

NEUROPROTECTIVE EFFECT OF ARB AND ACEI FOR HIGH BLOOD PRESSURE IN THE RETINA OF DIABETES MELLITUS TYPE 2 PATIENTS STUDIED BY MFERG

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- **introduction**

- Angiotensin II generated from angiotensin I by angiotensin-converting enzyme (ACE) induces vascular contraction and plays an important role in the regulation of blood flow.
- The renin-angiotensin system (RAS) may have a pathogenetic role at the sites of micro and macro vascular injury in diabetes.

- Major components of the RAS including angiotensin type 1 and angiotensin type 2 receptors have been identified in ocular tissues.
- There is also evidence that ACE is produced locally by vascular endothelial cells.
- Angiotensin II is a known stimulus for the expression of VEGF, which is associated with the induction of retinal neovascularisation.

- Losartan is an angiotensin receptor blocker (ARB)
- Enalapril is an angiotensin-converting enzyme inhibitors (ACEIs)
- These drugs not only control blood pressure in HBP but improve many other problems like proteinuria in diabetic nephropathy
- They are able to block vascular endothelial growth factor (VEGF) that promotes in vitro migration and tube formation of endothelial cells^{2,3} and plays a key role in hypoxia-induced angiogenesis

Context

- Diabetes is the most common cause of retinopathy and loss of vision in México
- In Mexico 50% of diabetic patients also have high blood pressure (HBP)

Description of study

- A cohort of 44 diabetic patients between 40 and 60 years of age were included.
- In the subclinical stage of diabetic retinopathy supported by fundus photograph.
- Ten or less years of diabetes mellitus.

Two groups of patients in the subclinical stage of diabetic retinopathy

23 patients were diabetic type 2

21 patients diabetic type 2 and high blood pressure:
9 were treated with enalapril and 11 with losartan

Description of study

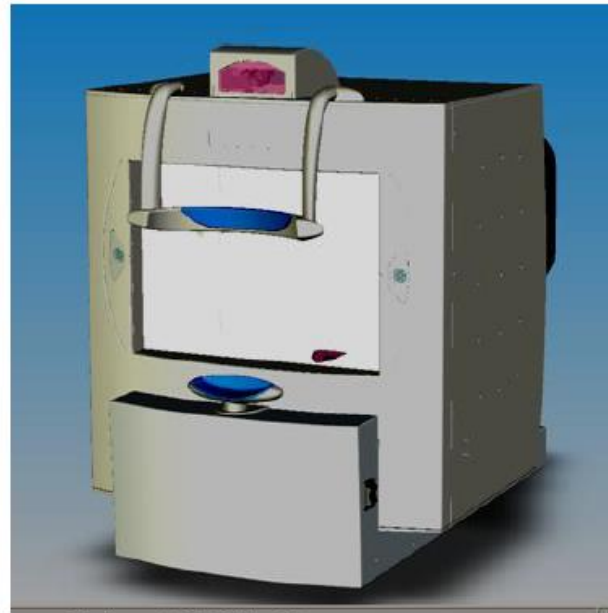
- The variables analyzed to compare their effect in the two groups were:
 - Age, gender, years of evolution, treatment, glycemia, glycosylated hemoglobin, tobacco smoking, dyslipidaemia, years of HBP, systolic and diastolic blood pressure level, recorded for three months.
- 88 eyes were evaluated by mfERG.

The mfERG was recorded with

ERG equipment
for standard electrophysiology



Compact unit for
ganzfeld, flash, pattern
and multifocal exams.



