

Transcranial Ultrasonography PFO and Migraine

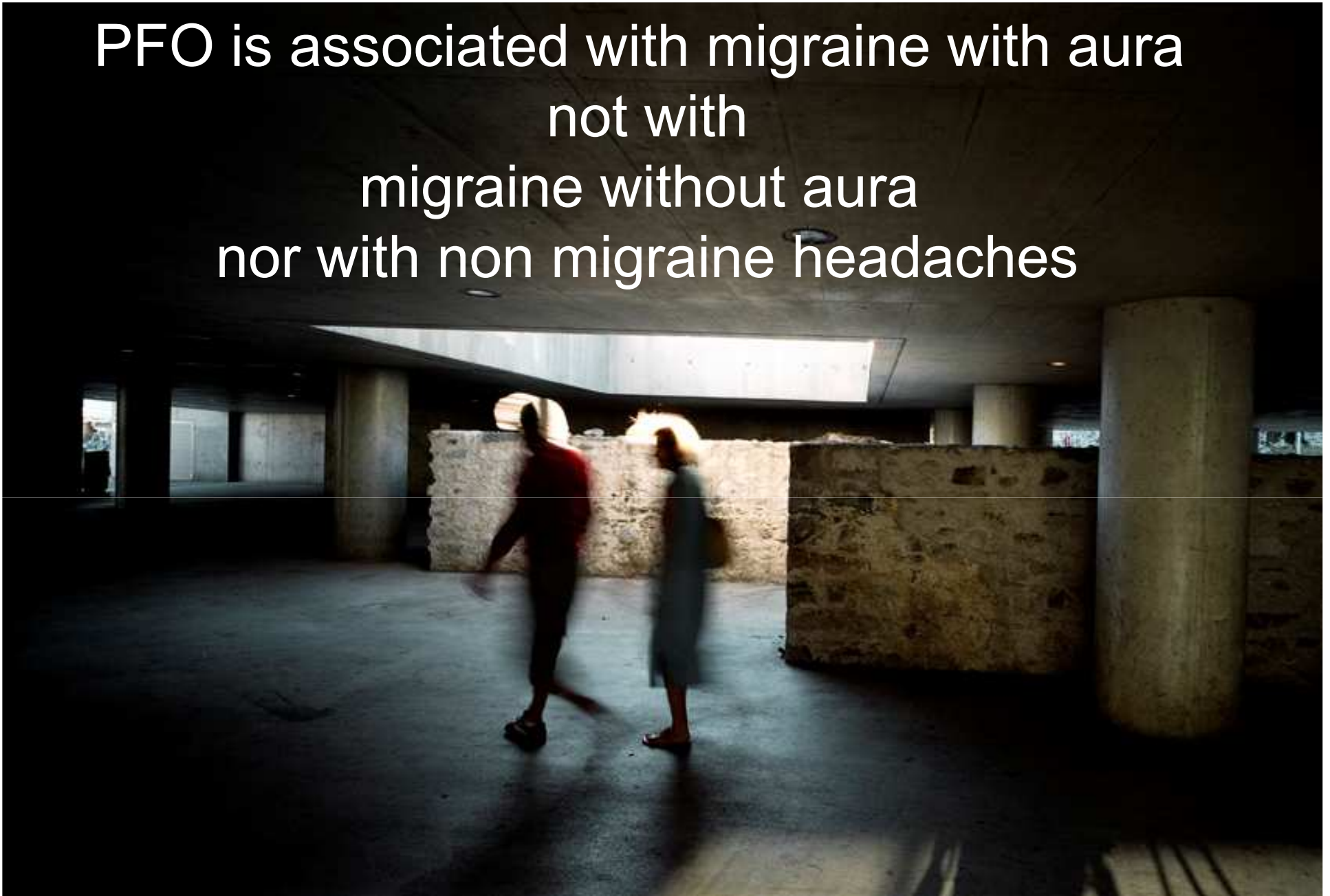
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- Association PFO-Migraine
- Characteristics of PFO in migraine
- Characteristics of migraine associated with PFO
- How does migraine change after PFO closure?
- Conclusion

The association of migraine with PFO

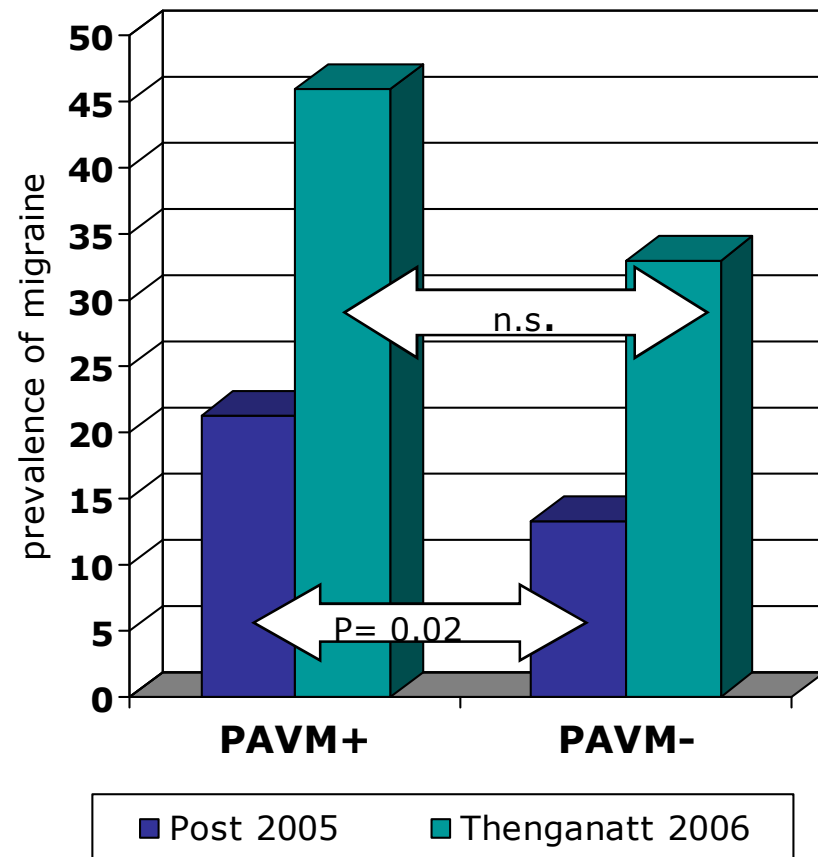
- In MA+ patients PFO is twice more frequent than in MA- and non migraineurs
- In subjects with PFO migraine is two to four
- In patients with cryptogenic stroke ar PFO migraine is twic more frequent than ir patients without PFO
- At least in some families PFO and migraine are inherited in association

PFO is associated with migraine with aura
not with
migraine without aura
nor with non migraine headaches



Migraine in patients with hereditary hemorrhagic telangiectasias with and without PAVM

- Migraine prevalence in PAVM+ ranging from 21 to 46% (Post 2005, Thenganatt 2006)
- Pulmonary AVMs significantly associated with migraine (OR 2,4 ; 95% CI 1,1-5,5, $p=0.04$) after adjustment for age and sex (Thenganatt 2006)
- **after PAVM embolization prevalence of MA+ decreased from 33,3 to 19% ($p=0.002$) (Post 2006)**



Characteristics of PFO in migraine

Prevalence and size of directly detected patent foramen ovale in migraine with aura

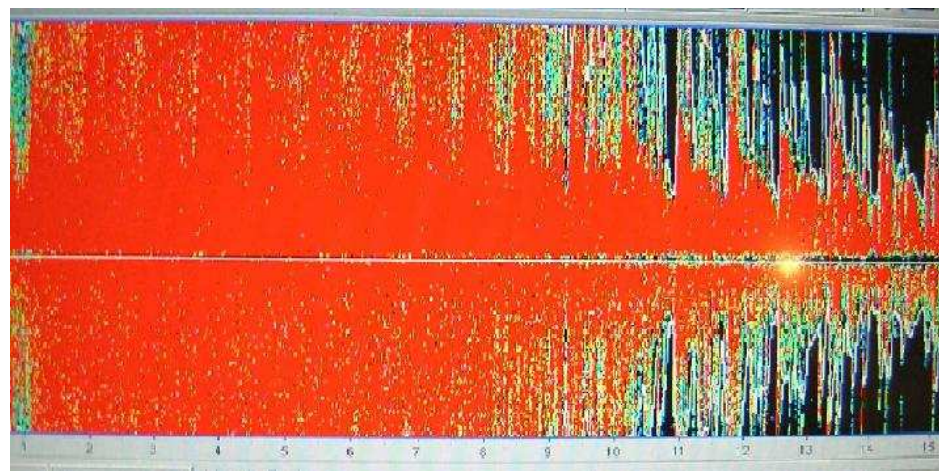
M. Schwerzmann, MD; K. Nedeltchev, MD; F. Lager, BSc; H.P. Mattle, MD; S. Windecker, MD; B. Meier, MD; and C. Seiler, MD

NEUROLOGY 2005;65:1-1

Table 2 Transesophageal echocardiography

	Migraine with aura, n = 93	Controls, n = 93	p Value*
Patent foramen ovale, n	44 (47%)	16 (17%)	<0.001
Small shunt, n	9 (10%)	9 (10%)	0.165
Moderate shunt, n	10 (11%)	4 (4%)	0.102
Large shunt, n	25 (27%)	3 (3%)	0.001
Atrial septal aneurysm, n	6 (6%)	2 (2%)	0.900
Prominent eustachian valve, n	6 (6%)	3 (3%)	0.831
Left ventricular hypertrophy, n	1 (1%)	0	1.000
Mitral valve prolapse, n	3 (3%)	2 (2%)	0.701

* p Values are calculated using conditional logistic regression analysis correcting for age, sex, and smoking.



