Letter

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Pseudoxanthoma elasticum is associated with cardiocirculatory inefficiency

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SUMMARY Pseudoxanthoma elasticum (PXE) is a rare, genetic, metabolic disease characterized by dystrophic calcification of elastic fibres in the skin, retina and vascular wall. Data on cardiac involvement are inconsistent. Hence, we aimed to evaluate cardiorespiratory response to incremental cardiopulmonary exercise testing (CPET) in PXE. A total of 30 PXE patients (54.0 ± 11.2 years, 40.0% male) and 15 matched controls underwent symptom-limited incremental CPET. PXE patients presented an impaired peak work rate as compared to controls (84.2 ± 16.0% *vs*. 94.7 ± 10.4%, $p = 0.03$) that was accompanied by a lower peak oxygen uptake (in % predicted and mL/min/kg), reduced increments in oxygen uptake per increments of work rate ($\Delta V'O_2/\Delta WR$, 8.4 ± 3.0 mL/min/W *vs*. 11.3 ± 4.9 mL/min/W, $p = 0.02$), lower peak oxygen pulse (78.0 ± 12.3% *vs*. 90.6 ± 19.6%, $p = 0.01$) and reduced minute ventilation at peak exercise ($V'E$, 66.2 ± 16.8% *vs*. 82.9 ± 25.2%, $p = 0.02$). To summarize, we presently observed impairment in mainly cardiocirculatory parameters, whilst no substantial ventilatory limitation was detected. The potential implications of this finding for PXE management warrant further study.

Keywords pseudoxanthoma elasticum, cardiopulmonary exercise testing, cardiocirculatory limitation

Pseudoxanthoma elasticum (PXE) is a rare, multisystem disorder with autosomal recessive inheritance in which ectopic calcification affects elastin-rich connective tissues such as the skin, eyes and cardiovascular system (*1,2*). First clinical manifestations of PXE occur in childhood to adolescence and comprise diverse cutaneous lesions. Ophthalmological changes become apparent in the third to fourth decade of life, affect the ocular fundus, predispose to choroidal neovascularization and entail the risk of blindness as early as in the fifth to sixth decade (*3*). Cardiovascular manifestations occur years after the onset of dermal and retinal lesions. They result from an extensive calcification of both the medial and intimal layer of small- and medium-sized arteries. Vascular symptoms primarily encompass intermittent claudication in consequence of peripheral vascular compromise. However, arterial narrowing has casuistically also been described to affect the coronary vascular bed (*4*). Moreover, autoptic studies have identified degenerated elastic fibres with calcification in the subendocardium, suggesting cardiac involvement in PXE (*1,5*). In keeping with this, the aim of the present study was to evaluate cardiorespiratory response to incremental cardiopulmonary exercise testing (CPET) in PXE patients and to compare the results with those obtained in matched healthy controls.

Between January and May 2018, 30 consecutive patients with PXE were included in this case-control study. PXE diagnosis relied on the revised diagnostic criteria by Plomp *et al*. (*6*). Exclusion criteria for study participation comprised preexisting cardiac disorders or symptomatology. 15 age-, gender- and body mass index-matched healthy controls were recruited from the general population by screening invitation. All study participants gave written informed consent for partaking in the study. The study was approved by the medical ethics committee of the University Hospital Bonn, Germany (No. 349/17) and complied with the Declaration of Helsinki. All subjects underwent symptom-limited incremental CPET (Cardiovit AT-104, Schiller, Feldkirchen, Germany) using a cycle ergometer in semi-supine position. The same step protocol was applied for patients and controls. It provided baseline measurements before exercise for 2 min, followed by an initial workload of 10–30 W which was increased by 10–20 W every 1–2 min. Participants were encouraged to exercise until exhaustion. Prior to CPET, detailed pulmonary function testing was performed. Statistical analyses were conducted using

Table 1. Demographics, PFT- and CPET-derived measurements in PXE patients and controls

Variables	PXE patients (n = 30)	Controls (n = 15)	p value
Demographics			
Age [years]	54.0 ± 11.2	56.6 ± 10.4	0.46
Male sex	12 (40.0%)	7 (46.7%)	0.67
BMI [kg/m²]	27.1 ± 4.2	24.7 ± 4.4	0.08
Pulmonary function testing			
TLC [L]	6.3 ± 1.3	7.1 ± 0.9	**0.04**
TLC [% predicted]	106.2 ± 15.7	112.5 ± 17.2	0.23
FVC [L]	3.8 ± 0.9	3.8 ± 0.9	0.90
FVC [% predicted]	101.7 ± 14.1	93.2 ± 14.5	0.07
FEV_1 [L]	3.2 ± 0.7	3.2 ± 0.7	0.76
FEV_1 [% predicted]	102.7 ± 14.2	95.4 ± 10.8	0.09
FEV_1/VC [%]	87.8 ± 8.7	83.8 ± 4.9	0.11
DL_{CO} [% predicted]	73.2 ± 13.5	80.3 ± 7.7	0.07
DL_{CO}/VA [% predicted]	81.0 ± 14.6	85.6 ± 12.6	0.31
CPET			
Work rate peak [W]	125.5 ± 40.1	141.1 ± 37.8	0.22
Work rate peak [% predicted]	84.2 ± 16.0	94.7 ± 10.4	**0.03**
RER peak	1.11 ± 0.11	1.13 ± 0.10	0.45
Heart rate peak [per min]	133.9 ± 16.1	143.3 ± 17.0	0.08
Heart rate peak [% predicted]	89.7 ± 10.3	100.2 ± 9.7	**0.003**
O_2 pulse peak [mL/beat]	10.7 ± 3.6	12.0 ± 2.1	0.22
O_2 pulse peak [% predicted]	78.0 ± 12.3	90.6 ± 19.6	**0.01**
$\dot{V}O_2$ peak [L/min]	1.41 ± 0.44	1.66 ± 0.39	0.08
$\dot{V}O_2$ peak [% predicted]	75.3 ± 11.6	89.5 ± 16.4	**0.002**
$\dot{V}O_2$ peak/kg [mL/min/kg]	18.1 ± 4.7	21.9 ± 3.7	**0.009**
$\dot{V}E$ peak [L/min]	41.7 ± 12.2	49.7 ± 13.1	0.05
$\dot{V}E$ peak [% predicted]	66.2 ± 16.8	82.9 ± 25.2	**0.01**
$\dot{V}E/\dot{V}CO_2$ (AT)	22.9 ± 4.4	22.0 ± 4.8	0.54
$\Delta\dot{V}O_2/\Delta$WR [mL/min/W]	8.4 ± 3.0	11.3 ± 4.9	**0.02**
Breathing reserve [%]	45.4 ± 15.9	43.7 ± 15.1	0.74
$PETO_2$ peak [mmHg]	105.4 ± 6.8	105.5 ± 5.2	0.96
$PETCO_2$ peak [mmHg]	42.2 ± 4.9	43.1 ± 4.3	0.55