Jacques Charier - © 2012 Metrovision
Electro-retinography

Characteristics of the analysis	
5 to 7 minutes per eye	Mf photopic responses 61B
Modes of stimulation	Areas covering 25° of the retina and scaled eccentrically to stimulate an array of 61 hexagons
Hexagons modulated	with a high 200 cd/m ² luminance according to a binary m-sequence
Stimulated fields	60 degrees horizontal and 46 degrees vertical
Standard stimulation	Black/white monochrome cathode ray tube monitor with blue background to minimize rod response and maximize cone responses
Frame frequency	120 Hz to provide higher temporal resolution
Refraction	Large field lenses correction for test distance
Stimulus frequency	Set at 17 Hz to optimize the amplitude of responses
Fixation stability	Monitored with an infrared camera

ISCEV guidelines for clinical multifocal electroretinography (2007 edition) Doc Ophthalmol, 116 (2008), pp. 1–11

results

Demographic characteristics of the two groups of diabetic patients: hypertensive and normotensive

Dato		Con HTA N= 21	Sin HTA N = 23	Valor de p
Género*				
	Masculino	7 (33.3)	10 (43.5)	0.54
	Femenino	14 (66.7)	13 (56.5)	
Edad en años ⁺		53.5 (6.4)	53.3 (6.8)	0.57
Años de diabetes ⁺		7.2 (3.2)	6.1 (4.3)	0.35
Hipoglucemiantes*				
	Metformina	21 (100)	23 (100)	1.00
	Glibenclamida	21 (100)	21 (91.3)	0.48
Glucemia central	mg/dL ⁺	143.5 (48.6)	120.2 (17.1)	0.04
%Hb glucosilada ⁺		7.7 (1.4)	7.9 (1.5)	0.71
Tabaquismo*		8 (38.1)	9 (39.1)	1.00
Dislipidemia*		18 (85.7)	14 (60.9)	0.09
Años hipertenso ⁺		7 (4.5)	- -	
TAS de los últimos 3 meses mmHg ⁺		124 (15.3)	119 (7.1)	0.16
TAD de los últimos 3 meses mmHg ⁺		75.6 (8.3)	77.1 (4.7)	0.45
Agudeza visual mejor corregida OD		0.9 (0.05)	0.9 (0.05)	0.33
Agudeza visual mejor corregida OI		0.9 (0.05)	0.9 (0.05)	0.31
Presión ocular OD mmHg ⁺		13.5 (1.8)	13.5 (2.2)	0.99
Presión ocular OI mmHg ⁺		14 (1.9)	14.2 (2.2)	0.73

