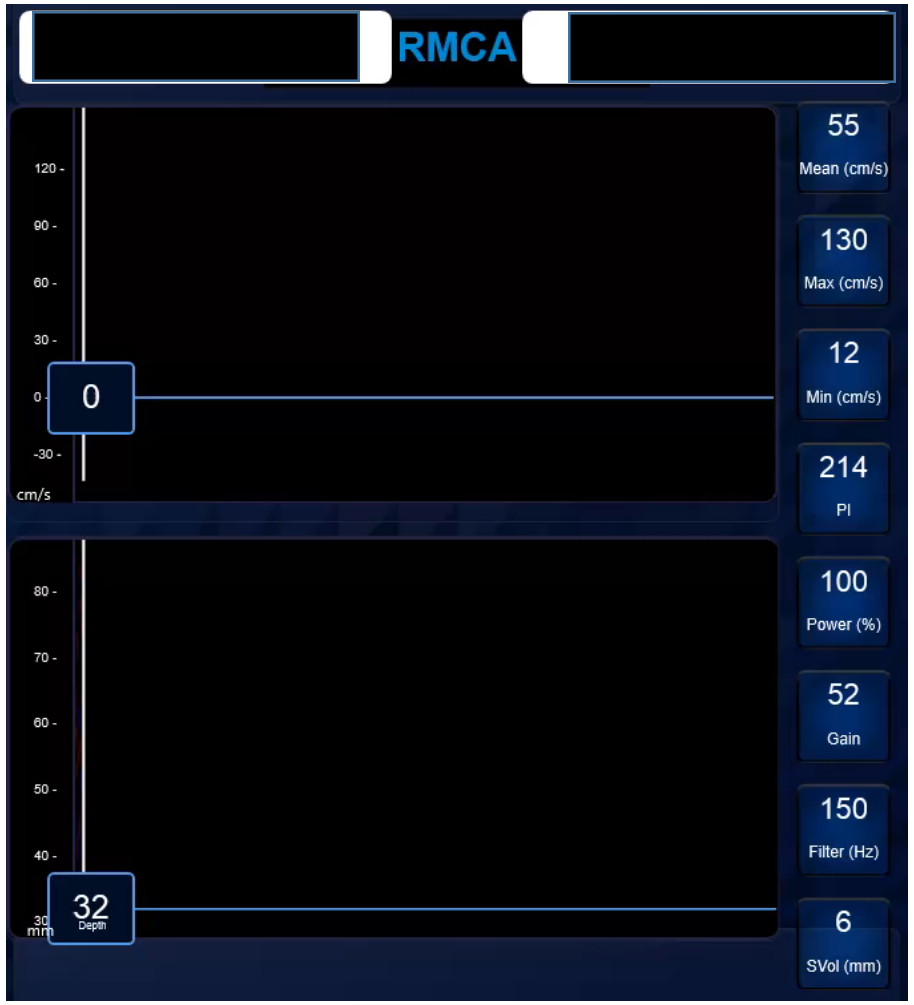
Low Flow- Day 4



Reversal of flow