Different degrees of right-to-left shunting predict migraine and stroke: Data from 420 patients

Abstract—The authors analyzed the extent of right-to-left shunting in patients with migraine, patients with cryptogenic stroke, and controls. Patients with both migraine and stroke had larger shunts than did patients with migraine without stroke ($p = 0.038$), patients with no migraine with stroke ($p = 0.007$), and control patients ($p < 0.0001$). Patients with migraine have overall larger shunts than nonmigraineurs, particularly if they have had a stroke. Right-to-left shunting may be causally related to migraine and to the increased stroke risk of migraine.

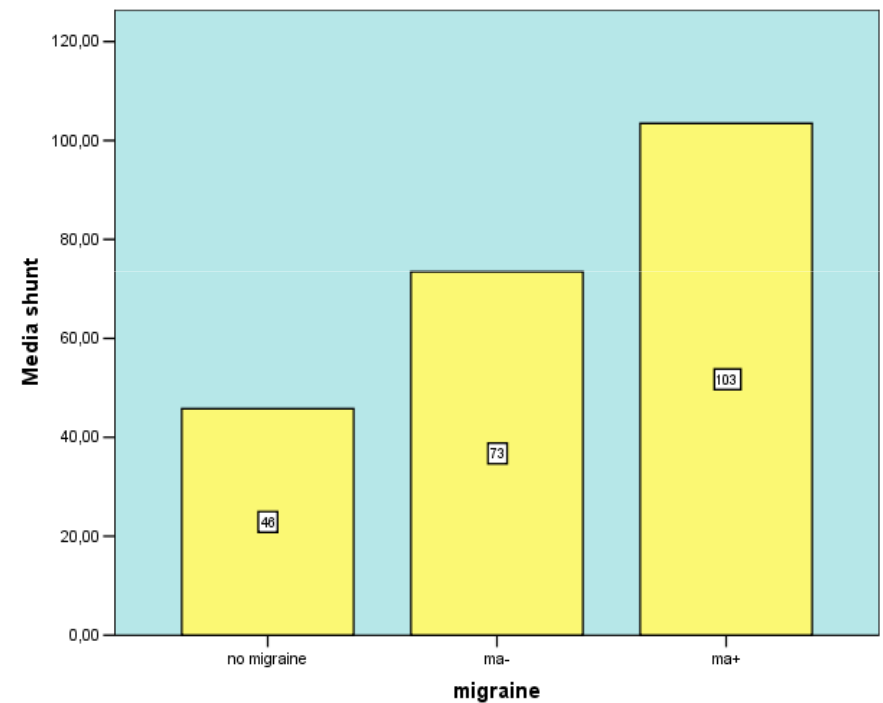
NEUROLOGY 2006;66:1–1

Gian Paolo Anzola, MD; Eva Morandi, MD; Francesco Casilli, MD; and Eustaquio Onorato, MD

Table 2 Age and shunt between Migraine and No-Migraine patients

	n	Sex, M/F	Age, mean $\pm$ SD, y	Shunt, mean bubble count (SE)
MA+	151	22/129	38 $\pm$ 12	104 (16)
MA–	84	17/67	41 $\pm$ 14	74 (11)
No Migraine	185	78/107	51 $\pm$ 16	46 (4)
All Migraine	235	39/196	39 $\pm$ 13	93 (11)
Total	420	117/303	44 $\pm$ 16	72 (6)

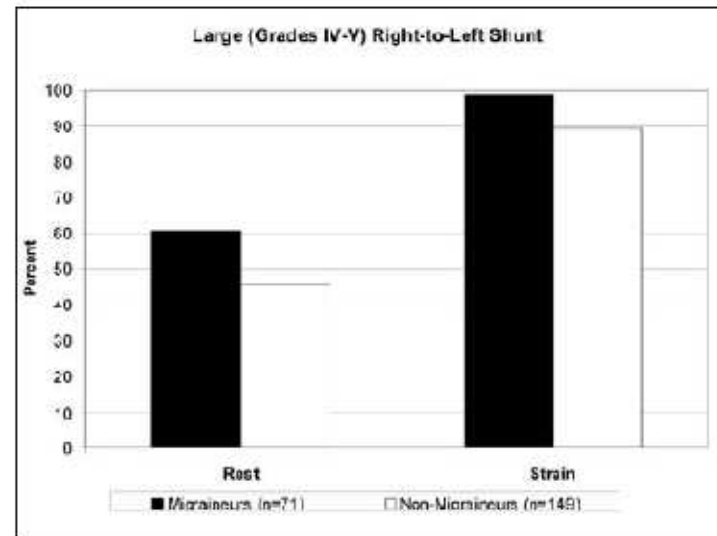
Age significant at $p < 0.0001$ between migraine with aura (MA+) and No Migraine and between migraine without aura (MA–) and No Migraine. Shunt between MA+ and No Migraine significant at $p < 0.0001$, between MA– and No Migraine at $p = 0.020$.



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Migraineurs with patent foramen ovale have larger right septal characteristics

J Headache Pain (2010) 10:1007-1015
DOI 10.1007/s10194-010-0100-0



The o
to as:

Fig. 1 Percent of migraineurs and non-migraineurs who had large (Grades IV–V) RLS at rest and following calibrated Valsalva (strain). At rest, migraineurs had a higher proportion of large RLS than non-migraineurs ($\chi^2=4.3$, $p=0.03$) and at strain ($\chi^2=5.9$, $p=0.01$)

Larger shunts but not ASA differentiated migraine from non migraine patients

J.T. Jesurum • C.J. Fuller • C.A. Velez •

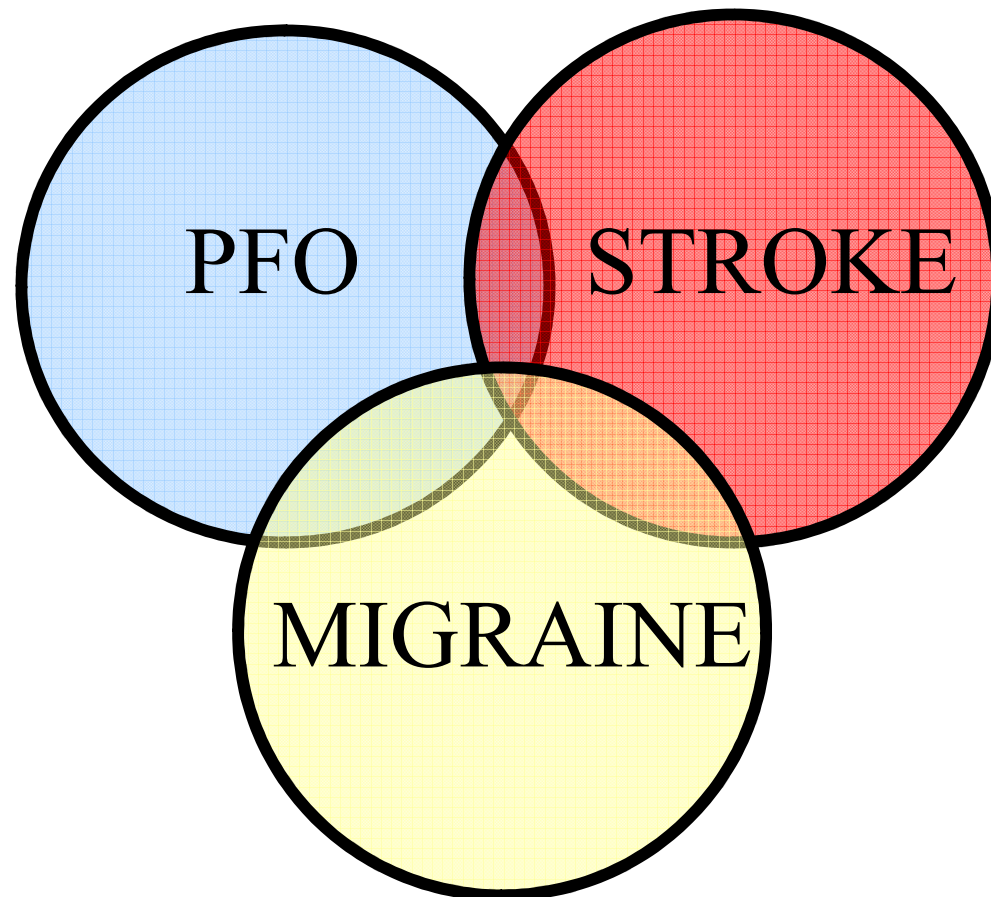
Table 2 Atrial septal characteristics and presence of large RLS in migraineurs with aura and non-migraineurs undergoing transcatheter closure of PFO

Atrial septal characteristic	Migraineurs with aura (n=52)	Migraineurs without aura (n=19)	Non-migraineurs (n=149)	p value ^a
Coexisting ASA ^b	18 (35)	8 (42)	49 (33)	NS ^c
ASA base pouch width (mm)	21±6	19±3	20±5	NS
ASA septal excursion (mm)	15±4	13±2	16±5	NS
Septal tunnel length (mm)	11±3	10±3	12±3	NS
Balloon stretch diameter (mm)	13±3	12±3	13±4	NS
Large RLS ^d (Grade IV or V) at rest	28 (54)	15 (79)	68 (46)	0.02
Large RLS (Grade IV or V) after calibrated, sustained Valsalva	51 (98)	19 (100)	133 (89)	NS

Risk of ischaemic stroke in people with migraine: systematic review
and meta-analysis of observational studies

Maythar Etmaman, Bahi Takkouche, Francisco Caamano Isorna, Ali Samii

Results 14 studies (11 case-control studies and 3 cohort studies) were identified. These studies suggest that the risk of stroke is increased in people with migraine (relative risk 2.16, 95% confidence interval 1.89 to 2.48). This increase in risk was consistent in people who had migraine with aura (relative risk 2.27, 1.61 to 3.19) and migraine without aura (relative risk 1.83, 1.06 to 3.15), as well as in those taking oral contraceptives (relative risk 8.72, 5.05 to 15.05).