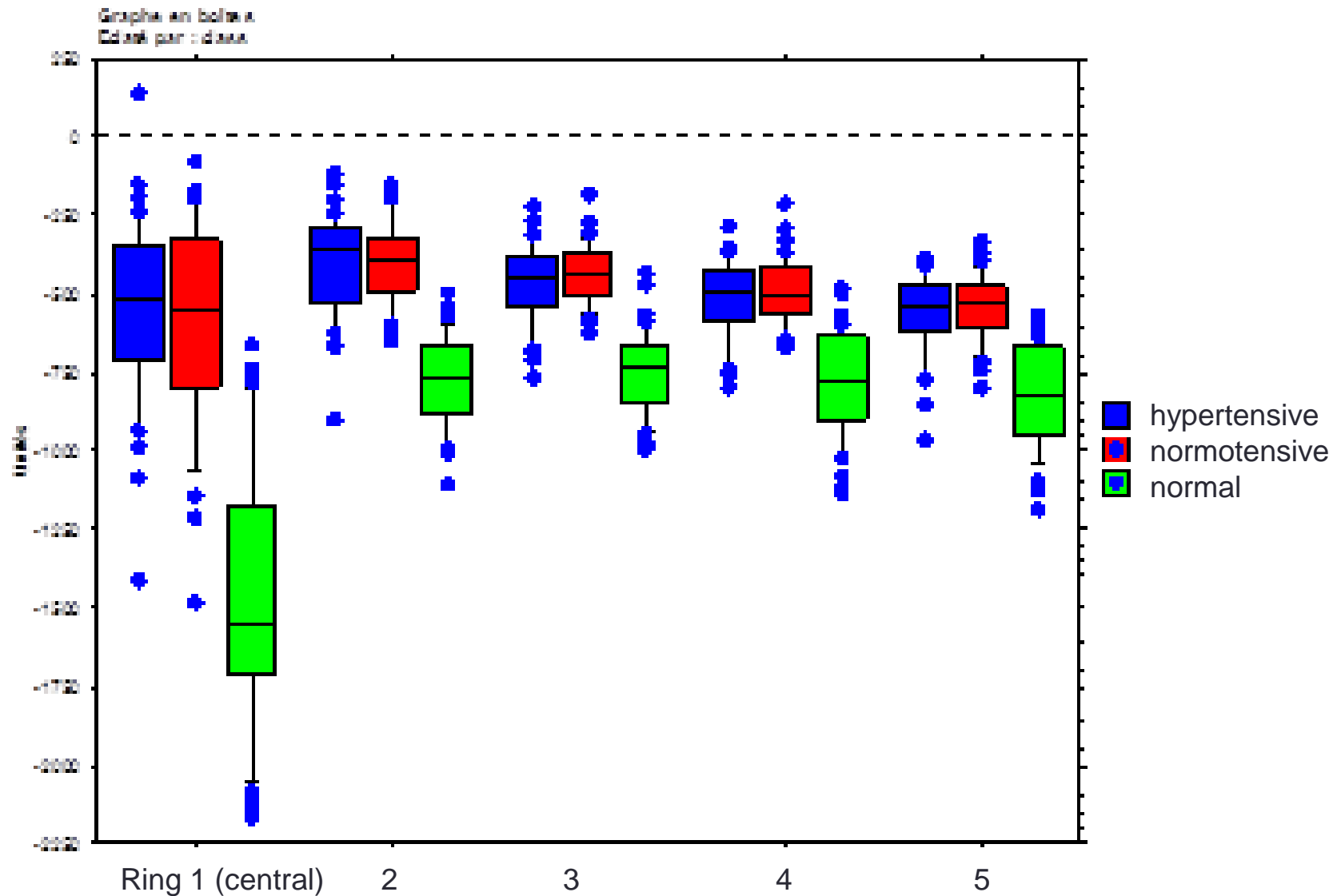
Nota: * n (%) prueba de Chi cuadrada; + media (1DS) prueba de t de student 1 cola.

Table 2. Amplitude and Implicit times of N1 and P1 in 88 eyes of diabetic patients with and without high blood pressure.

