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Pathomorphologic findings in left ventricular hypertrabeculation/noncompaction of adults in relation to neuromuscular disorders

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ABSTRACT

Background: Aim of this study was to assess pathomorphologic findings (PATHO) in patients with echocardiographically (ECHO) diagnosed left ventricular hypertrabeculation/noncompaction.
Methods: ECHO-criteria for LVHT were: >3 trabeculations, moving synchronously with the compacted myocardium, and forming the noncompacted part of a two-layered myocardium. At autopsy, the hearts were investigated according to the pathologists' preferences.
Results: Twelve patients (2 females, age 27–81 years) were included. Seven suffered from neuromuscular disorders, 5 patients were not investigated neurologically. The specimens were acquired after explantation during heart transplantation (n = 1), death due to heart failure (n = 6), sudden death (n = 2), pneumonia (n = 2) and stroke (n = 1). Eight hearts were investigated without fixation and 4 after formaldehyde fixation. The hearts were opened along the long-axis, in 3 hearts additional short-axis cuts were carried out.
At PATHO the trabecular meshwork was better visible in the formaldehyde-fixed hearts than in the fresh hearts. Differentiation from papillary muscles was easier on the long-axis cuts, whereas the two-layered structure was better visible on short-axis cuts. The trabecular pattern was similar in patients with neuromuscular disorders and those who did not undergo neurologic investigation. Subendocardial fibrosis was found in each case. Due to the complex three-dimensional geometry, it was impossible to count the number of trabeculations.
Conclusion: Formaldehyde-fixation should be performed when comparing ECHO with PATHO findings in LVHT. Long-axis as well as short-axis cuts should be carried out in order to assess the course of trabeculations and the extent of the two-layered structure. Subendocardial fibrosis in LVHT deserves further research.

1. Introduction

Left ventricular hypertrabeculation/noncompaction (LVHT) is a cardiac abnormality of unknown etiology, which is most frequently diagnosed by echocardiography, but can be also visualized by cardiac computed tomography, magnetic resonance imaging or ventriculography [1]. If systematically screened, LVHT is frequently associated with neuromuscular disorders (NMD) [2]. Pathoanatomic as well as imaging criteria for LVHT are still a matter of debate [3–5]. Furthermore, it is unknown if the morphology of LVHT differs between patients with and without NMD. Aim of this study was to assess pathomorphologic findings in patients with echocardiographically diagnosed LVHT from our database, to assess pathomorphologic findings of LVHT patients with NMD, and to compare our findings with patients reported in the literature.

2. Methods

2.1. Patients

We evaluated patients with echocardiographically diagnosed LVHT whose hearts were pathoanatomically investigated, either at autopsy or after cardiac transplantation. The patients were recruited from the LVHT-database of the echocardiographic laboratory of the Rudolfstiftung hospital, where LVHT cases were collected and registered since 1995 or from the German–Austrian "noncompaction registry", founded and initiated in 2007 by the "Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte" (ALKK). Clinical and demographic data were registered from the patients' records. All LVHT patients from the Rudolfstiftung hospital were invited for a neurological investigation carried out by a neurologist dedicated to NMD (JF). The neurologic investigation comprised the history and a clinical neurological examination, and further instrumental investigations if a NMD was suspected. A NMD was diagnosed if clinical or instrumental findings indicated the presence of a NMD. NMD was categorized as "specific" if a diagnosis could be established. Cases with a non-specific diagnosis were categorized as "NMD of unknown etiology".

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Table 1
Echocardiographic diagnostic criteria for left ventricular hypertrabeculation/noncompaction [5].

>3 trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in one echocardiographic image plane at end-diastole;
A two-layered myocardial structure with the trabeculations forming the noncompacted part, visible at end-systole;
Intertrabecular spaces perfused from the ventricular cavity, visualized on color Doppler imaging

2.2. Echocardiography

Two-dimensional and Doppler-echocardiographic criteria for the diagnosis of LVHT were: >3 trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in one echocardiographic image plane at end-diastole; trabeculations form the noncompacted part of a two-layered myocardial structure, best visible at end-systole; intertrabecular spaces perfused from the ventricular cavity, as visualized on color Doppler imaging (Table 1). Trabeculations were defined as structures moving synchronously with the ventricular contractions, distinct from ventricular bands, false tendons and prominent papillary muscles. The diagnostic criteria remained the same during the study period [5].

