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Atrial Fibrillation is Not A Dead Horse

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ABSTRACT

Prevalence and incidence of Atrial Fibrillation (AF) is high in western countries. It is apparently lower in developing countries, because of unrecognition, undertreatment and related complications and mortality. Studies in subjects wearing cardiac implantable electronic devices showed a wide burden of AF, ranging from subclinical episodes to permanent AF.

The aim of our study was to identify haematological and haemodynamic differences between Paroxysmal Atrial Tachyarrhythmias (PAT) compared to Non-Paroxysmal AF (NPAF), detected by 24 hours Holter ECG, and predictive negative factors associated with increased risk of evolution from paroxysmal to persistent or permanent AF.

Our data highlight the dynamic nature of PAT and NPAF. PAT in young subjects is a red flag, requiring at least changes in lifestyle and further diagnostic examinations to avoid progression to irreversible pathological myocardial electrical and structural remodeling. Comorbidities, scarce compliance, or inappropriate treatments account for high incidence of acute cerebrovascular events with disabling outcomes in elderly patients. Further studies are needed on genetic susceptibility and vulnerability. Educational campaign is the most effective, long-term strategy. Personalized approach and therapeutical scheme are recommended based on patient compliance and actual risk. A holistic approach to patient is the pillar for any clinical decision and practice.

Keywords
Atrial Fibrillation, Acute Cerebrovascular Events, Biomarkers, Haemodynamic features.

Introduction

The risk of stroke is increased 5-fold in patient suffering from Atrial Fibrillation (AF) [1]. The cause of ischemic stroke remains unknown (cryptogenetic stroke), despite a complete diagnostic evaluation in 20 to 40% of the cases [2]. The most frequent causes of cryptogenetic stroke are occult AF (6-23%) and AF (20-30%). Eighty percent of cardio-embolic stroke had AF [3]. AF duration longer than 24 h was associated with a significantly increased risk of stroke or systemic embolism of 3.1% per year compared to 0.5% in those with no AF detected in patients with recently implanted pacemaker or defibrillator [4]. In Kaplan et al. [5], rate of stroke and systemic embolism increased according with $CHAD_2DS_2VASc$ from a rate 0,37 per year with a score of 0 up to 2,55 per year for a score of 9. Annual rate of stroke and systemic embolism was 1% in patients with 6 minutes to 23.5 h of AF, 1.43% in patients with >23,5 h of AF. It was low in patients with $CHAD_2DS_2VASc$ of 0 and 1, regardless of device detected AF duration. However, it was>1% in patients with $CHAD_2DS_2VASc$ of 2 with >23,5 h of AF. In the group with a $CHAD_2DS_2VASc$ score of 3–4, the stroke rate rose with >6 min of AF. However, in the group with $CHAD_2DS_2VASc$ of 5 or greater, the stroke rate increased even in the absence of device-detected AF. A retrospective study showed a higher risk even in patients with resolved AF, although lower than in patients with AF. The incidence rate of TIA and stroke was 0,76 in patients with resolved AF vs 1,63 in patients with AF, the incidence rate of mortality was 0,6 in the former vs 1,13 in the latter [6].

Ganesan AN et al. [7] reported an annualized risk of stroke or systemic thromboembolism and mortality of 2,17% and 3,89% in non-paroxysmal (NPAF) compared 1,5% and 2,79% in paroxysmal AF (PAF), respectively. The risk resulted higher in not treated patients compared to those under oral anticlotting therapies.

CRYSTAL AF (Cryptogenic Stroke and underlying AF) study detected AF in 8.9% of patients in the Insertable Cardiac Monitor (ICM) group versus 1.4% of patients in the control group, undergone conventional follow-up, by 6 months, in 12.4% of patients in the ICM group versus 2.0% of patients in the control group, by 12 months after the index event (transient ischaemic attack or stroke) [2]. Recently, STROKE- AF study confirmed the higher rate of AF detected by ICM (12,1%) compared to usual care group (1,8%) over 12 months, in patients recruited within 10 days after both large and small-vessel acute stroke [8].

Patients affected with AF have a stroke mortality of about 20%. Around 50% of affected patients died within one year and about 60% of them remain permanently disabled [2].

AF may be subclinical [9,10] and emerges only when an acute event occurs. Number and duration of episodes and total percentage time in AF are extremely variable both in paroxysmal and persistent AF and conversion to sinus rhythm may occur also in previously defined permanent AF. Once resolved, recurrence may appear after spontaneous resolution, cardioversion, and ablation. Even after the last surgical procedure, AF recurrence may be observed in up to 80% of the patients [11,12]. Several authors reported a risk equivalence in intermittent compared to sustained AF [13,14]. This is not surprising because of high risk of embolization at re-establishment of sinus rhythm in the former and lower risk of embolization in the latter, under anticlotting therapy. Comorbidity significantly increases the risk [5,15], also shown in recent trials with Novel Oral Anti-Clotting therapies [16-18]. Then, the concept of a biological gradient of AF burden arised and its dynamic nature needs further investigations for primary and secondary prevention of complications [19].

Subclinical atrial tachyarrhythmias may precede clinical AF. A 6-fold increased risk of developing AF, a 2.8-fold increased risk of non-fatal stroke and death were reported in patients who had at least one episode of high atrial high-rate events (AHRE) (>220 b/min for 5 minutes) in sinus node dysfunction [20]. Six minutes of subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats/minutes longer than 6 minutes), over the course of 3 months, increased the risk of stroke and systemic embolism by 2,5-fold in patients with dual chamber pacemaker (for sinus-node or atrioventricular-node disease) or implantable cardiac device (for any indication). The risk of stroke continued to increase as the amount of subclinical atrial tachyarrhythmias burden increased [21]. AHRE are found in 60-70%, if AF patients are included, and 10-30%, if AF patients are excluded [22].

The aim of our study was to identify haematological and haemodynamic differences between Paroxysmal Atrial Tachyarrhythmias (PAT) compared to Non-Paroxysmal AF (NPAF) and predictive negative factors associated with evolution from paroxysmal events to persistent or permanent AF.

Materials and Methods

We recruited 143 other neuropsychiatric disorders (OND), 110 of which suffering from minor arrhythmias, as extrasystoles (46 females, age 53,6 sd 14,6, 64 males, age 49,5 sd 14) (ONDa), 354 patients affected with PAT, including P preserved atrial tachyarrhythmias, AF and atrial flutter, regardless of duration. Among these, there were 256 patients admitted for acute cerebrovascular diseases (ACV) (136 females, age 81,2 sd 7,8, $CHAD_2DS_2VASc$ 6,1 sd 1, HASBLED 3,7 sd 1,3; 120 males, age 75,6 sd 12,1, $CHAD_2DS_2VASc$ 4,8 sd 1,2, HASBLED 4 sd 1,3), 65 for chronic cerebrovascular diseases (CCVD, 33 females, age 78,6 sd 6,7, 32 males, age 76,6 sd 8,1), 33 for OND (23 females, age 58,1 sd 13,6, 10 males, age 57,2 sd 16,1). Other 561 patients were affected with NPAF, 474 of which admitted for ACV (273 females, age 84,2 sd 6,3, $CHAD_2DS_2VASc$ 6,9 sd 0,9, HASBLED 4,7 SD 1,1; 201 males, age 81,7 sd 8,8, $CHAD_2DS_2VASc$ 5,7 sd 1,1, HASBLED 4,8 sd 1,2), 87 for CCVD (43 females, age 84,7 sd 5,6, 44 males, age 81,8 sd 6,2). The following risk factors

were reported at case history by ACV patients: in PAT smoke 7/136 (5%) females vs 21/120 (18%) males, at least one alcoholic drink/day 13/136 (10%) females vs 46/120 (38%) males, arterial hypertension 121/136 (89%) females, 100/120 (83%) males, type 2 diabetes mellitus 31/136 (23%) females vs 27/120 (23%) males, in NPAF smoke 4/273 (1%) females vs 14/201 (7%) males, at least one alcoholic drink/day 20/273 (7%) females vs 84/201 (42%) males, arterial hypertension 268/273 (98%) females vs 189/201 (94%) males, type 2 diabetes mellitus 66/273 (24%) females vs 39/201 (19%) males (Table 1). Data on dyslipidemia are not reported because values were normal in most of the patients under statins.