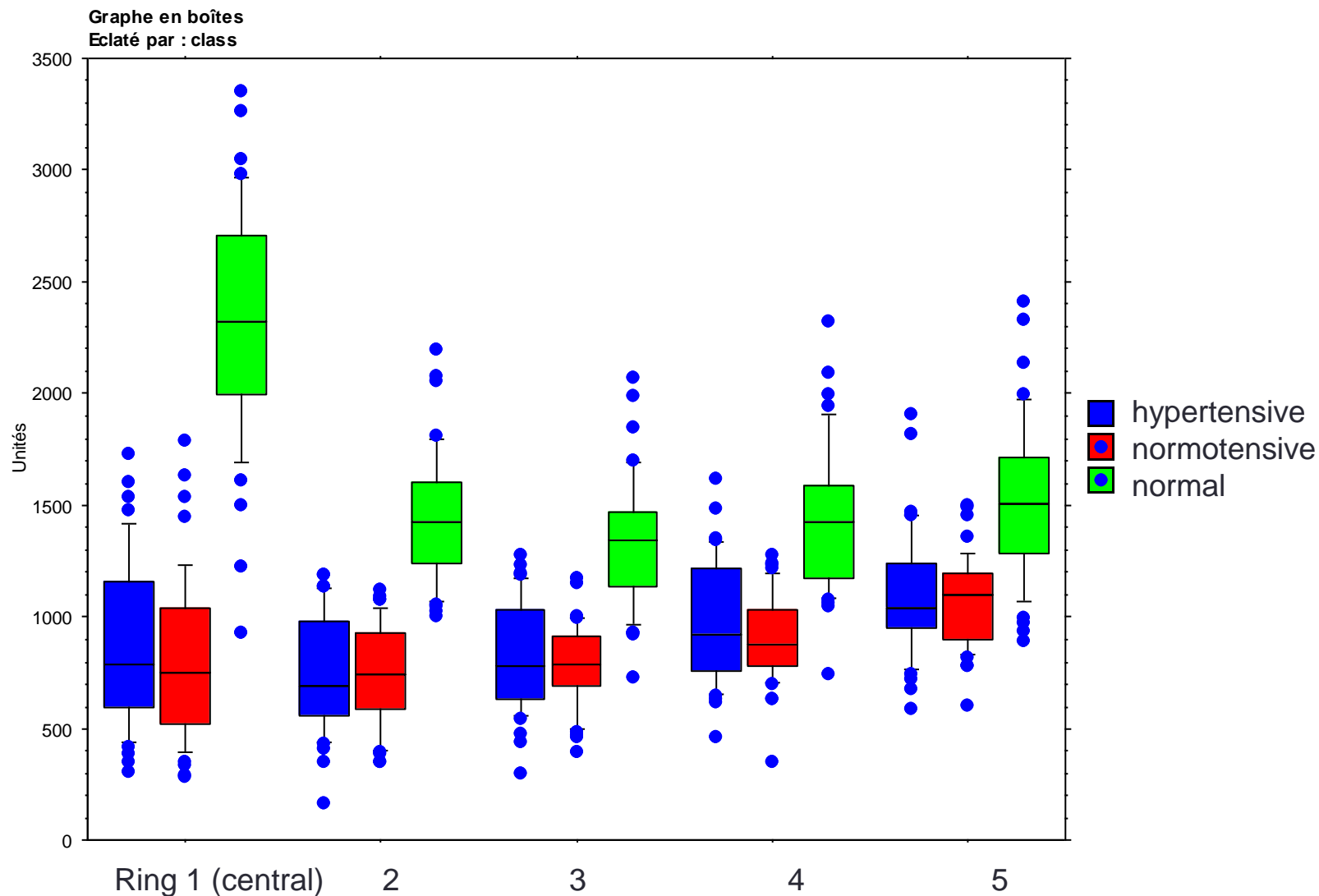
	With hypertension N= 42 ojos		Without hypertension N = 46 ojos		P value *	Normals N=10
	Average	(1 sd)	Average	(1.sd)		
N1						
Amplitude, nV/deg ²						
<2	-24.2	(15.3)	-23.1	(16.4)	0.75	-47.2
2 a 5	-19.3	(9.1)	-19.9	(7.3)	0.74	-31.1
6 a 10	-13.7	(5.0)	-13.8	(4.3)	0.92	-25.7
11 a 15	-10.5	(3.3)	-10.7	(2.7)	0.72	-21.2
>15	-8.9	(2.9)	-9.2	(2.5)	0.57	-17.6
Implicit time,ms						
<2	22.7	(6.7)	22.9	(6.8)	0.90	26.8
2 a 5	24.0	(1.8)	24.4	(1.9)	0.26	25.8
6 a 10	22.9	(1.6)	22.9	(4.0)	0.89	25.0
11 a 15	22.6	(1.5)	23.4	(1.8)	0.03	25.4
>15	22.5	(1.7)	22.8	(2.1)	0.41	25.6
P1						
Amplitude, nV/deg ²						
<2	61.5	(18.6)	51.9	(18.8)	0.04	97.8
2 a 5	51.9	(14)	49.9	(12.1)	0.29	84.0
6 a 10	39.6	(8)	36.8	(7)	0.17	71.5
11 a 15	29.9	(5)	28.1	(4.3)	0.19	55.7
>15	25.2	(3.8)	24.1	(4)	0.20	44.3
Implicit time, ms						
<2	43.4	(5.4)	37.3	(10.3)	0.01	43.0
2 a 5	43.6	(1.2)	44.1	(2.1)	0.17	43.0
6 a 10	42.5	(0.8)	42.7	(0.8)	0.17	42.7
11 a 15	41.9	(0.8)	41.9	(0.9)	0.48	42.6
>15	41.6	(0.9)	41.8	(0.9)	0.38	42.7