Different degrees of right-to-left shunting predict migraine and stroke: Data from 420 patients

Abstract—The authors analyzed the extent of right-to-left shunting in patients with migraine, patients with cryptogenic stroke, and controls. Patients with both migraine and stroke had larger shunts than did patients with migraine without stroke ($p = 0.038$), patients with no migraine with stroke ($p = 0.007$), and control patients ($p < 0.0001$). Patients with migraine have overall larger shunts than nonmigraineurs, particularly if they have had a stroke. Right-to-left shunting may be causally related to migraine and to the increased stroke risk of migraine.

NEUROLOGY 2006;66:1–1

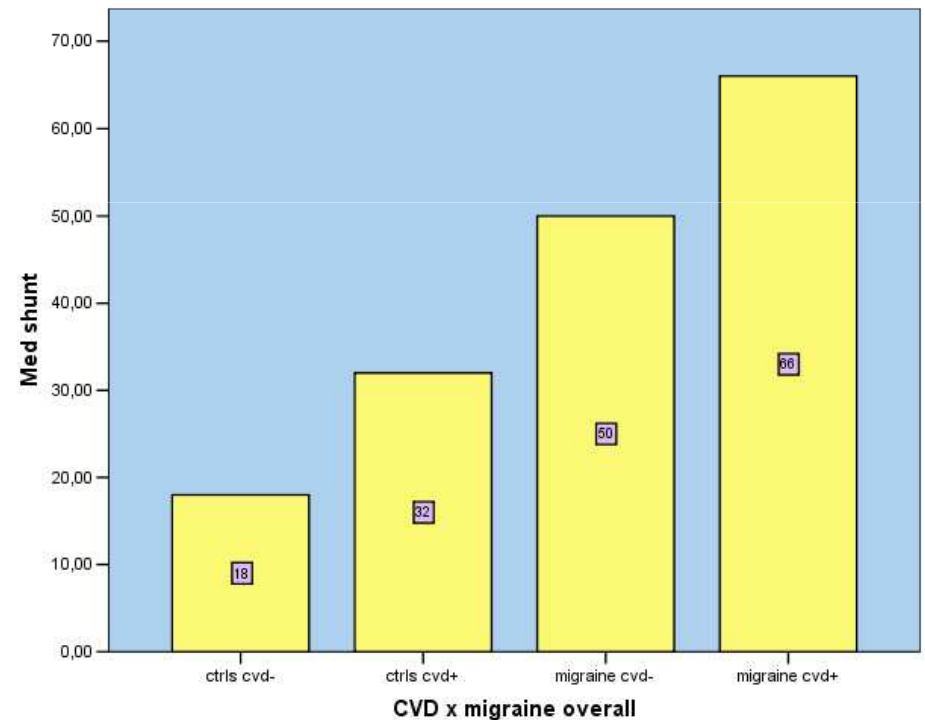
Gian Paolo Anzola, MD; Eva Morandi, MD; Francesco Casilli, MD; and Eustaquio Onorato, MD

Table 3 Age and shunt according to the CVD $\times$ Migraine condition

	No Migraine		Migraine	
	CVD–	CVD+	CVD–	CVD+
n	100	85	139	96
Sex, M/F	40/60	38/47	21/118	18/78
Age, mean $\pm$ SD, y	48 $\pm$ 17	55 $\pm$ 14	36 $\pm$ 14	42 $\pm$ 11
Mean bubble count (SE)	38 (5)	55 (8)	72 (8)	123 (24)

Age significantly different in all comparisons (p between <0.0001 and 0.023). Mean bubble count in Migraine CVD+ patients significantly larger than in any other group (p between <0.0001 and 0.038).

CVD = cerebrovascular disease.



Relation of Atrial Shunts to Migraine in Patients With Ischemic Stroke and Peripheral Emboli

Peter Wilmshurst, MB, ChB^{a,*}, Simon Nightingale, MD^a, Matthew Pearson, BSc(Hons)^a,
Lindsay Morrison, MD^b, and Kevin Walsh, MD^c

Table 1

Prevalence of clinically relevant atrial shunts in patients with stroke or migraine or both and in normal controls

Variable	Stroke and Migraine With Aura	Stroke and Migraine Without Aura	Stroke, No Migraine	Migraine With Aura, No Stroke*	Normal Controls [†]
Clinically relevant atrial shunt	21 (84%)	6 (75%)	15 (55.6%)	141 (38.1%)	15 (12.2%)
No atrial shunt or small atrial shunt	4 (16%)	2 (25%)	12 (44.4%)	229 (61.9%)	108 (87.8%)
Total	25 (100%)	8 (100%)	27 (100%)	370 (100%)	123 (100%)

* Data from Wilmshurst et al.³

In

conclusion, the increased incidence of stroke in subjects with migraine compared with the general population is because they have a higher prevalence of large atrial shunts and hence an increased risk for paradoxical embolism. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98:

Characteristics of migraine associated with PFO

Is shunt associated migraine a
clinical entity?

SAM **(Shunt Associated Migraine)** **STUDY**

Prospective

Multicenter

NON SPONSORED

Observational trial

Experimental design:

Prospective observational study in consecutive subjects referred to migraine clinics for migraine with (MA+) aura.

Inclusion criteria:

- diagnosis of MA+ (criteria of IHS – 2)
- age: 15-50 years
- consecutive subjects

Assessment:

1. Demographics (initials, gender, age)
2. Diagnosis (IHS criteria)
3. Standardised clinical assessment performed with the aid of computer based ACCESS data base (provided to all participants).
4. Transcranial Doppler for diagnosis of RLS, with classification into categories (at rest or after Valsava – small (<10 MES), medium (>10 MES, no curtain), large (> 10 MES, with curtain effect (Jauss and Zanette, 2000)).
5. MRI standard with FLAIR images.
6. Blood tests to assess thrombophilia: RBC, PLT, APTT, AT III, Protein C, Protein S, APCR, factor II and Factor V Leyden, homocysteine, mutation of MTHFR.



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Ambulatorio di Neurologia

Responsabile: Dott. Gian Paolo Anzola

DEMOGRAFICO

COGNOME ANZOLA NOME GIAN PAOLO SESSO M ETA' 50 DATA ESAME 25/10/2004
VIA: BERNINI 31 CITTÀ: BRESCIA TELEFONO: 030362160

CARATTERISTICHE
DEL DOLORE

ETA' ESORDIO CRISI: 15 FAMILIARITA' PER CEFALIA: SI
UNILATERALE: NO PULSATILE: SI FONO-FOTOFOBIA SI
ACCENTUATO DA SFORZO SI NAUSEA-VOMITO SI INTENSITA' MEDIA 2

FATTORI
SCATENANTI

ATTIVITA' FISICA NO OVULAZIONE:
MESTRUAZIONE WEEKEND
BEVANDE O ALIMENTI SI FARMACI
ALTITUDINE >1500 MT VALSALVA

NUMERO DI CRISI NEGLI ULTIMI 12 MESI

SENZA AURA 20 CON AURA 10

CARATTERISTICHE
DELL'AURA

VISIVA SI SENSITIVA MOTORIA
VERT. BASILARE AFASICA
LATO BILATERALE DURATA IN MINUTI 15
TIPO DI DOLORE DOPO L'AURA EMICRANICO

