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«IDIOPATHIC» ARRHYTHMIAS: biopsy-proved nosologic diagnosis, role of anti-heart antibodies, results of treatment

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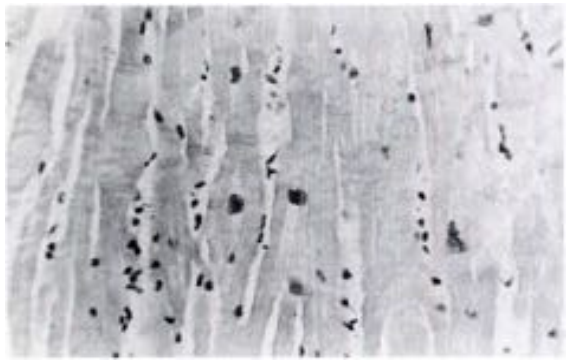
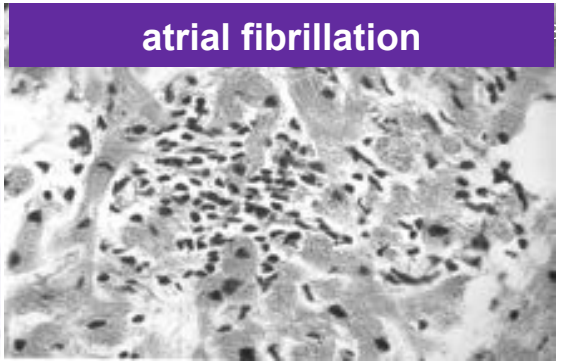
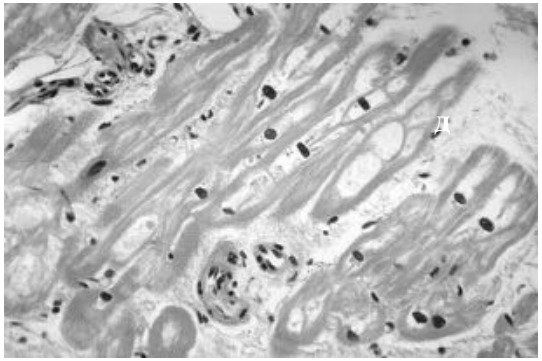
October 16-18, 2015, Venice, Italy

MYOCARDIAL BIOPSY IN «IDIOPATHIC» ARRHYTHMIAS



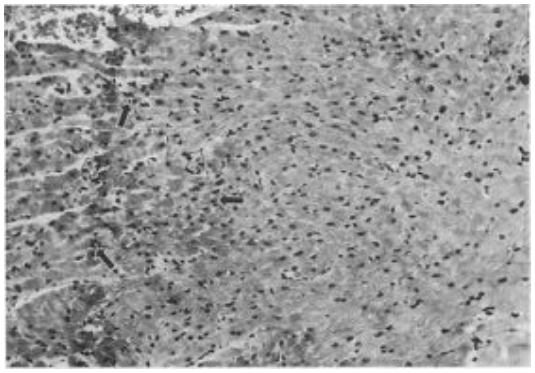
atrial fibrillation



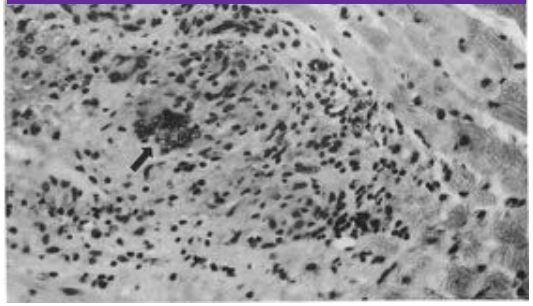


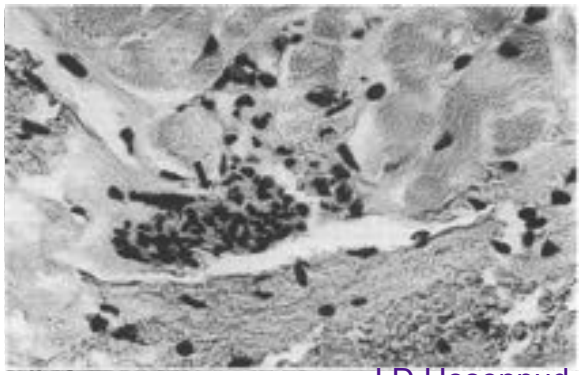
A.Frustaci, 1997

morphologic data	frequency	basic study
normal pattern	0-80%	F.Drago, 1999; J.Kazmierczak, 1998; A.Frustaci, 1994; V.Thongtang, 1994
myocarditis	0-78%	D.Sugrue, 1984; P. Vignola, 1984; M.Sekiguchi, 1992; A. Uemura, 2001; F.Drago, 1999; V.Thongtang, 1994
cardiomyopathy	17-42%	Vignola, 1984; M.Teragaki, 1999; HB Wiles, 1992
degeneration of cardiomyocytes	23-42%	A. Uemura, 2004; F.Drago, 1999; I.Segava, 1996; S.Peters, 1996; M.Di Biase, 1992
fibrosis	4-70%	J.Kazmierczak, 1998; M.Teragaki, 1999; I.Segava, 1996; S.Peters, 1996
lipomatosis	4-15%	F.Drago, 1999; S.Peters, 1996; C.Contini, 1992
vasculitis	0-8%	M.Di Biase, 1992



ventricular arrhythmias





J.D.Hosenpud, 1986

OBJECTIVE

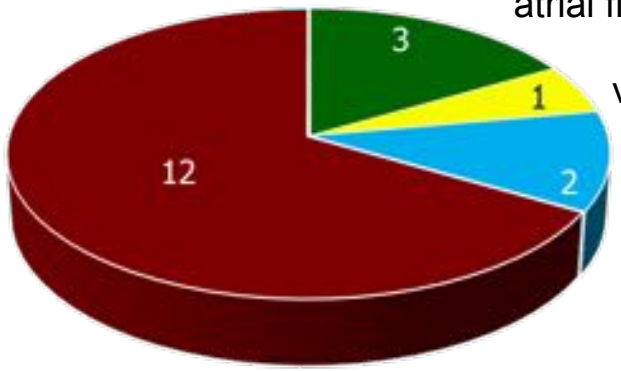
to perform instrumental and morphologic diagnostics of «idiopathic» arrhythmias' etiology by Endomyocardial Biopsy of right ventricle and to estimate effect of diagnosis-based treatment

STUDY GROUP

19 patients

9 women and 10 man, 42.6±11.3 years

14 patients received amiodarone, 2 patients had RFA of SVT/VT history



paroxysmal / persistent AF	2/2
paroxysmal AF + SVT + PAC	3
paroxysmal AF + PAC (+RBBB)	3 (1)
persistent AF + AV block (+RBBB)	1 (1)
paroxysmal AF + PAC + PVC + 1st degree AV block	1
paroxysmal AF + PAC + PVC + unsustained VT	2
PVC + VT	1
transient LBBB (+ SVT)	1 (1)