Table I

ACV	PAT		NPAF	
	females	*males*	*females*	*males*
Number	136	120	273	201
Age	81,2 sd 7,8	75,6 sd 12,1	84,2 sd 6,3	81,7 sd 8,8
$CHAD_2DS_2VASc$	6,1 sd 1	4,8 sd 1,2	6,9 sd 0,9	5,7 sd 1,1
HASBLED	3,7 sd 1,3	4 sd 1,3	4,7 sd 1,1	4,8 sd 1,2
Smoke	5%	18%	1%	7%
At least 1 alcoholic drink/ day	10%	38%	7%	42%
Arterial Hypertension	89%	83%	98%	94%
Type 2 Diabetes Mellitus	23%	23%	24%	19%

Table II		
	PAT	NPAF
VKA	2%	20%
NOAC	3%	9%
LMWH	2%	5%
ASA	34%	37%
Clopidogrel	4%	2%
Ticlopidine	3%	1%
DAPLT	3%	2%
Pacemaker	0%	38%

Holter ECG was completely normal only in 33/143 OND patients (23%) and were excluded because of the paucity of the sample. Forty-seven out of 256 (18%) PAT referred previous, brief, not significant episodes of PAF, detected at Holter ECG. Five of 256 PAT ACV patients (2%) were already treated with Vitamin K Antagonists (VKA), 7/256 (3%) with Novel Anti-Clotting drugs (NOAC), 5/256 (2%) with Low Molecular Weight Heparin (LMWH), 87/256 (34%) with ASA, 11/256 (4%) with clopidogrel (CL), 7/256 (3%) with ticlopidine (TC), 8/256 (3%) with dual antiplatelets (DAPLT) (7 with ASA+CL, 1 with CL+ticagrelor) (Table II). Twenty-nine out of 561 (5%) NPAF were recent (16 in females, 13 in males), 30/561 (5%) long-standing-persistent, 415/561 (74%) permanent (240 in females, 175 in males). Ongoing treatments in NPAF ACV patients were VKA in 94/474 (20%), NOAC in 44/474 (9%), LMWH in 22/474 (5%), ASA in 177/474 (37%), CL in 9/474 (2%), TC in 3/474 (<1%), 9/474 (2%) with DAPLT (6 with ASA+CL, 3 with CL+ticagrelor). Twenty-one out of 561 (38%) NPAF carried a pacemaker (Table II).

ACV in PAT included 26 (10%) transient ischaemic attacks (TIA) (9 in females, 17 in males), 107 (42%) lacunar strokes (LS) (60 in females, 47 in males), 117 (46%) medium- large vessel occlusions (M-LVO) (63 in females, 54 in males), 14 (5%) of which with haemorrhagic infiltrations (HI) (8 in females, 6 in males), 6 (2%) parenchymal haemorrhages (HAE) (4 in females, 2 in males), ACV in NPAF included 14 (2%) TIA (6 in females, 8 in males), 143 (25%) LS (77 in females, 66 in males), 304 (64%) M-LVO (182 in females, 122 in males), 40 (7%) of which with haemorrhagic infiltrations (23 in females, 17 in males), 13 (2%) HAE (8 in females and 5 in males) (Table III).

Table III

	PAT	NPAF
TIA	10%	2%
LS	42%	25%
M-LVO	46%	64%
HI	5%	7%
HAE	2%	2%

All the patients underwent blood withdrawal, standard ECG, Computerized Tomography (CT) within 24 hours, 24 hours Holter ECG, echocardiography and CT/Magnetic Resonance Imaging (MRI) within one week.

Blood cell counts (n x 10^3) were examined by XN 2000 Hematology Analyzer (Sysmex Corporation).

Glycosylated Haemoglobin (HbA1c) (%) was measured by Gold Standard non-porous ion exchange High Performance Liquid Chromatography by automated analyzer (HLC-723 G8, Tosoh Corporation, Bioscience Division). Cut off value was < 7%.

Fibrinogen was detected by immunoturbidimetric method, measured on Sysmex analyzer (Dade Thrombin Reagent, Dade Behring, Deerfield, Illinois, USA, Siemens Healthcare Diagnostics). Normal range value was 18-400 mg/dl.

D-dimer (d-Dim) was determined by immunoturbidimetric application with polystyrene particles, coated with monoclonal mouse antibodies against d-Dim, on Sysmex analyzer (d-Dim, Innovance, Dade Behring, Deerfield, Illinois, USA, Siemens Healthcare Diagnostics). Normal range value was 0-0,5 mg/L.

Different assays were used for high-sensitive Troponin (hs Tro) detection in serum. The first one (hs Tro1) was an electrochemiluminescence immunoassay with biotinylated monoclonal anti-mouse-T Tro specific antibodies labeled with ruthenium, which formed a sandwich complex. After addition of streptavidin-coated microparticles, it bound to solid phase. The microparticles were aspired and magnetically captured by an electrode, while unbound particles were removed. Voltage induced chemiluminescence was revealed by Cobas analyzer (Elecsys and Cobas, Roche). The cut off value to rule out myocardial infarction was < 15 pg/ml. The second electrochemiluminescence immunoassay (hs Tro2) was for cTnI (Access Immunoassay

AccuTnI System, Beckman-Coulter). Samples were incubated with paramagnetic microparticles covered by murine monoclonal antibodies against cTnI conjugated with alkaline phosphatase in a sandwich assay with solid phase murine monoclonal anti-cTnI antibodies, revealed by a chemiluminescence substrate (Lumi-Phos 530) (normal range value < 0,06 ng/ml). The third (hs Tro 3)was a sandwich electrochemiluminescence immunoassay for hs Tro (Beckman Coulter Access hsTnI, Brea, CA, USA). Alkaline phosphatase conjugated, sheep monoclonal antibodies anti- human-hsTro were incubated with the samples and mouse monoclonal anti-human-hsTro coated with paramagnetic microparticles. After removal of unbound materials and addiction of chemiluminescent substrate, light was measured with a luminometer (Access 2 Immunoassay System). Normal range value was <11,6 ng/L. N-Terminal-pro-BNP II levels (NT-pro-BNP) were measured by electrochemiluminescence immunoassay with biotinylated monoclonal anti-mouse-NT-pro-BNP-specific antibodies, by a method similar to the first hs Tro above described (Elecsys and Cobas, Roche). Normal range value of NT-pro-BNP were 0-125 pg/ml. Brain Natriuretic Peptide (BNP) was detected by capture paramagnetic microparticles covered by murine anti-BNP antibodies and murine antibodies anti-BNP marked with acridinium, preactivated by hydrogen peroxide and activated by sodium hydroxide. Electrochemiluminescence was measured in relative light unit (Architect BNP System, Abbott). Cut off value was 0-100 pg/ml.

Creatinine (Cre) was evaluated by reaction with sodium picrate and measurement of absorbance through Architect cSystem (Abbott, Wiesbaden, Germany). Normal range value was 0,7-1,2 mg/dl for men and 0,5-0,9 mg/dl for women.

