Cognitive Impairment and Ultrasound (US)

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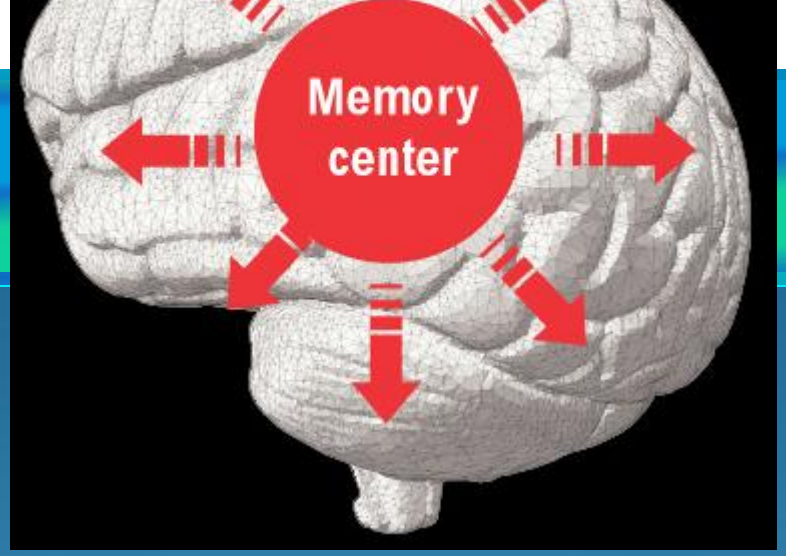
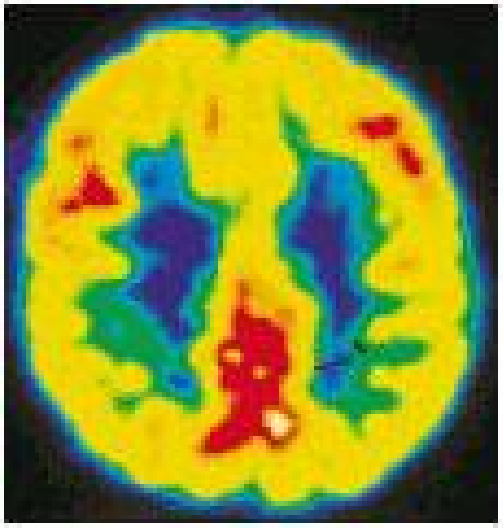
Tel Aviv Sourasky Medical Center, Tel Aviv University
Sackler Faculty of Medici

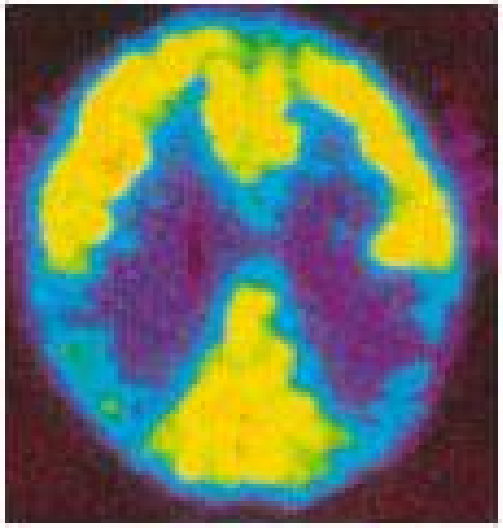
Dementia, a leading cause of memory impairment and disability



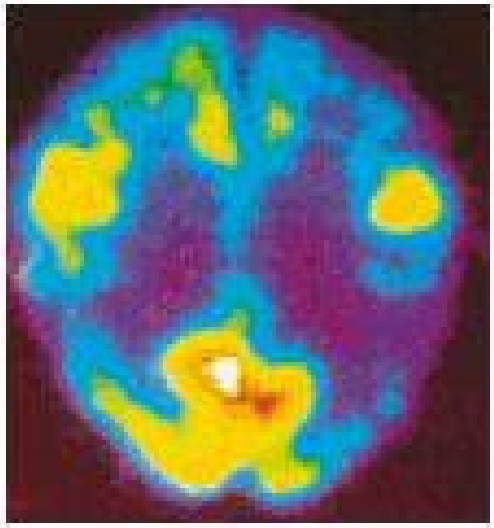
- Dementia is a clinical syndrome presenting with acquired, progressive cognitive impairment that may be related to several ethiopathogeneses, the two main leading causes being represented by degenerative Alzheimer's Disease (AD) and



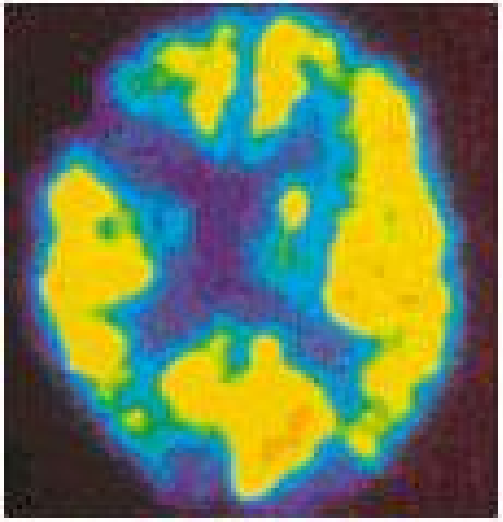
Healthy control



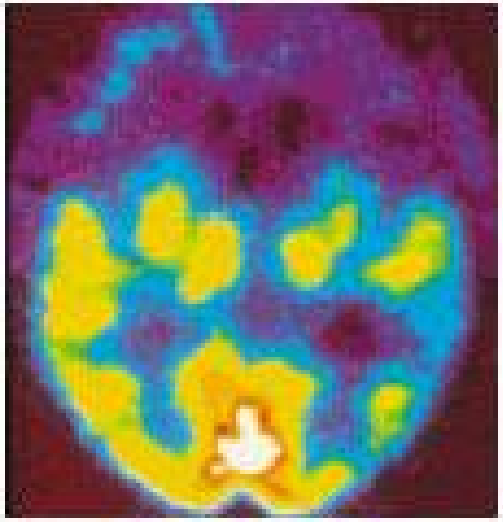
DAT
60 year old male



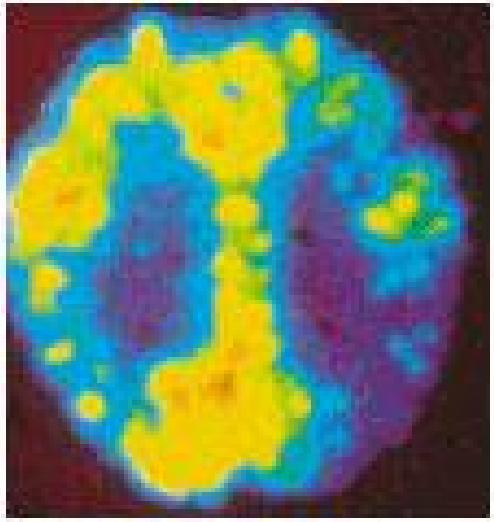
Severe DAT
64 year old female



MID [define]
50 year old male



Pick's disease
69 year old female

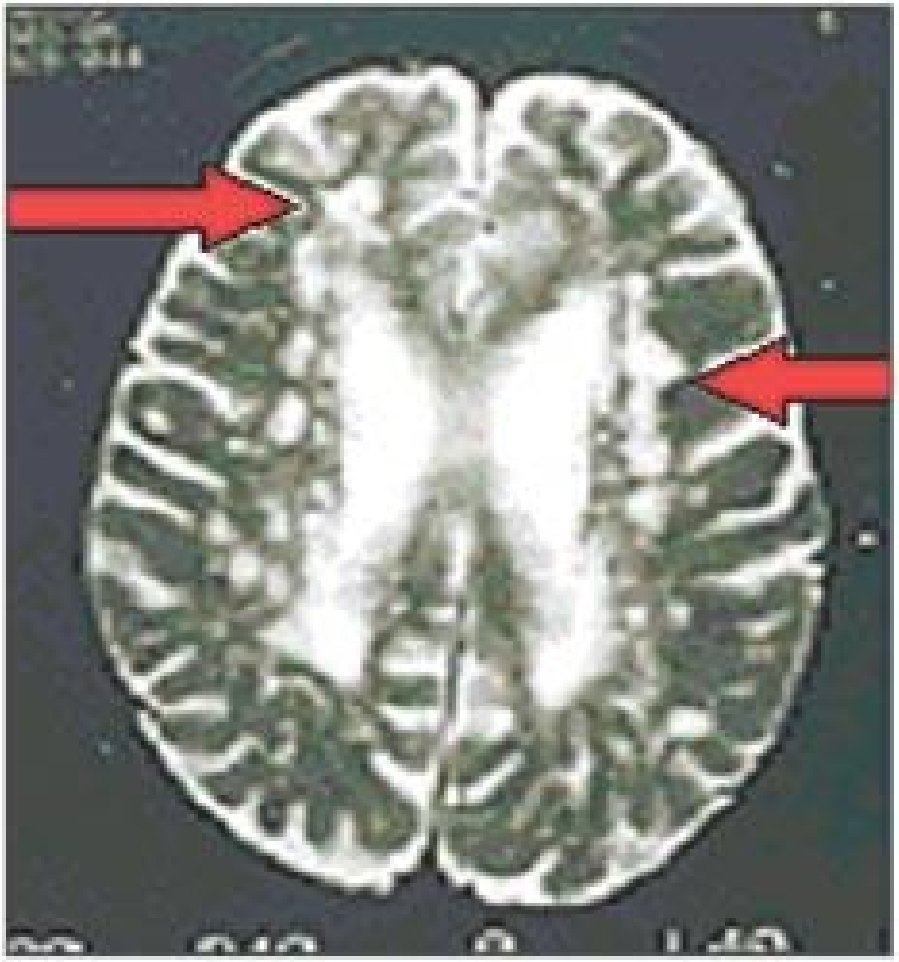


DAT aphasia
59 year old female

Problems arise when...

- The inside of the vessels becomes narrow, rigid or blocked.
- The blood vessels become damaged and blood leaks out of them.
- The heart doesn't pump forcefully enough.
- The blood thickens or clots too easily.

Searching for vascular dementia



A horizontal MRI scan of the brain in which brain regions with circulation problems appear as bright patches. This is typical of one type of vascular dementia in which multiple small vessels are blocked.

Source: Duke University, Dr. Murali Doraiswamy

The News & Observer

Vascular dementia (VaD)

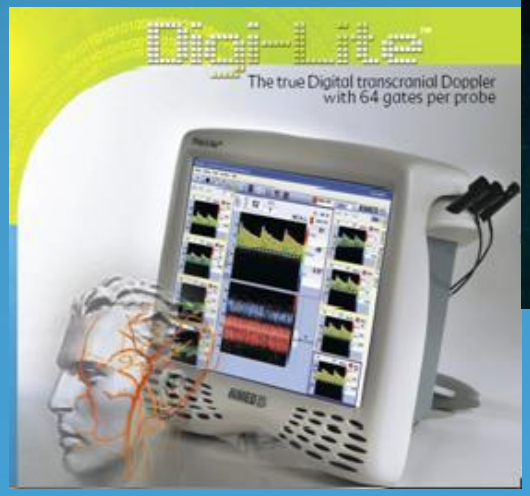
- Dementia is one of the common devastating sequels after stroke.
- 25% of post-stroke patients may develop cognitive impairment within 3 months following stroke.
- Patients with VaD have a higher mortality rate independently of age and co- morbidities.
- VaD diagnosed 3 months after stroke was also associated with an increased risk of stroke recurrence.

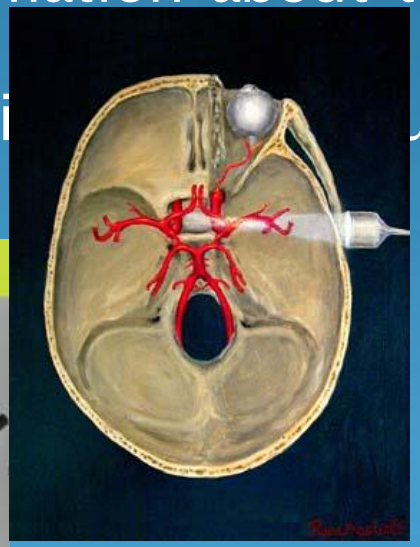
Lessons from the Nun Study

- Pure AD and pure VaD may represent the two extremes of the spectrum.
- A “mixed dementia” is actually consistent with the majority of cases.
- At least one third of AD cases h of cerebral infarction on autopsy.

Transcranial Doppler Sonography

- 1982, Aaslid –TCD tool for evaluation of the cerebral vasculature.
- TCD and more recently Transcranial Color Doppler and Power Imaging give detailed information about the flow velocity in brain arteries and veins.
- This hemodynamic information i used in diagnosis of cerebrovascular disease.

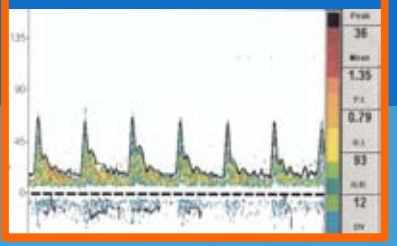




Procedures using TCD

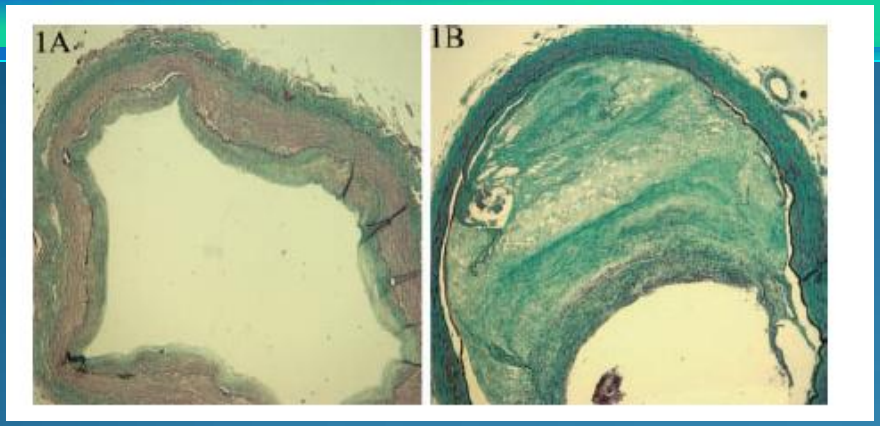
TCD

Routine TCD

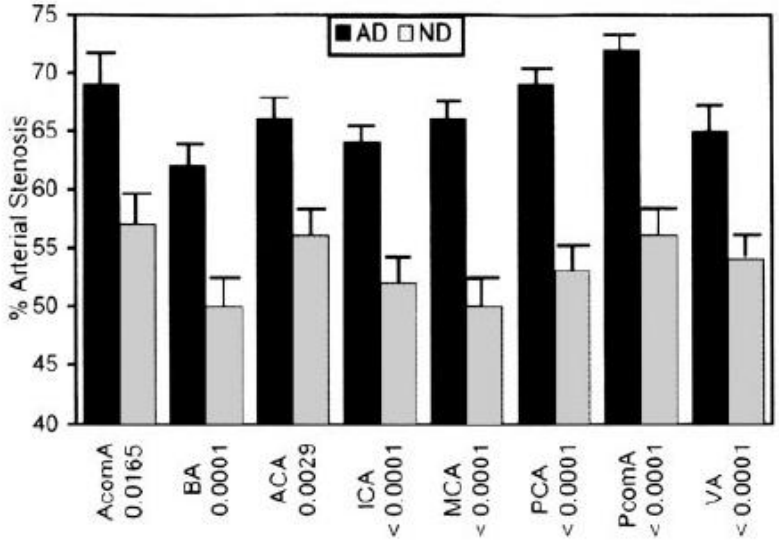


TCD and microembolic detection

Intracranial Atherosclerosis & AD



MCA: Healthy Control MCA: Patient with AD



HC

AD

Roher et al. Arterioscl Thromb Vasc Biol 2003;23:255-262

Routine TCD and Dementia

Multiinfarct and Alzheimer-type dementia investigated by transcranial Doppler sonography.