EXCLUSION CRITERIA

- LV dilatation (end-diastolic diameter > 5.5 cm) and systolic dysfunction (EF<50%)
- Myocardium infarction or acute coronary syndrome
- Congenital and valvular heart diseases (except nonsignificant atrial septal defect)
- Infective endocarditis
- Thyrotoxicosis
- LV hypertrophy >14 mm
- Hypertrophic cardiomyopathy
- Systemic autoimmune diseases and vasculitis
- Verified amyloidosis, sarcoidosis
- Storage diseases
- Lymphoproliferative diseases
- Chemotherapy with anthracyclines
- Heart surgery in the past two months (including angioplasty and radiofrequency ablation)
- Patient failure

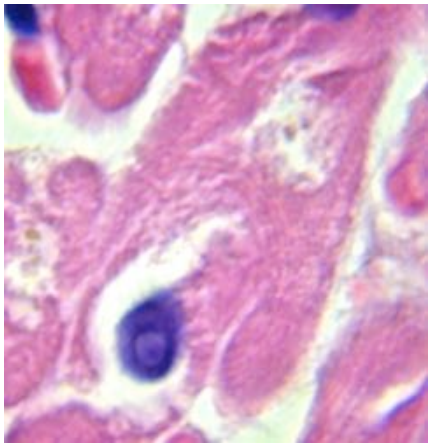
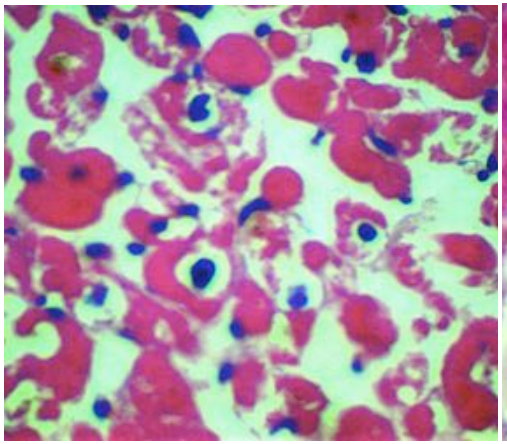
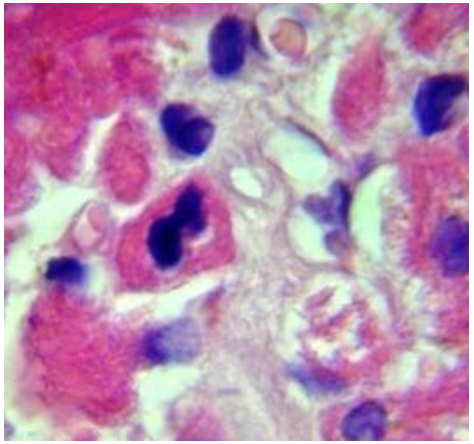
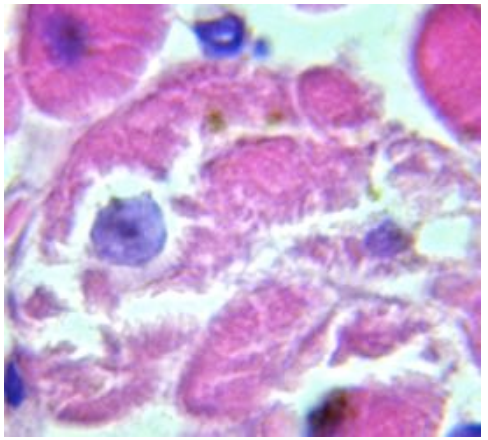
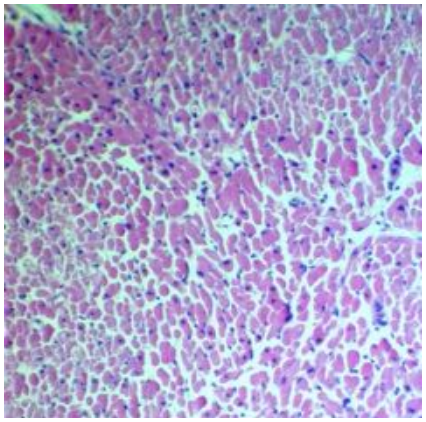
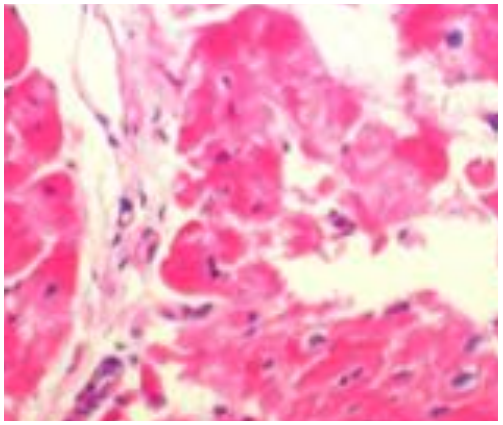
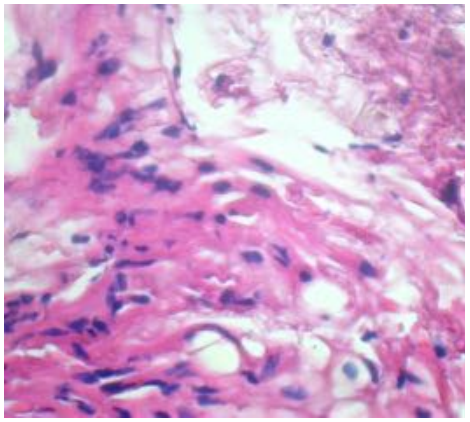
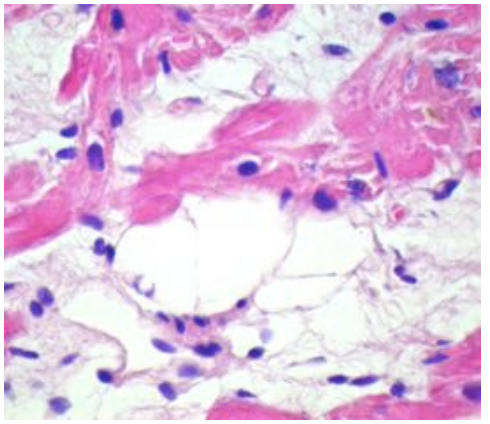
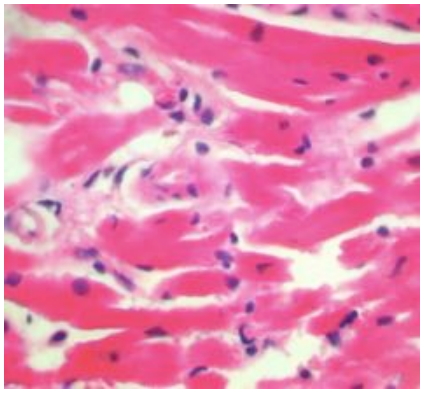
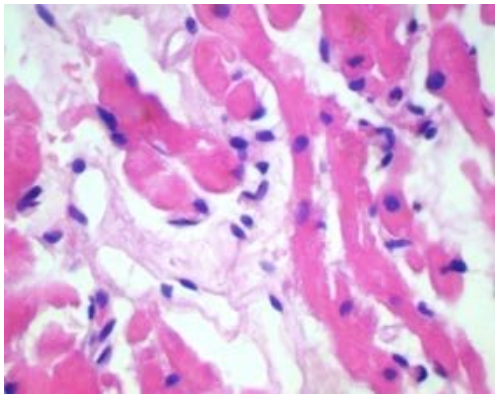
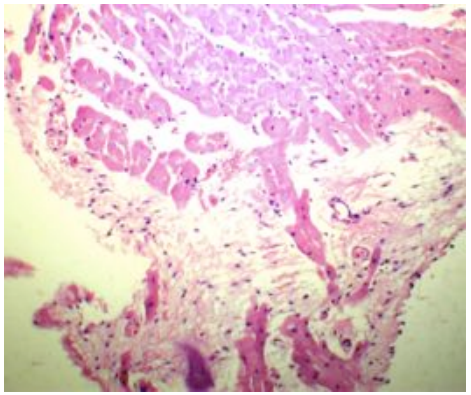
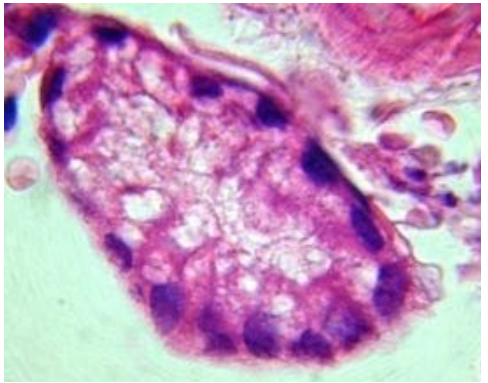
METHODS

