

Left Ventricular Systolic and Diastolic Function by Echocardiogram in Pseudoxanthoma Elasticum

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Pseudoxanthoma elasticum is an inherited systemic disease of connective tissue with possible cardiac involvement. Nineteen patients with pseudoxanthoma elasticum without a history of cardiac disease were investigated by echocardiography using standard measurements and tissue Doppler imaging. Systolic function was normal, but diastolic parameters were abnormal in 7 patients. Explanations for these abnormalities could be silent myocardial ischemia due to early coronary involvement and/or the direct consequences of ultrastructural defects of the elastic tissue of the heart. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;97:1535–1537)

Pseudoxanthoma elasticum (PXE) is an inherited systemic disease of connective tissue primarily affecting the skin, retina, and cardiovascular system.¹ PXE is characterized pathologically by the early and progressive mineralization and fragmentation of elastic fibers and clinically by high heterogeneity with regard to age at onset and the extent and severity of each organ's involvement.¹ PXE was recently related to mutations in the adenosine triphosphate-binding cassette subtype C number 6 (ABCC6) gene, which encodes an adenosine triphosphate-dependent transmembrane transporter. Its substrates are still unrecognized, but the current hypothesis considers PXE as an inherited metabolic disorder with undetermined circulating molecules interacting with the synthesis or turnover of extracellular matrix components.¹ Elastic fiber-rich walls of middle-sized arteries are involved in PXE, resulting in precocious and slow-evolving arterial narrowing indistinguishable from usual atheromatosis.² Whether heart involvement is common in PXE is unclear, but it seems logical considering the pathophysiologic process. We hypothesized that if lesions of elastic fibers do occur in the heart, changes in ventricular function could be detected by echocardiographic examination before any symptoms of cardiac insufficiency occur. Diastolic dysfunction is often the first preclinical manifestation. Recent methods such as tissue Doppler imaging (TDI) and color M-mode echocardiography detect these abnormalities accurately and noninvasively,³ and we therefore chose to use these techniques to assess diastolic function in patients with PXE.

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Consecutive asymptomatic patients with diagnoses of PXE were recruited from January 2004 to February 2005 by our French multidisciplinary group for PXE evaluation and treatment. The diagnosis of PXE was based on the demonstration of characteristic elastic fiber changes in skin biopsy samples and angioid streaks on eye fundusoscopic examination. ABCC6 mutation analysis was systematically performed according to our published procedure.⁴ Patients with hypertension or with known or suspected cardiac disease demonstrated by histories or symptoms were excluded from the study population. Coronary disease was ruled out by a standard treadmill test and/or by myocardial tomoscintigraphy. Nineteen patients (mean age 50 years; 10 women, 9 men) fulfilling these criteria were compared with a group of 30 normal subjects without a history of cardiac disease or hypertension.

Standard M-mode, bi-dimensional imaging, Doppler, and TDI measurements were performed in all patients using a commercial HDI 5000 system (Phillips Medical Systems, Andover, Massachusetts), according to the recommendations of the American Society of Echocardiography.⁵ Ventricular mass index was calculated according to the Devereux formula. The ejection fraction was estimated according to left ventricular volumes evaluated by Simpson's biplane method. Early (E) and atrial (A) peak velocities were measured. Wall motion velocities (E_m) were assessed by TDI at the level of the mitral annulus on the septal, lateral, inferior, and anterior walls in 2- and 4-chamber views. E_m was calculated according to measurements for each wall. Flow propagation velocity (V_p) was measured from color M-mode recordings. All findings were subsequently measured on digital recordings and were averaged on 3 to 5 cardiac cycles by 2 experienced echocardiographers blinded to the clinical information. Inter- and intraobserver variabilities had previously been tested (<5% for all parameters).⁶

Table 1 lists the echocardiographic findings for the 2 groups. Systolic function, indexed ventricular mass and

Table 1
Echocardiographic data

Variable	PXE	Normal	p Value
EF (%)	0.64	0.62	NS
VMI (g/m ²)	106	103	NS
CI (L/mm/m ²)	3.7	3.5	NS
E (m/s)	0.77	0.68	0.07
A (m/s)	0.66	0.59	NS
E/A (m/s)	1.22	1.23	NS
E _m (m/s)	0.11	0.14	0.02
E/E _m (m/s)	7.14	5.01	0.01
V _p (cm/s ²)	53	65	0.1

The ejection fraction (EF) is expressed as a percentage. Cardiac index (CI) is expressed in L/mm/m²; ventricular mass index (VMI) in g/m²; E, A, and E_m in m/s; and V_p in cm/s².

volume, and cardiac index were similar in the 2 populations. No endocardial calcifications were detected in our patients. Early mitral peak velocity was slightly greater in patients with PXE. In contrast, annular velocity was smaller in patients with PXE, leading to a significantly greater E/E_m ratio. There was a tendency to slower mitral flow propagation, but it did not reach significant statistical difference. Three patients in the PXE group had E/E_m ratios >12. Five patients also had reduced V_p (<40 cm/s). Consequently, 7 of 19 subjects with PXE had ≥1 classic criterion for diastolic abnormality (compared with none in normal subjects). No correlations between diastolic function and ABCC6 genotype or other cutaneous, ophthalmologic, or arterial involvement indicative of poor prognosis were found.

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The key finding of our study was that the prevalence of diastolic dysfunction in unselected asymptomatic inpatients with PXE is high (37% of our population).

Left ventricular diastolic function is a complex process, with many inter-related factors, such as preload and left ventricular compliance.⁷ There is no simple echocardiographic assessment of diastolic function, and multiple parameters are needed. Mitral valve flow is the first parameter used but has low sensitivity and specificity. Mitral valve TDI associated with the latter shows good correlation with left ventricular filling pressure.^{3,8} V_p is a simple, reliable, and preload-insensitive parameter.⁹

Cardiac involvement in PXE affects the coronary arteries, with fairly early onset, either by organic stenosis or, in rare instances, by spasm.¹⁰ Calcification of the elastic layer in the media of small and intermediate-sized arteries is followed by atheromatous disease. Fragmentation of the elastic layer in arteries has also been found in pathologic studies² and was suspected in a recent endocoronary echocardiographic study.¹¹ Coronary aneurysms have also been described.¹² Angina pectoris may be present and has even been reported in teenagers and young adults.^{13,14} Endocar-

dial lesions with intimal fibroelastic thickening, fragmentation, and calcification of elastic fibers have also been described in necropsy reports.^{2,15} In addition, heterozygosity for R1141X, the most frequent ABCC6 mutation in European patients with PXE, is also associated with the increased occurrence of premature coronary artery disease without skin or eye manifestations.^{16,17} PXE or heterozygote carriage of ABCC6 mutation should therefore be investigated in young patients with precocious coronary disease and no identified cardiovascular risk factors. Interestingly, PXE displays multivisceral vascular involvement comparable with metabolic diseases such as diabetes. The hypothesis of a deleterious circulating serum factor has been proposed.¹⁸

The reasons for diastolic dysfunction in PXE might therefore be multiple in our population without clinical cardiac disease, with either the preclinical involvement of coronary artery or endocardial disease or the direct consequences of ultrastructural serum-mediated defects of heart elastic tissue. We believe that serial echographic assessments with TDI are valuable in patients with PXE (maybe yearly), although no prophylactic treatment is available to date. The impact of heterozygosity for mutations of the ABCC6 gene (e.g., in relatives of patients with PXE) on diastolic function is still unknown and should also be investigated in further studies.

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