XXI CORSO NAZIONALE DI ULTRASONOLOGIA VASCOLARE DIAGNOSI E TERAPIA

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PREMIO LEONE POLI – I GIOVANI NELLA RICERCA

"Alterazione Della Reattività Vasomotoria Cerebrale Nell'ipertensione Resistente E «Non Resistente»: Il Ruolo Del Sistema Nervoso Autonomo."

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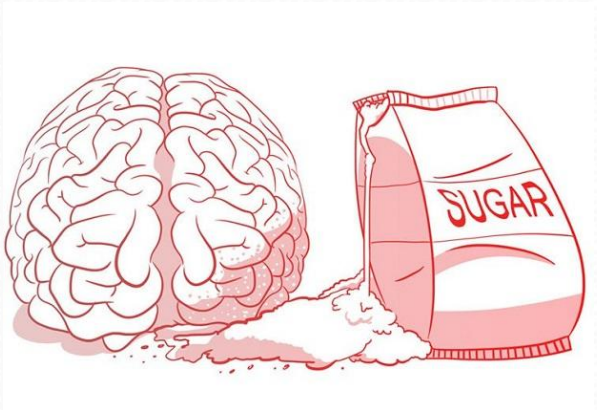
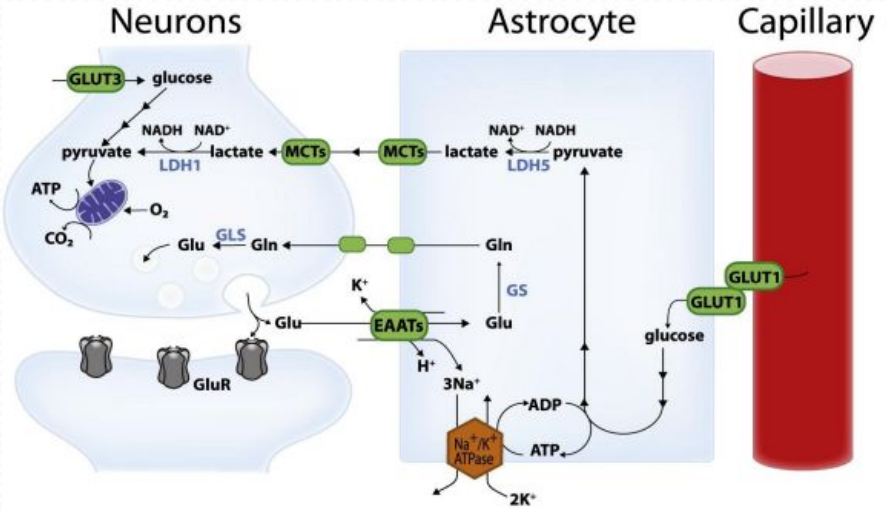
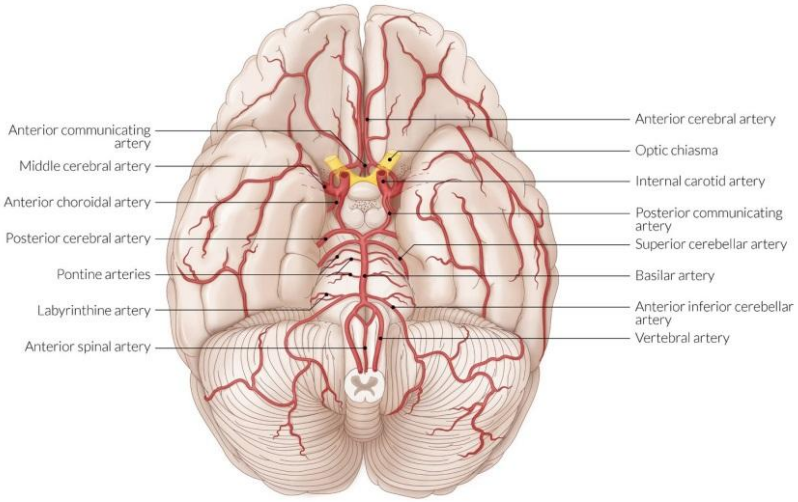
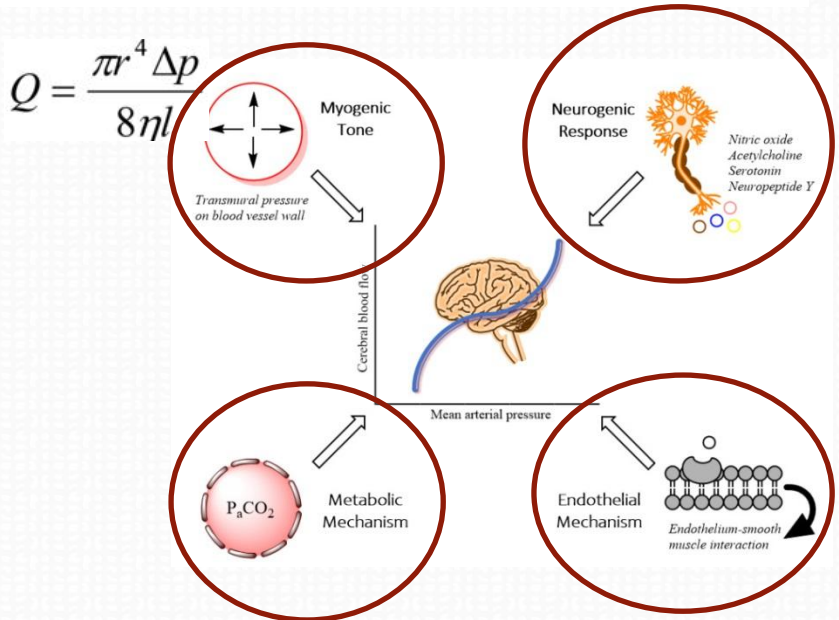
CEREBRAL METABOLISM