Proteinuria was determined by immunoturbidimetric assay (Architect cSystem, Abbott). Albuminuria was detected by a colorimetric assay by reaction with bromocresol green, forming a blue-green complex, whose intensity is directly proportional to albumin concentration in the sample, measured photometrically (ALB2, Cobas, Roche Diagnostics). Normal range value was 0-29 mg/L. Urinary light chains were revealed by immunoturbidimetry on Architec Plus CI 8200 with polyclonal rabbit antibodies anti-human κ and λ chains (Free Light Chains Kit, New Scientific Company Srl). Normal range values were: κ 0-5 mg/L, λ 0-5 mg/L.

Cardiovascular reactivity (CR) was defined by beat indices, ratio (R) or difference (D) between higher maximal or minimal heart rate on higher maximal or minimal pulse rate. A value < 1 or > 1 were considered as negative (NCR) or positive CR (PCR), respectively [23].

By transthoracic echocardiography, we gathered data on ejection fraction (EF, normal range 60-80%), pulmonary arterial pressure (PAP, normal < 25 mmHg), atrial dimension (AD, normal range 3.3 sd 0.5 cm).

Data were statistically analyzed by unpaired T-Test for standard description of baseline characteristics and differences among the studied groups, by Pearson correlation test and regression analysis, for identification of association among examined parameters.

Results

At admission, GCS was lower in females compared to males in both PAT and NPAF ACV (PAT, 12,8 sd 2,7 vs 13,7 sd 2,2, p 0,005; NPAF, 11,8 sd 3,2 vs 12,4 sd 2,7, p 0,02). Day 7 GCS significantly improved in both groups and genders (PAT females 13,7 sd 1,9 (+0,9), p 0,001, males 14,3 sd 1,6 (+0,6), p 0,01; NPAF females 12,4 sd 2,9 (+0,6), p 0,02, males 13,3 sd 2,5 (+0,9), p 0,002). Pre-MRS was higher in females compared to males in both PAT and NPAF ACV (PAT, 0,8 sd 1,5 vs 0,5 sd 1,1, p 0,02; NPAF, 1,4 sd 1,7 vs 0,8 sd 1,4, p 0,0004). Day 7 MRS increased in both groups and genders, significantly in PAT males (PAT females 1,8 sd 1,8 (+1), p ns, males 1,2 sd 1,6 (+0,7), p 0,0001; NPAF females 2,9 sd 1,7 (+1,5), p ns, males 2,1 sd 1,8 (+1,3), p ns) (Table IV).

Table IV

	PAT			**NPAF**		
	females	*males*		*females*	*males*	
day 1 GCS	12,8 sd 2,7	13,7 sd 2,2	*p 0,0005*	11,8 sd 3,2	12,4 sd 2,7	*p 0,02*
day 7 GCS	13,7 sd 1,9	14,3 s3d 1,6		12,4 sd 2,9	13,3 sd 2,5	
	p 0,001	*p 0,01*		*p 0,02*	*p 0,002*	
pre-MRS	0,8 sd 1,5	0,5 sd 1,1	*p 0,02*	1,4 sd 1,7	0,8 sd 1,4	*p 0,0004*
day 7 MRS	1,8 sd 1,8	1,2 sd 1,6		2,9 sd 1,7	2,1 sd 1,8	
	p ns	*p 0,0001*		*p ns*	*p ns*	

Blood cell counts (n x 10^3) showed higher number of neutrophils and lower number of lymphocytes in PAT (6,6 sd 3,4, p 0,0003; 1,7 sd 0,9, p 0,0001) and NPAF ACV (7,8 sd 3,9, p 0,001; 1,6 sd 1,5, p 0,001) compared to ONDa (4,8 sd 2,3; 2,2 sd 0,7) (Figure 1a). Glycosylated Hb (%) was higher in PAT (6,1 sd 1,1, p 0,01) and NPAF ACV (6,1 sd 1,1, p 0,0007) compared to ONDa (5,8 sd 0,8) (Figure 1b). Fibrinogen (mg/dl) was higher in PAT females ACV (387,3 sd 138 vs 311 sd 78,1, p 0,0004) and NPAF in both ACV genders (438 sd 157,1, p 0,003) vs ONDa (308,9 sd 80,3) (Figure 1c). D-Dimer (mg/l) was higher in PAT ACV (2,7 sd 7,7, p 0,02) and NPAF ACV (2,5 sd 4,9, p 0,0002) vs ONDa (0,5 sd 0,7) (Figure 1d).

Increased levels of hs Tro were present in 165/252 (65%, 67% females, 64% males) PAT and in 392/474 (83%, 81% females, 86% males) NPAF patients, natriuretic peptides in 146/248 (59%, 64% females, 53% males) PAT and in 396/411 (96%, 97% females, 96% males) NPAF patients. Higher levels of hs Tro were detected both in PAT and NPAF. Hs Tro 3 showed significant differences between PAT / NPAF ACV and ONDa. Increased levels of hs Tro 1 (pg/ml) were present both in ACV (PAT 28,9 sd 27 p 0,0006; NPAF 50,5 sd 77,7, p 0,0005) and CCVD (PAT 27,3 sd 34,1, p 0,0006; NPAF 32,5 sd 28,4, p 0,009) vs ONDa (7,4 sd 8,4); hs Tro 2 (ng/ml) predominantly in NPAF CCVD (1,2 sd 3, p 0,009) compared to ONDa (0,02 sd 0,04). Hs Tro 3 levels (ng/L) were: 45,9 sd 78,7 in PAT ACV (p 0,03), 27,5 sd 24,7 (p 0,02) in NPAF CCVD, 35,6 sd 35,1 (p 0,004) in NPAF ACV vs 11,2 sd 32 in ONDa (Figure 1e). Pro-BNP levels (pg/ml) were higher in females compared to males in ONDa (138,9 sd 165,6 vs 65,9 sd 63, p 0,04), in CCVD (1037 sd 2012,9, p 0,0001) and ACV (3516,5 sd 7628,4, p 0,002) PAT, in CCVD (2356 sd 7185,7, p 0,0004) and ACV (5724,6 sd 6752, p 0,0004) NPAF compared to ONDa (98,5