Foerstl H, Biedert S, Hewer W.
Zentralinstitut für Seelische Gesundheit, Mannheim, West Germany.

Primary degenerative dementia of the Alzheimer type and multiinfarct dementia exhibit differences in cerebrovascular blood flow velocity profiles, which were investigated by transcranial Doppler sonography. The pulsatility indices, as angle-independent parameters of peripheral vascular resistence, measured in middle cerebral and basilar arteries of patients with multiinfarct dementia were significantly increased (p less than 0.005) compared with cases of primary degenerative dementia of the Alzheimer type and with healthy age-matched controls.

Biol Psychiatry. 1989 Oct;26(6):590-4

Routine TCD and Dementia

Interaction of cardiovascular disease and neurodegeneration: transcranial Doppler ultrasonography and Alzheimer's disease.

Roher AE, Garami Z, Alexandrov AV, Kokjohn TA, Esh CL, Kalback WM, Vedders LJ, Wilson JR, Sabbagh MN, Beach TG.

- OBJECTIVE: Recent post-mortem studies have reported that the severity of atheromatous deposits in the circle of Willis is significantly greater, relative to non-demented (ND) elderly persons, in subjects with neuropathologically diagnosed Alzheimer's disease (AD). Additionally, the severity of intracranial atherosclerosis correlates significantly with the densities of neuritic plaques and neurofibrillary tangles. In this study, we examine the arteries of the circle of Willis by transcranial Doppler (TCD) ultrasonography.

- METHODS: TCD was used to measure, in 25 AD patients and 30 ND elderly subjects, mean flow velocities and pulsatility indices in 16 different segments of the circle of Willis. The data were compared with and without adjustment for age, gender and systolic blood pressure.

- RESULTS: The AD patients had systematically higher pulsatility indices ($p<0.005$) than the ND group.Incremental increases of pulsatility indices in these segments had odds ratios ranging from 1.8 to 48 for the presence of AD when adjusted for age, gender and systolic blood pressure. The left internal carotid artery siphon and the left posterior cerebral artery were the two vessels that were strongly associated with AD diagnosis. Mean flow velocities were generally lower in patients with AD but the differences did not reach the significance level.

- DISCUSSION: The pulsatility indices of the arteries of AD patients were generally greater than those of similarly-aged ND subjects. This difference is most likely due to increased arterial wall rigidity imposed by atherosclerotic changes. Atherosclerotic disease of intracranial arteries may be a risk factor for AD.

Neurol Res. 2006 Sep;28(6):672-8.

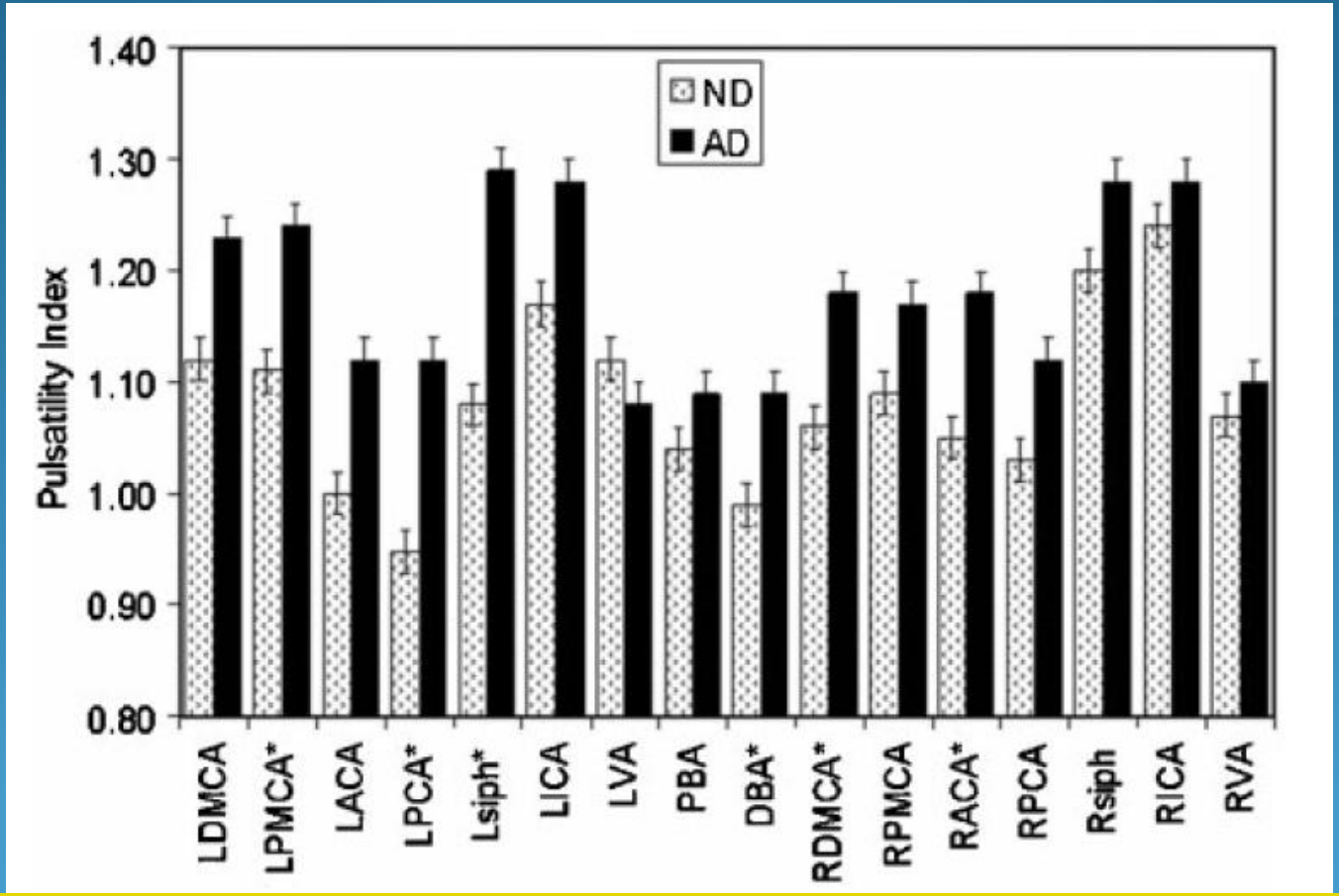
Intracranial Atherosclerosis & AD: Summary of Pathology Studies

Table 3: Proportions of dementia cases with AD, cerebral arteriosclerosis and mixed pathology, as reported by six historical studies[67]

Author	No.	Senile dementia (AD)	Cerebral arteriosclerosis	Mixed cases
Rothschild, 1941	60	21.7	23.3	55
Newton, 1948	22	50	31.8	18.2
Raskin and Ehrenberg, 1956	193	22.3	29.5	48.2
Peters and Struck, 1959	240	7.5	92.5	0
Delay and Brion, 1962	31	25.8	19.3	54.8
Simon and Malamud, 1965	50	24	22	54

Roher et al. Neurol Res 2006;28:672-678

Increased Pulsatility of Intracranial Arteries: Intermediate link between Atherosclerosis & AD



Intracranial Atherosclerosis=> Increased Stiffness of proximal intracranial arterie=> Increased PI

Roher et al. Neurol Res 2006;28:672-678

Association of increased PI with AD & VaD

Ageing Research Reviews 11 (2012) 271–277

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

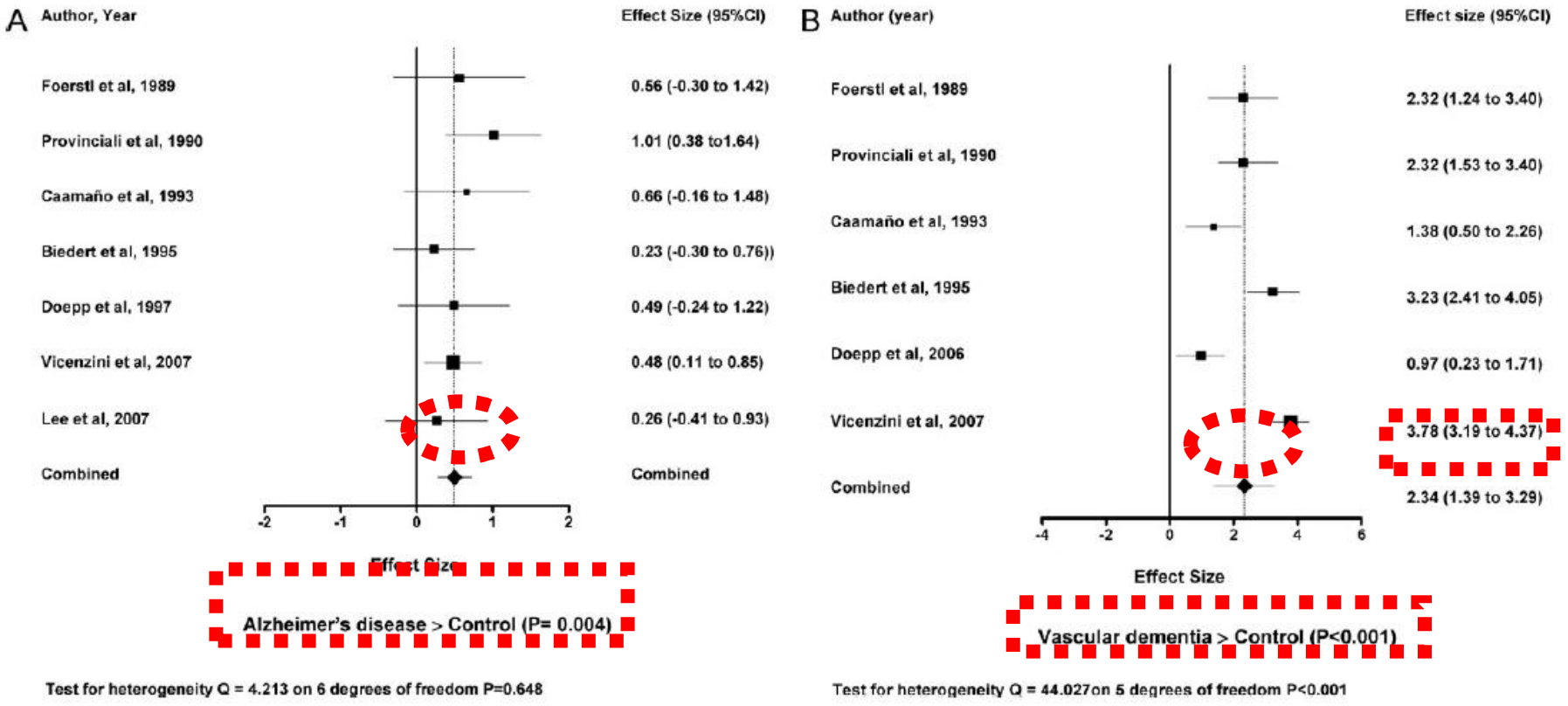
journal homepage: www.elsevier.com/locate/arr

Review

Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: A meta-analysis of transcranial Doppler studies

Behnam Sabayan[a,b,c,*], Steffy Jansen[a,b], Anna M. Oleksik[a], Matthias J.P. van Osch[c], Mark A. van Buchem[c], Peter van Vliet[a,d], Anton J.M. de Craen[a,e], Rudi G.J. Westendorp[a,b,e]

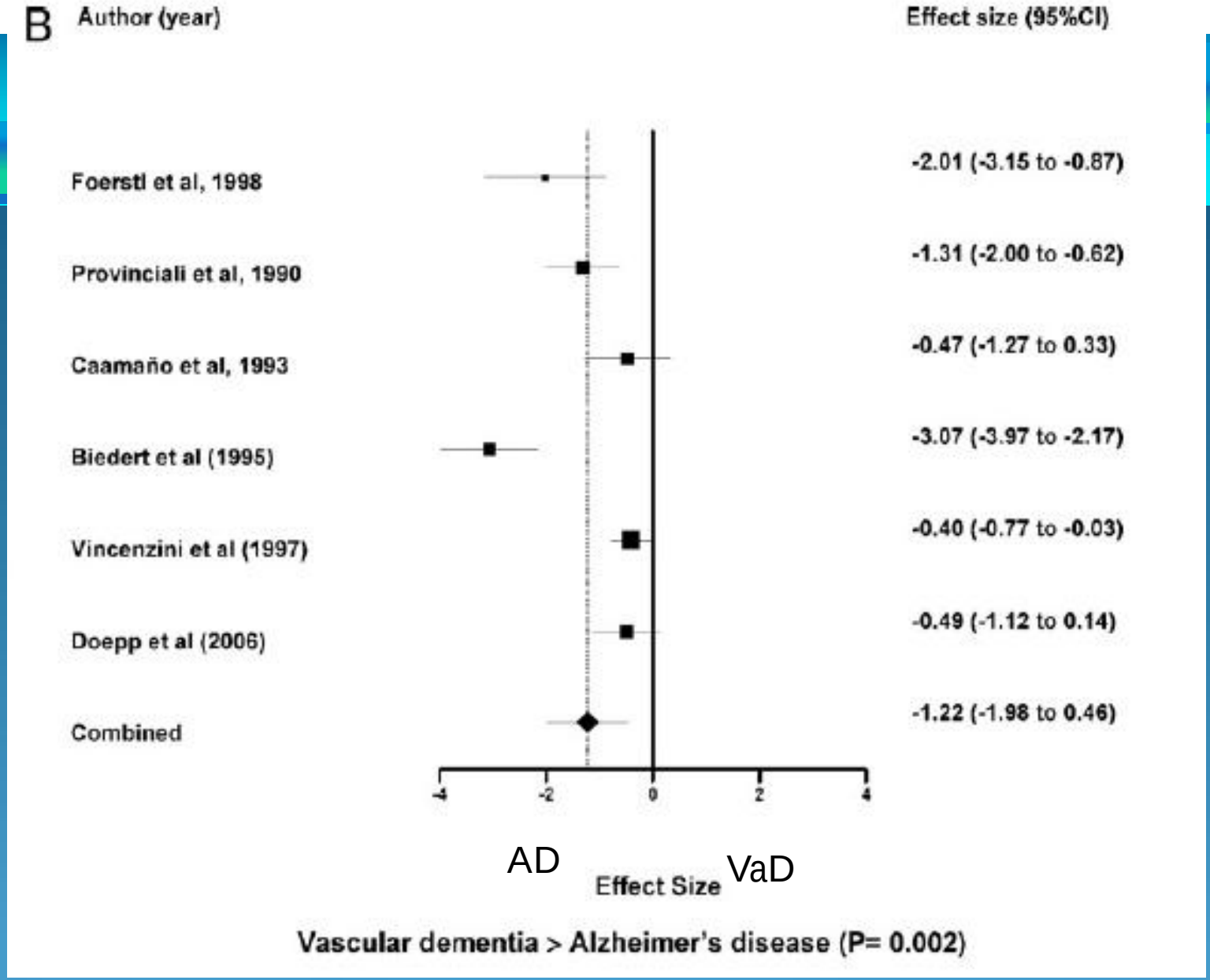
[a] *Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands*
[b] *Leyden Academy on Vitality and Ageing, Leiden University, Leiden, The Netherlands*
[c] *Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands*
[d] *Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands*
[e] *Netherlands consortium for healthy ageing, Leiden, The Netherlands*



PI AD> PI HC

PI VaD>> PI HC

Sabayan et al. Ageing Researc Reviews 2012;11:271-277



PI VaD> PI AD

Sabayan et al. Ageing Researc Reviews 2012;11:271-277

Routine TCD and Dementia

Transcranial Doppler ultrasonography in senile dementia: neuropsychological correlations.