- medical history, clinical examination
- standard blood examination (including thyroid function)
- ECG, Holter monitoring
- treadmill test (n = 5)
- transesophageal (n = 5) and intracardiac electrophysiological study (n = 3)
- Echo-CG
- measurement of the anti-heart antibodies (ELISA):
  - IgG to myocardial antigen (normal 1:100)
  - IgG to cardiomyocytes cytoplasmic protein CoS05-40 and membrane protein, CoM015-15; NO-synthase; β1-adrenergic receptor (n = 8, normal -30 to +20)
  - IgG to the antigens of endothelial cell, cardiomyocyte, smooth muscle, conduction heart system (normal 1:40), and antigen-specific anti-nuclear antibodies (ANA)
- viral genome detection in the blood (real-time PCR)
- measurement of the anti-streptococcal antibodies
- endomyocardial biopsy of the right ventricle
  - virus detection (real-time PCR)
  - morphological study with hematoxylin-eosin, Van Gieson, PAS staining, congo red
  - electron microscopy in some cases
- myocardial scintigraphy with ^{99}Tc-MIBI (n=10)
- multi-slice computer tomography of the heart (MSCT, n=3)
- magnet resonance imaging of the heart (MRI, n=3)
- coronary angiography (n=6)
- skin biopsy (n=1)
- otolaryngologist
- geneticist, DNA-diagnostic

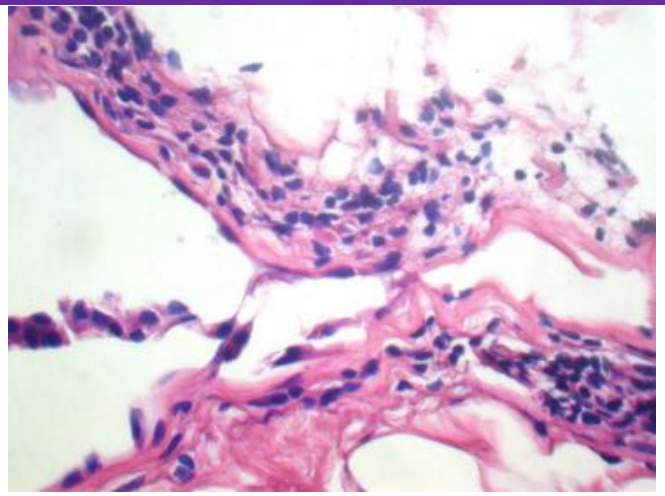
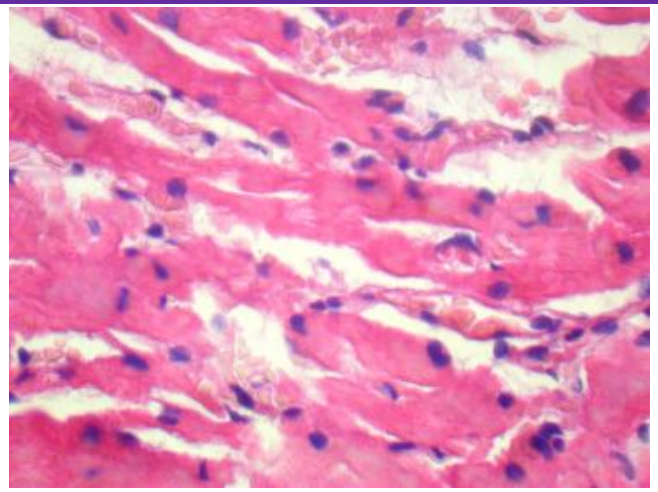
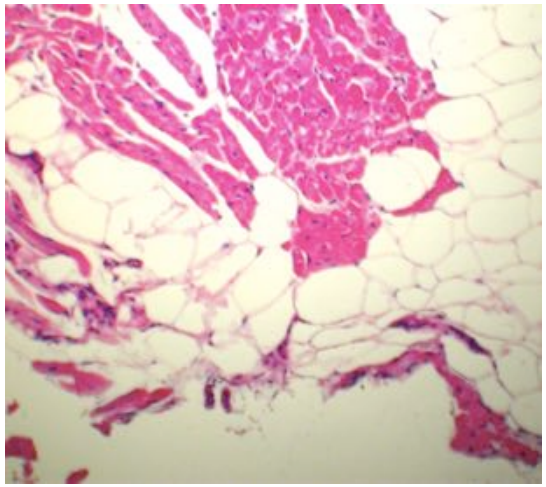
IMMEDIATE RESULTS OF THE MORPHOLOGICAL STUDY

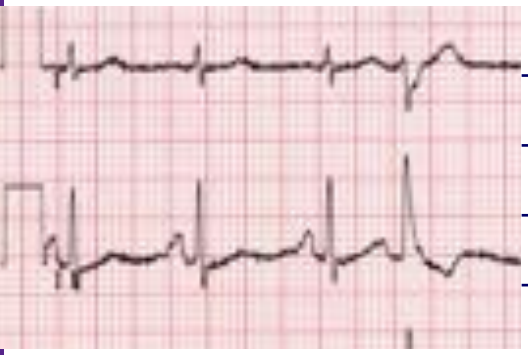
PCR results / morphological changes	n	%
parvovirus B19 / herpes simplex virus type 6 (PCR)	2/1 (from 18)	16.7%
endocardium sclerosis / thickening	8	42.1%
lymphocytic infiltration in endocardium	2	10.5%
subendocardial / interstitial lipomatosis	12	63.2%
interstitial lymphocytic infiltration (>14 and 7-10)	11/3	73.7%
necrosis of cardiomyocytes	6	31.6%
immune cytolysis (emperipolesis, peripolesis)	2	10.5%
mitosis in cardiomyocytes	1	5.3%
disarray of cardiomyocytes	2	10.5%
dystrophy of cardiomyocytes	14	73.7%
hypertrophy of cardiomyocytes	7	36.8%
productive vasculitis	7	36.8%
arteriosclerosis / angiopathy	7/1	36.8/5.3%
interstitial edema	12	63.2%
interstitial sclerosis	14	73.7%
fibro-fatty replacement	1	5.3%
PAS-positive substance in cardiomyocytes	1	5.3%
no changes	0	0
Total	19	100%