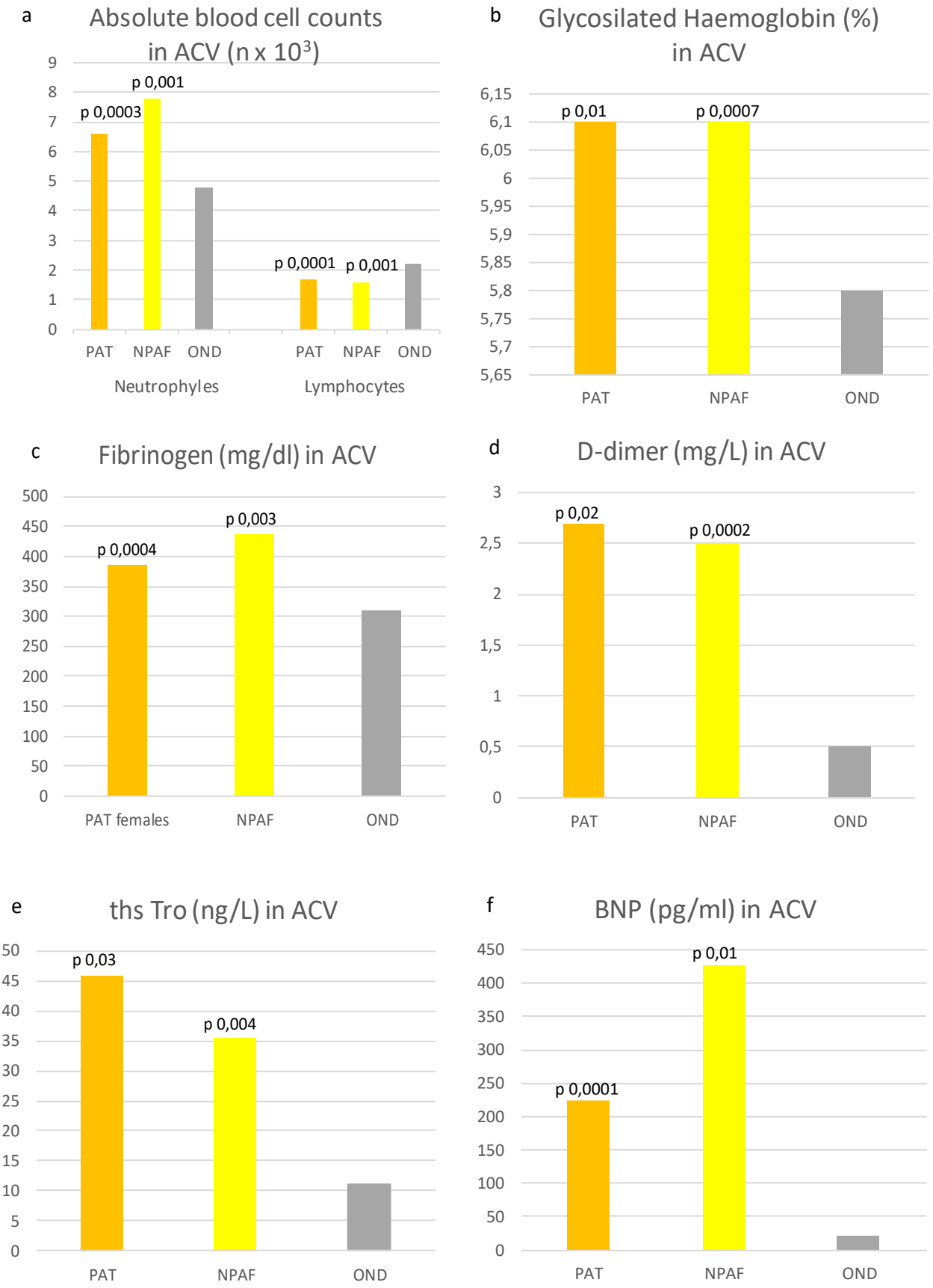
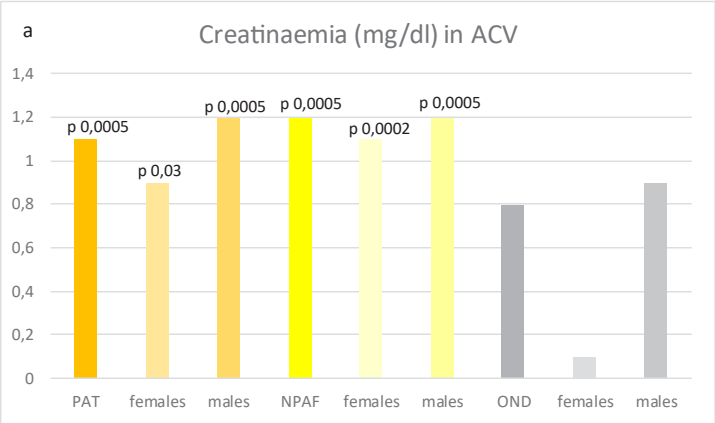

a
Absolute blood cell counts in ACV (n x 10³)
p 0,0003
p 0,001
p 0,0001
p 0,001
PAT
NPAF
OND
Neutrophyles
Lymphocytes
b
Glycosilated Haemoglobin (%) in ACV
p 0,01
p 0,0007
PAT
NPAF
OND
c
Fibrinogen (mg/dl) in ACV
p 0,0004
p 0,003
PAT females
NPAF
OND
d
D-dimer (mg/L) in ACV
p 0,02
p 0,0002
PAT
NPAF
OND
e
ths Tro (ng/L) in ACV
p 0,03
p 0,004
PAT
NPAF
OND
f
BNP (pg/ml) in ACV
p 0,0001
p 0,01
PAT
NPAF
OND