TERAPIA DELLA
CRISI

TRIPTANI EFFICACI ERGOT EFFICACI

TERAPIA PROFILATTICA
NEGLI ULTIMI 12 MESI

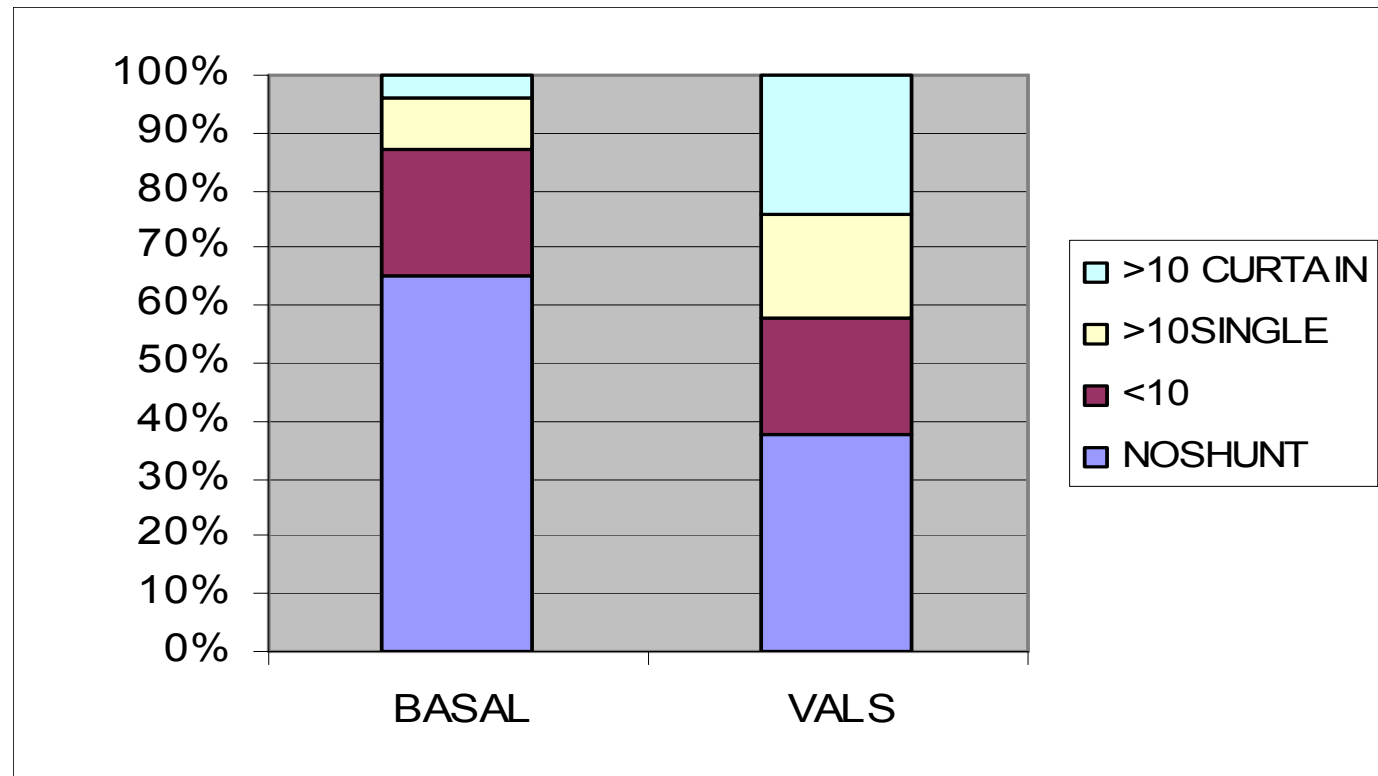
FANS EFFICACI SI
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FATTORI DI
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VASCOLARI

FARMACI UTILIZZATI
IPERTENSIONE NO DIABETE NO PILLOLA: NO
FUMO SI IPERCOLESTEROLEMIA NO
FAMILIARITA' PER CVD PREGRESSO TIA/ICTUS NO

MA+

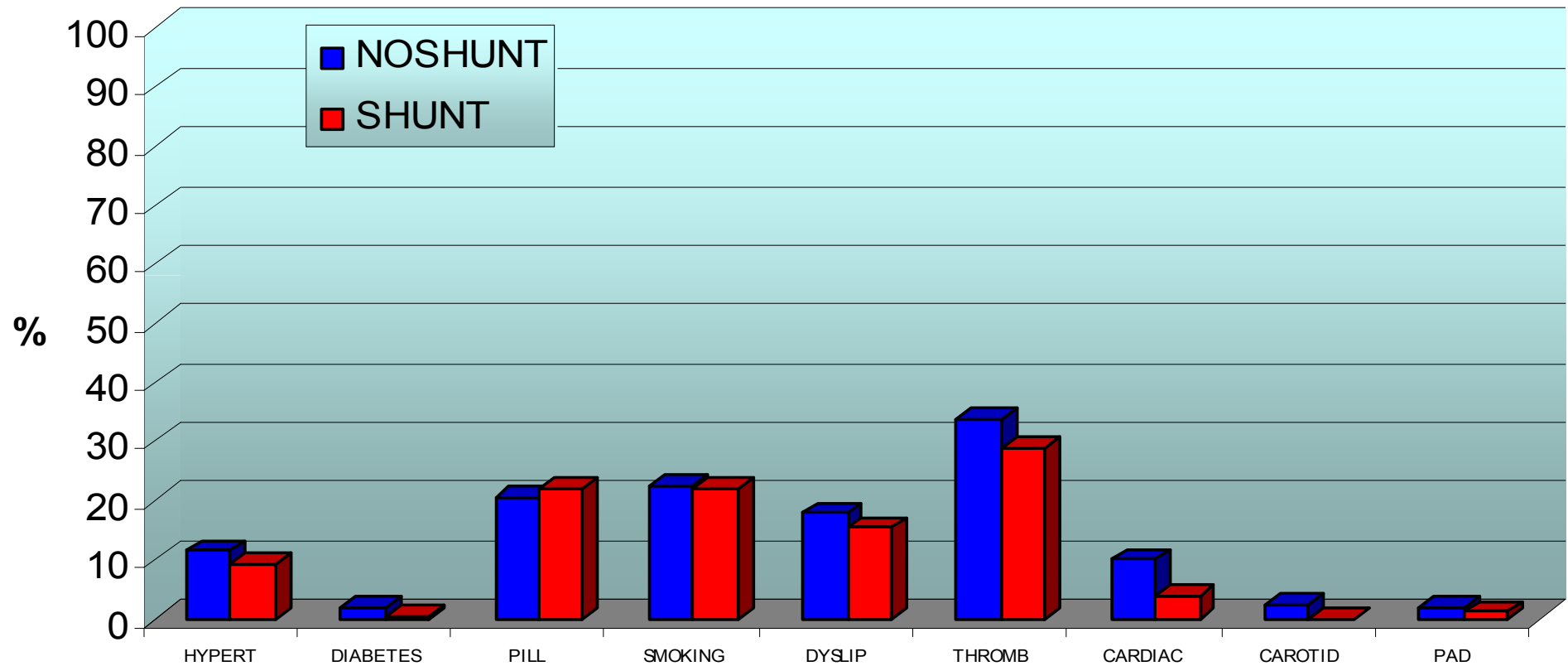
Total cohort	460
M	106
F	354
ETA'	35,9
SD	10,8



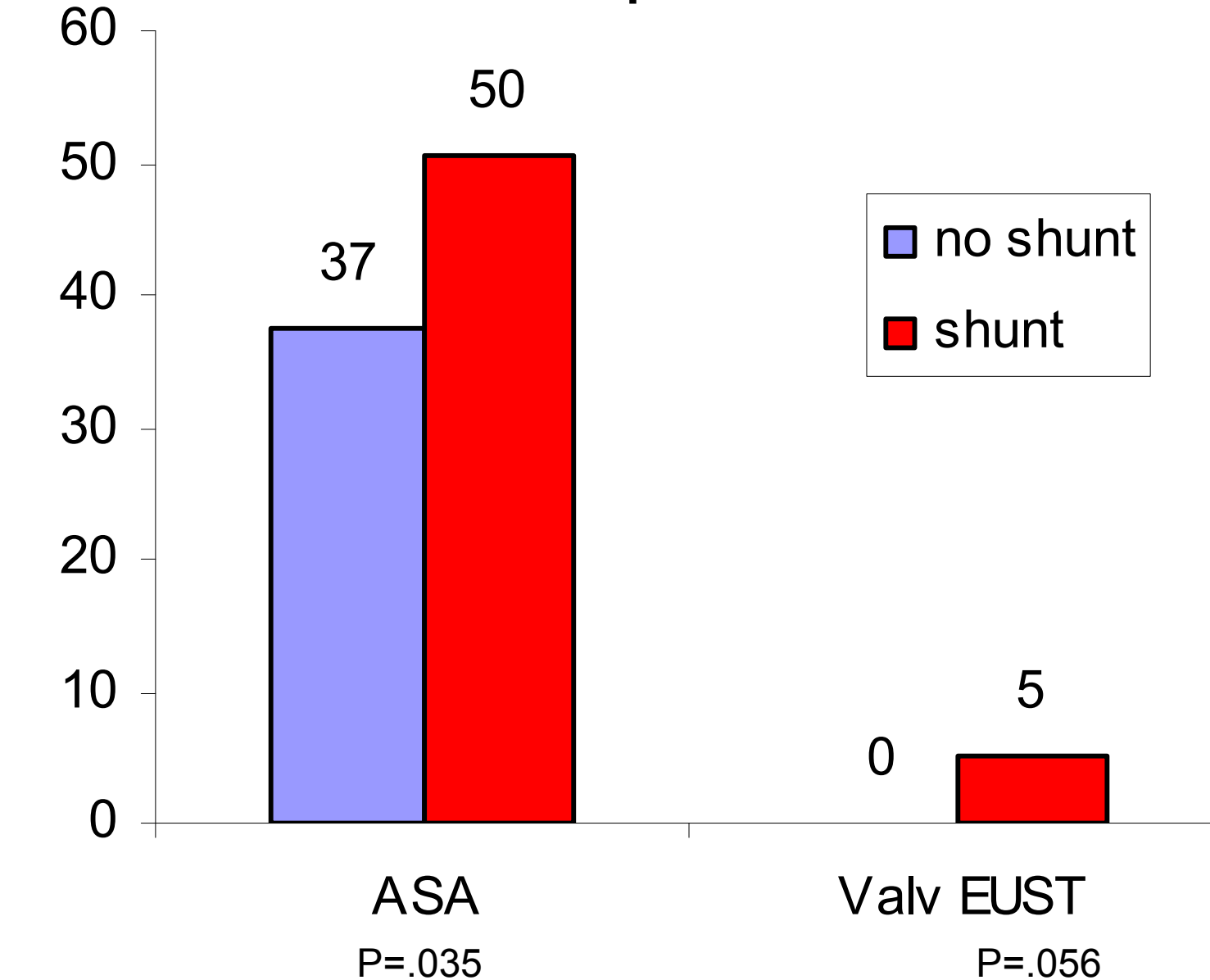
	BASAL	VALS	%	%
NOSHUNT	298	173	37,6	58
<10	99	92	20,0	
>10SINGLE	42	85	18,5	42
>10 CURTAIN	18	110	23,9	