MORPHOLOGIC SIGNS OF THE MYOCARDITIS

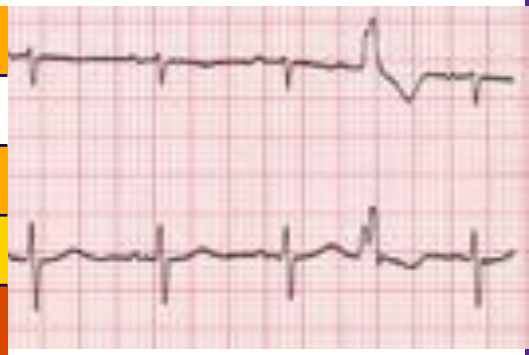













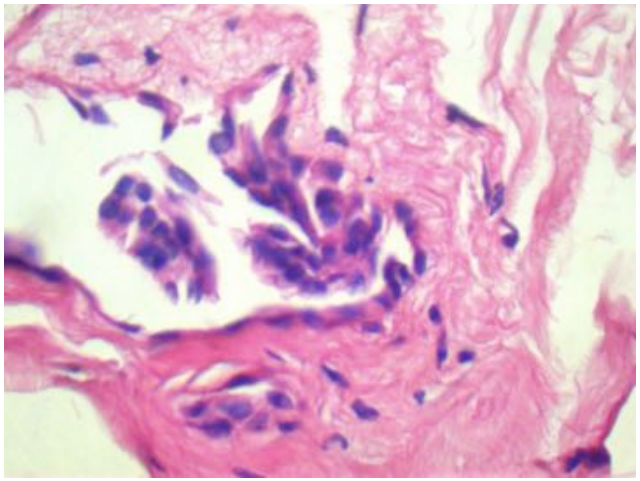
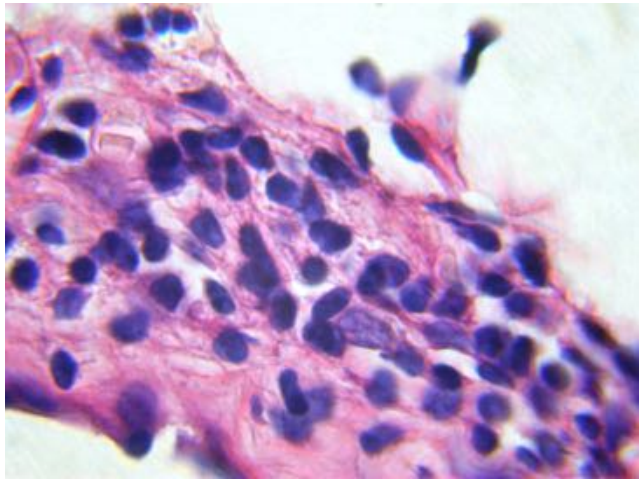
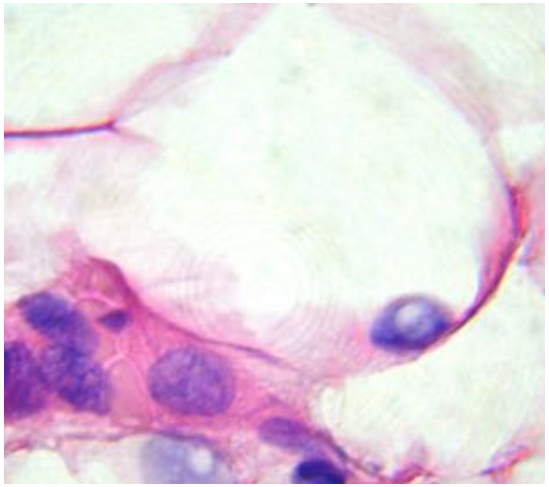
PARVOVIRUS-POSITIVE ENDOMYOCARDITIS



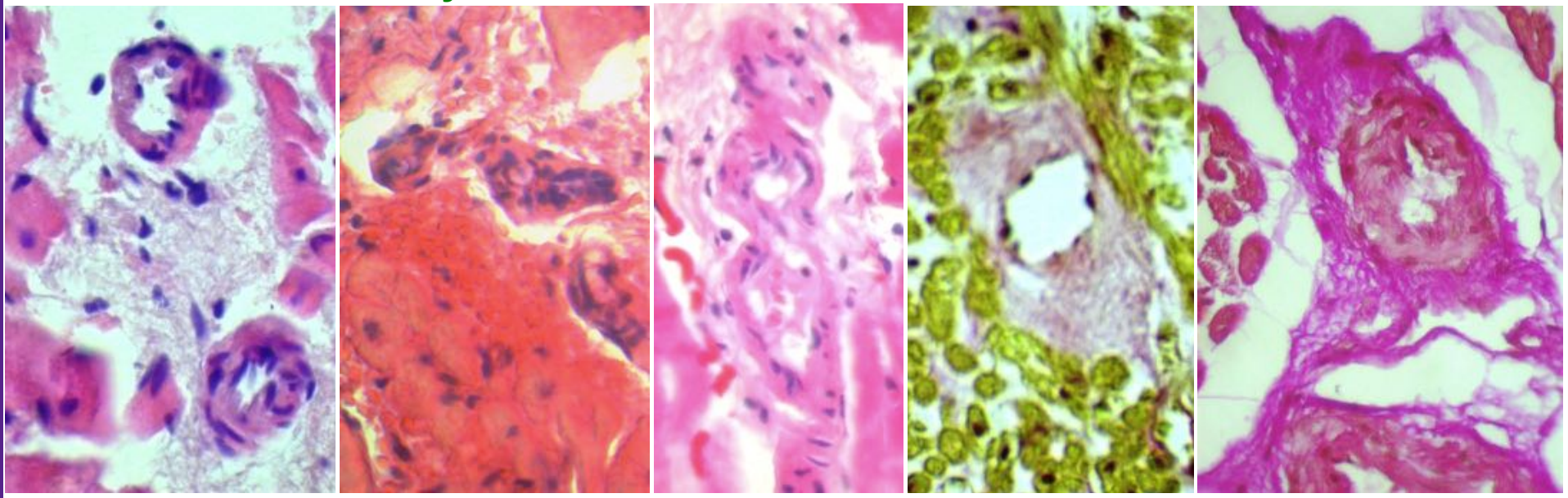
heart-specific anti-nuclear antibodies	1:160
IgG to the endothelial antigens	no
IgG to antigens of cardiomyocytes	1:160
IgG to antigens of smooth muscle	1:80
IgG to antigens of conductive system	1:320