Figure 1



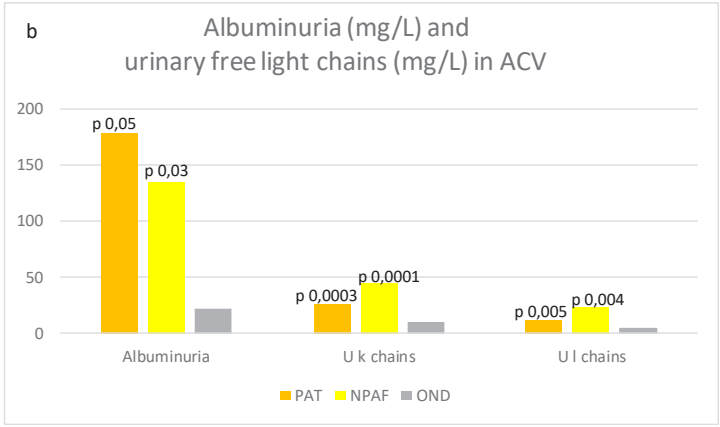


Figure 2

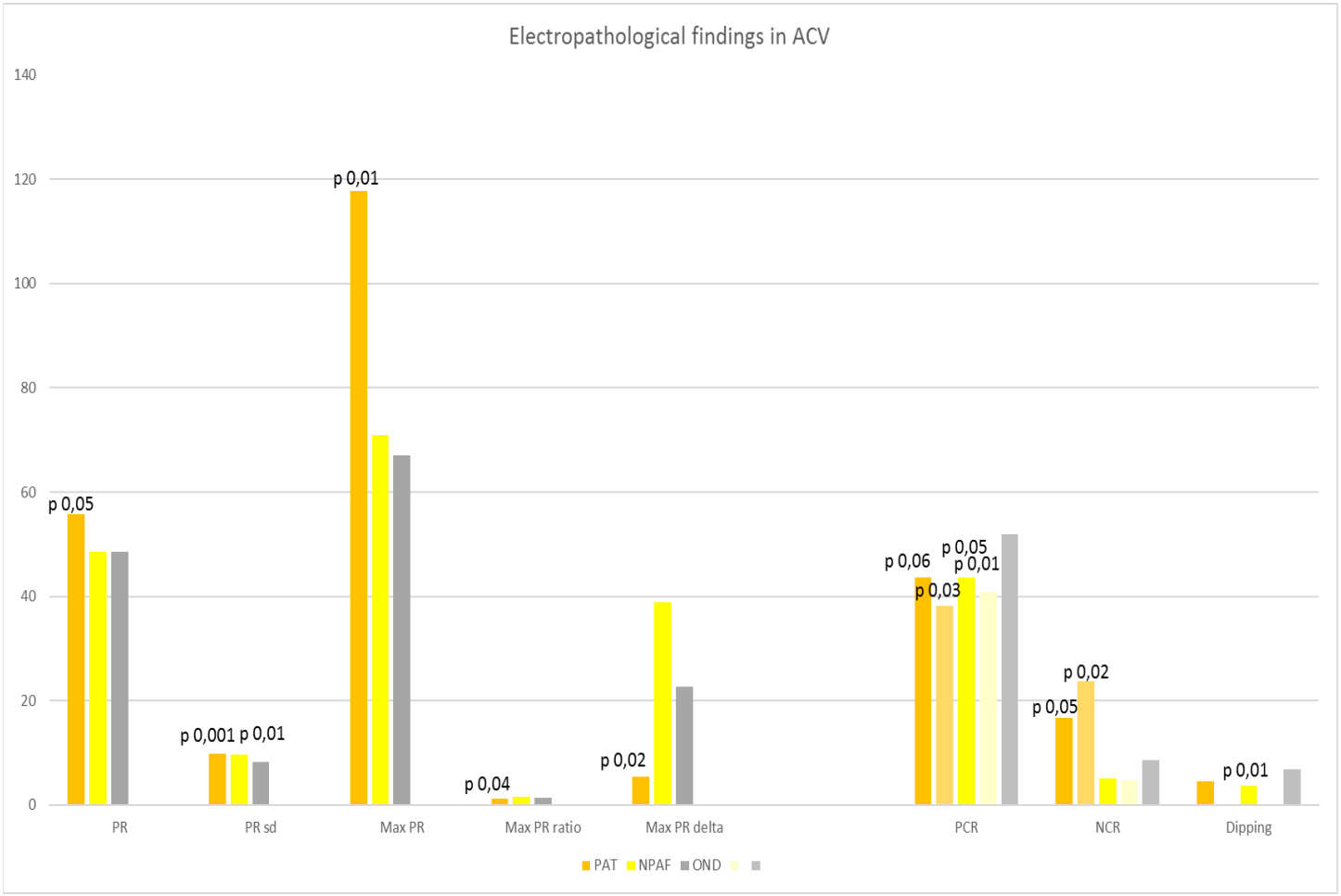


Figure 3

sd 124,2), as well as BNP levels (pg/ml) in females compared to males in ONDa (29,1 sd 29,7 vs 16,2 sd 11,6, p 0,02), in CCVD (65,3 sd 21,7, p 0,04) and ACV (222,7 sd 389,3, p 0,0001) PAT, in CCVD (328,7 sd 281,1, p 0,03) and ACV (426,7 sd 425, p 0,01) NPAF compared to ONDa (21,5 sd 11,6) (Figure 1f). Hs Tro 3 correlated with GCS at admission in PAT (r - 0,31), day 7 GCS in PAT (r -0,27) and NPAF (r -0,24) ACV, pre-MRS in PAT (r 0,36) and NPAF (r 0,24), MRS in PAT (r 0,49) and NPAF (r 0,36) ACV. BNP correlated with GCS at admission (r -0,33), day 7 GCS (r -0,39), pre-MRS (r 0,27), MRS (r 0,33) in PAT ACV. Then, in severe patients, as in NPAF, there were a reduced production of BNP and an increased release of hs Tro 3 by necrotic myocardial cells.

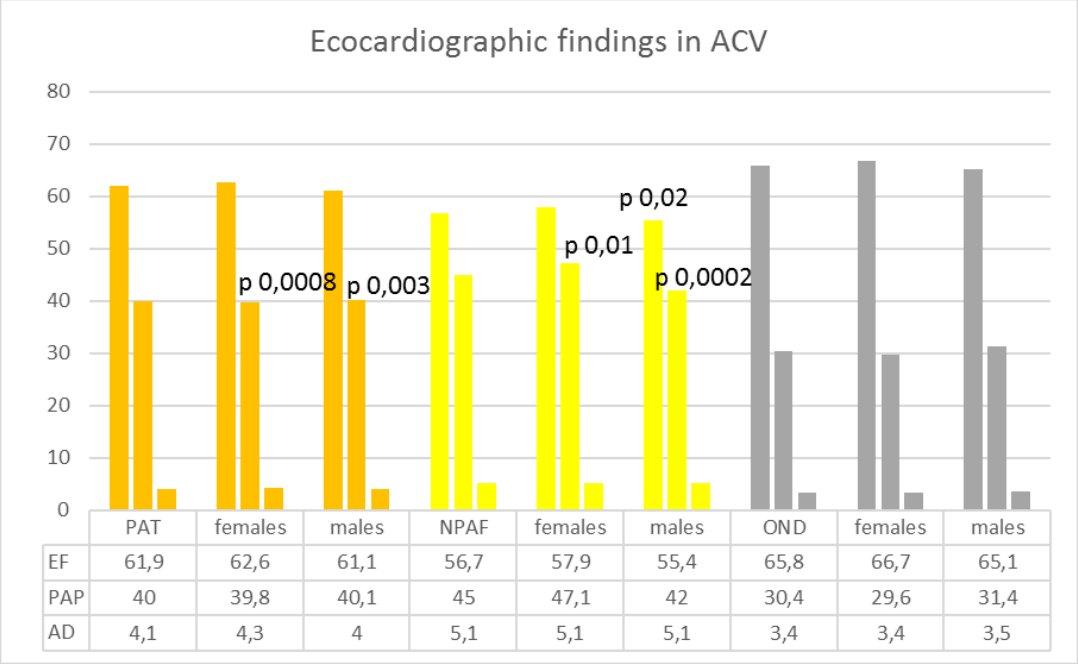
Creatinemia (mg/dl) was significantly higher in both PAT and NPAF, particularly in males, compared to ONDa (PAT 1,1 sd 0,6, NPAF 1,2 sd 0,7, vs OND 0,8 sd 0,1, p 0,0005; females/males

PAT 1 sd 0,9 / 1,2 sd 0,6, p 0,03 / p 0,0005, NPAF 1,1 sd 0,7 / 1,2 sd 0,7, p 0,0002 / p 0,0005, vs ONDa 0,8 sd 0,1 / 0,9 sd 0,1) (Figure 2a). Proteinuria (mg/dl) was higher in PAT ACV (25,4 sd 43,8, p 0,001; albuminuria (mg/l) 178,3 sd 188,1, p 0,05; urinary kappa chains (uκc, mg/l) 26,3 sd 44,6, p 0,0003; urinary lambda chains (uλc, mg/l) 11,3 sd 22, p 0,005), NPAF ACV (35,1 sd 61,3 p 0,0005, albuminuria 134,9 sd 143,4, p 0,03; uκc 44,7 sd 61,3, p 0,0001; uλc 23,4 sd 39,3, p 0,004) compared to ONDa (7 sd 16,4; albuminuria 22 sd 75,8; uκc 9,5 sd 13,1; uλc 5,1 sd 8,1), particularly in males (Figure 2b), (Table V).

HR, Max HR, Min HR (b/min) were higher in NPAF ACV (81 sd 14,5, p 0,0001; 111,7 sd 32,4, p 0,003; 61,6 sd 13,9, p 0,005) compared to ONDa (66,2 sd 6,8; 89,6 sd 23,1; 53,3sd 5,1). PR, PR sd, Max PR (b/min) were significantly higher in PAT ACV (55,8 sd 13,5, p 0,05; 9,9 sd 3,2, p 0,001; 117,8 sd 19,7, p 0,01) and, not significantly, in NPAF (48,6 sd 11,8, p ns; 9,7 sd 2,1, p 0,01; 71 sd 15,4, p ns) compared to ONDa (48,5 sd 12,7; 8,2 sd 2,2; 67 sd 13,7), max PR ratio and delta were lower in PAT (1,2 sd 0,4, p 0,04; 5,5 sd 29,9, p 0,02) compared to ONDa (1,4 sd 0,6; 22,7 sd 27,5). This was not surprising, considering episodes