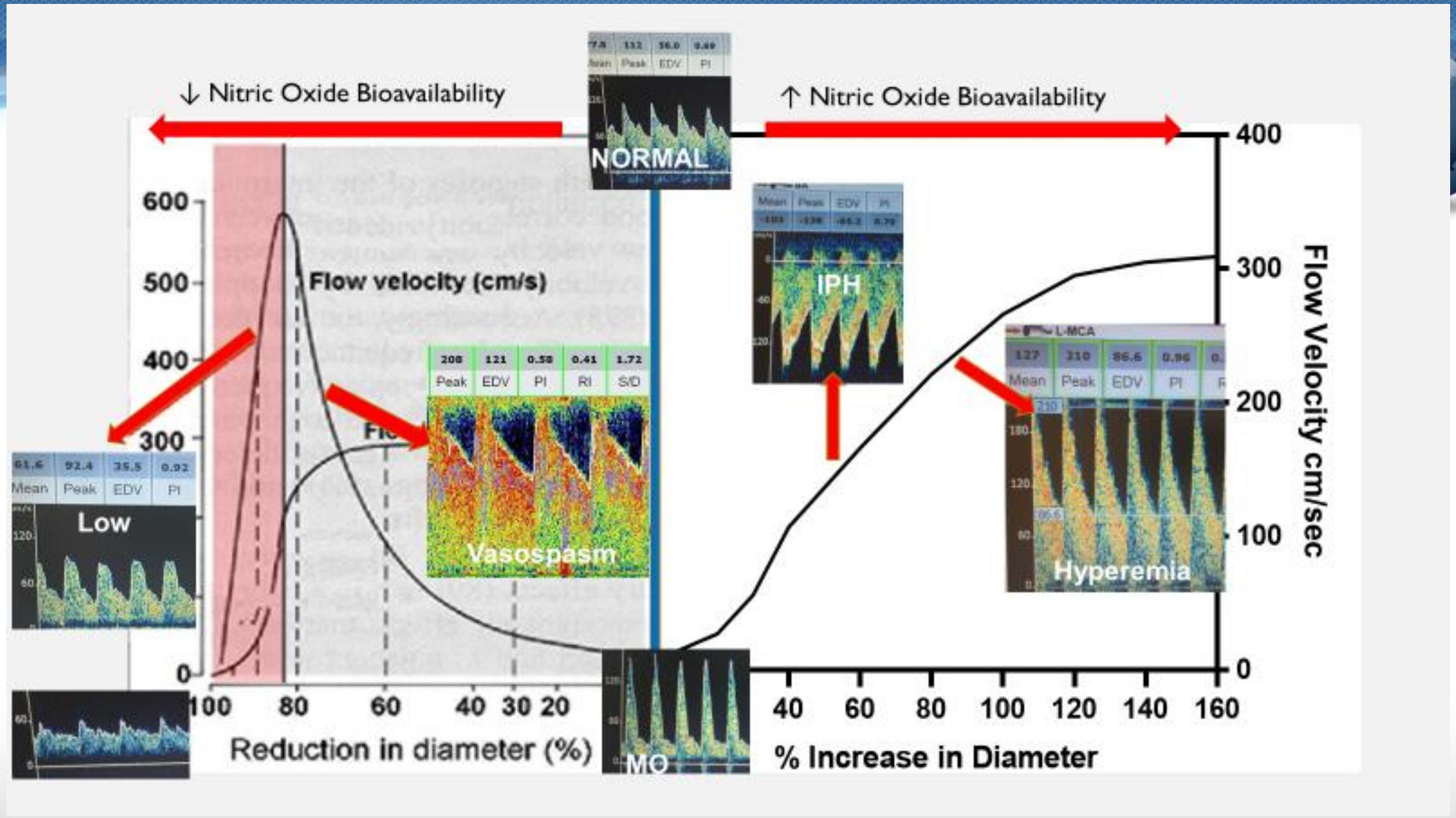
Catastrophic cerebral swelling with diffuse ischemia