Note * student test

N1 wave amplitude comparison between diabetic hypertensive and normotensive patients with normal individuals



P1 wave amplitude, comparison between diabetic hypertensive and normotensive patients with normal individuals



Implicit time N1 wave (figure A) y P1 wave (figure B), comparison between diabetic hypertensive and normotensive patients with normal individuals

Figure A

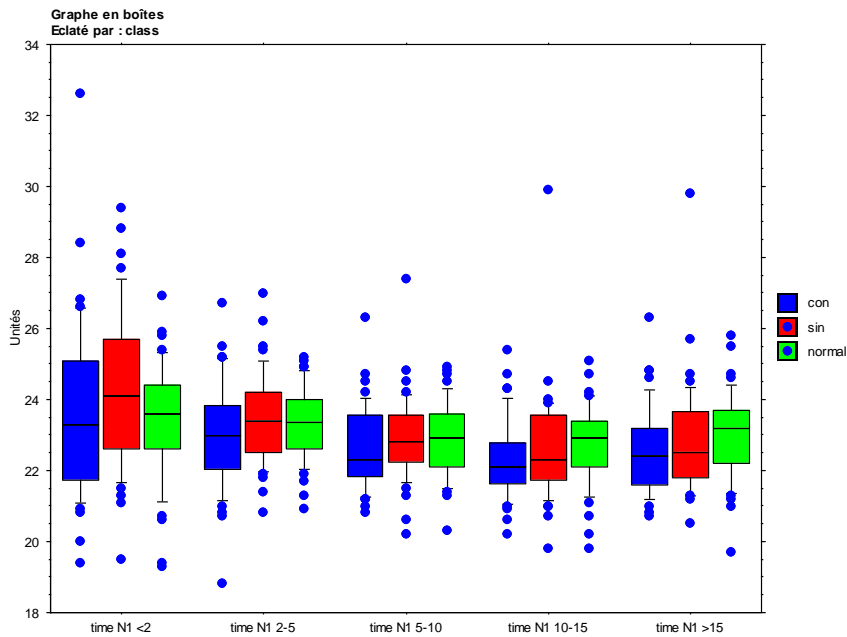
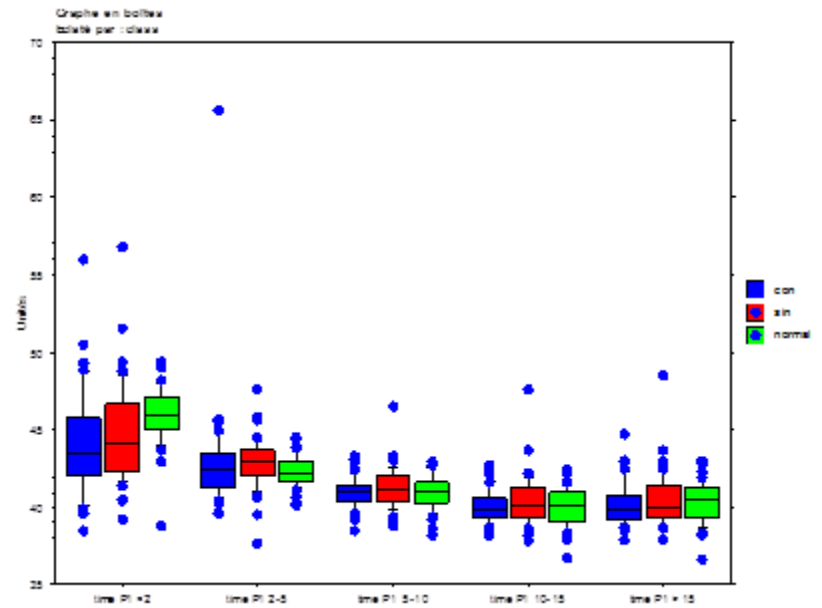