Table V

	PAT			**NPAF**			**OND**		
Neutrophils (n x 10^3)	6,6 sd 3,4		*p 0,0001*	7,8 sd 3,9		*p 0,001*	4,8 sd 1,3		
Lymphocytes (n x 103)	1,7 sd 0,9		*p 0,0001*	1,6 sd 1,5		*p 0,001*	2,2 sd 0,7		
Glycosylated Hb (%)	6,1 sd 1,1		*p 0,01*	6,1 sd 1,1		*p 0,0007*	5,8 sd 0,8		
		females	*males*		*females*	*males*		*females*	*males*
		6,1 sd 0,9	6,1 sd 1,3		6,2 sd 1,1	6,1 sd 1		5,7 sd 0,8	5,8 sd 0,8
					p 0,01	*p 0,03*			
Fibrinogen (mg/dl)	383,5 sd 138			438 sd 157,1		*p 0,003*	308,9 sd 80,3		
		females	*males*		*females*	*males*		*females*	*males*
		387,3 sd 138	379,2 sd 129,5		432,6 sd 160,1	445,1 sd 153		311 sd 78,1	307,4 sd 82,4
		p 0,0004							
D- dimer (mg/L)	2,7 sd 7,7		*p 0,02*	2,5 sd 4,9		*p 0,0002*	0,5 sd 0,7		
hs-Tro 3 (ng/L)	45,9 sd 78,7		*p 0,03*	35,6 sd 35,1		*p 0,004*	11,2 sd 32		
NT-pro-BNP (pg/ml)	3516,5 sd 7628,4		*p 0,002*	5724,6 sd 6752		*p 0,0004*	98,5 sd 124,2		
		females	*males*		*females*	*males*		*females*	*males*
		5441,9 sd 9484,4	903,6 sd 2127		6346,2 sd 7282,5	4805,7 sd 5797,7		138,9 sd 165,6	65,9 sd 63
		p 0,01	*p 0,05*		*p 0,0003*				
BNP (pg/ml)	222,7 sd 389,3		*p 0,0001*	426,7 sd 425		*p 0,01*	21,5 sd 11,6		
		females	*males*		*females*	*males*		*females*	*males*
		221,2 sd 382,5	224,3 sd 398,6		465,8 sd 432	380,3 sd 414,3		29,1 sd 29,7	16,2 sd 11,6
		p 0,01	*p 0,03*						
Creatinemia (mg/dl)	1,1 sd 0,6		*p 0,0005*	1,2 sd 0,7		*p 0,0005*	0,8 sd 0,1		
		females	*males*		*females*	*males*		*females*	*males*
		1 sd 0,9	1,2 sd 0,6		1,1 sd 0,7	1,2 sd 0,7		0,8 sd 0,1	0,9 sd 0,1
		p 0,03	*p 0,0005*		*p 0,0002*	*p 0,0005*			
Proteinuria (mg/dl)	25,4 sd 43,8		*p 0,001*	35,1 sd 61,3			7 sd 16,4		
		females	*males*		*females*	*males*		*females*	*males*
		21,8 sd 43,8	29,4 sd 49,3		32,8 sd 59,3	38,2 sd 61,3		3 sd 7	9,8 sd 20,3
		p 0,001	*p 0,002*		*p 0,0007*	*p 0,0003*			
Albuminuria (mg/L)	178,3 sd 708,4		*p 0,05*	134,9 sd 143,4		p 0,03	22,3 sd 75,8		
		females	*males*		*females*	*males*		*females*	*males*
		211,2 sd 956,6	140,9 sd 188,1		218,6 sd 216,9	114,8 sd 143,4		15,4 sd 15	27,1 sd 75,8
			p 0,0005		*p 0,001*	*p 0,0005*			
Urinary κ chains (mg/L)	26,3 sd 54,3		*p 0,0003*	44,6 sd 69,4		*p 0,0001*	9,5 sd 13,1		
		females	*males*		*females*	*males*		*females*	*males*
		23,4 sd 34,1	29,8 sd 54,3		43,9 sd 55	45,7 sd 69,3		9,8 sd 12,7	9,4 sd 13,4
		p 0,01	*p 0,003*						
Urinary λ chains (mg/L)	11,2 sd 22		p 0,005	23,3 sd 39,3		p 0,004	5,1 sd 8,1		
		females	*males*		*females*	*males*		*females*	*males*
		11,4 sd 24,8	11,1 sd 18,2		22,6 sd 28,2	24,3 sd 51		5,4 sd 10,1	4,9 sd 6,4
			p 0,009			p 0,002			



	PAT	females	males	NPAF	females	males	OND	females	males
EF	61,9	62,6	61,1	56,7	57,9	55,4	65,8	66,7	65,1
PAP	40	39,8	40,1	45	47,1	42	30,4	29,6	31,4
AD	4,1	4,3	4	5,1	5,1	5,1	3,4	3,4	3,5

Figure 4

of tachy-brady-arrhythmias, lower ejection fraction (EF) and higher pulmonary arterial pressure (PAP) in NPAF. Number of Positive Cardiovascular Reactivity (PCR) events were lower in PAT ACV (43,6 sd 23,9, p 0,06, especially in females 38,1 sd 29,3, p 0,03) and NPAF (43,7 sd 14,7, p 0,05, females 40,8 sd 15,4, p 0,01) compared to ONDa (51,9 sd 15,5), while number of Negative Cardiovascular Reactivity (NCR) events were higher in CCVD and ACV PAT (16,7 sd 17,7, p 0,05, females 35,2 sd 13,5, p 0,0001; 16,6 sd 21,6, p 0,05, females 23,7 sd 23,6, p 0,02) compared to ONDa (8,5 sd 12,7). Dipping (%) was lower in PAT (4,6 sd 13,1, p ns) and NPAF AS (3,6 sd 7,5, p 0,01) compared to ONDa (6,9 sd 6,2) (Figure 3a, Table VI).

The rate of PAF was slightly higher in females than in males both in ACV (0,6-fold) and CCVD (0,5-fold). EF (%) was lower in PAT ACV (females 62,6 sd 8,5, p 0,005, males 61,1 sd 9,7, p 0,007) and NPAF ACV (females 57,9 sd 10,5, p 0,03, males 55,4 sd 10,8, p 0,02), compared to ONDa (females 66,7 sd 4,7, males 65,1 sd 6,5), PAP (mmHg) was higher in PAT ACV (females 39,8 sd 10,9, p 0,0008, males 40,1 sd 9,6, p 0,003) and NPAF ACV (females 47,1 sd 14,3, p 0,01, males 42 sd 9,8, p 0,0002), compared to ONDa (females 29,6 sd 7,3, males 31,4 sd 6,7) (Figure 4). Contrarily to expected values, Atrial Dilatation (AD, cm) resulted not significantly different in ACV (PAT females 4,3 sd 0,6, males 4 sd 0,5, p ns, NPAF females 5,1 sd 1, males 5,1 sd 0,9, p ns, ONDa females 3,4 sd 0,5, males 3,5 sd 0,5) (Figure 4), while it was higher in PAT (females 4 sd 0,7, p 0,0006, males 4,1 sd 0,4, p 0,0001) and, tendentially, in NPAF (females 5,2 sd 0,7, males 4,8 sd 0,7, p 0,07) CCVD compared to ONDa (females 3,4 sd 0,5, p, males 3,5 sd 0,5).

Echocardiography showed the following findings in PAT and NPAF, respectively: 157/256 (61%) vs 71/474 (15%) mild mitral failure, 37/256 (14%) vs 217/474 (46%) moderate-severe mitral failure, 85/256 (33%) vs 82/474 (17%) mild aortic failure, 21/256 (8%) vs 34/474 (7%) moderate-severe aortic failure, 7/256 (3%) vs 20/474 (4%) mild aortic stenosis, 2/474 (<1%) mild mitral stenosis in NPAF, 7/256 (3%) vs 10/474 (2%) moderate-severe aortic stenosis, 1/256 (<1%) vs 1/474 (<1%) moderate-severe mitral stenosis, 10/256 (4%) vs 8/474 (4%) mild tricuspidal failure, 6/256 (2%) vs 93/474 (20%) moderate-severe tricuspidal failure, 9/256 (4%) vs 5/474 (<1%) floating interatrial septum, 3/256 (1%) vs 1/474 (<1%) aneurismatic septum, 9/256 (4%) vs 41/474 (9%) wall dyssynergias, 6/256 (2%) vs 12/474 (3%) valvular prosthesis, Amplatzer device for paten foramen ovale 1/256 (< 1%) in PAT (Table VI).