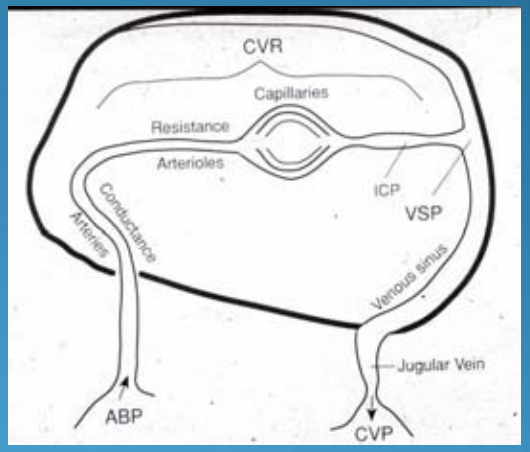
Caamaño J, Gómez MJ, Cacabelos R.

Department of Digital Diagnosis, Basic and Clinical Neurosciences Research Center, La Coruña, Spain.

- Blood flow velocities were measured in right and left middle cerebral arteries (MCAs) and in basilar artery (BA) on rest conditions by transcranial Doppler ultrasonography in three groups of patients: Alzheimer's disease patients (AD, N = 12, age = 63.5 +/- 6.6 years), b) patients with multi-infarct dementia (MID, N = 12, age = 72.8 +/- 9.0 years), and c) control subjects (CS, N = 12, age = 57.20 +/- 7.5 years).
- TCD measures were taken through the temporal window for MCA recordings, and transforaminal approach for BA recordings, with a 2 MHz ultrasonic probe using a TC-2000S (EME).
- A significantly ($p < 0.05$) decrease in TCD measures was found in right and left MCA and BA of dementia patients with respect to controls. Data analysis included a significant correlation between blood flow velocities and Hachinski scores ($p < 0.016$) in multi-infarct dementia patients.
- These results appear to show a general hypoperfusion pattern in the brain of senile dementia patients.

Cerebral Vasomotor Reactivity

- The cerebral vasculature has a unique ability to dilate during hypercapnia and to constrict during hypocapnia.
- The differences between cerebral blood flow (CBF) at rest and after the induction of hypercapnia reflect the state of cerebral vasomotor reactivity (VMR) and, hence cerebrovascular reserve capacity.
- VMR can be considered as a shift between cerebral blood flow velocity (BFV) before and after the administration of a potent vasodilatory stimulus test.
- Assessment of VMR could provide the valuable information regarding hemodynamic patterns of cerebral autoregulation and collateral circulation



Definitions of CVR

- CVR is the capacity of the brain to increase cerebral blood volume (CBV) in order to maintain a constant cerebral blood flow (CBF) in the face of low cerebral perfusion pressure (CPP)
- CBF=CPP/VR
- CPP=MAP-ICP

Powers WJ. Ann Neurol 1991;29:231-240

Evaluation of CVR

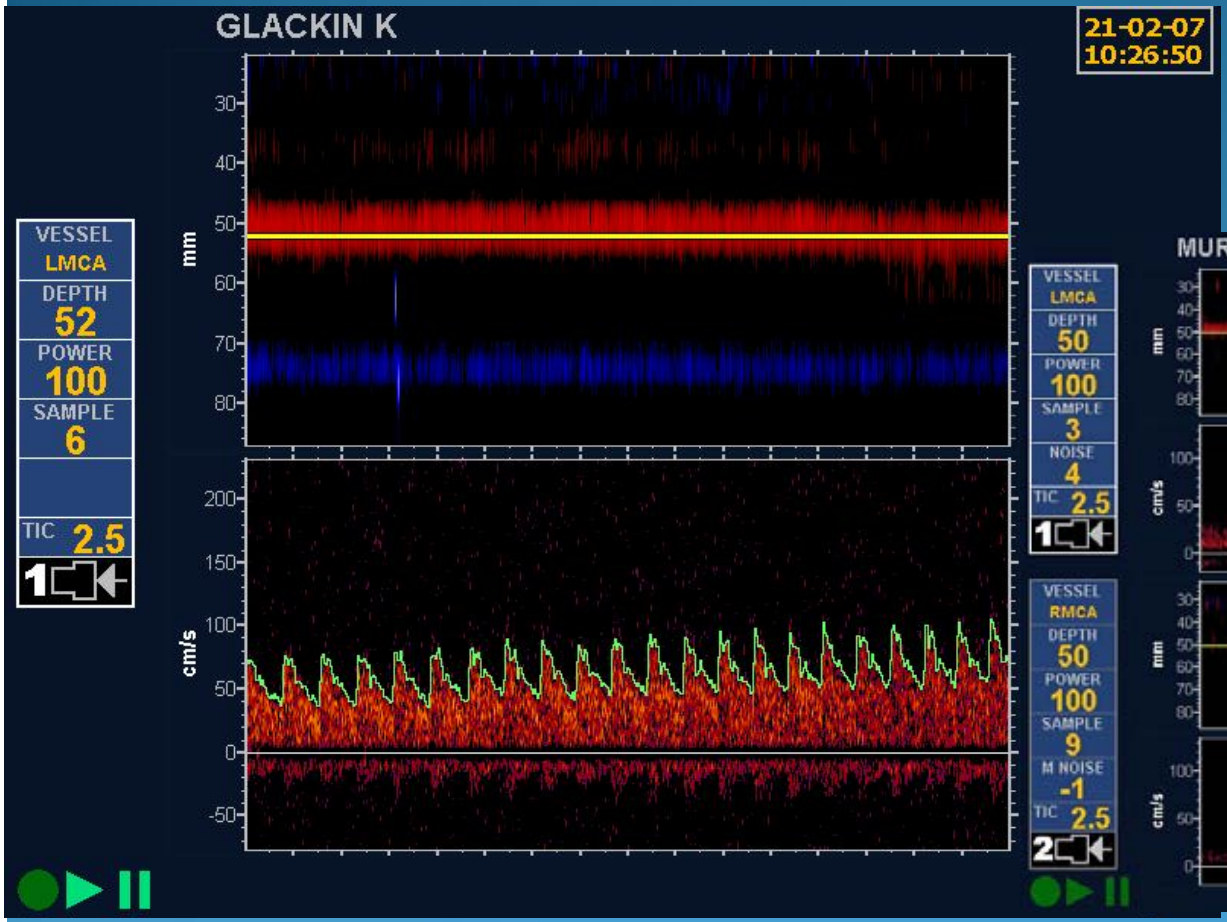
- PET
- SPECT
- TCD
- Xenon-CT, Perfusion CE CT
- Dynamic CE MRI

Tsivgoulis G & Alexandrov AV. Neurotherapeutics 2007;4:420-427
Momjian-Mayor I & Baron JC. Stroke 2005;3:567-577

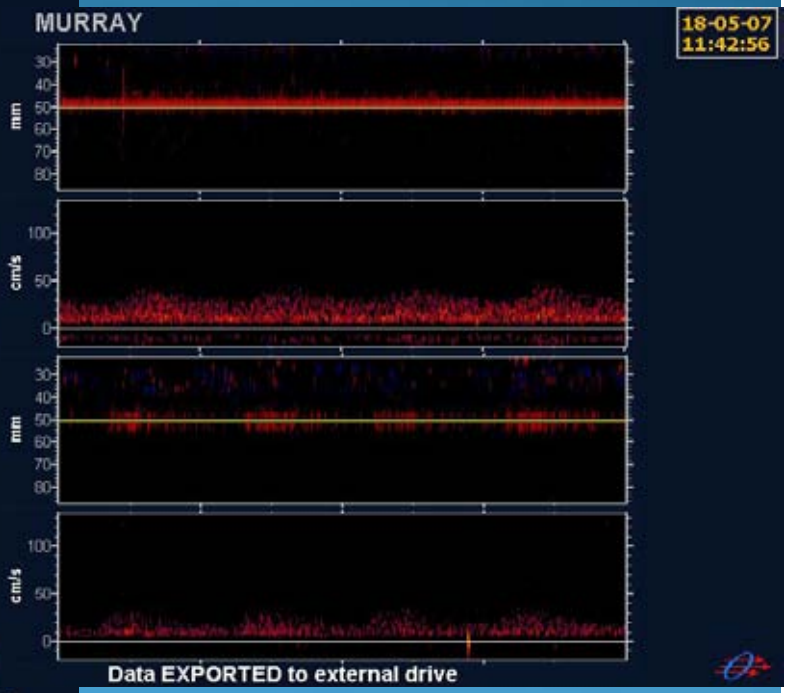
Vasodilatadory Test

- Apnea-breath holding test
- CO2 inhalation
- Diamox (acetazolamide) tes
- L-Arginine test

TCD & Estimation of CVR



NORMAL VMR



EXHAUSTED VMR

Tsivgoulis G. & Alexandrov AV. J Vasc Interv Neurol 2008;1:65-69

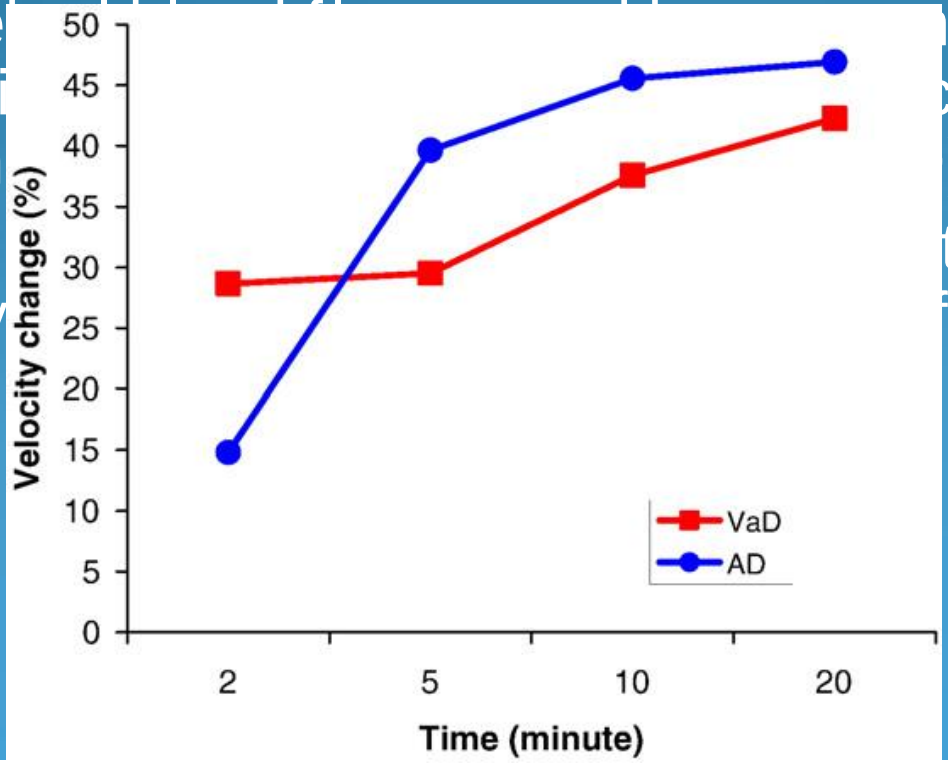
Cerebral hemodynamic patterns during stimuli tasks in multi-infarct and Alzheimer types of dementia

- Cerebral reactivity to apnea was significantly lower in the multi-infarct group.
- These data suggest that cerebrovascular reactivity to apnea could be an additional criterion for discriminating between MID and DAT patients. Transcranial Doppler assessment during cognitive and motor tasks could provide useful complementary information for comprehension changes in cerebral activity in patients with dementia.

Acta Neurol Scand; 1998 Jun;97(6):374-80.

Vasoreactivity induced by acetazolamide in patients with vascular dementia versus Alzheimer's disease

- Acetazolamide vasoreactive test measures the increment of cere satory vasodilatation abili can be detected by tran).
- Con tive test using TCD may fferentiate VaD from AD.



Journal of the Neurological Sciences 283 (2009) 32–35

The value of TCD to investigate the influence of dementia treatment on vasomotor reactivity

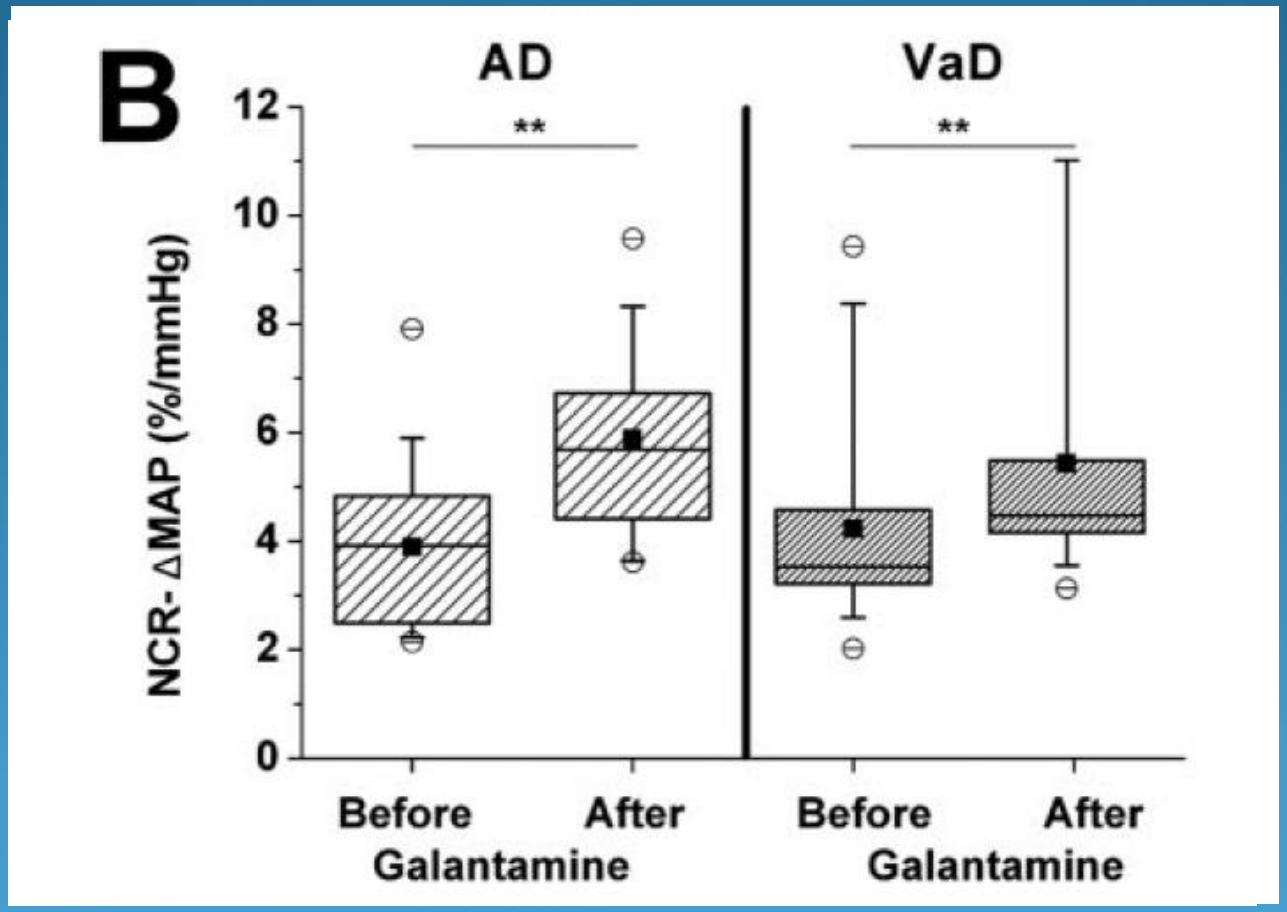
Influence of galantamine on vasomotor reactivity in Alzheimer's disease and vascular dementia due to cerebral microangiopathy.