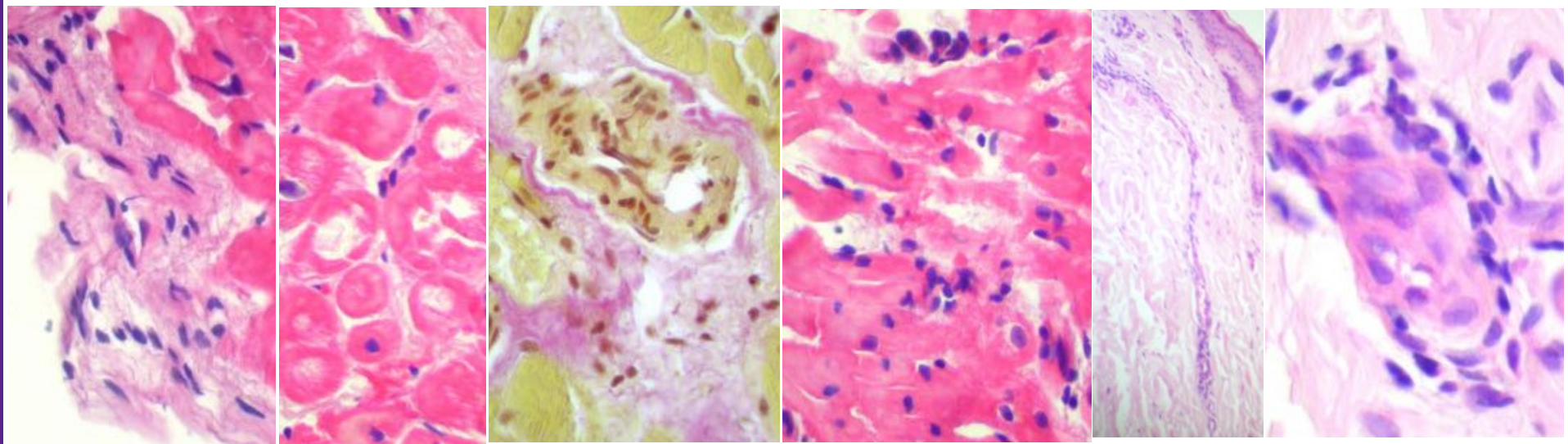




VASCULAR PATHOLOGY IN THE MYOCARDITIS

intramyocardial vasculitis with bulbous sclerosis

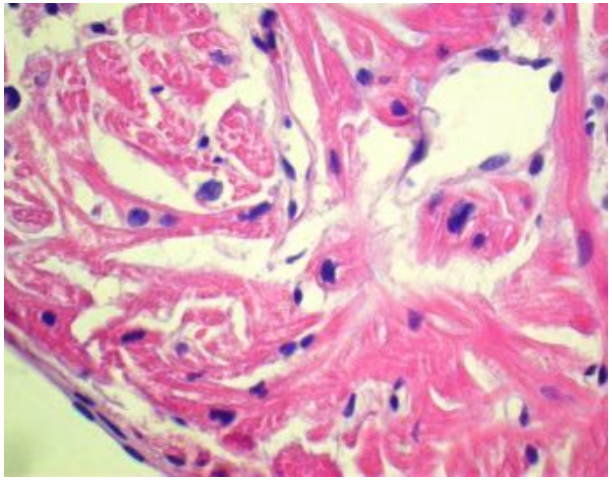
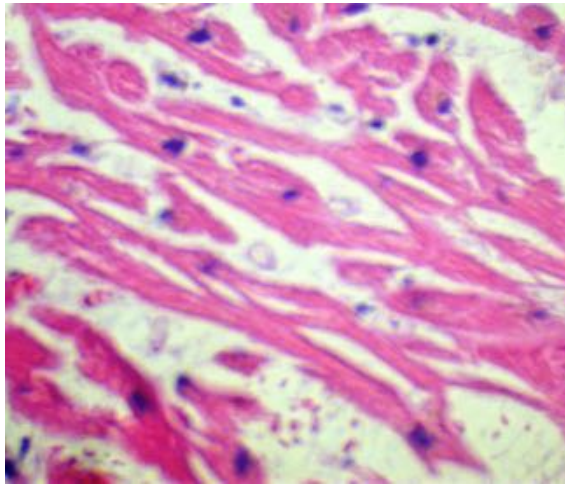
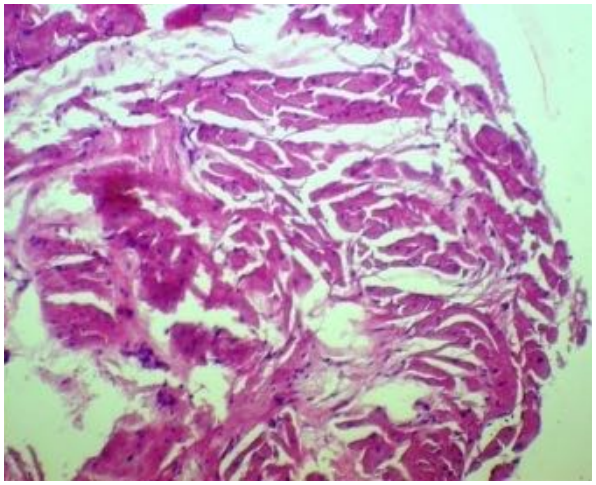


hypersensitive vasculitis with myoendocarditis

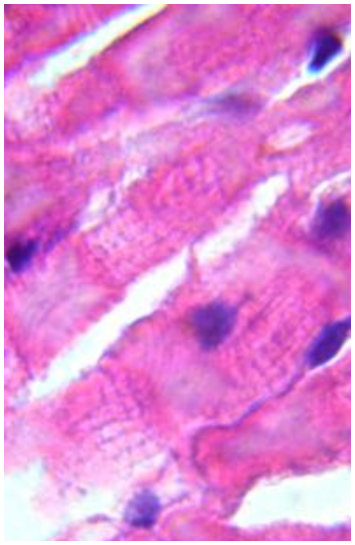
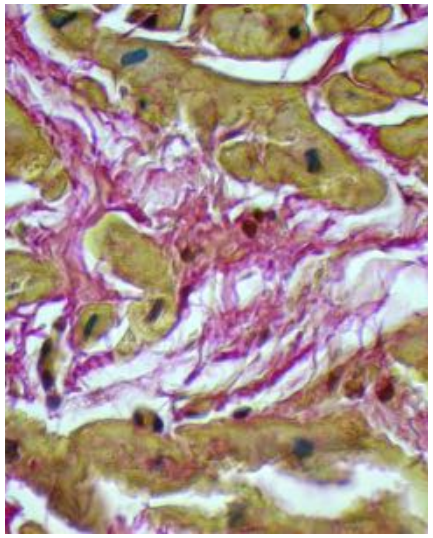


MORHOLOGIC SIGNS OF GENETIC CARDIOMYOPATHIES

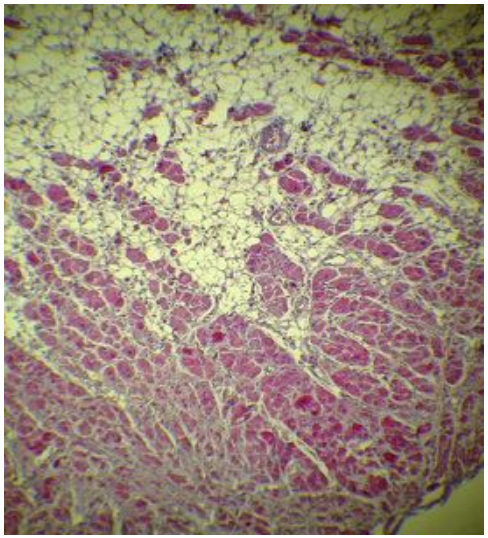
disarray of cardiomyocytes (unverified cardiomyopathy)