The human brain comprises only 2% of body weight but consumes more than 20% of oxygen and glucose at rest. The brain has no storage of oxygen and only limited storage of glycogen. It, therefore, needs a constant supply of nutrient.





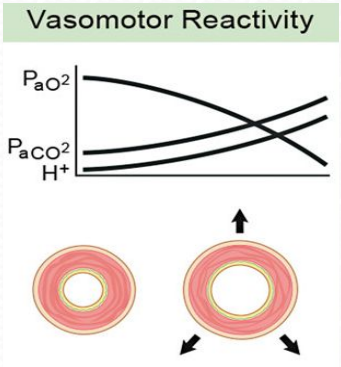




REGULATION OF CEREBRAL BLOOD FLOW

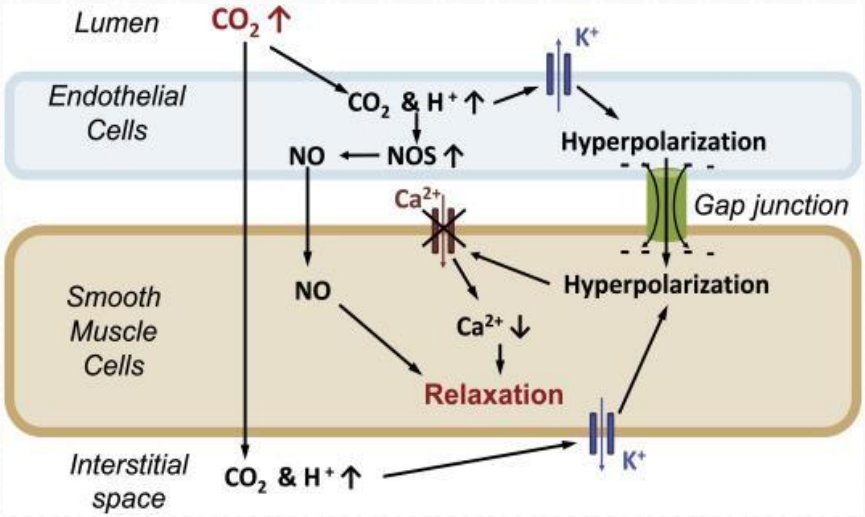
METABOLIC VASOMOTOR REACTIVITY

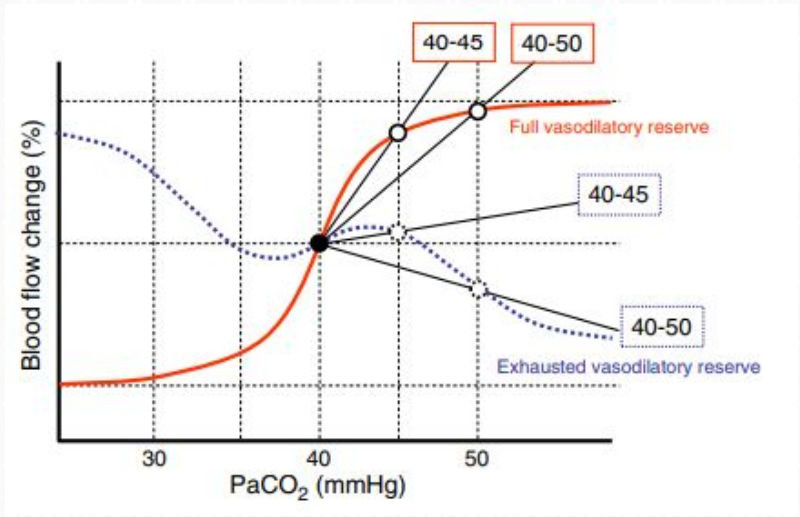
The metabolic "coupling" pathway has been described as a "feedback system," where changes in O_2, CO_2, pH, and other vasoactive substances [i.e., adenosine, nitric oxide (NO), prostanoids, and potassium ion] drive local vasodilation and increase CBF.



The highly sensitive distribution of CBF in response to changes in PaCO2 , termed cerebrovascular CO2 reactivity, is a vital homeostatic function that helps regulate and maintain central pH and, therefore, affects the respiratory central chemoreceptor stimulus. In this sense, elevations in CBF with hypercapnia "wash out" CO2 from brain tissue, thereby attenuating the rise in central PCO2

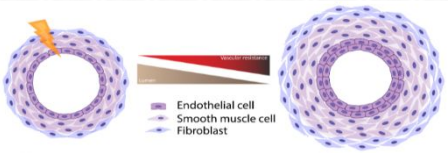