Data are presented as n (%) or mean ± standard deviation. P values are significant at < 0.05. Statistically significant differences are given in bold. *Abbreviations*: BMI: body mass index; CPET: cardiopulmonary exercise testing; DL_{CO}: diffusion capacity of the lung for carbon monoxide; $\Delta\dot{V}O_2/\Delta$WR: increments in oxygen uptake per increments in work rate; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; $PETO_2$: end-tidal oxygen tension; $PETCO_2$: end-tidal carbon dioxide tension; PFT: pulmonary function testing; PXE: pseudoxanthoma elasticum; RER: respiratory exchange ratio; RV: residual volume; TLC: total lung capacity; VA: alveolar volume; $\dot{V}E$: minute ventilation; $\dot{V}E/\dot{V}CO_2$ (AT): minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide) at anaerobic threshold; $\dot{V}O_2$: oxygen uptake.

SPSS statistics version 26.0 (IBM, Armonk, NY, USA). Continuous variables were evaluated by use of unpaired *t*-test, categorical parameters by Pearson's Chi-squared test. Statistical significance was assumed when the null hypothesis could be rejected at $p < 0.05$.

Demographic and clinical data are displayed in Table 1. Overall, PXE patients were middle-aged (54.0 ± 11.2 years) with slight female predominance (n = 18/30, 60.0%). Pre-CPET, detailed pulmonary function testing revealed no substantial intergroup differences in measurements, except for absolute lung capacity that was significantly lower in the patient group than amongst controls (6.3 ± 1.3L *vs*. 7.1 ± 0.9L, $p = 0.04$). In terms of CPET results, PXE patients presented an impaired peak work rate as compared to controls (84.2 ± 16.0% *vs*. 94.7 ± 10.4%, $p = 0.03$) that was accompanied by a lower peak oxygen uptake (in % predicted and mL/min/kg), reduced increments in oxygen uptake per increments of work rate ($\Delta\dot{V}O_2/\Delta$WR, 8.4 ± 3.0 mL/min/W *vs*. 11.3 ± 4.9 mL/min/W, $p = 0.02$), lower peak oxygen pulse (78.0 ± 12.3% *vs*. 90.6 ± 19.6%, $p = 0.01$) and reduced minute ventilation at peak exercise ($\dot{V}E$, 66.2 ± 16.8% *vs*. 82.9 ± 25.2%, $p = 0.02$). By contrast, end-tidal oxygen and carbon dioxide tensions did not differ between groups.

This is the first study to investigate functional capacity by CPET in PXE patients. Of note, we presently observed impairment in mainly cardiocirculatory parameters, whilst no substantial ventilatory limitation was detected. Maximum respiratory exchange ratio (RER) slightly exceeded 1.10, implying excellent exercise effort in both study groups. The vast majority of PXE patients (n = 23/30, 76.7%) exhibited exhaustion as exercise limiting factor, only 1 patient aborted CPET due to claudication in lower limbs. By now, available evidence on cardiac involvement in PXE is inconsistent. Whilst Prunier *et al*. reported no elevated number of cardiac complications in PXE (*7*), other trials have reiteratedly observed diastolic dysfunction in PXE patients (*8,9*). Cardiovascular disease, foremost accelerated atherosclerosis, at an early age despite the absence of established risk factors has been described by Lebwohl and colleagues (*10*). Our findings support

the assumption that cardiac dysfunction seems to be truly related to PXE and not just coincidental. Potential underlying pathophysiological mechanisms that have previously been proposed comprise subendocardial deposition of altered elastic fibres affecting ventricular relaxation (*5*), silent myocardial ischaemia derived from premature atherosclerosis and compromised myocardial oxygen supply by disturbed myocardial microcirculation.

Study limitations arise from the relatively small number of patients studied inherent to the rarity of the disease. Additional cardiac imaging would have been a valuable adjunct to further define CPET observations.

To summarize, our data suggest that PXE is accompanied by cardiocirculatory inefficiency. The potential implications of this finding for PXE management warrant further study.

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