	No shunt	Shunt	p
n.	265	195	
age	37,1	34,1	.002
Migraine onset	21	19,4	ns
Aura delay (years)	2,7	1,4	ns
M/F	65/200	41/154	ns
Family history for migraine yes/no	173/87	140/45	.045
Family history for CVD yes/no	105/153	81/102	ns
Personal history for CVD yes/no	15/245	16/170	ns
BMI	23,01	22,43	ns

Vascular RF



% Associated septal abnormalities

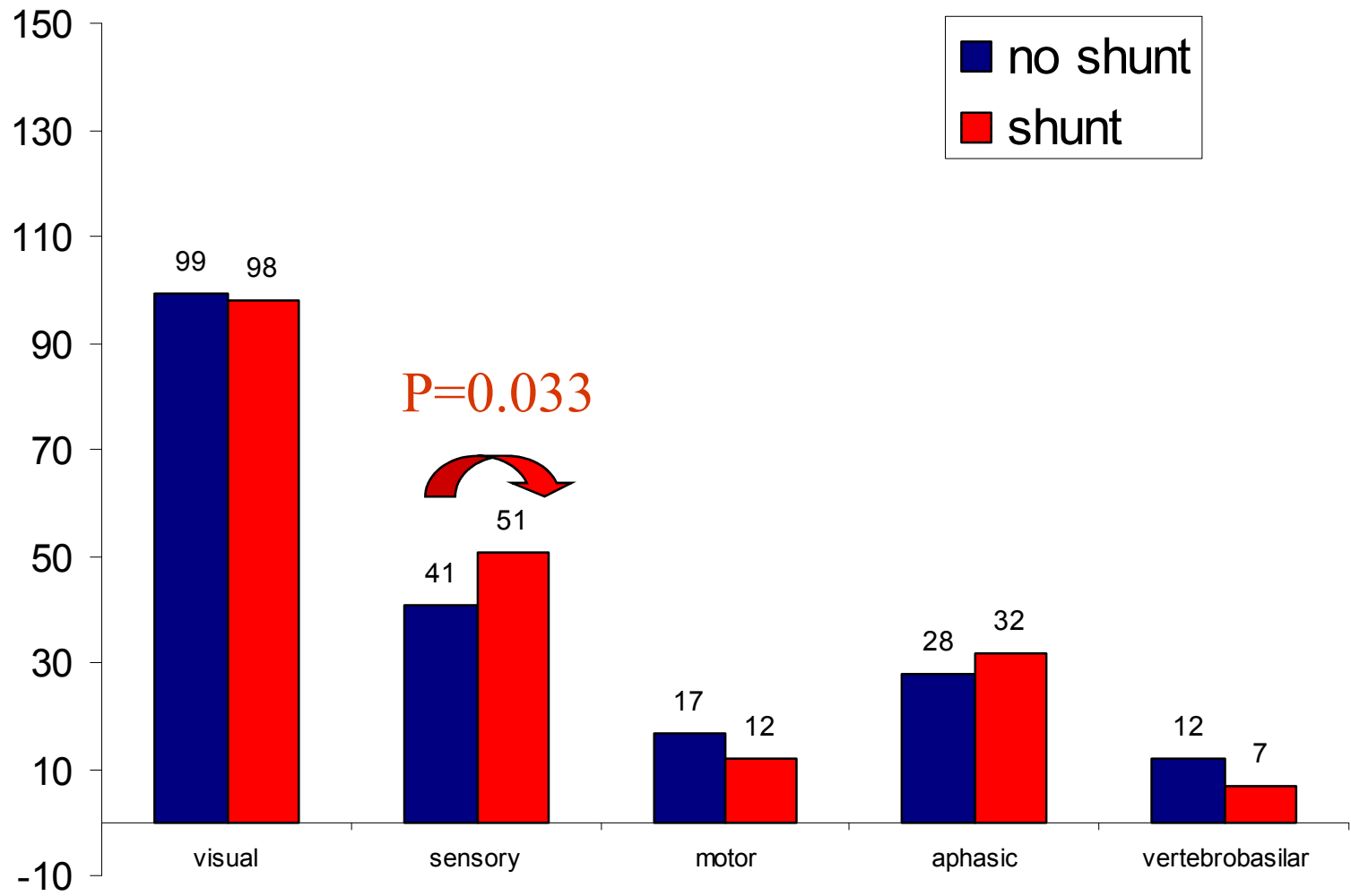


Characteristics of headache

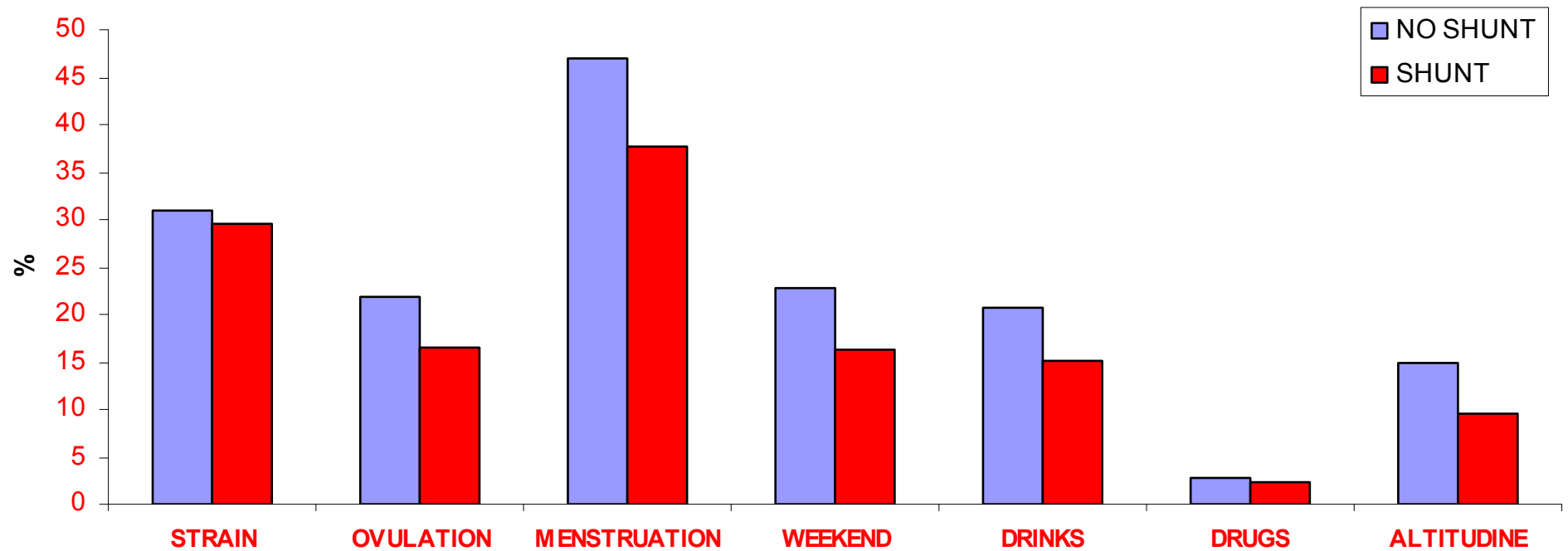
	No shunt	shunt	p
Median aura dur. Min.	20	20	ns
Median aura complexity	2	2	ns
Mean pain severity	2,5	2,5	ns
Median n. attacks overall*	24	20	ns
Median n. with aura*	8	7,5	ns
Relative aura frequency %	60	64	ns

* In the last 12 months

AURA



Triggers

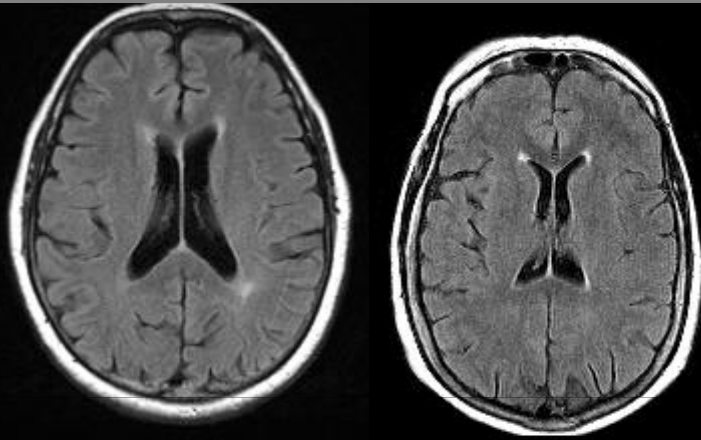


MRI ABNORMALITIES

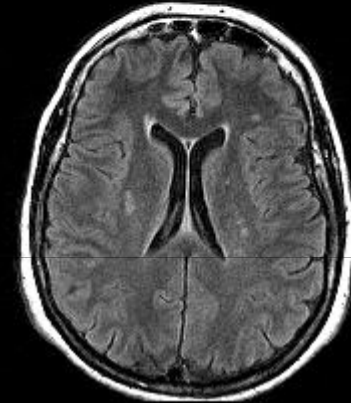
Entire SAM cohort		MRI protocol	
N.	460	N.	185
F	77%	F	77%
age	35,9	age	36
SD	10,8	SD	11
RLS +	43%	RLS +	44%