Cerebral blood flow is particularly sensitive to partial pressure of arterial CO2 as reflected in a 1-mm Hg increase or decrease from eupnoeic CO2 levels leading to a 3,6% elevation or a 1,3% reduction in CBF, respectively, for ranges of PaCO2 between 35-55 mmHg.



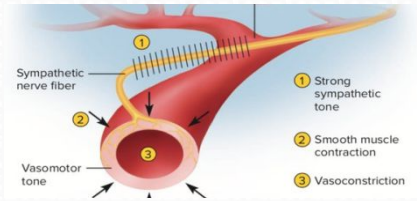


CVR IN HYPERTENSION

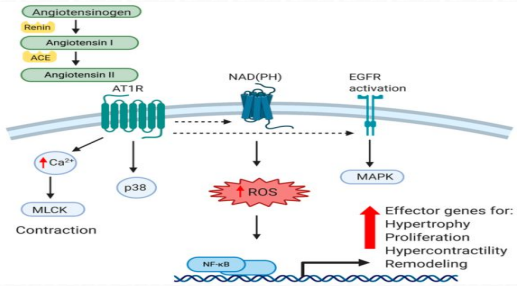
Endothelial dysfunction



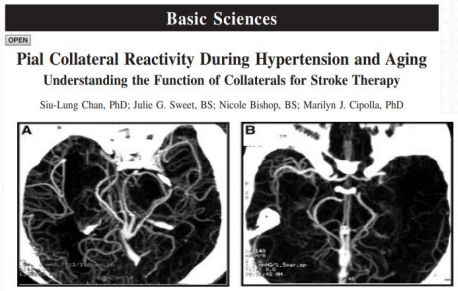
Hyperactivation of SNS



Increased levels of Angiotensine II



Lack of collateral circles



Basic Sciences

OPEN

Pial Collateral Reactivity During Hypertension and Aging

Understanding the Function of Collaterals for Stroke Therapy

Siu-Lung Chan, PhD; Julie G. Sweet, BS; Nicole Bishop, BS; Marilyn J. Cipolla, PhD

8.1 Resistant hypertension

8.1.1 Definition of resistant hypertension

Hypertension is defined as resistant to treatment when the recommended treatment strategy fails to lower office SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively, and the inadequate control of BP is confirmed by ABPM or HBPM in patients whose adherence to therapy has been confirmed.