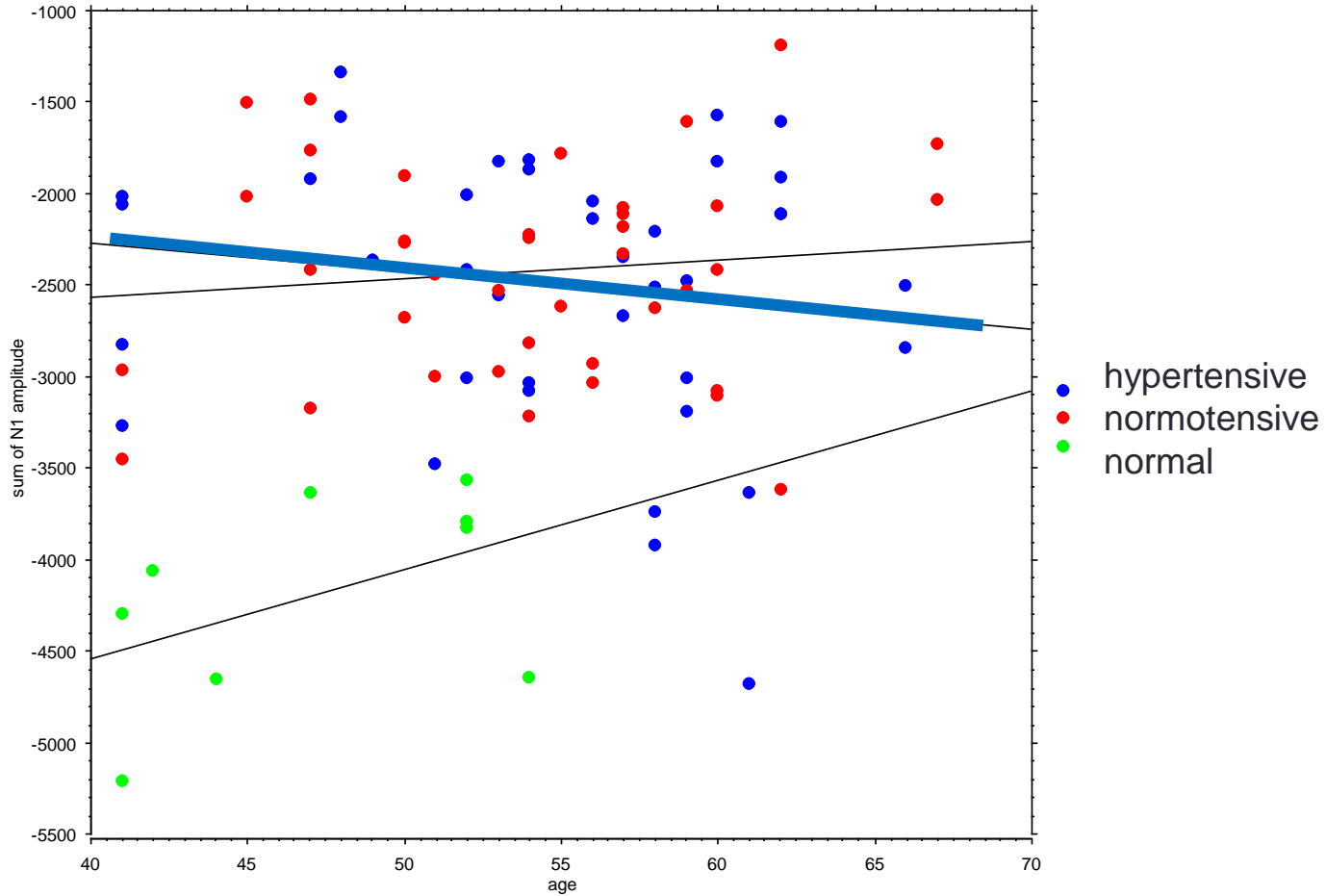
Figure B



Nuage de points avec régression

Eclaté par : class

Critère d'inclusion : only older than 40 de laluz_data.svd



N1 wave amplitude - age corrected

P1 wave amplitude (age corrected)