Table VI

	PAT		**NPAF**		**OND**
HR	66,6 sd 10,5		81 sd 14,5	*p 0,0001*	66,2 sd 6,8
Max HR	84,3 sd 16,1		117,7 sd 32,4	*p 0,003*	89,6 sd 23,1
Min HR	54,2 sd 9,3		61,6 sd 13,9	*p 0,005*	53,3 sd 5,1
PR	55,8 sd 13,5	*p 0,05*	48,6 sd 11,8		48,5 sd 12,7
PR sd	9,9 sd 3,2	*p 0,001*	9,7 sd 2,1	*p 0,01*	8,2 sd 2,2
Max PR	117,8 sd 19,7	*p 0,01*	71 sd 15,4		67 sd 13,7
Max HR / Max PR ratio	1,2 sd 0,4	*p 0,04*	1,6 sd 0,6		1,4 sd 0,6
Max HR / Max PR delta	5,5 sd 29,9	*p 0,02*	38,9 sd 35,1	*p 0,07*	22,7 sd 27,5
PCR	43,6 sd 23,9	*p 0,06*	43,7 sd 14,7	p 0,05	51,9 sd 15,5
females	38,1 sd 29,3	*p 0,03*	40,8 sd 15,4	p 0,01	57,6 sd 12
NCR	16,6 sd 21,6	*p 0,05*	5 sd 11,3		8,5 sd 12,7
females	23,7 sd 23,6	*p 0,02*	4,7 sd 11,2		4,7 sd 6,9
EF					

females	61,7 sd 11,7	*p 0,02*	58,4 sd 10,7	p 0,0001	66,7 sd 4,7
males	56,7 sd 11,8	*p 0,0001*	55,5 sd 9	p 0,003	65,1 sd 6,5
PAP					
females	39,8 sd 10,9	*p 0,0008*	47,1 sd 14,3	*p 0,001*	29,6 sd 7,3
males	40,1 sd 0,6	*p 0,003*	42 sd 9,8	*p 0,0002*	31,4 sd 6,7
AD					
females	4,3 sd 0,6	*p ns*	5,1 sd 1	*p ns*	3,4 sd 0,5
males	4 sd 0,5	*p ns*	5,1 sd 0,9	*p ns*	3,5 sd 0,5
Mild mitral failure	61%		15%		
Moderate-severe mitral failure	14%		46%		
Mild aortic failure	33%		17%		
Moderate-severe aortic failure	8%		7%		
Mild aortic stenosis	3%		4%		
Mild mitral stenosis	0%		1%		
Moderate-severe aortic stenosis	1%		1%		
Moderate-severe mitral stenosis	3%		2%		
Mild tricuspidal failure	4%		4%		
Moderate-severe tricuspidal stenosis	2%		20%		
Floating interatrial septum	4%		1%		
Aneurismatic septum	1%		1%		
Wall dyssinergias	4%		9%		
Valvular prosthesis	2%		3%		

Underdose of NOAC was referred by 8 patients (4 under apixaban, 3 under rivaroxaban, 1 under dabigatran). At emergency department, most of the patients under VKA (96%) were out of the therapeutic window (INR 1,24 sd 0,34), in a minority of patients (3%) INR was 3,51 sd 0,24 (Table 2). Only in one patient, INR was 4,3 and was associated with cerebral haemorrhage.

The rate of rehospitalization was 12/354 (3%) (1 OND, 4 CCVD, 7 ACV) in PAT, 42/561 (7%) (5 CCVD, 38 ACV) in NPAF. Among these patients, twelve (9 females and 3 males) were previously classified as PAT and readmitted in NPAF. A significant increase of hs Tro (> 20%) was detected in 2/12 readmitted patients before first discharge. Five ACV recurrent events occurred under ASA, 5 under NOAC and 2 under VKA.

Discussion

Our data highlight the wide burden of PAT and NPAF merely detected by standard and 24 hours Holter ECG. If wearable devices or insertable cardiac monitor were applied, the incidence and prevalence of AF would have been terrifically high. At admission, neurological conditions were more severe in females compared to males, although biomarkers of chronic conditions, as creatinine and proteinuria, were higher in the latter. No differences in mean age between genders were present. As previously reported, levels of brain natriuretic peptides are early warning markers of an increased overload with subsequent risk of ischaemic sufferance [24]. Abnormal haematological parameters (blood cell counts, fibrinogen, high-sensitive troponin, brain natriuretic peptides, glycosylated haemoglobin, creatinemia, proteinuria) were detected both in PAT and NPAF, particularly in the latter. The significant increase in pulse rate reflects the abnormal cardiac excitability (increased bathmotropism, reduced dromotropism) because of lower coronary perfusion time and increased time of repolarization in PAT. A loss of contractility function is already established in NPAF, responsible of cardiac overload with structural damage (loss of chronotropism and inotropism). In these patients, atrial dilatation may be apparently not significant, because of predominant pulmonary arterial hypertension, higher in females compared to males. The main echocardiographic differences between PAT and NPAF were the presence of a higher percentage of patients with moderate-severe valvular cardiopathy and right cardiocirculatory failure. In our population, NPAF was associated with a 2,6-fold increased rate of large-medium vessel occlusion and a 2,5-fold increased rate of heamorrhagic infiltration compared to PAT. Nonetheless, even brief episodes of PAT may become remarkable if $CHAD_2DS_2VASc$ and concomitant risk factors are present. Often P preserved PAT are intermingled by PAF. The impairment of circulatory condition in hospitalized patients may be underestimated, considering that Holter ECG is recorded at rest, under control of modifiable risk factors of daily life, as stress, smoking, alcohol abuse, sleep disorders. The role of erroneous lifestyle is remarkable in males. Even small amount of alcohol was associated with increased risk of AF [25]. Binge drinking, eating or other addictive behaviours should be considered. Preliminary data showed no differences in the rate of permanent AF in hysterectomized vs no-hysterectomized females (18%) AS, while 2,8- fold higher rate of PAT was present in the latter (17%) compared to the former (6%) and PAT were also detected in no hysterectomized OND (11%). Haemodinamic factors may contribute to acute worst conditions in females, requiring careful management, which may be realized by “pink triage” and dedicated care during hospitalization. No differences were present in patients with prostatic pathologies under treatments vs those with a negative case history. The most common findings in this countryside, hard-working, conservative, long-lived population of the south of Italy were thyreopathies, aging and neurological related constipation, diverticulosis, dysbiosis, which may account for underlying proinflammatory response, related to increased cardio- and cerebrovascular risk and worst prognosis. Other comorbidities may negatively interfere with recovery, worsen quality of life and shorten life expectancy. The susceptibility and vulnerability to AF may be related to genetic predisposition. Having a parent with AF doubled the risk of AF in offspring in 4-year time [26]. Gain or loss of function mutations in genes encoding for ionic channels (NA, K, Ca), involved in Ca homeostasis, extracellular matrix remodeling, cardiogenesis, cell-cell coupling, cell structure is reported. Genome Wide Association Studies (GWAS) identified over 100 genetic loci associated with AF [27]. Additional risk may be related to epigenetic factors. Indeed, multiple microRNAs, regulating gene expression post-transcriptionally, have been linked to the course of AF [28].