Bär KJ, Boettger MK, Seidler N, Mentzel HJ, Terborg C, Sauer H.

- BACKGROUND AND PURPOSE: Recent reports suggest that vascular factors play a crucial role in the development and progression of Alzheimer's disease. We aimed to assess vasomotor reactivity in patients with Alzheimer's disease and vascular dementia due to microangiopathy using transcranial Doppler sonography and near-infrared pectroscopy during a CO(2) exposition task.
- METHODS: The normalized CO(2) reactivity assessed at the middle cerebral artery and the oxygenated and deoxygenated hemoglobin of the frontal cortex were obtained. To investigate the impact of cholinergic deficiency known for Alzheimer's disease on vasomotor reactivity, both groups were reinvestigated during treatment with the acetylcholine esterase inhibitor galantamine.
- RESULTS: Transcranial Doppler analysis revealed significantly reduced normalized CO(2) reactivity for Alzheimer's disease and vascular dementia. Vasomotor reactivity assessed by near-infrared spectroscopy was decreased in patients with vascular dementia, but not in Alzheimer's disease. Galantamine treatment showed a beneficial effect, normalizing these parameters close to age-matched control levels.
- CONCLUSIONS: Our results suggest that Alzheimer's disease is associated with a lack of vasomotor reactivity, which might be associated with disturbed autoregulation indicating a potential risk for a decreased protection of brain tissue against blood pressure changes. Additionally, a diminished increase of cortical oxygenated hemoglobin during the CO(2) test was apparent in patients with vascular dementia. Galantamine treatment influenced vascular reactivity in the CO(2) test, thus providing evidence for the cholinergic deficiency, thereby adding to vascular dysregulation in Alzheimer's disease, but also indicating an important role of cholinergic system dysfunction for vascular dementia.

Stroke. 2007 Dec;38(12):3186-92.

AchEIs Improved VMR in AD & VaD I



Baseline VMR assessment

Bar KJ et al. Stroke 2007;38:3186-3192

AchEIs Improved VMR in AD & VaD I

	Patient group	Baseline	Donepezil 5 mg	Donepezil 10 mg
Resting flow velocity (cm/s)	47±15	40±13	41±10	44±11
Gain (%)	16±7	13±4	11±3	10±4
Attenuation	0.4±0.2	0.64±0.2**	0.58±0.3*	0.4±0.2
Natural frequency (1/s)	0.22±0.06	0.20±0.04	0.21±0.07	0.24±0.07
Rate time (s)	3.6±2.4	4.4±1.2	3.7±2.3	3.4±1.9

?á ATTENUATION<=> ?=VMR

Rosengarten B et al. J Neurol 2006;253:58-64

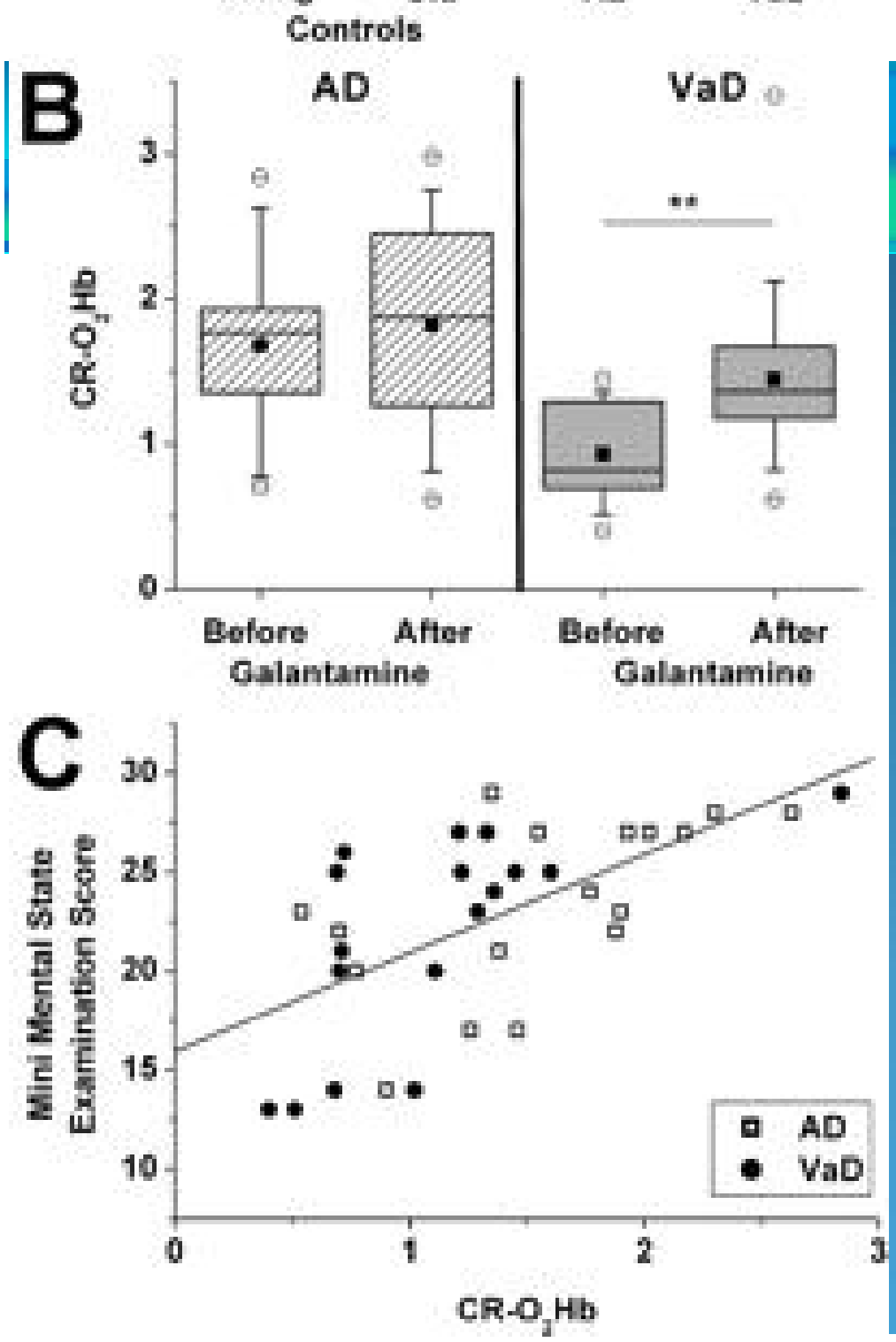
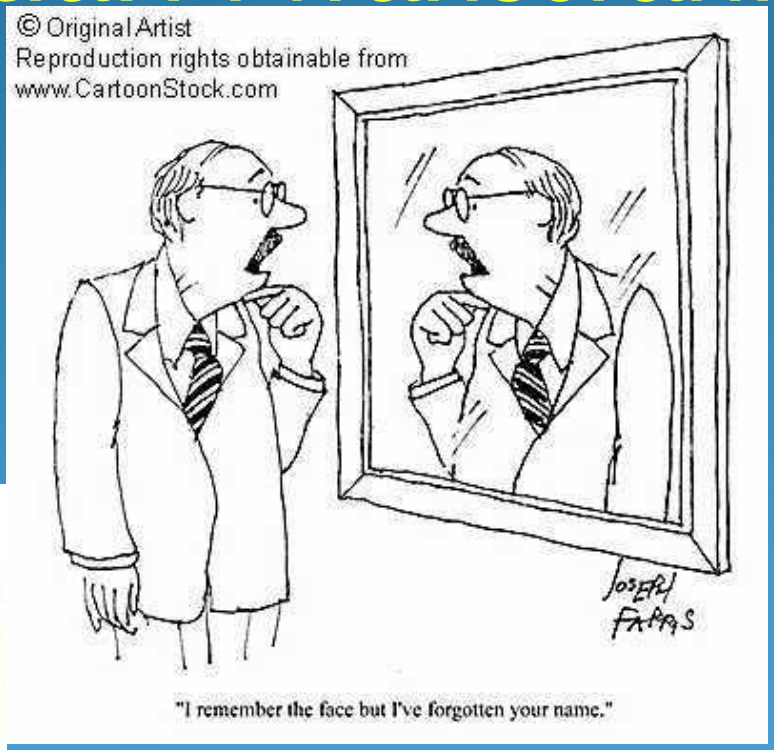
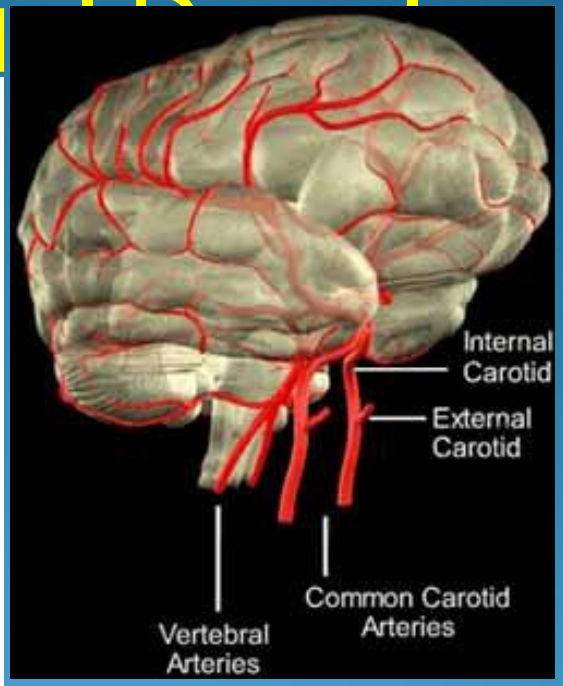


Figure 2. NIRS. Differences for CR-O_2Hb between control subjects (old: control subjects matched with respect to age and sex, n=20; young: control subjects from a different age population, n=20) and patients with AD disease (n=17) and VaD (n=17) are depicted as box plots (A). Into NCR, no significant difference was obvious between old control subjects and AD, but between control subjects and VaD. The effect of galantamine treatment is depicted in (B) showing an increase of oxygenated hemoglobin in VaD to the level of patients with AD, but no significant change in AD itself. NIRS parameters showed significant correlations to Mini-Mental State Examination scores (C) for both patients with AD (empty squares) and patients with VaD (filled circles) as well as when including both in the analysis as shown here. Boxes in (A) and (B) indicate data between the 25th and 75th percentile with the horizontal bar reflecting the median (=mean; o=1st and 99th percentile; —=minimum and maximum of data; *P<0.05; **P<0.01; ***P<0.001).

Cerebrovascular Reactivity in Degenerative and Vascular Dementia: A Transcrani



"I remember the face but I've forgotten your name."



Eur Neurol 2007;58:84–89

Cerebrovascular Reactivity in Degenerative and Vascular Dementia: A Transcranial Doppler Study

- 60 AD and 58 VaD patients and 62 nondemented controls. Both AD and VaD subjects showed lower flow velocities (FV) and higher pulsatility indices (PI) as compared with controls.
- Lower total vasomotor reactivity and lower response to hypercapnia were observed in the AD and VaD groups as compared with controls.
- AD and VaD patients did not show significant differences in FV, PI values or cerebral vasoreactivity.

Cerebrovascular Reactivity in Degenerative and Vascular Dementia: A Transcranial Doppler Study

Table 3. Vasoreactivity in right and left MCA during hyper- and hypocapnic conditions in AD, VaD and controls

	VaD		AD		Controls	
	right	left	right	left	right	left
Total VMR, %	62.1 ± 12.9*	61.8 ± 14.9*	63.8 ± 14.2*	60.1 ± 15.6*	81.4 ± 16.8	80.1 ± 15.7
RI CO_2	3.1 ± 1.7*	2.8 ± 1.5*	3.5 ± 1.9*	2.5 ± 1.5*	5 ± 1.4	4.8 ± 1.2
RI Hp	3.2 ± 1.6	3.1 ± 1.4	3.0 ± 1.6	2.9 ± 3.6	3.6 ± 0.8	3.6 ± 0.8

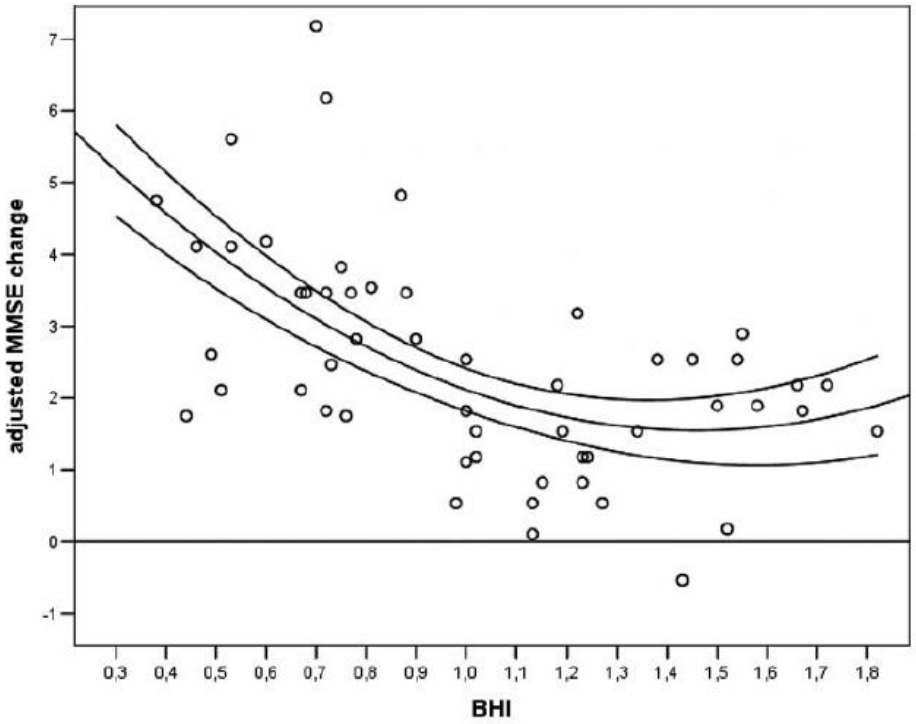
Values are means ± SD. Total VMR = Total vasomotor range; RI CO_2 and RI Hp = reactivity index to hypercapnia and hypocapnia, respectively, calculated as percentage per millimeter mercury column. * $p < 0.0001$ compared with controls.