2.3. Pathologic investigation

At autopsy, the hearts were investigated according to the pathologists' preferences and the pathoanatomic findings were documented by photography. Thickness of the compacted and noncompacted myocardial layers were measured and the presence of subendocardial fibrosis was evaluated at pathoanatomic inspection [6,7]. Additionally it was attempted to count the number of trabeculations according to the method described by Boyd et al. [8]. For measurements the software ImageJ (Rasband W.S., U.S. National Institutes of Health, Bethesda, Maryland, USA, http://imagej.nih.gov/ij/, 1997–2012) was used.

Either at autopsy or by reviewing the photographs, the extension of subendocardial fibrosis was described as "diffuse" or "patchy" and semiquantitatively assessed as "mild", "moderate" or "severe". Echocardiographic and pathomorphologic findings were compared and methodological problems were recorded.

2.4. Patients reported in the literature

A literature search was carried out by systematically screening MEDLINE for publications with the key words "noncompaction", "non-compaction", "hypertrabeculation" from 1990 to 2013. Reference lists and older references generated from initial papers were also considered. Longitudinal studies, case series and case reports were included. Included were patients >20 years of age in whom a pathomorphologic description of the heart with or without images was reported. Excluded were cases where the pathomorphologic data could not be exactly assigned to clinical data.

3. Results

3.1. Patients

Twelve patients (2 females, 10 males, mean age 63 years, range 27–81 years) were included. Several findings of these patients have been reported previously [9–15]. Ten patients were from the Rudolfstiftung database and 2 from the ALKK registry. The specimens were acquired after explantation during heart transplantation (n = 1), death due to heart failure (n = 6), sudden death (n = 2), death from pneumonia (n = 2) and death after stroke (n = 1). Death or cardiac transplantation had occurred between 2002 and 2011. The clinical and pathomorphologic characteristics are listed in Table 2. One patient suffered from Duchenne muscular dystrophy, one patient from mitochondrial myopathy, 5 patients from NMD of unknown etiology and 5 patients were not investigated neurologically.

3.2. Pathologic investigation

At autopsy, 8 hearts were investigated without previous fixation and 4 after formaldehyde fixation. The hearts were opened along the long-axis by performing either the classical "inflow-outflow" method or cutting the heart longitudinally in an anterior and posterior half. In 3 hearts, after the posterior and anterior half were repositioned and glued together, additional short-axis "breadloafing" cuts were carried

Table 2
Characteristics of the included patients.

Initials/sex	Age at diagnosis/death, years	HTN	DM	CAD	NMD	Cause of death	Autopsy technique	Heart weight	N/C ratio (patho)	Endocardial fibrosis	Pub
BL/m	40/47	0	0	0	U	Pneumonia	Native, LA	1100 g	1.5	Diffuse severe	[9]
BR/m	63/67	+	+	0	U	Heart failure	Formalin, LA + SA	730 g	1.06	Diffuse severe	
HR/f	80/80	+	+	−	U	Stroke	Native LA	650 g	1.5	Diffuse severe	[10]
KG/m	56/57	+	+	−	NI	Heart failure	Native LA	600 g	0.87	Diffuse moderate	[11]
LA/m	27/28	0	0	−	E	Pneumonia	Native LA	600 g	1.4	Focally severe, mild to moderate	[12]
PN/m	77/78	+	0	+	U	Heart failure	Native LA	760 g	1.6	Diffuse severe	[13]
RM/f	74/75	+	+	−	U	Heart failure	Native LA	710 g	1.0	Diffuse mild	[14]
AO/m	61/61	+	+	0	NI	Explantation	Formalin, LA	750 g	1.22	Diffuse severe	[15]
HH/m	57/57	−	−	−	NI	SCD	Native, LA	850 g	1.1	Patchy	
ES/m	62/62	−	−	−	NI	SCD	Native, LA	520 g	Not measured	Diffuse mild to moderate	
GO/m	51/64	0	+	0	E	Heart failure	Formalin, LA + SA	420 g	0.61	Patchy	
AP/m	81/81	+	+	−	NI	Heart failure	Formalin, LA + SA	790 g	0.58	Diffuse mild	

CAD = Coronary artery disease.
DM = Diabetes mellitus.
E = specific neuromuscular disorder.
HTN = arterial hypertension.
LA = long axis.
N/C ratio = ratio of noncompacted to compacted myocardial layer.
NI = not investigated.
NMD = neuromuscular disorder.
SA = short axis.
U = neuromuscular disorder of unknown etiology.