PAT in young subjects is a red flag, requiring at least changes in

lifestyle and further diagnostic examinations to avoid progression to irreversible pathological myocardial electrical and structural remodeling. A retrospective study showed higher risk of ischaemic stroke or arterial thromboembolism in PAF, related to time in AF or atrial flutter, not treated with OAC, independently on other risk factors: the highest tertile of atrial fibrillation burden (11.4%) was associated with higher adjusted rate of thromboembolism compared with the combined lower two tertiles of atrial fibrillation burden (adjusted hazard ratios, 3.13 [95%CI, 1.50-6.56] and 3.16 [95%CI, 1.51-6.62], respectively) [29]. The dilemma on prescription of drugs to reduce high rate or anti-arrhythmic agents is present on daily practice. Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4, antiarrhythmic drugs, ablation) in AF diagnosed < 12 months showed lower risk of death from cardiovascular causes, stroke or hospitalization for heart failure or acute coronary syndrome in treated arm compared to usual care over a follow-up time longer than 5 years [30]. However, recurrence, episodes of bradycardia or bradyarrhythmia may occur, because of decreased vagal tone. Moreover, since anti-arrhythmics are not atrial selective, QRS and QT prolongation may increase the risk of torsade de pointes. The availability of ICM is still limited, the patient may be not compliant to the device or suffer from procedure- related adverse effects, as pain, infection. Handheld, wearable devices recording may be imprecise in real world setting and need ECG verification. In the RAte Control versus Electrical cardioversion for persistent atrial fibrillation studies, the paradigm "shock and forget" is counterbalanced by the novel concept of "look beyond the ECG, treat the patient" with an omnicomprehensive approach (rhythm control, anticoagulation, lifestyle changes, rehabilitation, nurse-led care, home care) [31]. Moderate physical activity is protective as well as control of vascular risk factors. Lifetime AF risk for a patient without risk factors is 20%, while it is 38% in the presence of just one risk factor [32]. Inclusion criteria for catheter ablation are symptomatic recurrences, AF class (<= 80% success rate for paroxysmal vs < 50% for persistent and longstanding persistent), heart failure. Long term success of atrial defibrillator in symptomatic, drug-refractory AF are uncertain. Permanent atrial pacing is recommended only for bradycardia, bradyarrhythmia, and sick sinus syndrome [33]. Biological phenomena underlying AF is probably related to bursts of depolarization and delayed repolarization, followed by altered conduction and refractory time, facilitation of re-entry rotors. Longer the duration, higher the probability of ongoing structural disarrangement, with subsequent increased risk of persistence, due to loss of atrial mechanical function, atrial dilatation and remodelling, inflammation, stasis, which may be followed by accelerated and irregular ventricular rhythm, increased risk of clot formation and embolization, necrosis/apoptosis of myocytes and fibrosis. Then, temporary anticlotting therapy in PAT might be prescribed to prevent progression of PAT to sustained AF and continued till the normalization of standard and Holter ECG, repeated as needed at general or cardiological office and at scheduled follow up, according to current findings of AF episodes. NOACs might be the drugs of choice in these "minor" but potentially evolving dysrhythmias. World Health Organization added the non-vitamin K antagonist oral anticoagulants (NOACs) to the Essential Medicines List [34]. Comorbidities, scarce compliance, or inappropriate treatments account for high incidence of ACV and disabling outcomes, especially in NPAF elderly patients. Electropathological findings of NCR may herald a negative prognosis before haematological parameters. Patients suffering from tachycardia and PAT patients with NCR seems to have a higher risk of conversion to NPAF. Moreover, patients with NCR have a higher probability of AS and/or CCVD (AS OR 4, CCVD OR 6) [35,36]. One limit of our study is related to the lack of healthy controls, which may increase statistical significance. Moreover, a technical device with cardiac and pulse electrodes may be more precise in recording cardiovascular reactivity. Four stages of ischaemic lesional burden may be conceived: I - Preserved ejection fraction (prEF), high CR (high HR, slightly reduced PR) / low Vascular Encephalopathy (VE) risk; II – PrEF, low CR / transition phase, characterized by heart overload, preceding nephrosic syndrome and increased risk of hyperviscosity; III - Reduced EF, low CR / high VE risk (no- perfusion, no-collateral compensation); IV – Reduced EF, apparently high CR (high HR, low PR), irreversible ischaemic damage. The relation of HR, PR with age and VE may be represented by U and reversed U curves, respectively. This model may be exploited for decision making on implantation of cardioverter defibrillators and pacemakers. Current guidelines allow the prescription of NOACs for stroke prevention in non-valvular AF. However, this strict restriction is attenuated considering the exclusion criteria, in which the term non-valvular refers to AF in the absence of mechanical prostheses or moderate- severe mitral stenosis, usually of rheumatic origin. Trials with NOAC in patients suffering from valvular cardiopathies or undergone to surgical procedure, as bioprosthetic valve/valve repair, transcatheter aortic valve implantation, are ongoing [37]. Efficacy and safety of NOACs fostered their off-label prescription. Our preliminary results on NOACs in valvular cardiopathies confirm their safety. Their efficacy may be lessened in moderate-severe ones. Further studies are needed to validate the reduction in mortality in the absence of traumatic events. However, the paradox of no differences in the rate of haemorragic infarction related to the entity of anticlotting effect of VKA treated patients, in the absence of traumatic events, highlights that the increased risk of bleeding is more related to the underlying cardiological dysfunction and late recanalization rather than to intrinsic VKA risk of bleeding [35,36]. Oral anticoagulant (OAC) therapy in AF is recommended if CHA_2DS_2VASc score is ≥2 in men or ≥3 in women. It should be considered if CHA_2DS_2VASc score is 1 in men or 2 in women, while it is contraindicated if CHA_2DS_2VASc score is 0 in men or 0–1 in women. In this regard, evaluation of body mass index, cardiac biomarkers, renal function, echocardiographic findings, clinical history, both thromboembolic and bleeding risk evaluation support decision making [38,39]. Echocardiographic signs of fibrin nets, clots, polydistrictual vulnerable plaques, may require VKAs. Both in NOACs and VKAs treated patients, risk of thromboembolism and bleeding is higher in decompensated heart failure. Cardio-respiratory rehabilitation, regular physical activity, dietary restriction and upstream and downstream pharmacological therapy, scheduled counseling may optimize success of any medical intervention [3,40].

Conclusions

Personalized approach and therapeutical scheme are recommended based on patient preference and actual risk, because of the dynamic nature of PAT-PAF-NPAF. Neuropsychological asset may help in decision making to avoid the paradox of increasing anxiety in compliant patients and reinforcement of self-reassurance in patients at risk for pathological behaviours. Primary and secondary prevention is recommended in high-risk patients, according to risk factors, CHAD2DS2VASc and HAS BLED. Final decision should be tailored on short-, intermediate- and long-term cost/benefit analysis. Unhealthy behaviors beget AF more than AF itself. By aging, once AF is established, the risk of dementia is further increased [41]. Temporary OAC may be safer in case of high risk of recurrence and shift from NOACs to VKAs or vice versa is conceivable according to clinical conditions and disease course. A cost-benefit analysis on wearable devices for arrhythmias is mandatory. AF care is not a dead horse. The most powerful strategy for keeping a tight rein on AF are educational plans. CR evaluation, secondary prevention and human resources for elderly patients may be considered anti-seismic measures for limiting the risk of heart quake. As predicted, AF epidemic approached the physician 'door [42]. Several large-scale AF screening studies are ongoing [43]. They will shed further light on lifetime risk in general population and risk factors related to AF development and they will point out strategies for primordial prevention. A holistic approach to patient is the pillar for any clinical decision and practice.

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