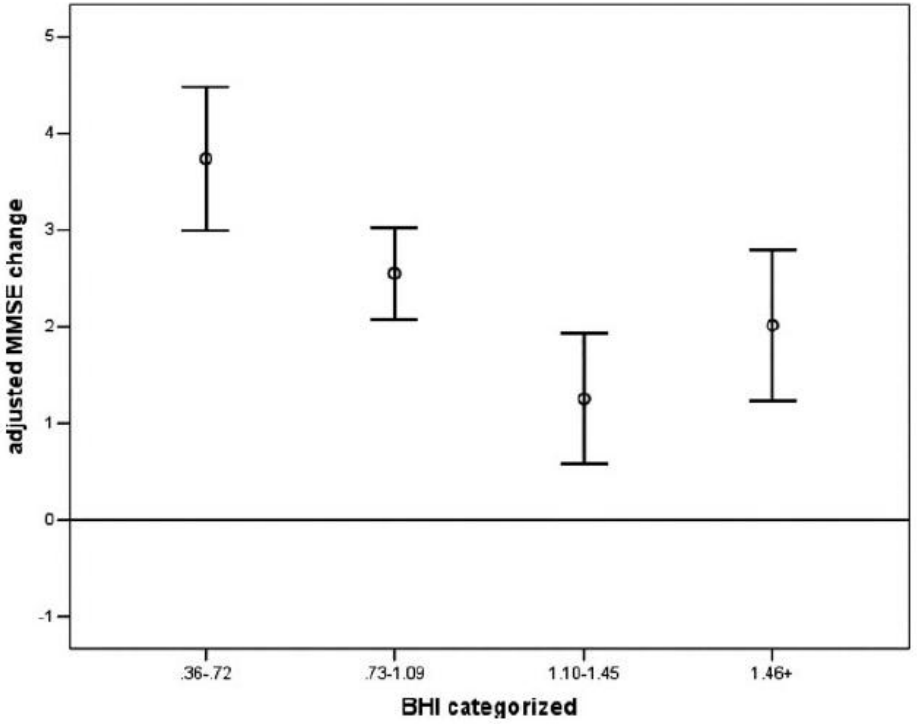
Cerebrovascular Reactivity and Cognitive Decline in Patients with AD

- The aim of the study was to explore the contribution of cerebral hemodynamics to the evolution of cognitive impairment in patients with AD.
- 53 patients with AD were investigated.
- The evolution of cognitive decline over 12 months was evaluated by means of changes in Mini Mental State Examination and AD Assessment Scale for Cognition scores.
- These results show an association between impaired cerebral microvessels functionality and unfavorable evolution of cognitive function in patients with AD.

Silvestrini et al. Stroke, 2006; 37;1010-5

Impaired VMR & Cognitive Decline in AD





?á BHI<=> ? VMR

Silvestrini M. et al. Stroke 2006;37:1010-1015

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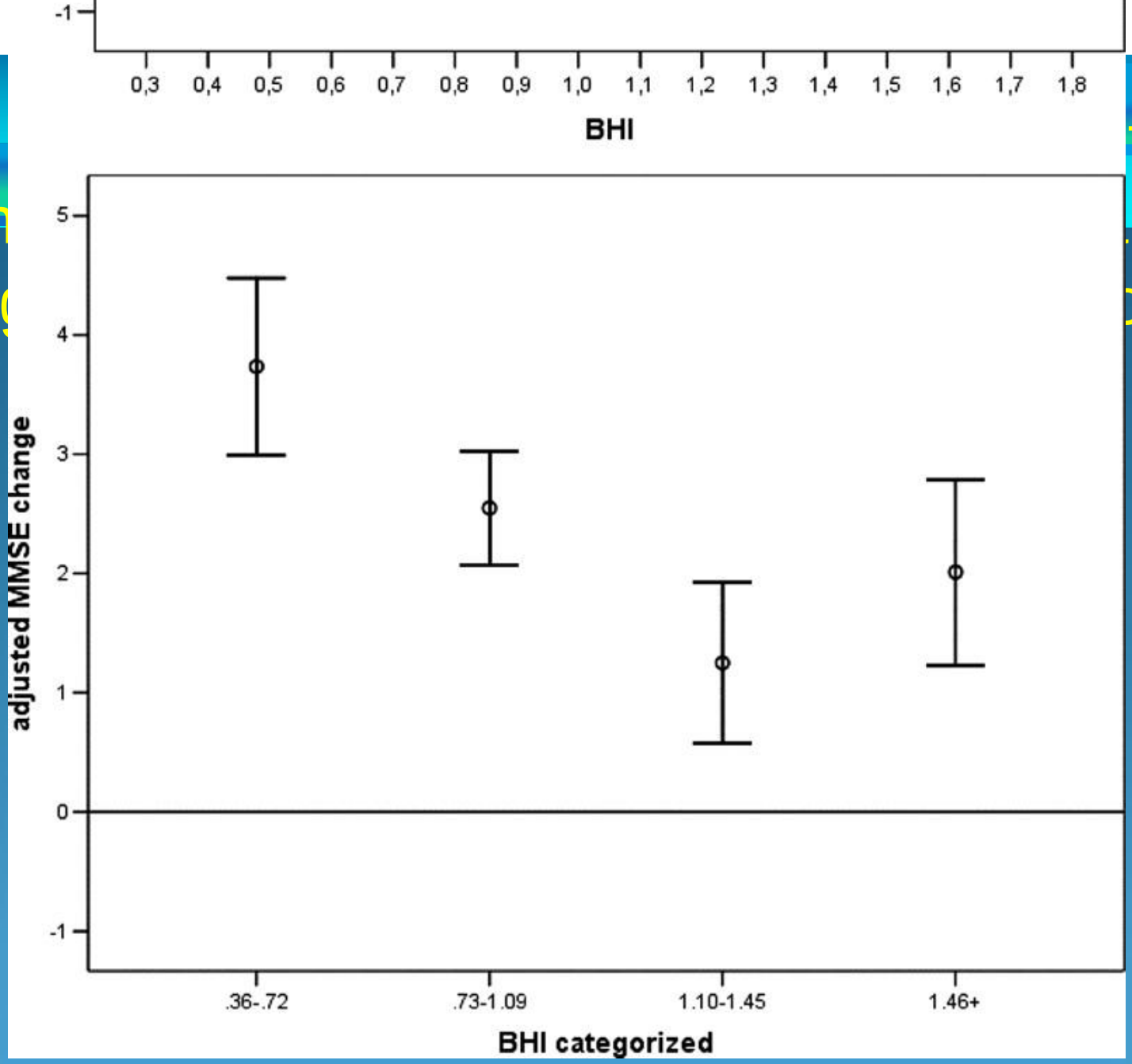


American Stroke Association®
A Division of American Heart Association

Silvestrini, M. et al. Stroke 2006;37:1010-1015

Differentiation of Multiinfarct and AD by Intracranial hemodynamic parameters

- BACKGROUND AND PURPOSE: The differentiation between the Alzheimer and multi-infarct types of dementia may still be equivocal considering clinical criteria, neuropsychological tests, and imaging techniques. Cerebral microangiopathic alterations underlying multi-infarct dementia should allow the characterization of dementia subgroups.

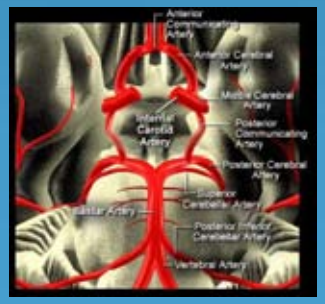
- METHODS: Patients with a diagnosis of multi-infarct dementia (n = 17; mean age, 69.1 +/- 8.5 years) or Alzheimer dementia (n = 24, mean age, 65.8 +/- 9.0 years) according to standard testing criteria, clinical findings, and neuroimaging techniques (computed tomography and magnetic resonance imaging) were investigated prospectively by transcranial Doppler sonography and compared with a normal reference group (n = 64; mean age, 61.0 +/- 11.1 years). Transcranial Doppler sonography allows an indirect evaluation of peripheral flow resistance in the microcirculatory bed by quantifying pulsatility characteristics, as reflected in the effective pulsatility range (time-averaged mean blood flow velocity minus the peak-systolic to end-diastolic amplitude, in centimeters per second).

- RESULTS: A total of 204 vessels were investigated in 105 subjects. Mean and diastolic blood flow velocities as well as the effective pulsatility range were significantly lower in the multi-infarct dementia group compared with the Alzheimer and the normal reference groups ($p < 0.001$). By using receiver operating characteristic analysis, a cutoff point for effective pulsatility range values of -5 cm/sec gives a side-dependent sensitivity of 90.48-95.24% and a specificity of 64.71-70.59% in diagnosing Alzheimer-type dementia; the corresponding sensitivity and specificity for a value of -2 cm/sec are 82.35-88.24% and 80.95-90.48%, respectively.

- CONCLUSIONS: Pulsatility changes as reflected by the effective pulsatility range are a noninvasive additional criterion in the differential diagnosis of dementia.

Stroke. 1993 Feb;24(2):228-35

Cerebral Vasomotor Reactivity and Cognitive Decline in Patients After Ischaemic Stroke. Israeli-Turkish Collaborative Study



A.Y. Gur,[1] D. Gücüyener [2], N.Üzüner [2], Y. Gilutz [1] . Özdemir [2], A.D. Korczyn [1], N.M. Bornstein[1]

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Cerebral Vasomotor Reactivity and Cognitive Decline in Patients After Ischaemic Stroke

- Aim of the Study: To assess and compare VMR findings in patients with and without dementia after suffering IS.
- Patients:
  - 11 Patients with first-ever acute (within 72 hours of stroke onset)
  - 20 Patients within 3-36 months after IS
- Methods:
  - TCD and the Diamox test (1g acetazolamide IV).
  - VMR is defined as a shift between cerebral blood flow (CBF) or cerebral blood flow velocity (BFV) before and after administration of a potent vasodilatory stimulus test.
  - Dementia was diagnosed based on DSM-IV and the MMSE scale.
  - The VMR% values of patients with and without dementia were compared using the ANOVA test.

Cerebral Vasomotor Reactivity and Cognitive Decline in Patients After Ischaemic Stroke

- Diamox Test:
  - Full cooperation is not essential
  - Easy performing

  Blood gases monitoring is not essential
- Results:
  - VMR% on the side of brain infarct in the AIS group with and without dementia after 6 months of follow-up.

AIS group n=11	Mean VMR%	
without dementia n=9	40.7±29.1%	
with dementia n=3	33.3±21.5%	P=NS

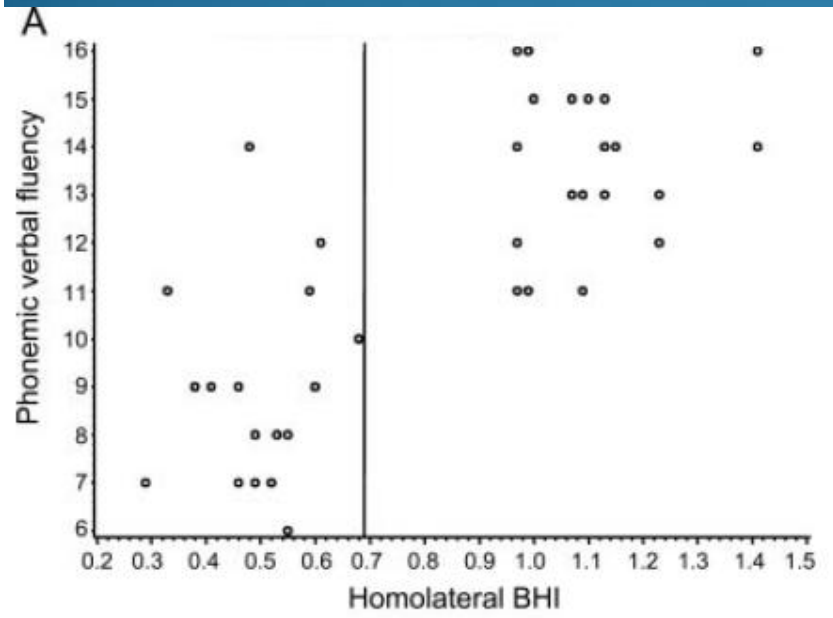
Cerebral Vasomotor Reactivity and Cognitive Decline in Patients After Ischaemic Stroke

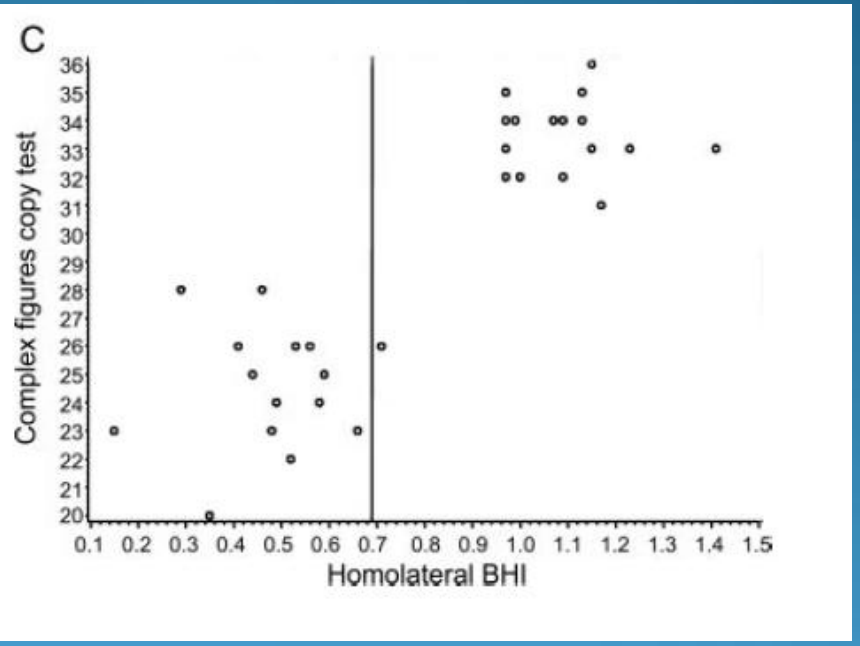
- Results: VMR% on the side of brain infarct in the PIS group with and without dementia

PIS group n=20	Mean VMR%	
without dementia n=10	43.7±29.8%	P=NS
with dementia n=10	36.4±28.5	

- Conclusion: VMR values assessed in the acute phase or late phases of stroke neither predict nor correlate with cognitive decline

Impaired VMR & Cognitive Performance in Asymptomatic Carotid Stenosis





Side of stenotic Artery: Left

Side of stenotic Artery: Right

Silvestrini M. et al. Neurology 2009;72:1062-1068

Impaired VMR & Cognitive Decline in Severe Carotid Artery Stenosis I

Table 2 Multiple linear regression model predicting decrease in Mini-Mental State Examination score

Variable	Coefficient	Standard error	t	p Value	95% Confidence interval
Pathologic breath-holding index	1.59	0.15	10.77	<0.001	1.29 to 1.88
Age	−0.01	0.15	−0.44	0.661	−0.04 to 0.02
Diabetes	0.13	0.16	0.82	0.410	0.18 to 0.45
Education	−0.03	0.02	−1.56	0.120	−0.07 to 0.01
Constant	2.03	1.06	1.92	0.056	−0.05 to 4.10

BHI<0.69<=> IMPAIRED VMR

Balestrini S. et al. Neurology 2013;80:2145-2150

Impaired VMR & Cognitive Decline in Severe Carotid Artery Stenosis II

Table 3 Logistic regression model predicting 3 points or more decrease in Mini-Mental State Examination score

Variable	Odds ratio	Standard error	z	p Value	95% Confidence interval
Pathologic breath-holding index value	14.89	5.15	7.82	<0.001	7.57-29.32
Age	0.97	0.04	−0.86	0.388	0.90-1.04
Diabetes	2.06	0.79	1.89	0.059	0.97-4.36
Education	0.99	0.05	−0.32	0.752	0.89-1.08

BHI<0.69<=> IMPAIRED VMR

Balestrini S. et al. Neurology 2013;80:2145-2150

European Journal of Neurology 2012, **19:** 1318–1324 doi:10.1111/j.1468-1331.2012.03728.x