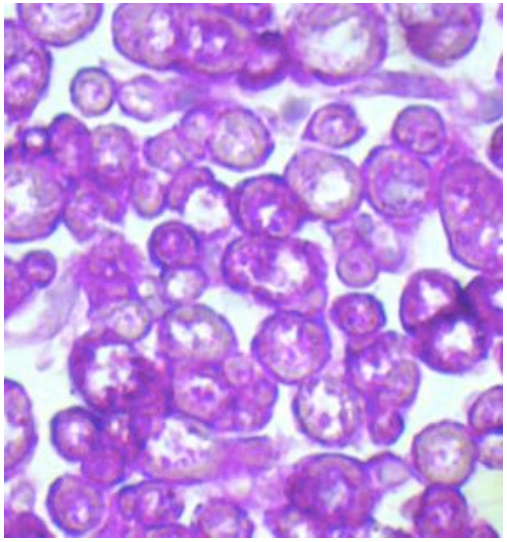
viral inclusions and fibrosis

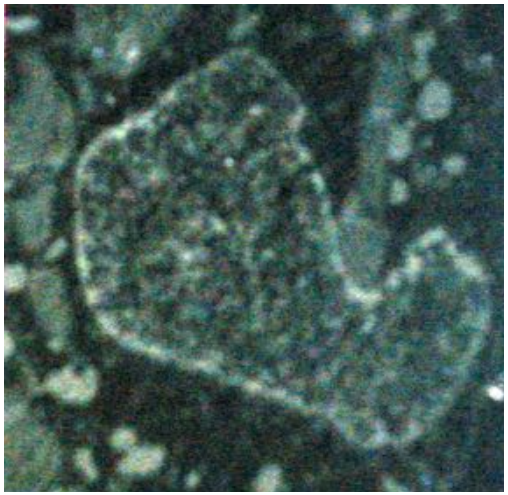
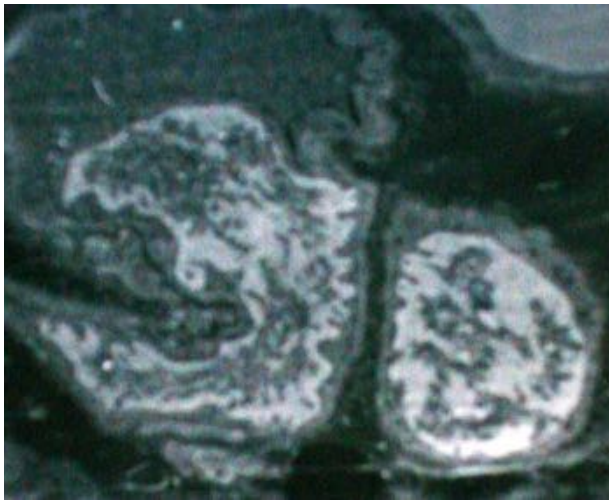
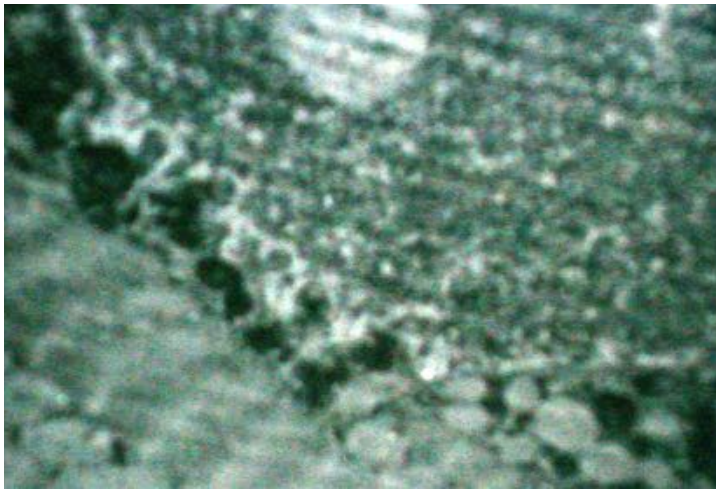
fibro-fatty replacement



«PAS+» substance



ELECTRON MYCROSCOPY

cardiomyocytes:

lysosomal myolysis, microbodies in cardiomyocytes,

mitochondrial wrinkling, cristae adhesion, absence of matrix

vessels:

vascular endothelium swelling,

thickening of the microvessels basic membrane,

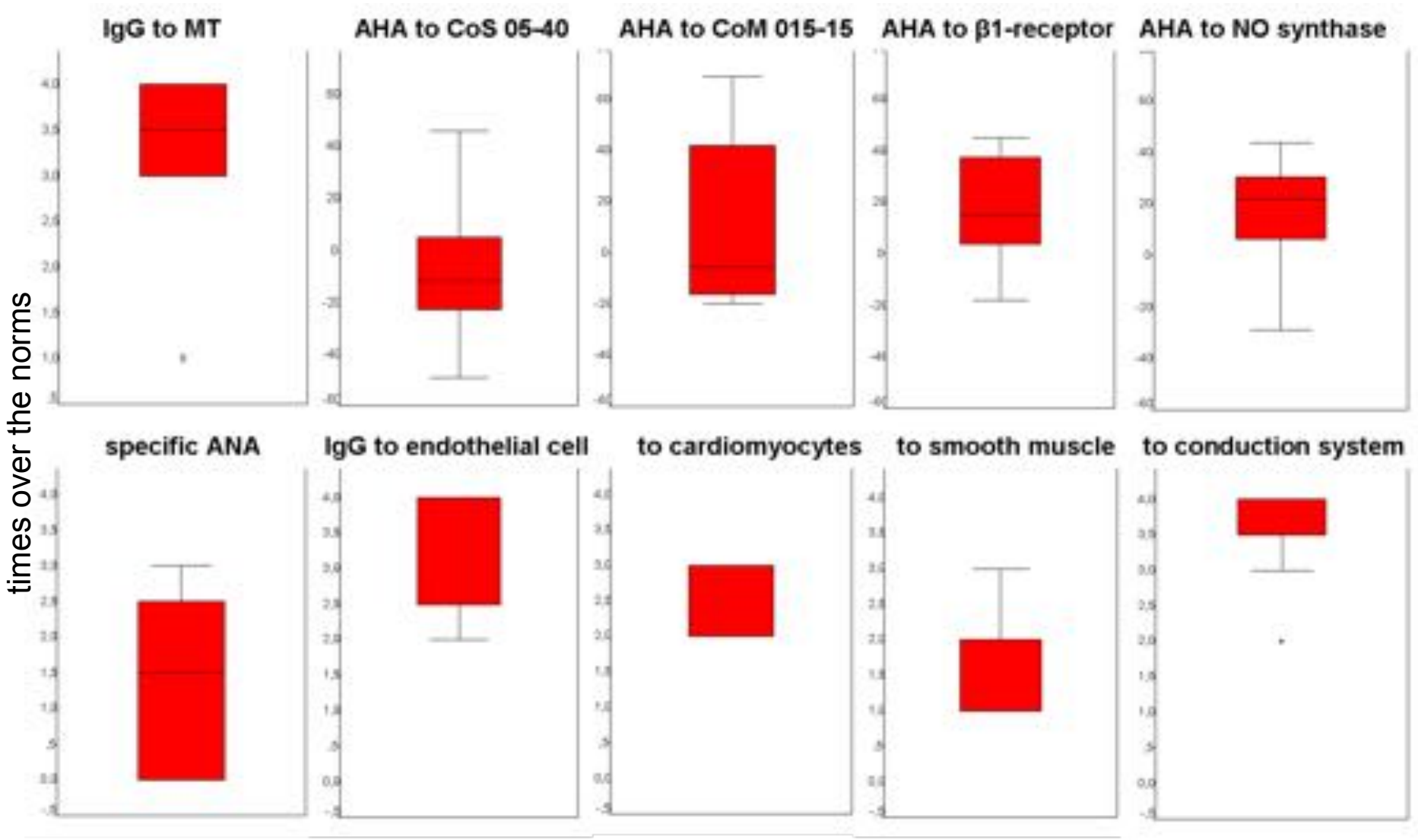
precipitate on the endothelium surface,

increased pinocytosis

BIOPSY PROUVED DIAGNOSIS (n=19)

initial diagnosis	diagnosis according to EMB	genetic diagnosis	n	%	
myocarditis?	**chronic / subacute infectious-immune myocarditis, including** virus-positive (parvo B19 in myocardium/ EBV in the blood) active / borderline lupus-myocarditis		**11** 2 6 3	**57,89%**	**78,9%**
	chronic viral autoimmune endomyocarditis (parvo B19)		**1**	**5,26%**	
myocarditis with predominant vasculitis?	**systemic vasculitis, including** hypersensitive		**2**	**10,53%**	
	myocardial vasculitis (with minimal signs of myocarditis)		**1**	**5,26%**	
myocarditis? genetic cardiomyopathy?	**viral (HHV6) + genetic cardiomyopathy**	**unverified**	**1**	**5,26%**	
	genetic cardiomyopathy	**unverified**	**1**	**5,26%**	
	Fabry disease	***X-GAL:*** p. Q283K	**1**	**5,26%**	**21,1%**
myocarditis? ARVD?	**arrhythmogenic right ventricular dysplasia**	***DSG2:*** p.V533I и ***DES:*** p.A213V	**1**	**5,26%**	

LEVELS OF ANTI-HEART ANTIBODIES



DIAGNOSTIC VALUE OF DIFFERENT CRITERIA

diagnostic criteria of the myocarditis

	sensitivity	specificity	+ predictive	- predictive
anamnestic triad	16.7%	100%	100%	25%
onset correlation with infection	50%	75.0%	87.5%	30%
history of tonsillitis	50%	75%	87.5%	30%
systemic immune signs	35.7%	100%	100%	30.8%
microvascular angina / ischemia	35.7%	100%	100%	30.8%
increased level of anti-O-streptolysin	21.4%	100%	100%	26.4%
increased CRP	14.3%	100%	100%	25%
non-specific inflammatory signs	35.7%	75%	83.3%	25%
viral genome in the blood	7.1%	75%	50%	18.8%
specific ANA	78.6%	66.7%	91.7%	40%
anti-endothelial cell IgG ≥ 1:160	78.6%	66.7%	91.7%	40%
anti-cardiomyocyte IgG ≥ 1:160	64.3%	100%	100%	37.5%
anti-conduction system IgG ≥1:160	92.9%	66.7%	92.9%	66.7%
isolated atriomegaly	64.3%	75%	90%	37.5%
pericardial effusion	21.4%	75%	75%	21.4%
focal defect of perfusion (scintigraphy)	33.3%	100%	100%	14.3%

diagnostic criteria of the genetic cardiomyopathy

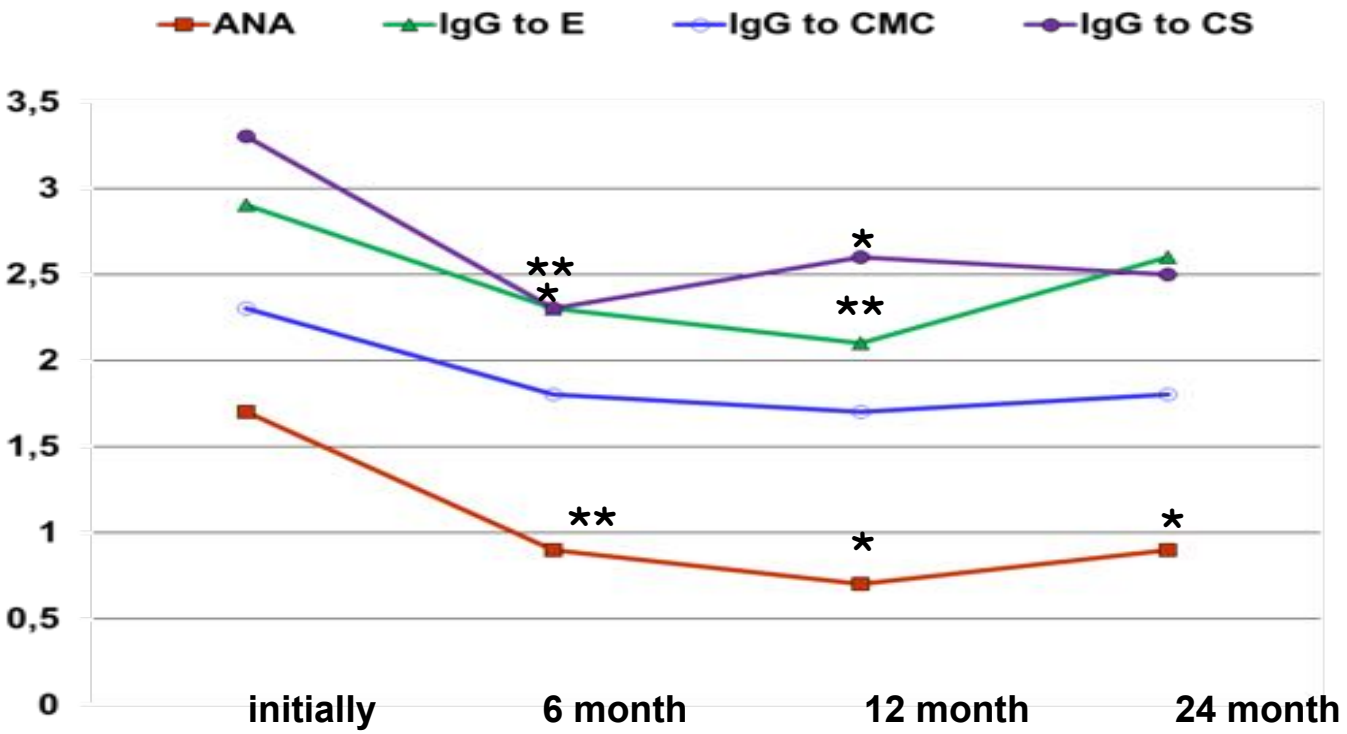
age younger than 40 years	75%	57.1%	33.3%	88.9%
isolated kinds of arrhythmia	75%	71.4%	42.9%	90.9%
family history	25%	100%	100%	82.4%
possible genetic markers	50%	100%	100%	87.5%
early repolarization syndrome	50%	78.6%	40%	84.6%