Cerebral Vasomotor Reactivity Impairment in Resistant And Non-Resistant Hypertension: The Role Of The Autonomic Nervous System.

Subtitle: Cerebrovascular Reactivity in Resistant Hypertension

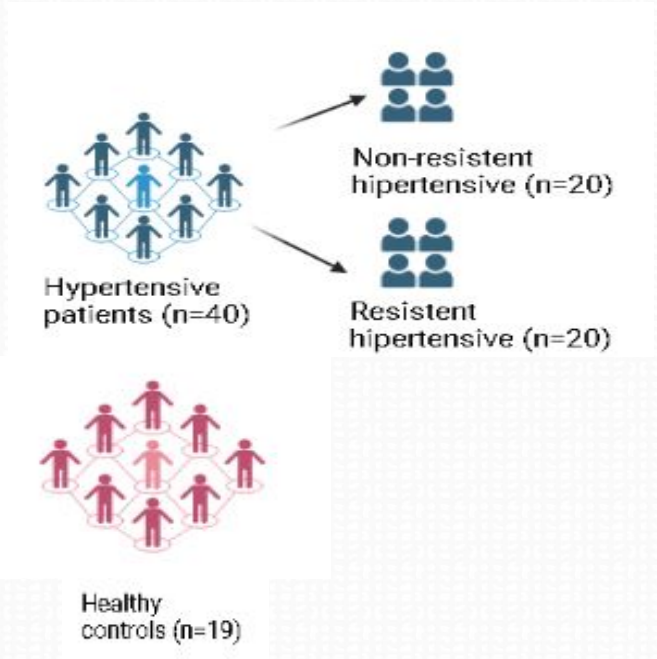
ORIGINAL ARTICLE

Giuseppe MICELI [a *], Mariachiara VELARDO [a *], Alessandra CASUCCIO [a], Maria Grazia BASSO [a], Antonino TUTTOLOMONDO [a].

Purpose: Hypertension reduces the ability of the vessel wall to constrict or dilate in response to one of many possible stimuli. Cardiovascular autonomic impairment contributes to the development of hypertension and it can influence cerebral vasomotor reactivity. Little is known about the effect of resistant hypertension.

Aim of this study is to analyze the role of sympathovagal imbalance in a cohort of patients with resistant (RH) and non-resistant hypertension (NRH) and its influence on cerebral vasomotor reactivity.

METHODS- POPULATION



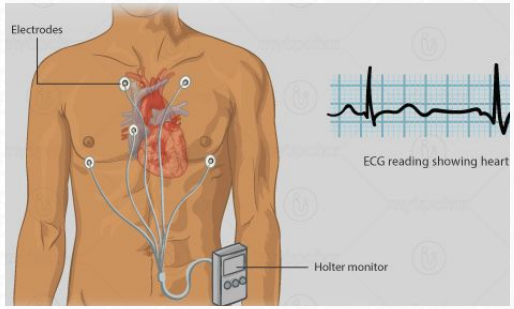
Demographic, anthropometric, clinic, echographic and echocardiographic characteristics in hypertensive patients (HP) and in health subjects (HS).

Variable	HS (n=19)		HP (n=40)		*p*
Age (years)	53,26 [37 - 73]		66,48 [40 - 83]		0,167
SBP (mmHg)	116,57		143,12		0,032
DBP (mmHg)	67,36		75,62		0,048
	n	%	n	%	
Gender	M 8 F 11	42% 58%	M 22 F 18	55% 45%	0,125
COPD	0	0	8	20%	0,036
CAD (eliminare?)	0	0	7	17,5%	0,052
CHF	0	0	9	22,5%	0,025
Previous Stroke	0	0	4	10%	0,153
CKD	0	0	8	20%	0,036
Liver disease	0	0	2	5%	0,321
Carotid atherosclerosis	6	31,5%	30	75%	0,001
Hemodinamically significant stenosis of ICA	0	0	4	10%	0,153
BHI < 0,69	0	0	16	40%	0,001
LVH	4	21%	29	72,5%	<0.0001
Altered diastolic function	6	31,5%	30	75%	0,001