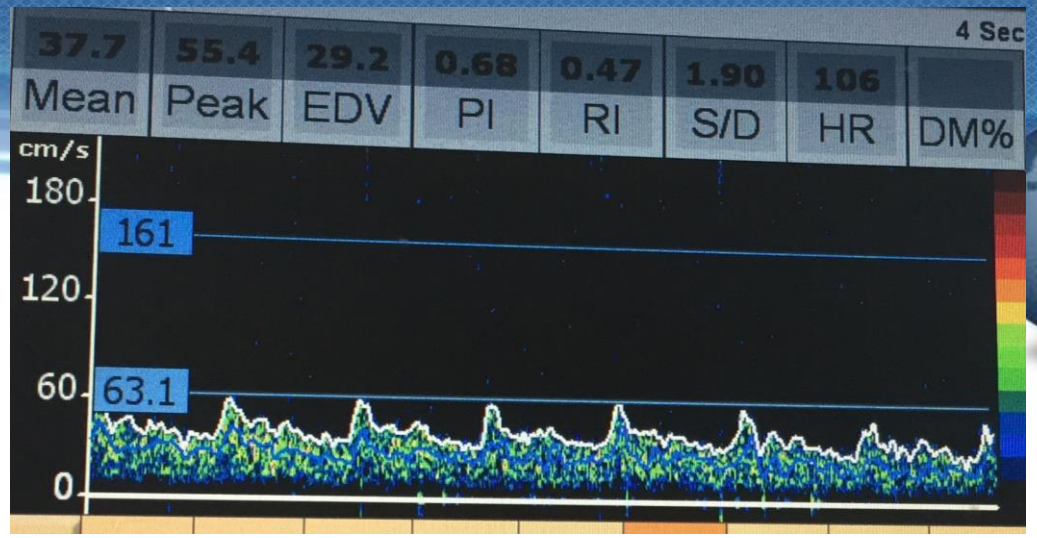


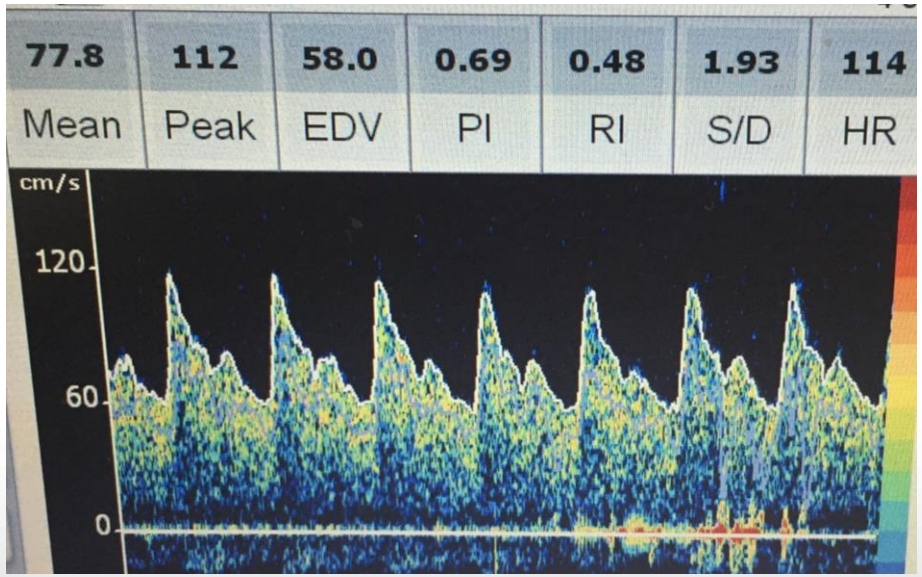


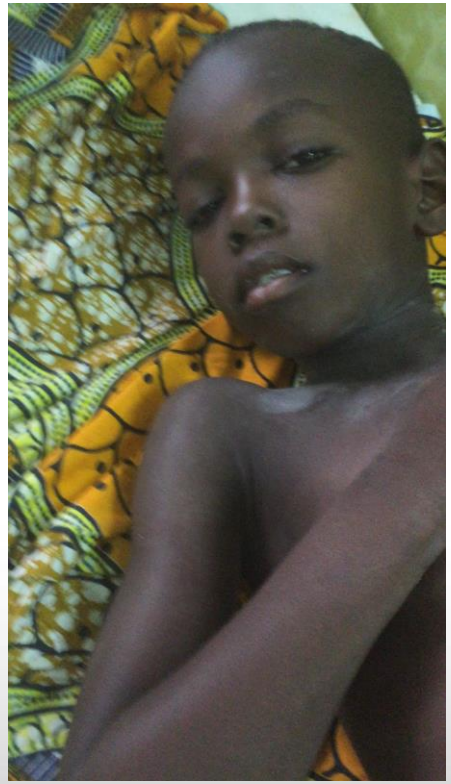
	All TCD phenotypes	Hyperemia	IPH	Low	Vasospasm	MO	p
Age, median (IQR)	49.0 [31.0, 74.0]	46.0 [30.2, 73.5]	41.0 [24.8, 66.5]	51.5 [35.0, 75.0]	55.0 [29.0, 95.0]	51.5 [40.0, 65.8]	0.750
Gender, N (%)	58 (49.6%)	25 (59.5%)	6 (37.5%)	18 (56.2%)	6 (46.2%)	3 (21.4%)	0.105
Temp, median (IQR)	38.3 [37.4, 39.2]	38.2 [37.4, 38.9]	38.4 [37.6, 39.4]	38.0 [37.2, 39.2]	39.0 [38.3, 39.5]	38.5 [37.6, 39.2]	0.125
HR, median (IQR)	141 [123, 160]	140 [125, 152]	139 [122, 164]	149 [124, 162]	135 [127, 165]	134 [119, 151]	0.804
RR, median (IQR)	35.0 [30.0, 41.0]	33.5 [28.5, 40.0]	37.0 [29.5, 45.8]	36.0 [31.2, 43.2]	40.0 [32.0, 45.0]	33.0 [32.0, 38.0]	0.372
O2 sat, median (IQR)	97.0 [96.0, 99.0]	97.0 [96.0, 98.0]	98.0 [96.0, 99.0]	97.5 [96.0, 99.0]	96.0 [95.0, 98.0]	98.0 [96.2, 98.0]	0.630
On Oxygen, N (%)	44 (37.6%)	14 (33.3%)	6 (37.5%)	12 (37.5%)	5 (38.5%)	7 (50.0%)	0.870
Mean BP, median (IQR)	77.0 [71.0, 86.0]	78.0 [71.2, 83.0]	76.0 [71.0, 85.2]	77.0 [66.8, 90.2]	82.0 [74.0, 90.0]	74.0 [66.5, 82.8]	0.591
Convulsions, N (%)	85 (72.6%)	29 (69.0%)	11 (68.8%)	23 (71.9%)	11 (84.6%)	11 (78.6%)	0.851