Carotid artery plaque progression and cognitive decline: the Tromsø Study 1994–2008

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Keywords:
Alzheimer's disease, atherosclerosis, carotid plaques, cognitive function, cohort studies, dementia, vascular dementia

Received 20 November 2011
Accepted 13 March 2012

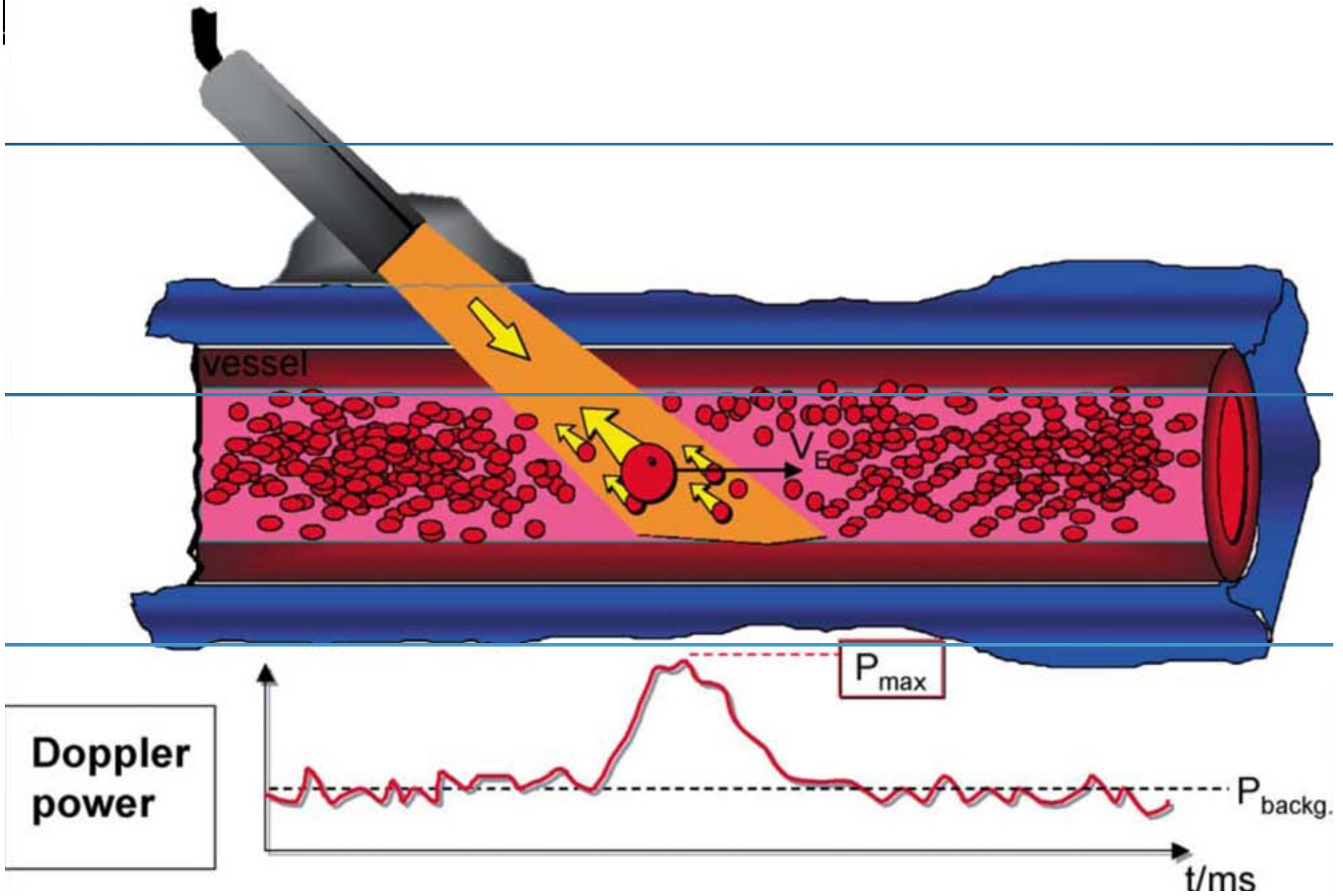
Background: Carotid atherosclerosis is a risk factor for stroke and cognitive decline, but knowledge on how progression of carotid atherosclerosis affects cognitive function in stroke-free individuals is scarce.

Methods: In the population-based Tromsø study, we calculated the change in ultrasound-assessed carotid plaque number and total plaque area from baseline (survey 4) to follow-up 7 years later (survey 5) in 4274 middle-aged stroke-free subjects. Cognitive function was assessed at follow-up by the verbal memory test, the digit-symbol coding test, and the tapping test and repeated after an additional 6 years in a subgroup of 2042 subjects (survey 6). Associations between the average of survey 4 and survey 5 plaque scores and the progression of plaque scores and cognitive test scores were assessed in regression analyses adjusted for baseline age, sex, education, depression, and cardiovascular risk factors.

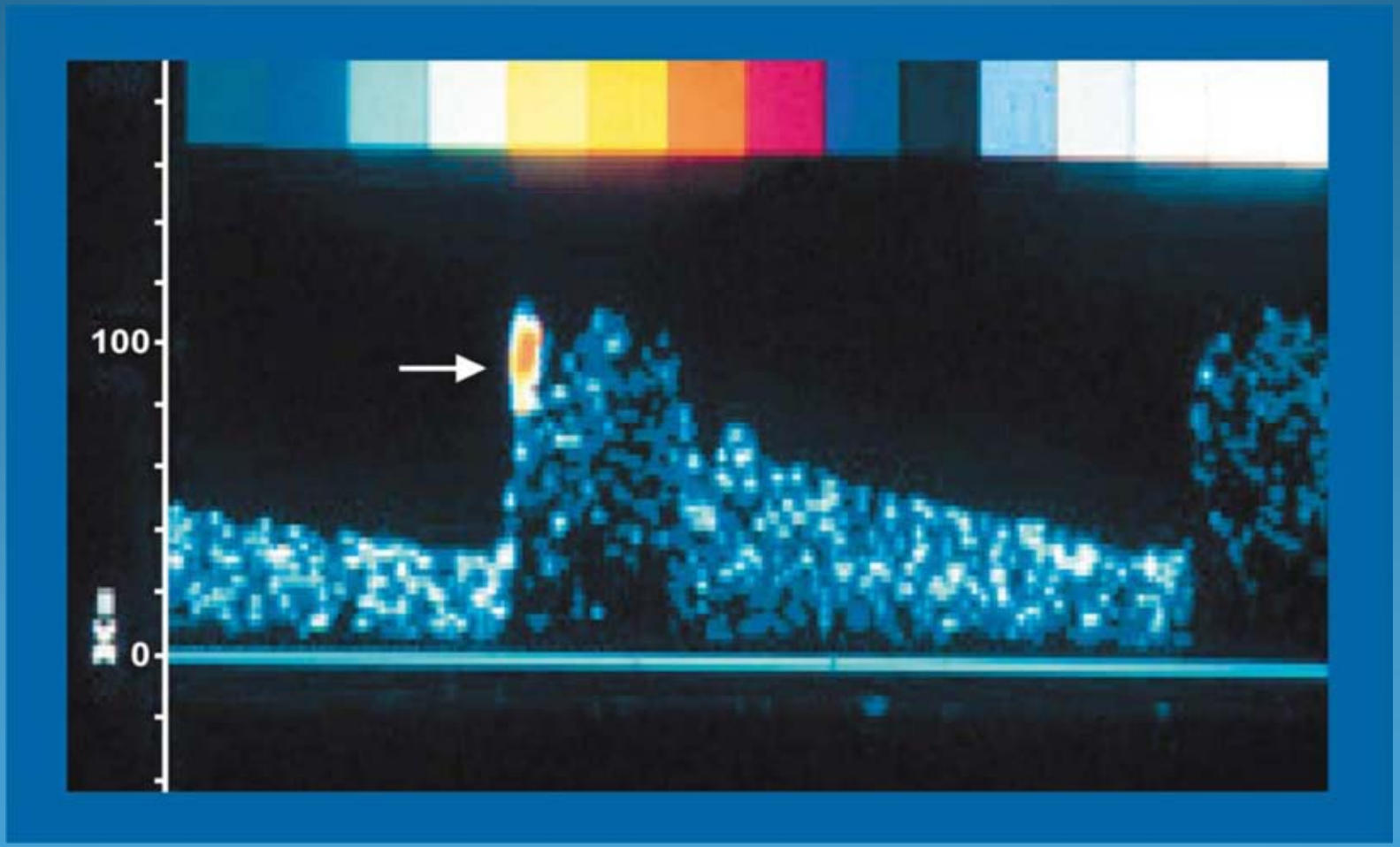
Results: Progression of total plaque area was associated with lower scores in the digit-symbol coding test (multivariable adjusted standardized β, −0.03; 95% CI, −0.05 to −0.00; $P = 0.04$) and the tapping test (β, −0.03; 95% CI, −0.06 to −0.00; $P = 0.03$). Similar results were seen for progression of plaque number. The average plaque scores were associated with lower scores in all cognitive tests (P-values ≤ 0.01). No association was found between plaque scores and cognitive decline.

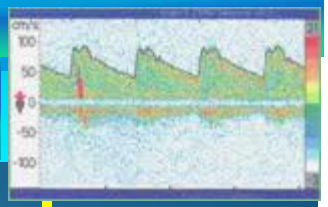
Conclusions: The average plaque scores were associated with lower scores in all cognitive tests. Progression of plaque scores was associated with lower scores in the digit-symbol coding test and the tapping test, but not with the verbal memory test or with cognitive decline.

Cerebral microembolus detection



– Fig. 2. A cerebral microembolus (arrow) passing through the middle cerebral artery during one heart cycle. Colour scale in decibels (top). Embolus (red), red blood cells (blue), Horizontal axis = time. Vertical axis = velocities (cm/sec).





The value of TCD with microemboli detection to investigate potential causes of vascular dementia

Methods of detecting potential causes of vascular cognitive impairment after coronary artery bypass grafting.

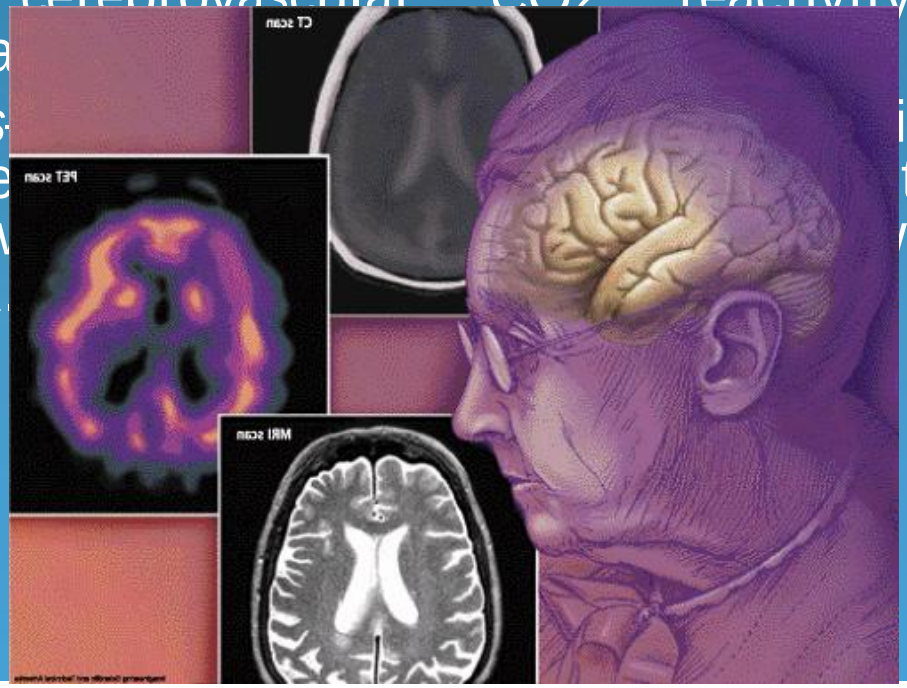
Russell D, Bornstein N.

Coronary artery bypass grafting (CABG) is the most common major surgical procedure performed worldwide. Neuropsychological deficits are frequent following CABG occurring in up to 80% in the early postoperative period, 20-50% at 6 weeks and 10-30% of patients at 6 months. Transcranial Doppler monitoring is well suited for monitoring the brain during surgery. It has been shown that both solid and gaseous microemboli are frequent during, surgery especially during clamping and declamping of the aorta. This method can also monitor cerebral hemodynamics during surgery and alert the surgical team when a fall in perfusion pressure occurs. Magnetic resonance imaging (MRI) studies have found evidence which suggests increased water content in the brain following "on-pump" CABG. New postoperative cerebral lesions have also been found in many patients using diffusion-weighted MRI.

J Neurol Sci. 2005 Mar 15;229-230:69-73. Epub 2004 Dec 23.

Changes of Cerebrovascular CO2 Reactivity During Normal Aging

- *D*uring the past decade, transcranial Doppler sonography has widely been used to assess blood flow velocities in the basal intracranial arteries and cerebrovascular reactivity (CR) to various stimuli.
- Although numerous studies have shown a decline of cerebral blood flow velocity with age, the age dependency of CR, including cerebrovascular CO2 reactivity, however, is controversia
- *Conclusions*- ing normal aging in men, whe the 4th to the 5th decades in v omen appears to enhance CR



Andreas Kastrup et al

Stroke, 1998;29:1311-1314

Cerebral Microemboli and Cognitive Impairment

- Transcranial Doppler Ultrasound (TCD) may be used to detect cerebral microemboli in patient groups with an increased stroke risk and during invasive cardiovascular examinations and operations.
- Although these microemboli do not cause immediate symptoms, there is growing evidence which suggests that they may cause cognitive impairment if they enter the cerebral circulation in significant numbers.
- This has been studied in detail in patients who have had coronary artery bypass surgery. In these patients, an association has been found between the number of intraoperative cerebral microemboli detected by transcranial Doppler and postoperative neuropsychological outcome. It is also possible that cerebral microemboli may be the cause of cognitive impairment in patients with cerebrovascular disease. Cerebral microemboli are often found in patients with atherosclerosis, especially of the carotid arteries and aortic arch, and in patients with heart disease.
- There is also an increased risk for silent strokes and cognitive impairment in these patients. Prospective clinical studies are therefore required to determine if continuous cerebral microembolization to the brain will lead to progressive cognitive impairment.

David Russell Journal of the Neurological Sciences 203–204 (2002) 211 –214

Asymptomatic Cerebral Microembolization in AD & VaD

Table 4 Spontaneous cerebral emboli (SCE)

Detection of SCE	Alzheimer's disease		Vascular dementia		All dementia	
	Cases (n=80)	Controls (n=80)	Cases (n=83)	Controls (n=83)	Cases (n=167)	Controls (n=145)
No (%) SCE positive*	32 (40)	12 (15)	31 (37)	12 (14)	65 (39)	21 (15)
Odds ratio (95% CI); P value	3.22 (1.52 to 6.81); 0.002		4.80 (1.83 to 12.58); 0.001		3.76 (2.15, 6.57); <0.001	
Adjusted odds ratio (95% CI); P value	2.70 (1.18 to 6.21); 0.019†		5.36 (1.24 to 23.18); 0.025†		3.46 (1.84, 6.52); <0.001‡	

*Numbers of case-control pairs corresponding to presence/absence of SCE: Alzheimer's disease +/+ (n=3), –/– (n=39), +/– (n=29), –/+ (n=9), discordance rate=48%; vascular dementia +/+ (n=7), –/– (n=47), +/– (n=24), –/+ (n=5), discordance rate=35%.