Esclusion criteria:

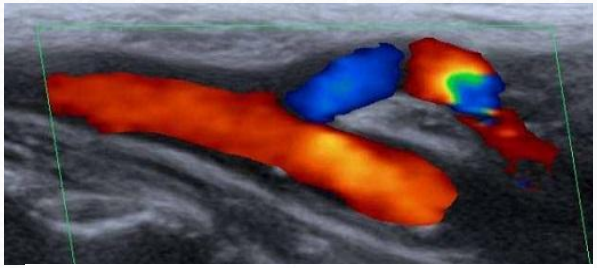
Persistent supraventricular arrythmias, acute heart failure, acute and recent ischemic heart disease, severe chronic kidney disease, type 2 diabetes mellitus, acute stroke, occlusion or subocclusion of internal carotid artery or other intracranial vessels, respiratory failure, OSAS, secondary hypertension, poor adherence to treatment.

METHODS-MEASUREMENTS

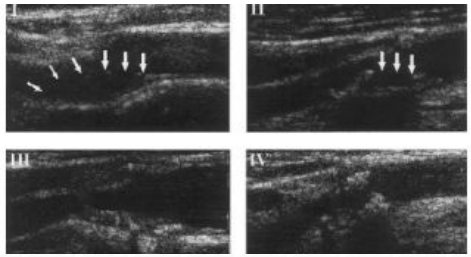


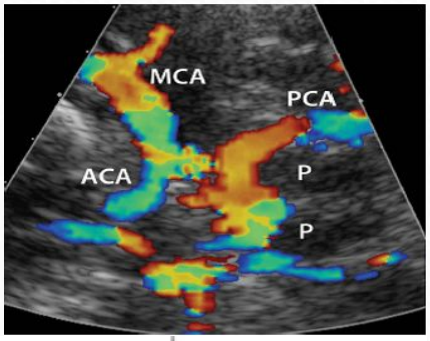
HRV MEASURES OF TIME DOMAIN

SDNN ms
pNN50%
RMSSD ms
ASDNN ms
SDANN ms

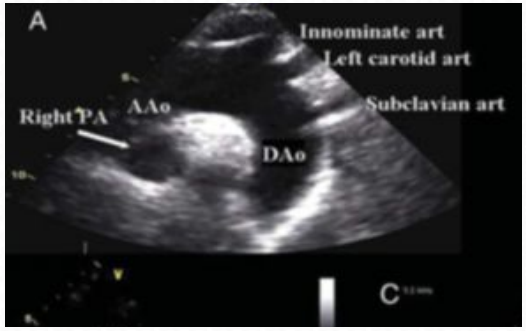


GRAY WEALE CLASSIFICATION





TRANSCRANIAL DOPPLER ULTRASOUND



TRANSCUTANEOUS DETECTION OF ARCH AORTIC ATHEROMAS BY SUPRASTERNAL HARMONIC IMAGING

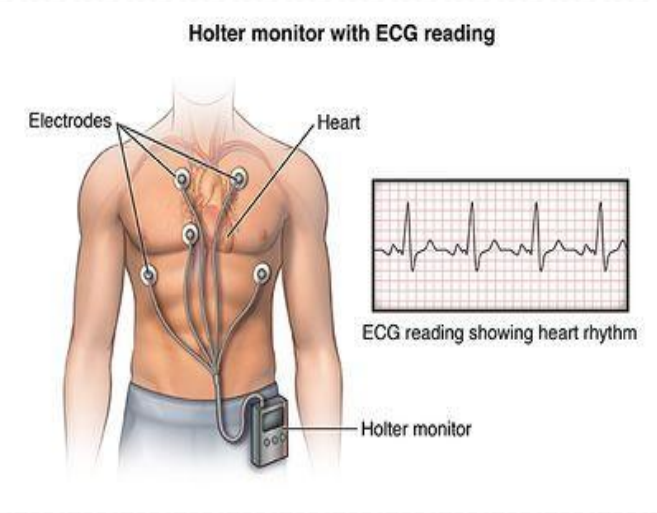
French Study Of Aortic Plaques In Stroke Group's Classification