PCV lowest, median (IQR)	26.0 [21.0, 30.0]	23.5 [20.0, 28.8]	24.5 [20.8, 28.0]	27.5 [22.0, 32.0]	28.0 [24.0, 31.0]	27.5 [24.2, 30.8]	0.111
MPS, median (IQR)	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	1.00 [1.00, 2.00]	0.509
Gluc, median (IQR)	5.50 [4.30, 6.40]	5.35 [4.32, 5.97]	5.90 [4.07, 7.35]	5.10 [4.22, 6.50]	6.30 [5.40, 6.50]	5.30 [4.38, 8.82]	0.323
Lactate, median (IQR)	4.30 [2.20, 6.90]	4.40 [2.60, 6.45]	3.25 [1.98, 5.85]	4.30 [2.18, 7.40]	5.10 [2.20, 10.6]	2.90 [2.00, 6.12]	0.901
pH, median (IQR)	7.40 [7.34, 7.47]	7.38 [7.34, 7.44]	7.46 [7.29, 7.49]	7.41 [7.33, 7.44]	7.38 [7.32, 7.39]	7.47 [7.40, 7.50]	0.263
CO2, median (IQR)	28.5 [23.8, 37.0]	28.0 [21.9, 37.0]	30.0 [25.0, 36.5]	28.0 [25.0, 34.0]	30.5 [26.2, 38.2]	28.0 [26.0, 30.5]	0.931
BE, median (IQR)	-5.00 [-8.00, -2.00]	-5.50 [-8.62, -2.80]	-4.30 [-7.00, -2.50]	-5.20 [-8.25, -2.75]	-5.90 [-10.02, -0.75]	-3.00 [-3.45, -1.40]	0.602
Na, median (IQR)	138 [135, 142]	139 [136, 144]	138 [135, 142]	140 [135, 142]	136 [132, 140]	137 [135, 139]	0.327
Bicarb, median (IQR)	17.0 [13.0, 20.0]	16.0 [13.0, 18.0]	18.0 [13.5, 20.0]	16.0 [13.0, 19.0]	17.5 [16.0, 21.0]	19.0 [13.0, 20.0]	0.654