MRI ABNORMALITIES

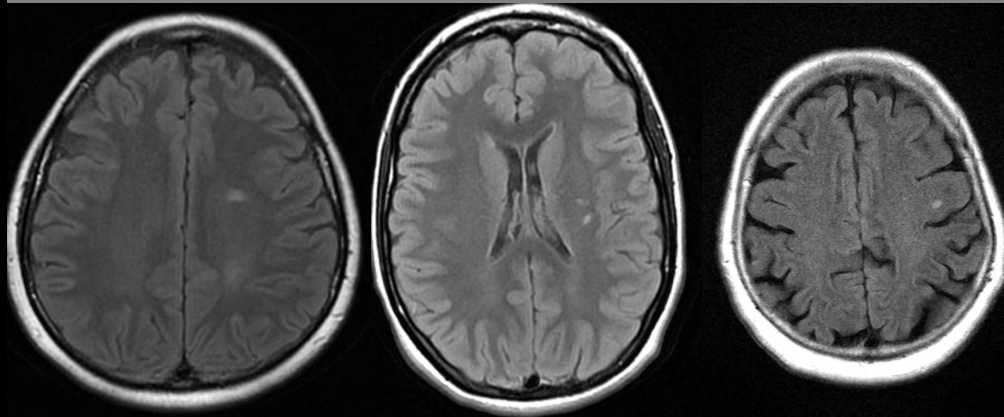
PERIVENTRICULAR PV-WML
35 pt = 19%



PV-WML and D-WML
21 pt = 11%



DEEP WHITE MATTER D-WML 86 pt = 47%



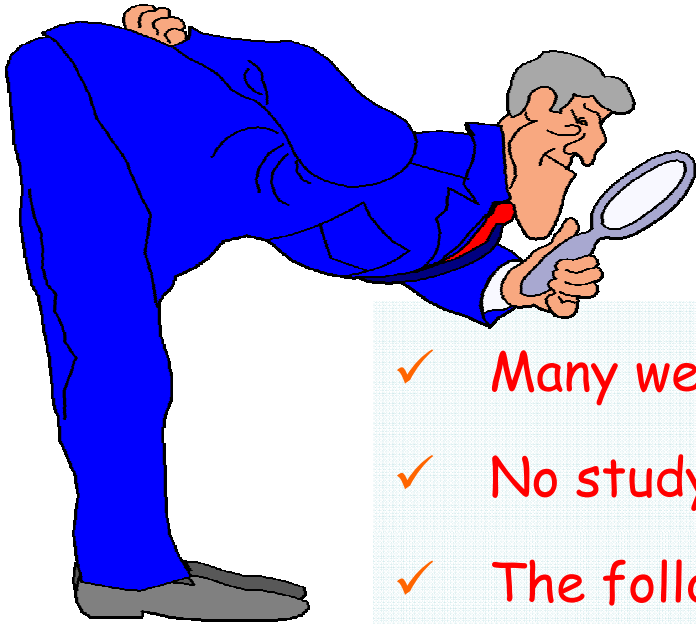
	PV-WMLS		D-WMLS	
	Yes (n=35)	No (n=150)	Yes (n=86)	No (n=99)
Demographics				
Age	40±11	35±10*	41±10	31±9†
Females	25 (71)	118 (79)	68 (79)	75 (76)
Clinical Features				
Years from first attack	14 (8-21)	14 (7-21)	16 (10-29)	11 (5-18)†
Nr. of aura/yr	6 (2-18)	10 (3-24)	9 (4-24)	10 (3-20)
Nr. of migraine attacks/yr	20 (6-48)	24 (12-46)	29 (13-48)	23 (9-46)
Nr. of migraine attacks/yr (women only)	22 (8-48)	28 (12-50)	32 (16-52)	24 (10-47)
Risk Factors				
Hypertension	9 (26)	14 (9)*	17 (20)	6 (6)*
Diabetes	0	4 (3)	0	4 (4)
High Cholesterol	8 (23)	28 (19)	19 (22)	17 (18)
Smoke	7 (20)	25 (17)	16 (19)	16 (16)
Contraceptive use	6 (23)	30 (26)	11 (16)	25 (34)*
Cardiopathy	5 (14)	13 (9)	13 (15)	5 (5)*
Increased BMI	23 (21-24)	22 (21-25)	23 (21-25)	22 (21-24)
Coagulation abnormalities	7 (22)	32 (24)	18 (23)	21 (24)
Prior prophylactic treatment	21 (60)	90 (61)	37 (43)	35 (36)
Basal RLS				
No RLS	22 (63)	77 (51)	52 (60)	47 (48)
<10 microbubbles	7 (20)	49 (33)	23 (27)	33 (33)
>10 microbubbles Single Spikes	5 (14)	16 (11)	7 (8)	14 (14)
>10 Shower or Curtain	1 (3)	8 (5)	4 (5)	5 (5)
RLS after Valsalva				
No RLS	12 (34)	51 (34)	32 (37)	31 (31)
<10 microbubbles	6 (17)	34 (23)	20 (23)	20 (20)
>10 microbubbles Single Spikes	6 (17)	22 (15)	11 (13)	17 (17)
>10 Shower or Curtain	11 (32)	43 (29)	23 (27)	31 (31)

In a multivariate logistic regression analysis correcting for sex, vascular risk factors (hypertension, diabetes, smoking, contraception), duration of migraine and TCD parameters only the **age** of the patients was strongly associated with PV- and D-WML load ($p < 0.001$. OR 1.1 95%CI: 1.0-1.2).

EFFECT OF PFO CLOSURE ON MIGRAINE

AUTHOR	YEAR	TYPE OF STUDY	N. of pts.	Mean f-up months	Resolution %	Improved %
Wilmshurst et al.	2000	retrospective	21	17	48	38
Morandi et al.	2003	prospective	17	12	29	59
Post et al.	2004	retrospective	26	6	84	N/a
Schwerzmann et al.	2004	retrospective	47	24	N/A	83
Azarbal et al.	2005	retrospective	37	3	60	40
Reisman et al.	2005	retrospective	50	12	56	14
Giardini et al.	2006	retrospective	35	20	83	8
Kimmelstiel et al.	2007	retrospective	24	3	N/A	57
Overall			257	12	60	43
Anzola et al.	2006	prospective	50	12	38	48

MIGRAINE: What is the evidence?



BUT...

- ✓ Many were retrospective
- ✓ No study but two had a control group included
- ✓ The follow-up was as short as six months
- ✓ All of the patients in retrospective studies had had a stroke
- ✓ Migraine severity was subjectively rated
- ✓ The possible effect of aspirin given post procedurally was not taken into account

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Migraine Intervention With STARFlex Technology (MIST) Trial. A Prospective, Multicenter, Double-Blind, Sham-Controlled Trial to Evaluate the Effectiveness of Patent Foramen Ovale Closure With STARFlex Septal Repair Implant to Resolve Refractory Migraine Headache

Andrew Dowson, Michael J. Mullen, Richard Peatfield, Keith Muir, Arif Anis Khan, Christopher Wells, Susan L. Lipscombe, Trevor Rees, Joseph V. De Giovanni, W. Lindsay Morrison, David Hildick-Smith, Giles Eltrington, W. Stewart Hillis, Iqbal S. Malik and Anthony Rickards