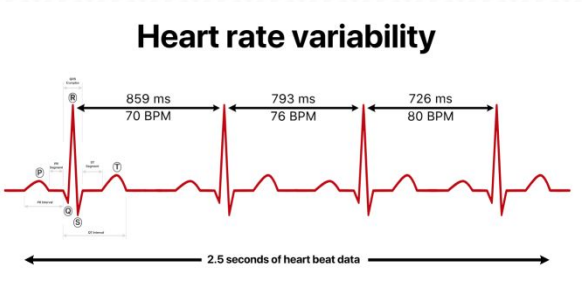
Tiype 1: lack of significant atherosclerotic lesions
Tipe 2: arch aortic atheromas < 3,9 mm
Tiype3: arch aortic atheroma ≥ 4mm o < 4 mm with flottant component

METHODS-MEASUREMENTS

EVALUATION OF AUTHONOMIC IMBALANCE

Heart rate variability (HRV) reflects beat-to-beat changes in RR intervals, which are related to the ongoing interplay between two arms of the autonomic nervous system (Task Force, 1996, Kleiger et al., 2005, Bilchick and Berger, 2006, Lahiri et al., 2008).





Time-domain analysis

Variable	Units	Description
SDNN	ms	Standard deviation of all normal-to-normal (NN) intervals
SDANN	ms	Standard deviation of the averages of NN intervals in all 5 minute segments of the entire recording
RMSSD	ms	Square root of the mean of the sum of the squares of differences between adjacent NN interval
pnn50	%	Percentage difference between adjacent NN intervals that are greater than 50 ms

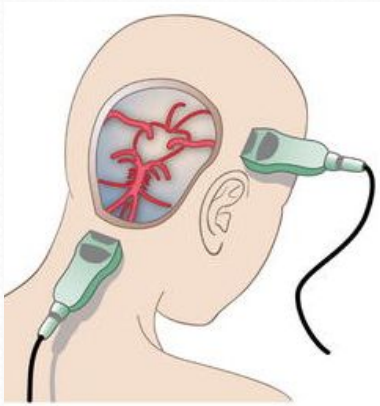
Frequency-domain analysis

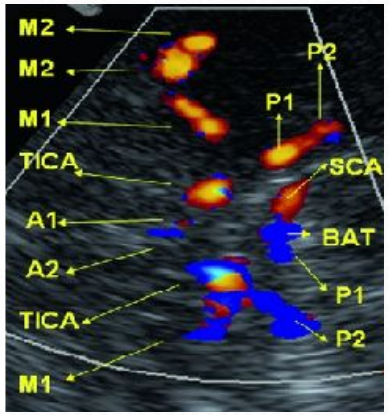
Total power	ms^2	Variance of all NN intervals < 0.4 Hz
ULF	ms^2	Ultra low frequency < 0.003 Hz
VLF	ms^2	Very low frequency < 0.003–0.04 Hz
LF	ms^2	Low frequency power 0.04–0.15 Hz
HF	ms^2	High frequency power 0.15–0.4 Hz
LF/HF	Ratio	Ratio of low–high frequency power

METHODS-MEASUREMENTS

EVALUATION OF CEREBROVASCULAR REACTIVITY

TCD to measure CBF velocity (typically using the middle cerebral artery) has become a popular technique to measure dynamic cerebral blood flow evaluation.