	All TCD phenotypes	Hyperemia	IPH	Low	Vasospasm	MO	p
SVI, median (IQR)	38.0 [33.0, 44.0]	42.0 [36.0, 44.5]	40.0 [35.0, 42.5]	33.0 [29.0, 36.0]	39.0 [31.0, 41.0]	44.5 [38.8, 51.0]	0.015
CI, median (IQR)	5.20 [4.38, 6.00]	5.30 [4.95, 6.10]	5.40 [4.70, 5.90]	4.50 [3.70, 4.90]	5.40 [3.85, 6.35]	5.55 [5.18, 6.37]	0.028
SVRI, median (IQR)	1302 [1002, 1580]	1272 [975, 1353]	1337 [1199, 1465]	1484 [1201, 1902]	1385 [1284, 1656]	991 [962, 1160]	0.06
Pulse Pressure, median (IQR)	39.0 [35.0, 47.0]	43.5 [39.2, 54.8]	38.5 [35.8, 44.0]	36.0 [31.5, 43.5]	37.0 [35.0, 39.0]	36.5 [34.0, 43.2]	0.005
EEG Seizures, N (%)	5 (4.72%)	1 (2.70%)	0 (0.00%)	1 (3.70%)	2 (15.4%)	1 (7.14%)	0.300
Papilledema, N (%)	6 (5.88%)	2 (5.26%)	0 (0.00%)	2 (8.00%)	0 (0.00%)	2 (14.3%)	0.575
ONSD, median (IQR)	0.47 [0.44, 0.51]	0.47 [0.44, 0.52]	0.45 [0.42, 0.50]	0.46 [0.44, 0.49]	0.46 [0.44, 0.50]	0.50 [0.47, 0.53]	0.446
Brain Volume Score, median (IQR)	6.00 [5.00, 6.75]	6.00 [5.00, 6.50]	6.00 [5.50, 6.25]	5.00 [4.75, 6.25]	5.50 [5.00, 6.00]	6.00 [5.00, 7.00]	0.963
OP on LP, median (IQR)	16.0 [12.0, 21.0]	14.0 [11.0, 19.0]	18.5 [15.5, 22.5]	16.5 [12.0, 20.2]	16.0 [15.0, 27.0]	18.0 [14.0, 19.0]	0.154
Outcome, (%):							0.057
Moderate/Severe	26.5%	16.2%	6.25%	43.8%	29.1%	14.3%)	

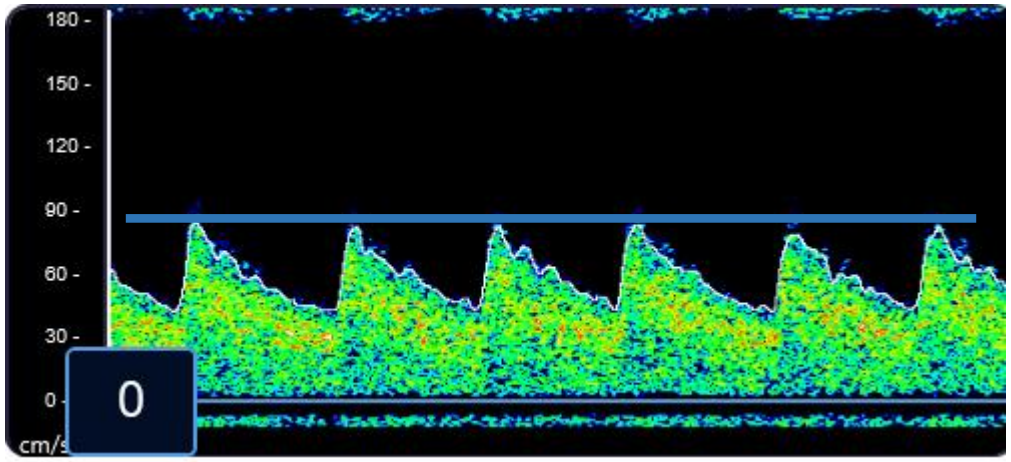

↓ Nitric Oxide Bioavailability
↑ Nitric Oxide Bioavailability
NORMAL
IPH
Low
Vasospasm
Hyperemia
MO
Flow velocity (cm/s)
600
500
400
300
0
100 80 60 40 30 20
Reduction in diameter (%)
40 60 80 100 120 140 160
% Increase in Diameter
400
300
200
100
0
Flow Velocity cm/sec


37.7
55.4
29.2
0.68
0.47
1.90
106
4 Sec
Mean
Peak
EDV
PI
RI
S/D
HR
DM%
cm/s
180
120
60
0
161
63.1