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MIST I Trial Design

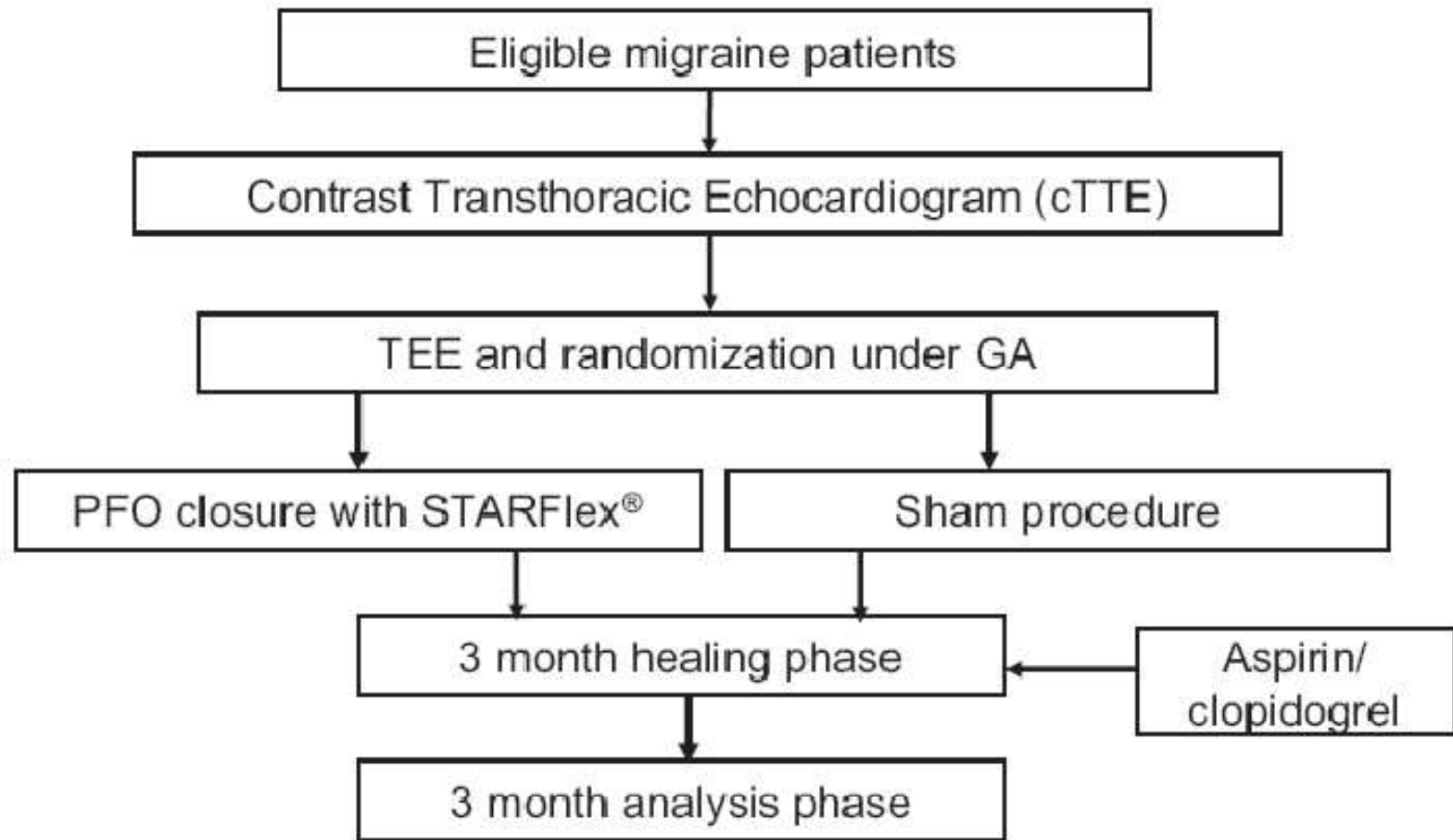


Figure 1. Patient flow through the study. cTTE indicates contrast transthoracic echocardiography; TEE, transesophageal echocardiographic assessment; and GA, general anesthesia.

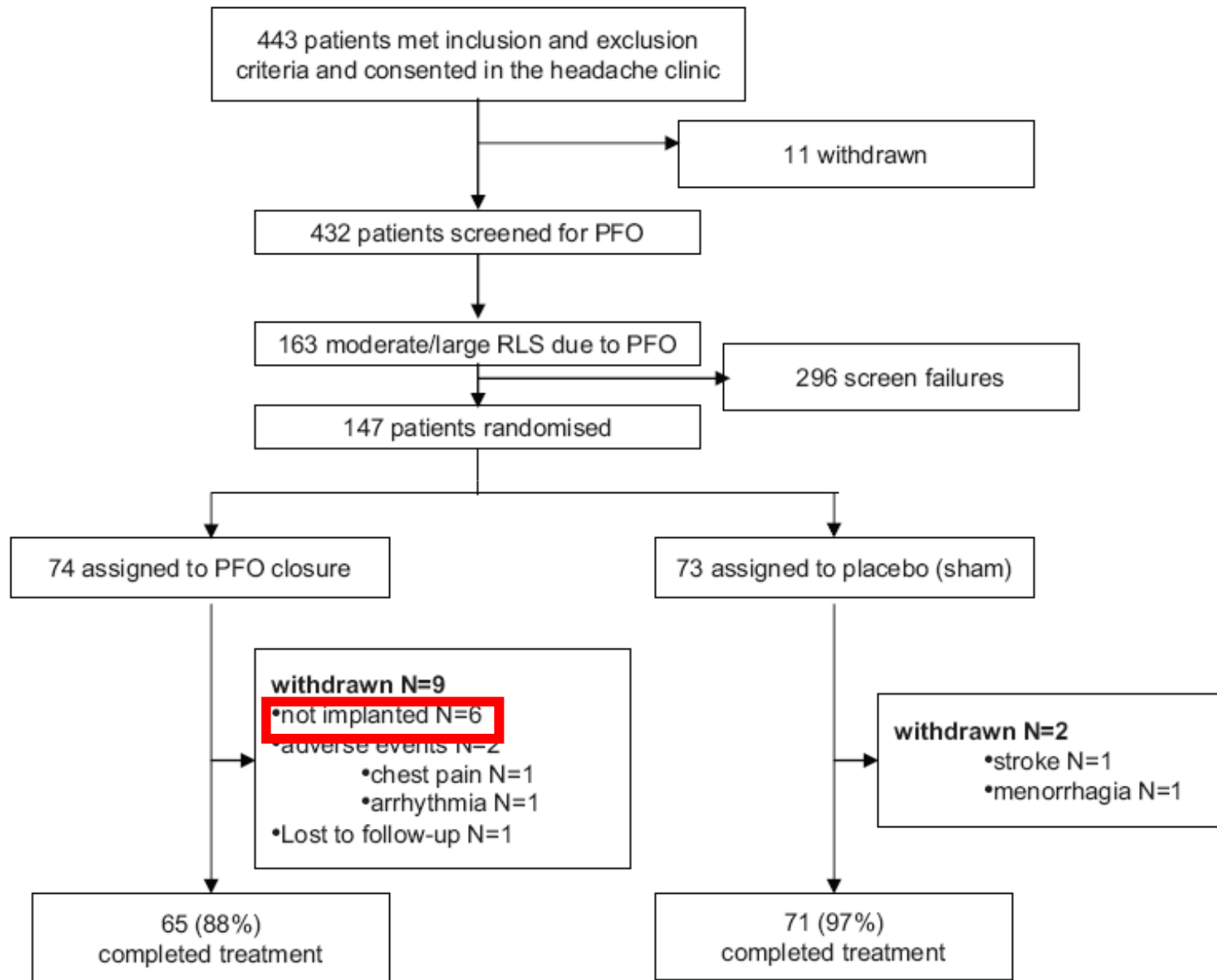


Table 3. Efficacy Analyses: Intention-to-Treat Population

	Implant (n=74)		Sham procedure (n=73)		Statistical Analyses*	
	Baseline	Analysis Phase	Baseline	Analysis Phase	Difference Between Implant and Sham Arms (95% CI)	P
Patients with no migraine attacks, n	0	3	1	3	−0.06% (−6.45–6.34)	1.0
Frequency of migraine attacks/mo, mean±SD	4.82±2.44	3.23±1.80	4.51±2.17	3.53±2.13	0.45 (−0.16–1.05)	0.14
n	66	66	73	73	...	...
Total MIDAS score, median (range)	36 (3–108)	17 (0–270)	34 (2–189)	18 (0–240)	1 (−11–10)	0.88
n	66	67	69	72	...	...
Headache d/3 mo (MIDAS), median (range)	27 (0–70)	18 (0–90)	30 (5–80)	21 (0–80)	1 (−5–6)	0.79
n	66	67	69	72	...	...
HIT-6 total score, mean±SD	67.2±4.7	59.5±9.3	66.2±5.1	58.5±8.6	0 (−3–2)	0.77
n	67	67	69	73	...	...

Missing data were replaced by last observation carried forward. CI indicates confidence interval.

Table 4. Efficacy Analyses: Per-Protocol Population

	Implant (n=64)*		Sham (n=71)		Statistical Analyses	
	Baseline	Analysis Phase	Baseline	Analysis Phase	Difference Between Implant and Sham Arms (95% CI)	<i>P</i>
Patients with no migraine attacks, n	0	3	1	3	0.46% (−6.50–7.42)	1.0
Frequency of migraine attacks/mo, mean±SD	4.88±2.43	3.26±1.82	4.55±2.18	3.55±2.14	0.47 (−0.15–1.08)	0.13
n	64	64	71	71	...	...
Total MIDAS score, median (range)	40 (3–108)	16 (0–270)	34 (2–189)	18 (0–240)	1 (−10–10)	0.89
n	57	64	67	71	...	...
Headache d/3 mo (MIDAS), median (range)	26 (0–70)	19 (0–90)	30 (5–80)	21 (0–80)	1 (−5–6)	0.85
n	57	64	67	70	...	...
HIT-6 total score, mean±SD	67±4.6	60±10	66±4.9	59±8.8	0 (−3–2)	0.79
n	57	64	67	71	...	...
Total migraine headache d/m,† median (range)	6.0 (1–17.0)	3.8 (0–13.3)	5.0 (0–20.0)	3.7 (0–16.7)	1.3 (0–2.3)	0.027
n	62	62	70	71	...	...

Missing data were replaced by last observation carried forward. CI indicates confidence interval.

*One subject was missing baseline diary cards.

†Determined as follows: No. of headaches/month)×(average length in hours)/24, rounded up to nearest day. Two outliers were removed.



..and even the MIST trial...

- Primary end-point too hard for patients with an exceedingly high frequency of migraine with aura (>5 days/month)
- Tension-type cases (unresponsive to PFO closure) included?
- Failure rate not stated
- TTE may be not ideal for differentiating true PFO from ASD → brain impact of shunt better with TCD
- Worsening of migraine not stated

In 5 patients, the PFO was not crossed.