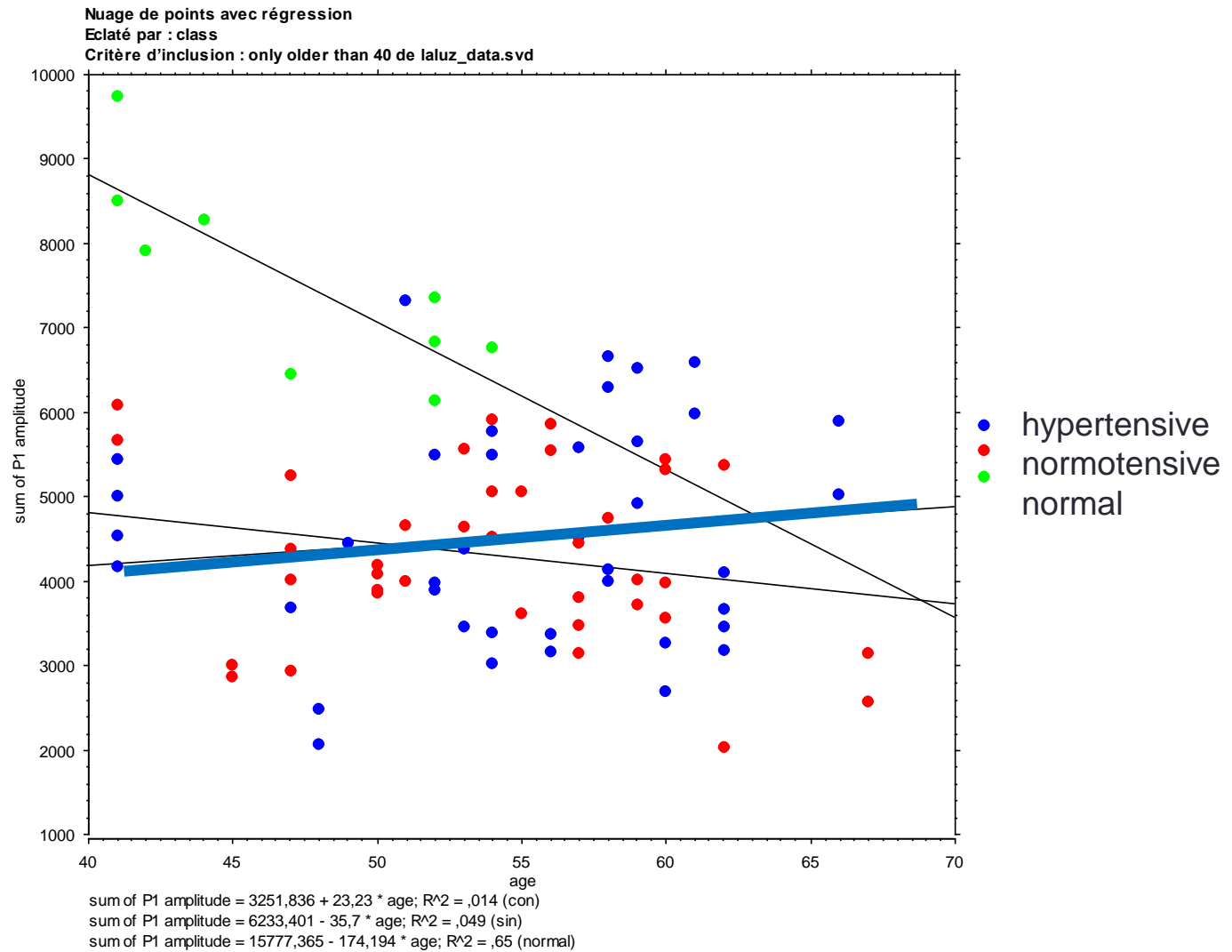


Table 3 - Multiple Linear Regression of amplitude of N1 and P1 waves for each ring.