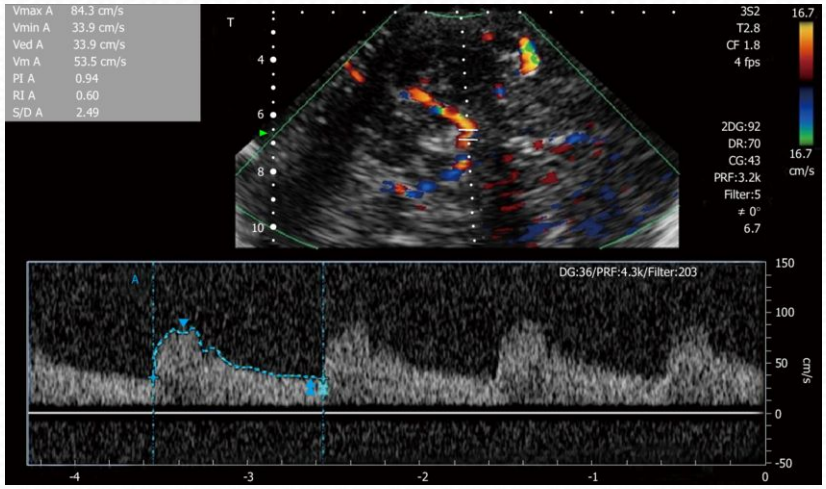




Artery	Window	Depth, mm	Direction	MFV, cm/s
MCA M1 (M2)	Temporal	40-65		<80
ACA A1	Temporal	62-75		<80
PCA	Temporal	60-68		<50
ICA Siphon	Orbital	60-64		<70
OA	Orbital	50-62		Variable
BA	Suboccipital	80-100		<60
VA	Suboccipital	45-80		<50

Breath-Holding Index

The BHI was obtained according to a previously reported protocol.[4] Once stable baseline velocities and CO_2 measurements were obtained, subjects were instructed to hold their breath for 30 seconds after a normal inspiration (to avoid a Valsalva maneuver). Mean flow velocities were then recorded. BHI was calculated by dividing the percentage increase of time-averaged mean flow velocity (MFV) after breath-holding by seconds of apnea. We considered values of BHI <0.69 as impaired.[4]



RESULTS

BHI and HRV measures of «time-domain» mean values comparison between healthy subjects (HS) and hypertensive patients (HP).

	HS (n=19)	HP (n=40)	p
BHI	**1,32 ± 0,41**	**0,92 ± 0,65**	**0,018**
SDNN ms	**137,87 ± 27,5**	**108,44 ± 26,48**	**<0,0001**
SDANN ms	**125,76 ± 24,96**	**87,65 ± 20,63**	**<0,0001**
PNN50%	12,28 ± 9,61	13,75 ± 16,77	0,723
ASDNN ms	57,67 ± 17,48	62,70 ± 28,33	0,480
RMSSD ms	45,36 ± 26,47	55,81 ± 43,60	0,341

BHI and HRV measures of frequency domain mean values comparison between non-resistant hypertensive patients (NRH) and resistant hypertensive patients (RH).

	NRH (n=20)	RH (n=20)	p
BHI	**1,15 ± 0,65**	**0,70 ± 0,58**	**0,027**
SDNN ms	**118,48 ± 26,01**	**98,41 ± 23,47**	**0,015**
SDANN ms	**95,09 ± 22,12**	**80,21 ± 16,36**	**0,021**
PNN50%	11,75 ± 12,54	15,76 ± 20,30	0,457
ASDNN ms	60,83 ± 28,75	64,57 ± 28,51	0,682
RMSSD ms	53,89 ± 40,72	57,73 ± 47,28	0,785

RESULTS

	BHI > 0.69 (n=24)	BHI < 0.69 (n=16)	p
SDNN ms	112,53 ± 24,74	102,31 ± 28,61	0,236
SDANN ms	91,06 ± 20,07	82,53 ± 21,03	0,204
PNN50%	9,79 ± 11,54	19,70 ± 21,56	0,067
ASDNN ms	59,88 ± 27,37	66,93 ± 30,09	0,448
RMSSD ms	51,49 ± 34,85	62,29 ± 54,82	0,450

Comparison of HRV parameters between the subgroup of patients with severe dysfunction of cerebral hemodynamic autoregulation and the subgroup of patients with minor dysfunction.

Variable	BHI > 0.69 (n=24)		BHI < 0.69 (n=16)		
	n	%	n	%	p
COPD	5		3		0,872
CAD	1		6		**0,007**
CHF	3		6		0,064
Previous Stroke	1		3		0,132
CKD	6		2		0,333
Liver disease	1		1		0,767
Carotid atherosclerosis	16		14		0,136
Hemodinamically significant stenosis of ICA	2		2		0,667
Grey-Weale 1-2	0		3		**0,027**
Grey-Weale 3-4	15		13		0,205
Aortic arch arherosclerosis	6		6		0,398
LVH	17		12		0,772
Altered diastolic function	18		12		1

Comparison of clinical characteristics between minor and severe dysfunction of cerebral hemodynamic autoregulation in hypertensive patients.