What is already known on this topic

Considerable overlap exists between Alzheimer's disease and vascular dementia

Vascular risk factors may be involved in the causation of both conditions

Spontaneous cerebral emboli are associated with increased risk of stroke and cognitive impairment in patients having carotid or cardiac surgery

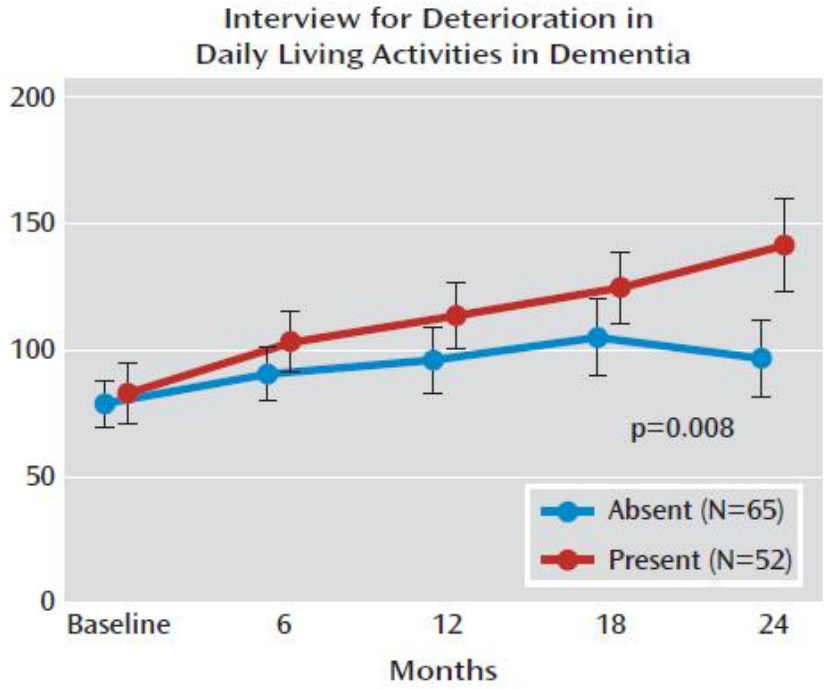
What this study adds

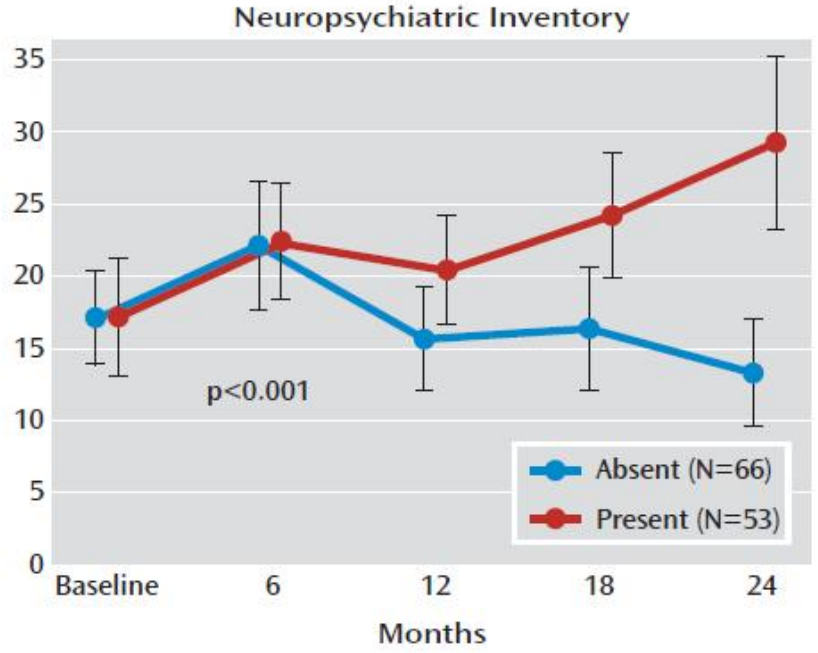
Spontaneous cerebral emboli are significantly associated with both Alzheimer's disease and vascular dementia and may be involved in the pathophysiology of both conditions

Spontaneous cerebral emboli may represent potentially preventable or treatable cause of both types of dementia

Purandare N et al. BMJ 2006;332:1119-1124

Asymptomatic Cerebral Microembolization & AD/VaD Progression





Purandare N et al. Am J Psychiatry 2012;169:300-308

Microemboli in cerebral circulation and alteration of cognitive abilities in patients with mechanical prosthetic heart valves

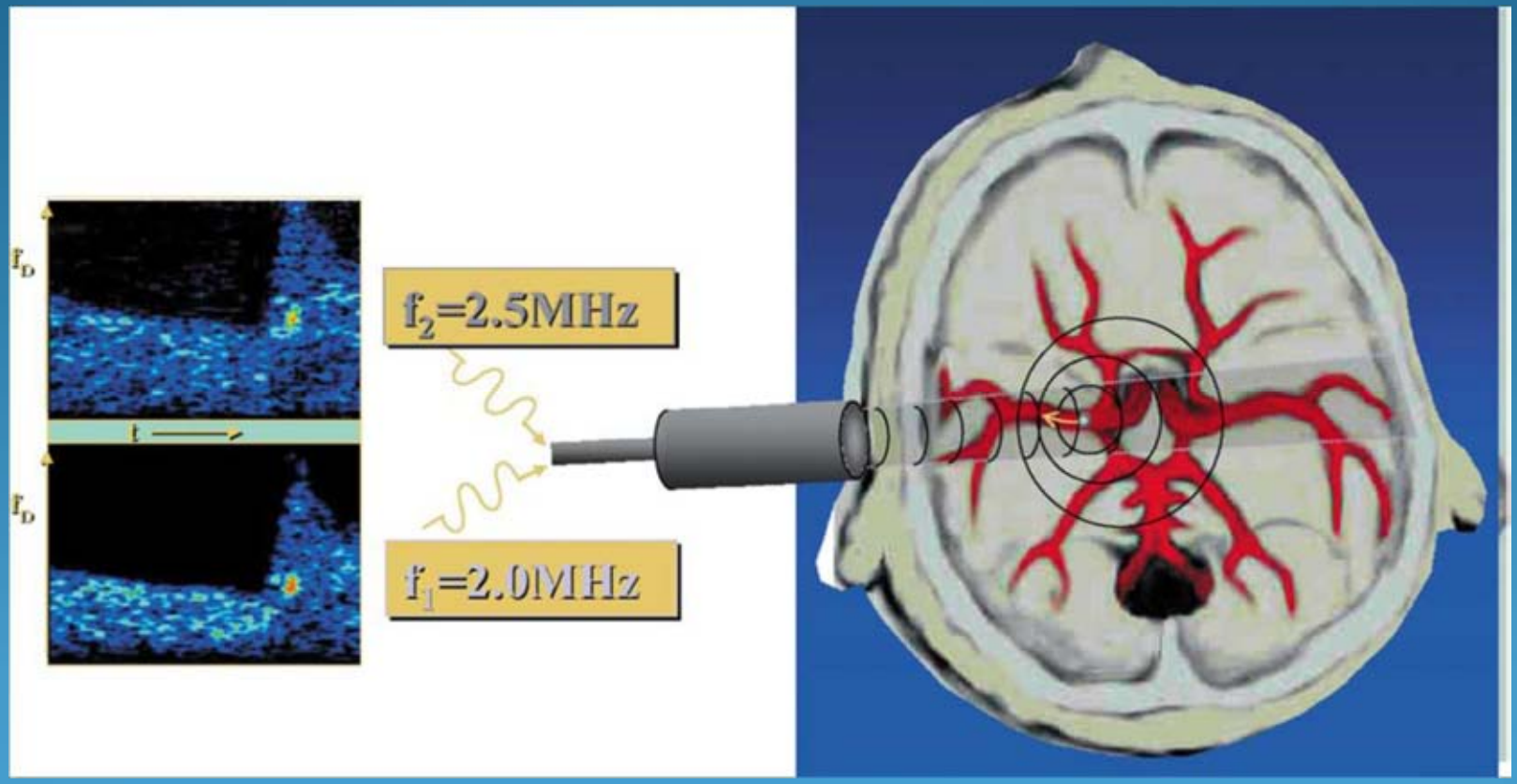
- BACKGROUND AND PURPOSE: It has been shown previously that cerebral microemboli may occur frequently in patients with a normal mechanical heart valve (MHV) without prior history of stroke. Some arguments strongly suggest that these microemboli have a gaseous origin. In other circumstances such as extracorporeal circulation or decompression in divers, it has been demonstrated that cerebral microbubbles could lead to some deterioration in cognitive functions. Therefore, we have studied attention and memory, which are among the most impaired cognitive functions as demonstrated in previous studies, in patients with an MHV.

- METHODS: Three groups of 12 volunteers each were composed of patients with an MHV and embolic signals in the cerebral circulation (group 1), patients with biological prostheses (group 2), and healthy subjects (group 3). Groups were carefully matched for age and verbal intellectual abilities. For each group, a transcranial Doppler examination was performed and a set of cognitive tests assessing sustained and selective attention and episodic and working memory was administered.

- RESULTS: The mean embolic rate was 29 per hour in patients with an MHV. No embolus was detected in the other 2 groups. Episodic memory was significantly modified in both groups 1 and 2 compared with the control group for tasks that required high-processing resources. Working memory performance was significantly decreased in MHV patients. No between-groups differences were observed for the other parameters.

- CONCLUSIONS: Alteration of episodic memory can be attributed to a long-term effect of the surgical procedure. Deterioration of working mem[illegible]he presence of cerebral microemboli in MHV patients.

Stroke. 1998 Sep;29(9):1821-6. Links



D. Russell / Journal of the Neurological Sciences 203–204 (2002) 211–214

Take Home Message

- The potential usefulness of US (TCD) in the diagnosis and management of patients with dementia has been clearly shown.
- The value of TCD in the differential diagnosis of AD and VaD is still controversial.
- Cerebral microemboli detection by TCD may be used to determine potential causes of cognitive impairment.

Classification system of CVR

Stage 0 -

CPP, CBF, CBV, OEF, MTT: N

Stage I -

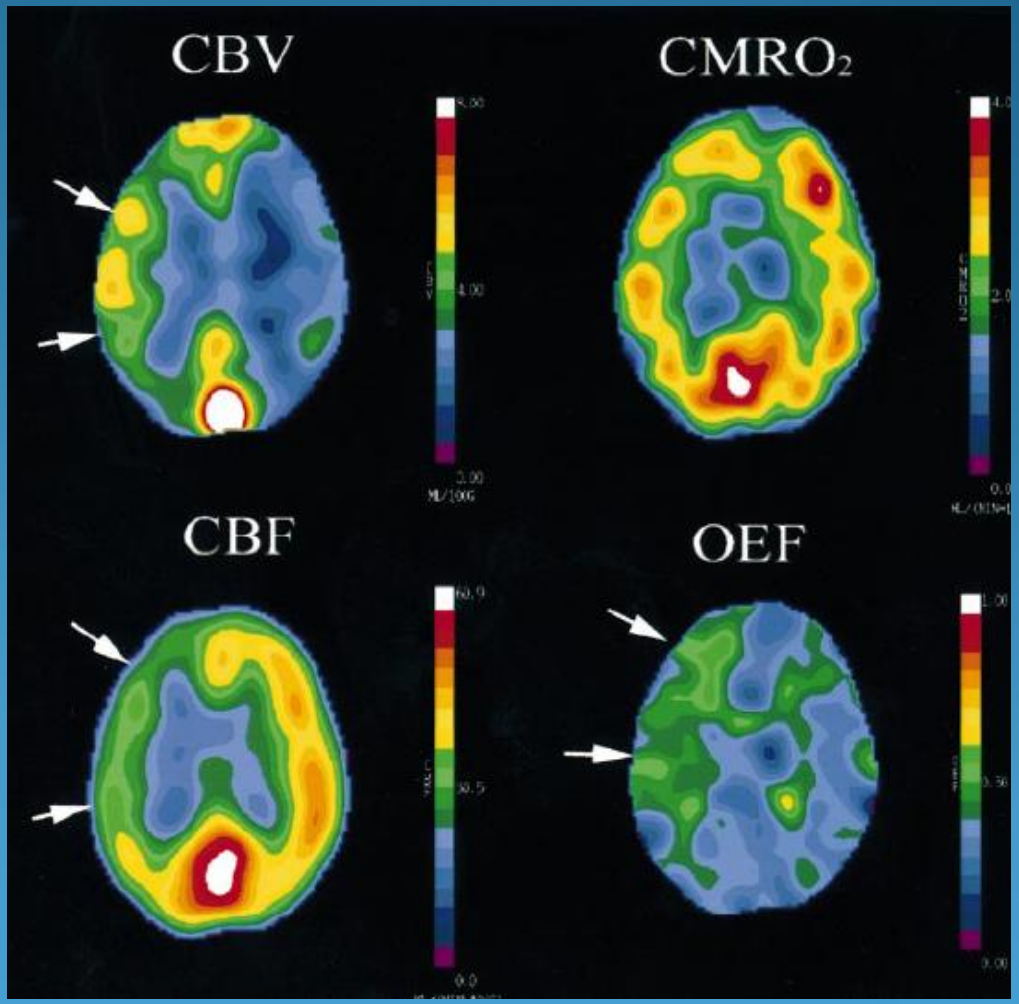
?á CPP, CBF ct, ?º CBV, ?º MTT, OEF ct

Stage II -

?áCPP, ?- CBF, ?- MTT,?- OEF

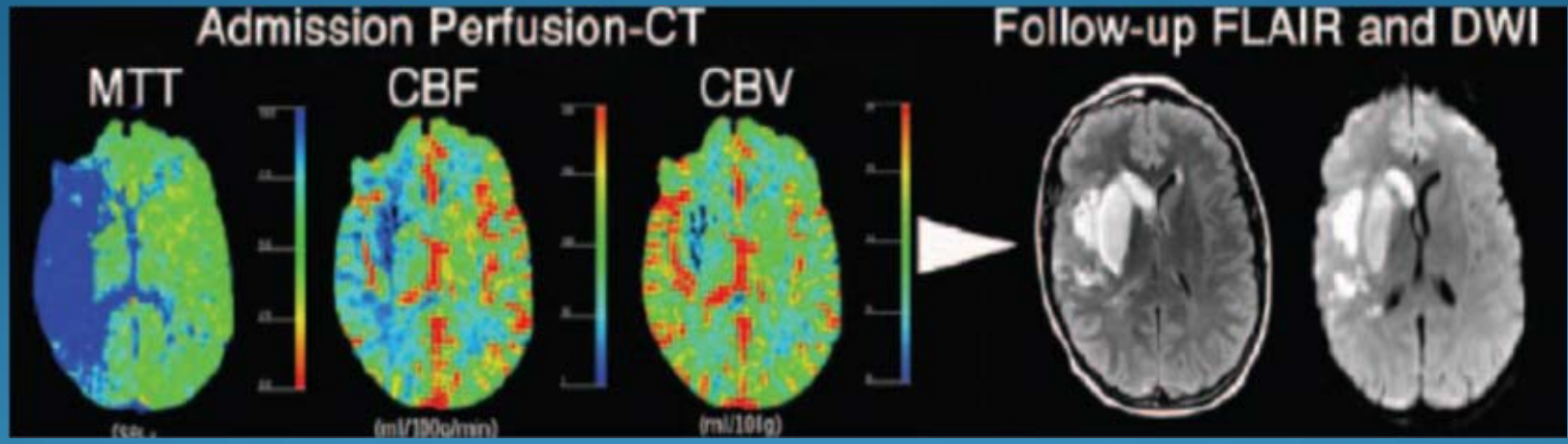
Powers WJ. Ann Neurol 1991;29:231-240
Momjian-Mayor I and Baron JC. Stroke 2005;3:567-577