MEDICAMENT TREATMENT

medication	n	%
antivaral therapy	**4**	**21.1**
IV gancyclovir 500 mg/day № 7-14	1	
IV aciclovir 800-1200 mg	2	
aciclovir 1600-2000 mg/day	1	
IV immunoglobulin 5-20 g	**2**	**10.5**
immunosupressive treatment	**15**	**78.9**
pulse therapy (steroids 1000 mg №3)	1	
corticosteroids (31,1±12,5 mg/day)	14	
azatioprine 150 mg/day	2	
hydroxychloroquine 200 mg/day	15	
ACE inhibitors	**7**	**36.8**
β-blockers	**10**	**52.6**
antiarrhythmic drugs	**14**	**73.7**
IC class (aethacizine, allapinine, propafenone)	10	
amiodarone	4	
anticoagulants	**9**	**47.4**

IMMEDIATE RESULTS OF BASIC THERAPY

decreasing of the anti-heart antibodies level



*p<0.05, **p<0.01 compared with the initial data

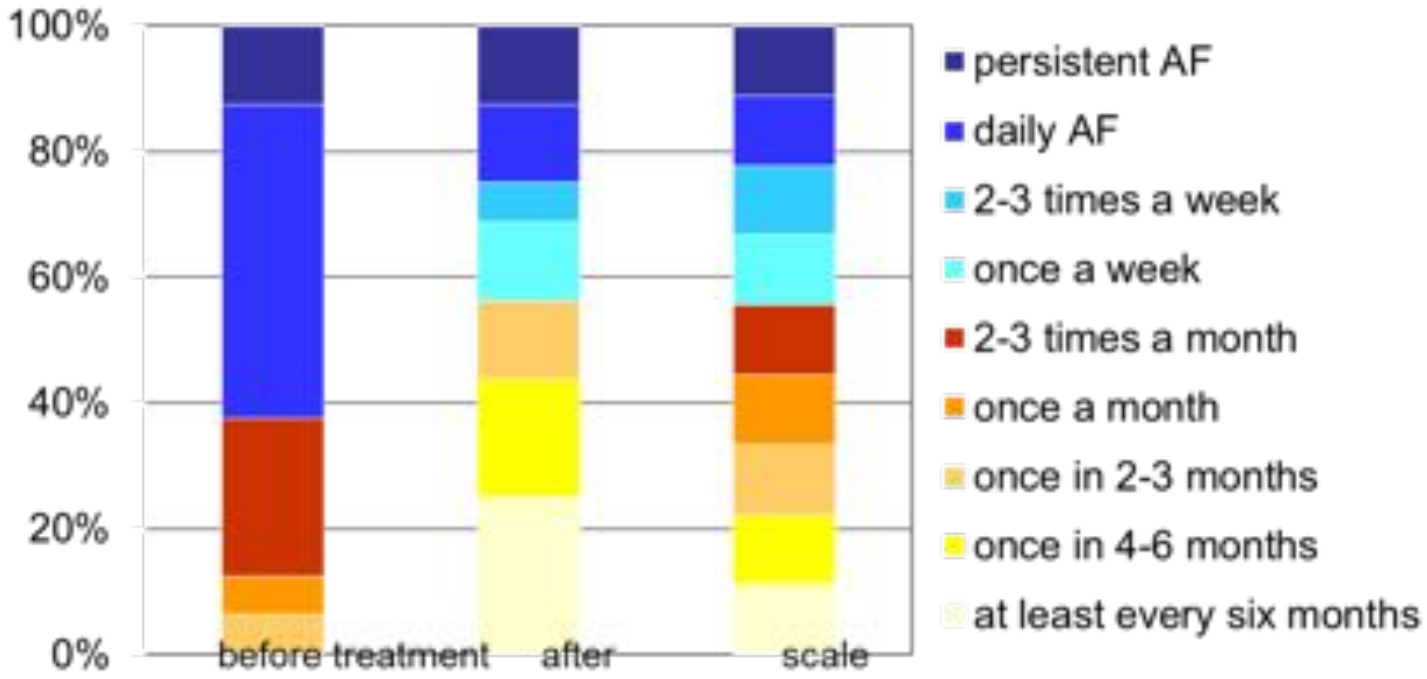
frequency of viral DNA elimination in the blood

virus type	PCR after 1 course of therapy	finally PCR
Epstein-Barr virus	negative	negative
Human herpes virus type 6	positive	positive
Bath (total effect)	50%	50%

CLINICAL RESULTS OF TREATMENT

the mean follow-up 48,0 [31,0; 62,0] months

decreasing of AF frequency



- decrease of AF frequency (from several times per day to 1 per month) was noted in 56.3 % of patients
- in one case stress-induced left bundle branch block disappeared
- none of the patients with immunosupressive therapy had chronic form of AF
- recurrence of arrhythmia due to infection or therapy withdrawal was noted in 60%
- in 5 patients (including those with ARVD) RF ablation was successfully performed
- 2 pacemakers and 1 ICD (in patient with ARVD) were implanted

PREDICTORS OF EFFECTIVE THERAPY

- relatively recent history of arrhythmia (less than five years)
- easy suppression arrhythmia using antiarrhythmics
- the presence of microvascular ischemia
- high levels of anti-heart antibodies
- significant reduction in the level of specific ANA due to immunosuppressive therapy

causes of the insufficient treatment

- high morphological activity of myocarditis
- irreversible structural changes (fibrosis, lipomatosis)
- viral persistence
- insufficient dose and duration of immunosuppressive therapy
- relapse due to infection

CONCLUSIONS

- EMB of the right ventricle allows nosological diagnosis in all patients with «idiopathic» arrhythmias (predominantly AF, as well as PVCs and LBBB)

- EMB revealed the immune-inflammatory nature of «idiopathic» arrhythmias (AF) in 78.9% of patients and genetic cardiomyopathy in 21.1%

- level of various anti-heart antibodies, including specific ANA, had the highest diagnostic value among noninvasive markers

- lack of correlation of arrhythmia onset with infection, acute onset, and coronary atherosclerosis and hypertension could not rule out myocarditis; more than half of the patients had primary chronic myocarditis

- antiviral and immunosuppressive therapy appointed according to myocarditis activity, could improve the effectiveness of antiarrhythmic therapy in patients resistant to antiarrhythmic drugs or prepare them for the RFA

- the best results of therapy had patients with a recent history of arrhythmia, relatively easy suppression of arrhythmia using antiarrhythmic drugs and high immune activity

- basic therapy of myocarditis, the underlying «idiopathic» arrhythmias, should be conducted continuously considering the chronic course of the disease and its tendency to relapses