Correlation between HRV parameters and clinical characteristics

NRH patients

		SDNN ms	SDANN ms	PNN5 0%	ASDNN ms	RMSSD ms
Age	**p**	0,633	**0,022**	0,605	0,769	0,264
	R	-0,114	**-0,509**	-0,123	-0,070	0,262
COPD	**p**	0,354	0,354	0,868	0,271	0,201
	R	0,219	0,219	-0,040	0,259	0,299
CAD	**p**	0,959	0,383	0,506	0,506	0,799
	R	-0,012	-0,206	0,158	0,158	-0,061
CHF	**p**	0,879	0,879	0,382	0,442	0,574
	R	-0,036	-0,036	0,206	0,182	0,134
Previous Stroke	**p**	0,233	0,647	0,158	0,278	0,799
	R	0,279	0,109	0,328	0,255	0,061
CKD	**p**	0,077	0,103	0,268	0,216	0,464
	R	-0,405	-0,376	-0,260	-0,289	-0,173
Carotid atherosclerosis	**p**	0,874	0,937	0,154	0,524	0,781
	R	0,038	0,019	0,331	0,151	0,066
Aortic arch atherosclerosis	**p**	0,585	1	0,358	0,465	0,229
	R	0,130	0,000	-0,217	-0,173	0,282

RH patients

		SDNN ms	SDANN ms	PNN5 0%	ASDNN ms	RMSSD ms
Age	**p**	0,457	**0,007**	0,114	0,157	0,104
	R	0,176	**-0,581**	0,365	0,329	0,374
COPD	**p**	0,467	0,970	0,261	0,172	0,261
	R	-0,173	0,009	-0,264	-0,318	-0,264
CVD	**p**	0,071	0,585	0,025	0,134	0,056
	R	-0,412	-0,130	-0,499	-0,347	-0,434
CHF	**p**	**0,035**	0,142	0,424	0,634	0,524
	R	**-0,473**	0,341	-0,189	-0,114	-0,151
Previous Stroke	**p**	0,201	0,450	0,934	0,145	0,934
	R	-0,298	-0,179	-0,020	-0,338	-0,020
CKD	**p**	0,225	0,068	0,044	0,751	0,296
	R	0,284	0,416	-0,454	-0,076	-0,246
Carotid atherosclerosis	**p**	0,162	**0,005**	0,716	0,694	0,716
	R	-0,325	**-0,607**	-0,087	-0,108	-0,087
Aortic arch atherosclerosis	**p**	0,075	**0,041**	0,711	0,502	0,552
	R	-0,407	**-0,460**	0,088	-0,159	0,142

LIMITATIONS

- ***Small sample*** *of the population study;*
- *The* ***absence of a prospective design*** *though our population was accurately selected and we used several and precise exclusion criteria;*
- *Since we chose a cross-sectional study design,* ***associations we found cannot imply causation****;*
- *TCCD with breath holding test and Holter ECG monitoring* ***were performed during pharmacological treatment*** *but this approach was primarily used for ethical reason;*
- ***The absence of CO2 monitoring*** *during the TCCD.*

CONCLUSIONS

Resistant hypertension is associated with impairment in homeostasis of both sympathovagal balance and cerebral vasomotor reactivity. *We also found a* ***progressively affected CVR from normotensive to non-resistant and resistant hypertension****, showing a higher degree of imbalance in cerebral hemodynamic reactivity with the lowest values of BHI in comparison to non-resistant hypertensive and normotensive individuals.*

AND WHAT FOR FUTURE?

A reduction in specific heart rate variability time domain parameters (SDANN) in patients with RH could represent in the ***future an indicator for increased cardio and cerebrovascular risk*** *and could be associated with a worse prognosis.*

Autonomic imbalance and cerebral vasomotor reactivity in RH could guide clinicians toward a ***comprehensive treatment of hypertension and prevention of organ damage****.*

A reduction in HRV parameters or BHI could represent important tools to ***early identify high risk hypertensive patients****.*