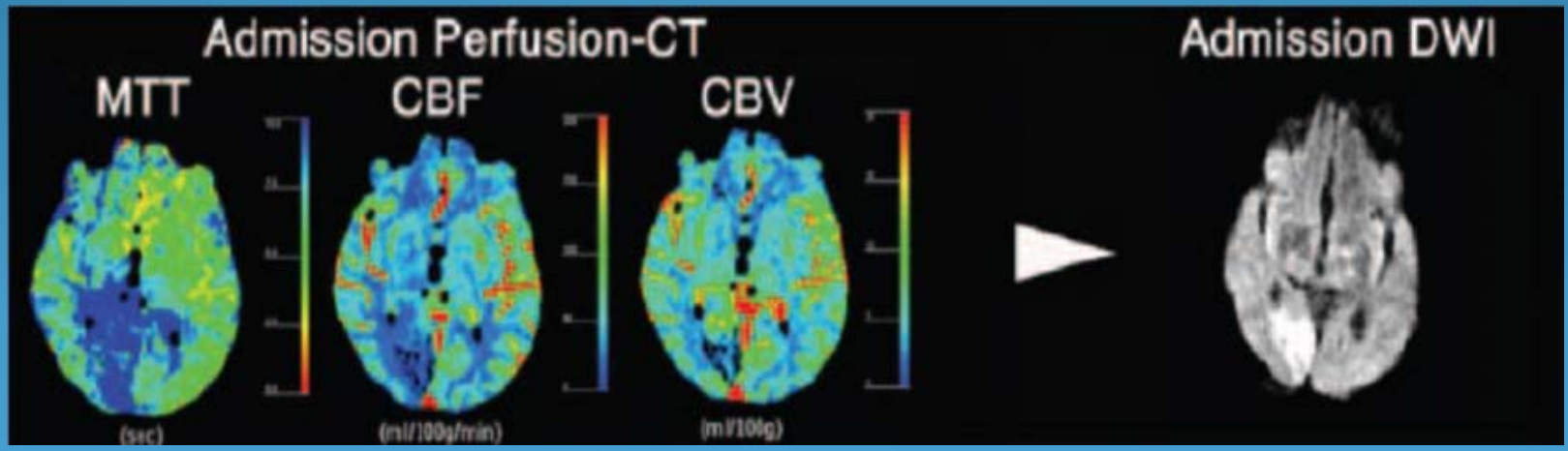
PET & Estimation of CVR



Derdeyn CP. et al. Brain 2002;125:595-607

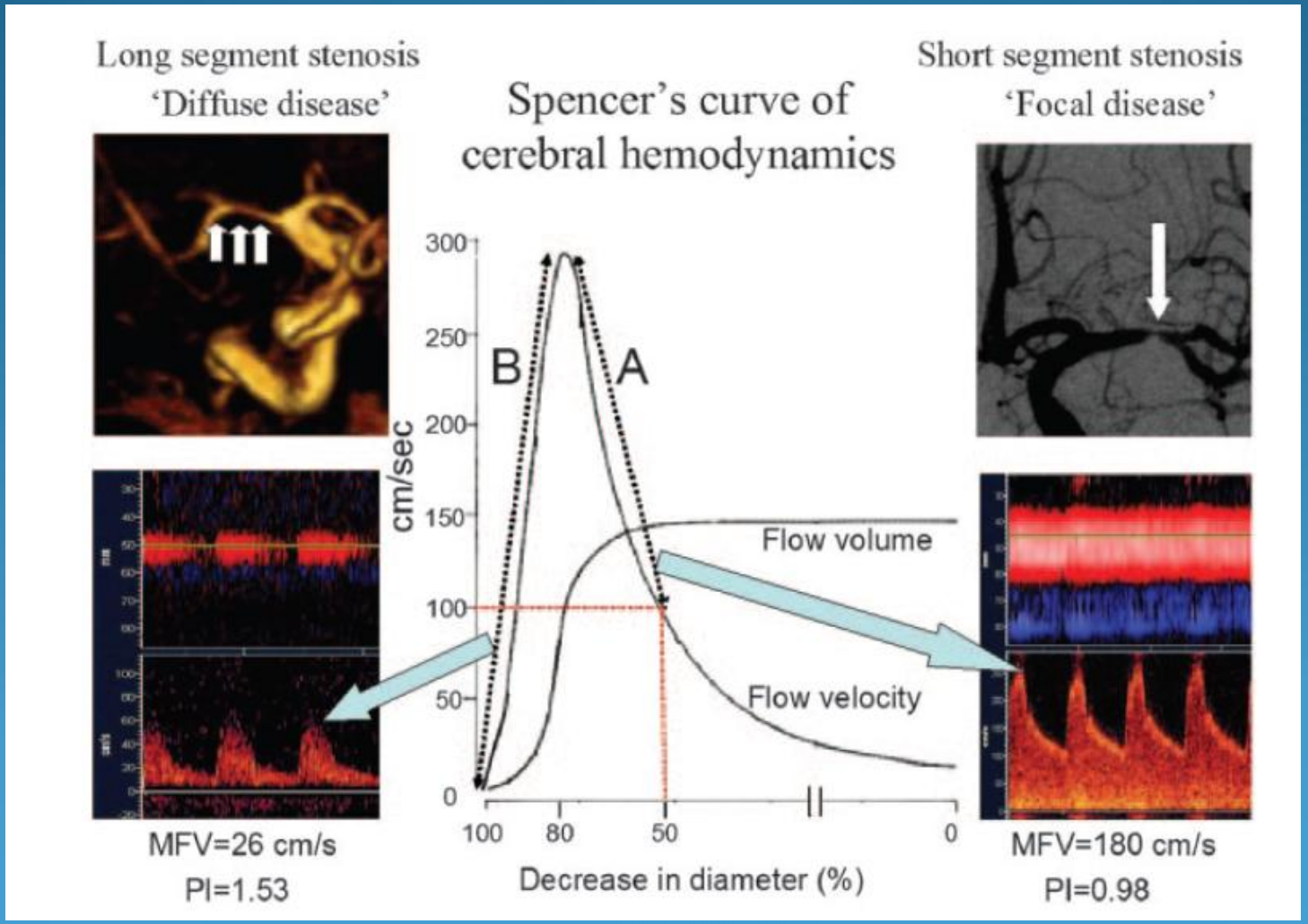
CTP & Estimation of CVR





Wintermark M. et al. Stroke 2006;37:979-985

Increased Pulsatility in ?2 Intrac/nial Arteries: Non-Invasive Marker of Diffuse Intrac/nial Atherosclerosis



Sharma VK, Tsivgoulis G et al. Stroke 2007;38:3175-3181

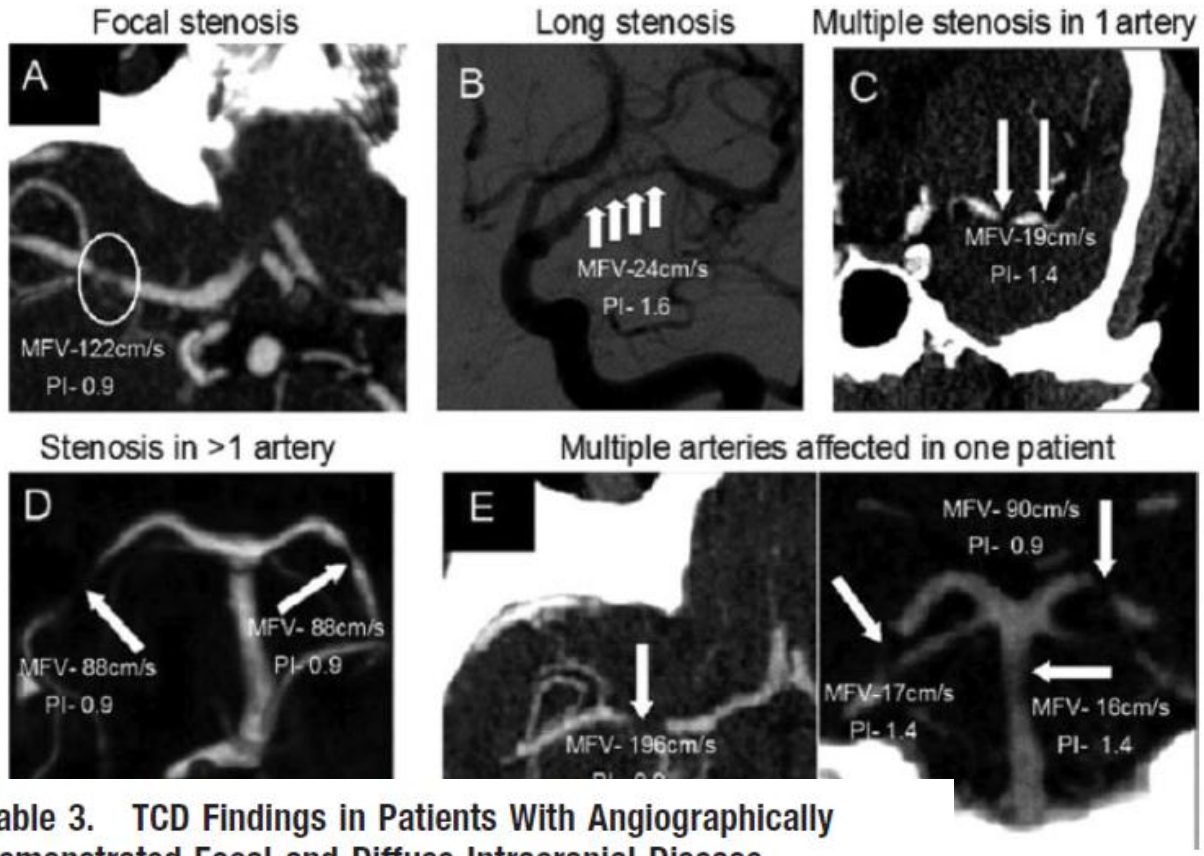


Figure 3. Spectrum of focal and diffuse intracranial lesions on contrast angiography with corresponding flow velocity and PIs. A, A focal stenosis in the M1 segment of the right MCA. B, A long (>1 cm) stenosis in the left MCA. C, Multiple segments with focal stenoses in left MCA. D, Stenoses in multiple segments of posterior circulation arteries. E, Multiple stenoses in both anterior and posterior circulation vessels.

Table 3. TCD Findings in Patients With Angiographically Demonstrated Focal and Diffuse Intracranial Disease

	Contrast Angiography	
TCD Findings	Focal Disease	Diffuse Disease
High MFV/variable PI	67%	21%
Low MFV/high PI	13%	58%
Normal MFV and PI	20%	21%

Fisher exact test=8.593, df=2, P=0.014.

Sharma VK, Tsivgoulis G et al. Stroke 2007;38:3175-3181

CEREBRAL MICROEMBOLIZATION & TCD

TCD can reliably detect in real-time asymptomatic embolic signals (ES) in cerebral circulation (HITS)

Asymptomatic cerebral embolization can be detected by TCD in 7%-71% of pts with AIS

Prevalence of ES : LAA>CE>LAC

ES predict recurrent stroke risk in acute stroke, symptomatic carotid stenosis and post-operatively after CEA or CABG.

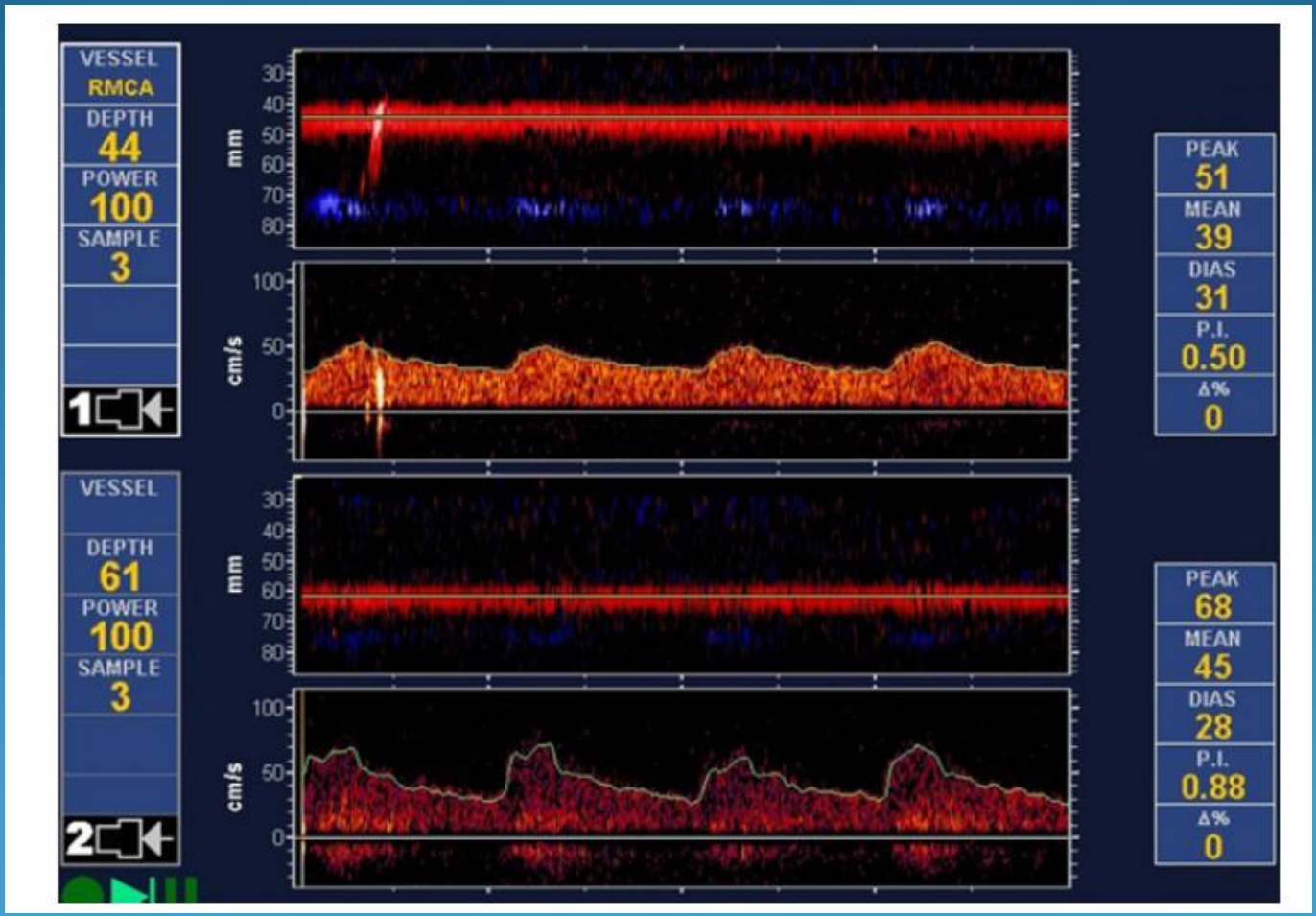
ES predict cognitive decline post-operatively after CEA or CABG

ES predict first-ever stroke risk in patients with asymptomatic carotid stenosis

ES have been used for risk stratification and assessment of therapeutic efficacy in the former conditions

Markus & Mackinnon. Stroke 2005;36:971-975

Markus et al. Lancet Neurology 2010;9:663-671



Tsivgoulis G. et al. Stroke 2012;43:1957-1960