Anillo	Coefficiente Beta para presencia HTA	Intervalo de confianza (95%)	Valor p
Onda N1			
< 2 °	-3.4	(-10.7 a 3.9)	0.35
2 a 5 °	0.38	(-3.4 a 4.2)	0.84
6 a 10°	-0.05	(-2.2 a 2.1)	0.95
11 a 15°	0.51	(-0.8 a 1.8)	0.45
>15°	0.57	(-0.6 a 1.7)	0.34
Onda P1			
< 2 °	16.7	(4.7 a 28.8)	0.007
2 a 5 °	3.2	(-5 a 11.4)	0.44
6 a 10°	3.3	(-1.8 a 8.4)	0.20
11 a 15°	1.1	(-2 a 4.2)	0.48
>15°	0.46	(-2.3 a 3.2)	0.74

Regresión ajustada con: edad en años, tiempo de evolución en años, tabaquismo (si o no), Niveles de hemoglobina glucosilada, dislipidemia (si y no) y ojo evaluado (derecho e izquierdo)

Table 4 - Multiple Linear Regression of implicit time of N1 and P1 waves for each ring.

Anillo	Coefficiente Beta para presencia HTA	Intervalo de confianza (95%)	Valor p
Onda N1			
< 2 °	-0.03	(-3.1 a 3)	0.98
2 a 5 °	-0.44	(-1.3 a 0.43)	0.31
6 a 10°	0.37	(-1.06 a 1.8)	0.60
11 a 15°	-0.79	(-1.5 a -0.05)	0.03
>15°	-0.22	(-1.08 a 0.64)	0.61
Onda P1			
< 2 °	9.3	(3.4 a 15.2)	0.002
2 a 5 °	-0.5	(-1.7 a 0.7)	0.39
6 a 10°	-0.4	(-0.9 a 0.13)	0.14
11 a 15°	0.15	(-0.4 a 0.8)	0.63
>15°	0.08	(-0.5 a 0.7)	0.77

Regression adjusting by all the exposure variables: edad en años, tiempo de evolución en años, tabaquismo (si o no), Niveles de hemoglobina glucosilada, dislipidemia (si y no) y ojo evaluado (derecho e izquierdo)

TABLE 5- Multiple Linear Regression of amplitude and Implicit time for central ring

	Coeficiente Beta estandarizados	Valor p
IMPLICIT TIME		
HAS	0.35	0.002
Years of evolution of diabetes	-0.17	0.16
Age	-0.14	0.21
Level of glycated hemoglobin	-0.08	0.49
Tobacco	-0.18	0.49
Dyslipidemia	-0.27	0.03
AMPLITUDE		
HAS	0.30	0.007
Years of evolution of diabetes	-0.26	0.03
Age	-0.13	0.23
Level of glycated hemoglobin	0.23	0.04
Tobacco	-0.17	0.15
Dyslipidemia	-0.32	0.01

Conclusions

- It has been reported before, and we proved too, that mfERG is abnormal long before clinical manifestations of diabetic or hypertensive retinopathy
- The amplitude of N1 and P1 waves decrease with age
- The biological meaning of central ring findings may implicate that the fovea has different metabolic needs, and foveal damage provokes abnormal mfERG before other retinal areas.
- In the logistic regression analysis adjusted by all the variables the HBP showed a protective effect, which might be attributed to a vascular effect of enalapril or losartan, given to treat these patients

Thank you

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