77.8
112
58.0
0.69
0.48
1.93
114
Mean
Peak
EDV
PI
RI
S/D
HR
cm/s
120
60
0



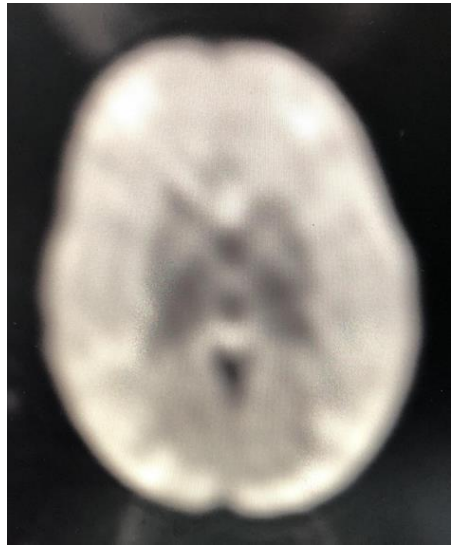
Low Flow- 4yo female, 2 days of fever and 4 episodes of seizures

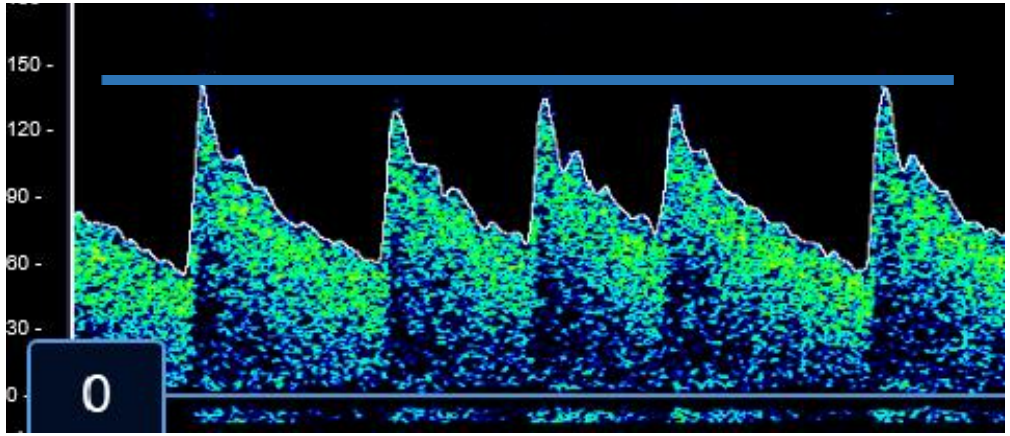


Day 1- MCA peak flows in the low 90's (<4SD) from age normal

Temp 37.1, HR 158, BP 89/52, MP ++, PCV 24, Lactate 4.7, Gas 7.35/46/-3, BCS 1
OP 18, ONSD 0.51

MRI with brain volume score 5, watershed infarcts on diffusion weighted images



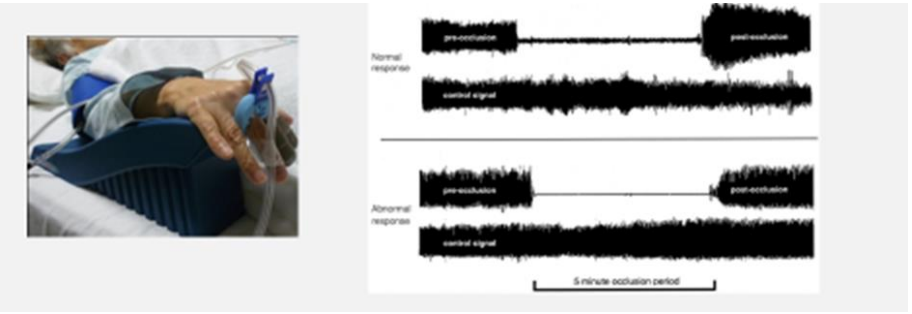


Day 1- With adjunctive therapy of 30ml/kg NS, adrenaline infusion 0.05mcg/kg/min, MCA peak flows normalized and BCS improved to 4

Survived with no gross neurologic deficits

What's next?

- Ongoing evaluation to rule out "known" pathophysiological contributors to TCD phenotypes
  - Further evaluation of SVR between groups
  - Reactive hyperemia/tonometry



- Plasma and CSF samples
  - Evaluation of kynurenine pathway
  - DAF-2 assay to evaluate for NO function
  - Evaluation of human mesenteric vessel response to plasma and CSF samples by phenotype

Transcranial Doppler Ultrasound Centers of Excellence

Thank you to NOVASIGNAL!