NEGATIVE EFFECTS

- Scintillating scotoma (Anzola 2004) → PFO
- Transformation of preceding migraine with aura in chronic headache with protracted aura (Yankovsky 2003, Riederer 2005, Sharifi 2005, Wilmshurst 2005, Wertman 2006) → ASD
- De novo appearance of headache (Rodès-Cabeau 2003, Wilmshurst 2000, Wertman 2006) → ASD

1. Course usually benign and limited to 2-3 months post implantation
2. Dramatic response to clopidogrel

Proposed mechanisms

- Nickel toxicity
- Secretion of neuromediators (e.g ANP)
- Nickel allergy promoting local inflammatory response with release of neuromediators in the left atrium
- Platelet activation and microembolization

Does PFO cause migraine ?

- NO, because PFO may be another manifestation of a more generalized endothelial dysfunction.
- YES, because platelet aggregates may bypass the pulmonary filter and trigger the attack (minor ischemia ?)
- OR chemical triggers (serotonin, NO, endothelin I, isoprostanes etc) may escape the lung and reach the arterial side

The CADASIL story

European
Neurology

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**Very High Prevalence of
Right-to-Left Shunt on
Transcranial Doppler in an
Italian Family with Cerebral
Autosomal Dominant
Angiopathy with Subcortical
Infarcts and
Leukoencephalopathy**

Angeli et al.

Results: A very high prevalence of RLS was found in CADASIL patients (4/5, 80%), as opposed to young subjects with ischemic stroke (15/40, 37%), asymptomatic subjects with migraine (32/80, 40%) and normal controls (8/50, 16%). **All the subjects with CADASIL and migraine (4/4) showed RLS.** The difference between CADASIL patients and controls was highly significant ($p = 0.006$).

Conclusions: We suggest an association between CADASIL and RLS, possibly due to the abnormal development of the endocardial cushion influenced by Notch 3 mutation. Our hypothesis needs to be tested in larger samples.

The CADASIL story

Right-to-Left Shunt in CADASIL Patients Prevalence and Correlation With Clinical and MRI Findings

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Silvia Bianchi, PhD; Gabriele Cevenini, PhD; Massimo Gistri, BSc; Nicola De Stefano, MD;
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Background and Purpose—A high prevalence of right-to-left shunt (RLS) was described in a family of patients with CADASIL, a rare cerebral arteriopathy attributable to Notch3 gene mutations. The aim of this study was to determine the prevalence of RLS in patients with CADASIL and possible relation to clinical phenotype and cerebral MRI lesion load.

Methods—Twenty-three CADASIL patients underwent Transcranial Doppler with gaseous contrast to assess RLS. Correlations between RLS, clinical features, and MRI lesion volume (LV) were determined.

Results—Large RLS was diagnosed in 47% of patients. No significant clinical or MRI differences were found between patients with and without RLS.

Conclusion—We found a high prevalence of RLS in our group of CADASIL patients. This may not be a coincidence, but can be rather related to the role of the Notch receptor family in the development of cardiovascular system. (*Stroke*. 2008; 39:000-000.)

Key Words: right-to-left shunt ■ patent foramen ovale ■ Transcranial Doppler ■ CADASIL

The CADASIL story

Table 2. Descriptive Statistics of Clinical Characteristics and Volume of T1-W and T2-W Lesions in Patients (n=21) With and Without RLS

	RLS-Positive Patients, n=15 (71%)	RLS-Negative Patients, n=6 (29%)	Odds Ratio (95% CI)	P Value
Demographic characteristics				
Age, mean±SD	45±10	54±11	...	0.17
Sex	12 males 3 females	3 males 3 females	...	0.16
Disease duration, mean±SD	5±5	6±7	...	0.99
Clinical characteristics				
TIA/stroke (95% CI)	10 (67%) (42 to 85)	4 (67%) (30 to 90)	1 (0.134 to 7.4514)	0.500
Migraine (95% CI)	4 (27%) (11 to 52)	2 (33%) (10 to 70)	0.75 (0.097 to 5.817)	0.613
Cognitive impairment (95% CI)	6 (40%) (20 to 64)	2 (33%) (10 to 70)	1.35 (0.186 to 9.872)	0.381
Behavioral dysfunction (95% CI)	9 (60%) (36 to 80)	4 (67%) (30 to 90)	0.74 (0.101 to 5.389)	0.619
T1-W LV, mean±SD	26.3±29.3	25.4±30.5	...	0.59
T2-W LV, mean±SD	56.9±55.8	45.4±50.1	...	0.54

Values are mean±SD or n (%).

CADASIL, migraine and right-to-left-shunt: lack of evidence for an association in a prevalence study.

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2008

Table 1. Demographic, genetic and clinical characteristics of CADASIL patients tested for RLS								
Subject	Mutation	Exon	EGF	Sex	Age	Migraine	Stroke/TIA	RLS
1	Cys174Tyr	4	4	m	49	-	+	-
2	Cys174Tyr	4	4	f	46	-	-	-
3	Cys174Tyr	4	4	m	40	-	-	-
4	Cys174Tyr	4	4	f	49	-	+	-
5	Cys174Tyr	4	4	m	43	-	+	-
6	Arg141Cys	4	4	m	48	+	+	+
7	Arg141Cys	4	4	m	61	-	+	+
8	Cys146Arg	4	3	f	55	+	-	+
9	Cys146Arg	4	3	f	63	+	-	-
10	Cys146Arg	4	3	m	56	+	+	-
11	Cys146Arg	4	3	m	51	-	+	-
12	Arg133Cys	4	3	f	65	-	+	-
13	Arg207Cys	4	5	m	59	+	+	-
14	Ser396Cys	7	10	m	68	-	+	-
15	Arg607Cys	11	15	m	62	+	-	-
16	Gly1013Cy	19	26	m	36	+	+	+

7/16

40%

4/16

25%

The "venous" theory of migraine

Wilmshurst and Nightingale Headache 2006

Table 1.—Mechanisms of Migraine Pathogenesis

-
-
1. Venous agents bypassing the lung filter through an atrial defect or pulmonary shunt.
 2. Venous agents causing migraine in the absence of a shunt by overwhelming the lung filter or due to particular sensitivity of the brain to the venous agent.
 3. Activation of platelets in the left heart beyond the lung filter.
 4. Venous agents or platelet activation play no part in the production of migraine.
-

However, although in a small proportion of cases, the “bubble” test may trigger a typical migraine with aura attack

Cerebrovascular Diseases

ABSTRACTS



13th Meeting of the
European Society of Neurosonology and Cerebral Hemodynamics



5th National Congress of the
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Migraine with Aura Attack after Diagnostic Microbubbles Injection

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There is a well-known association between migraine with aura (MA) and right-to-left shunt (RLS) due to patent foramen ovale (PFO). Recent reports described either an improvement of MA after percutaneous PFO closure or the occurrence of MA attacks after microbubbles injection (MBj) during Transcranial Doppler exam (TCD) in two subjects. Confirming the latter data, we describe the occurrence of MA attacks after diagnostic MBj during TCD, in a sample of MA patients.

One-hundred and twenty consecutive patients with MA (M:F 28:92; mean age 37.5 ± 11.3 ; ICHD-II) attending Headache Center in the years 2006–2007, underwent contrast TCD to disclose a RLS. RLS was revealed in 52/120 patients (about 52%). Persistent RLS was in 44/62 (71%), whereas latent RLS in 18/62 (29%) patients. We observed the occurrence of a typical MA attack, immediately after the MBj, in 8/120 patients (6.6%), (M:F 2:6, mean age 37.1 ± 7.2). All these patients exhibited a persistent RLS; six of them had a large RLS with a shower/curtain pattern, the remaining two, a small RLS with a "single spikes" one. Two of these patients, having a large and a small RLS, respectively, repeated TCD in another instance. MA attack occurred again right after MBj. No correlation between MA attack after MBj and thrombophilia was observed. A late occurrence of MA after MBj in the remaining patients was excluded by a telephone interview.

A possible physiological hypothesis would indicate the MBj as trigger of MA attack. This hypothesis seems to be confirmed by the occurrence of MA attack after MBj observed in two patients who repeated TCD. According to what recently published and to the occurrence of a typical MA attack after MBj, we would rule out an ischemic mechanism. Further studies need to be assessed in order to observe a wider correlation.

Trying to build up a coherent picture

- Migraine (particularly with aura) tends to co-segregate with PFO.
- PFO in migraine sufferers is larger than in non migraineurs.
- The association with PFO could partly explain the increased risk of stroke of female migraineurs.
- However, SAM does not increase the risk of getting “bright spots” on MRI

Trying to build up a coherent picture

- In shunt associated migraine (SAM), right –to-left shunt may be a trigger for aura.
- But SAM cannot be identified on clinical grounds.
- Closing PFO in SAM may provide a relief (how much clinically relevant and how long sustained presently unknown)→ more RCTs needed. Need to identify patients most likely to benefit (migraine with aura, larger shunt on TCD, with family history of both conditions, females, with complex auras).

Working hypothesis I

- Among SAM patients there exists a subgroup of migraine with a genetically determined sensitivity to shunted chemicals.
- These patients have large shunts and positive family history (for MA+ and RLS).
- Migraine attacks may be started by the bubble test.
- Genetic linkage studies needed
- Bubble migraine with special features ?

Working hypothesis II

- In CADASIL RLS and migraine do not necessarily co-segregate.
- Studies on genotype-phenotype characterization are warranted.
- RLS might be associated with the **Arg141Cys** mutation
- Migraine particularly with **Cys146Arg** but probably with a larger number of mutations.

Thank you for your attention !!!

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