Restrictive spirometry pattern and abnormal cardiopulmonary response to exercise in transthyretin cardiac amyloidosis

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To the Editor:

Cardiac amyloidosis originates primarily from the accumulation of insoluble misfolded protein deposits within the myocardial interstitium [1–3]. While >30 proteins are known to be capable of aggregating as amyloid *in vivo*, nonmutated (ATTRwt) and variant transthyretin (ATTRv) are the most frequent amyloidogenic proteins impacting the heart. Both ATTRwt and ATTRv cardiac amyloidosis can elicit restrictive cardiomyopathy, leading to poor outcomes including heart failure and death [1–3]. While myocardial dysfunction is often cited as the predominant mechanism for dyspnoea and exercise intolerance in patients with cardiac amyloidosis, growing evidence suggests that extracardiac causes, including abnormal lung function, may also be responsible for these clinical symptoms [1–3].

Until now, clinical and biomarker scoring systems have been used accurately to stratify disease severity [1, 2, 4, 5]. Besides these well-established risk models, several authors [6–8] have brought to light the pertinence of reduced peak aerobic capacity (peak V'_{O_2}) in identifying cardiac amyloidosis patients with poor prognosis. The aim of this study was to characterise baseline patient profile, spirometry, and cardiopulmonary exercise (CPET) parameters according to the presence of a restrictive spirometry pattern in ATTR cardiac amyloidosis patients.

The present multicentre study involves three referral centres for cardiac amyloidosis management, namely the University Hospital of Toulouse (France), the University Hospital of Martinique (France) and the Fondazione Toscana G. Monasterio (Pisa, Italy). We included ATTRwt and ATTRv cardiac amyloidosis patients, with available data on spirometry and CPET between 2015 and 2020. Informed consent was obtained from all patients and an institutional review board approved all study procedures (00006477, APHP, France).

ATTR amyloidosis was diagnosed by cardiac uptake on technetium-99m-labelled phosphate bone scintigraphy in the absence of monoclonal gammopathy or abnormal free light chains in blood and urine. ATTR amyloidosis was confirmed by histological demonstration of amyloid fibrils and genetic testing. Cardiac involvement was evoked on ventricular hypertrophy and decrease in longitudinal global strain with abnormal apical texture characterised as a speckled appearance. The validated three-stage biomarker staging score was calculated for each patient [5].

Standard spirometry was performed according to the European Respiratory Society (ERS) guidelines [9] immediately before CPET on stable patients (no hospitalisation for cardiac decompensation or any other cause in the 6 months prior to spirometry and CPET) during regular routine follow-up visits at the three participating centres.

Spirometry was considered as normal (forced vital capacity in 1 s (FEV_1)/forced vital capacity (FVC) ⩾0.70 and FVC ⩾80% predicted) or restricted (FEV_1/FVC ⩾0.70 and FVC <80% pred) [10] using Global Lung Initiative/ERS predicted values [11]. CPET was performed using standardised procedures as recommended by the American Thoracic Society [12].

Shareable abstract (@ERSpublications)
Restrictive spirometry pattern and abnormal cardiopulmonary response to exercise might prove insightful in better understanding the functional profile of transthyretin cardiac amyloidosis
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TABLE 1 Main characteristics of transthyretin cardiac amyloidosis patients according to restrictive spirometry pattern

	All ATTR patients	No restrictive spirometry pattern	Restrictive spirometry pattern	p-value
Patients, n	46	21	25	
Age, years	72±11	68±14	74±8	0.231
Male	39 (85)	16 (76)	23 (92)	0.220
BMI, kg·m^{-2}	24±4	24±4	25±4	0.765
NYHA III/IV	28 (61)	8 (38)	20 (80)	**0.004**
Nonsinusal rhythm	15 (33)	4 (19)	11 (44)	0.072
Permanent atrial fibrillation	12 (26)	6 (29)	6 (24)	0.749
Pacemaker	6 (13)	2 (10)	4 (16)	0.673
Echocardiography				
IVS thickness, mm	16±3	15±3	17±3	0.756
LV mass, g·m^{-2}	169±55	155 ±58	179±51	0.052
LVEF, %	54±15	55±14	53±16	0.657
E/e′ ratio	14±6	13±7	14±5	0.414
Lung function and CPET				
FEV_1, % pred	74±18	88±12	63±13	**<0.0001**
FVC, % pred	76±18	91±9	62±12	**<0.0001**
FEV_1/FVC, %	79±9	78±11	80±7	0.549
Peak workload, %	57±20	65±24	50±13	0.073
Peak V'_{O_2}, mL·kg^{-1}·min^{-1}	16 ±4	18±4	14±3	0.106
Predicted peak V'_{O_2}, %	67±18	77±17	59±13	**0.001**
Peak V'_{O_2}/Watt slope	10±2	10±3	11±2	0.054
Peak RER	1.2±0.1	1.1±0.1	1.2±0.1	0.094
Peak V'_E/V'_{O_2}	44±8	39±6	47±7	**0.004**
Peak V'_E/V'_{CO_2}	37±5	35±5	39±4	**0.011**
Peak breathing frequency, breaths·min^{-1}	36±7	32±8	39±5	**0.0003**
Peak V_T/FVC, %	55±15	56±20	55±13	0.828
Ventilatory reserve, %	32±19	41±19	24±17	**0.027**
$V'_EV'_{CO_2}$ slope	38±6	36±7	39±4	**0.017**
Peak oxygen pulse, %	76±17	82±17	72±15	0.218
Peak heart rate, %	83±14	80±14	86±13	0.875
Biological parameters				
eGFR, mL·min^{-1}·1.72 m^{-2}	77 (57–117)	86 (57–129)	77 (56–94)	0.168
Cardiac troponin T, ng·L^{-1}	65 (40–122)	53 (33–94)	98 (42–338)	0.074
NT-proBNP, ng·L^{-1}	3002 (1222–5060)	1222 (266–2026)	3698 (3321–5365)	**0.0002**
ATTR biomarker staging II+III *versus* I[#]	18 *versus* 12	2 *versus* 11	16 *versus* 1	**<0.0001**
Medication				
ACE inhibitor or ARB	32 (70)	13 (62)	19 (76)	0.349
β-blockers	2 (4)	1 (5)	1 (4)	1.000
Amiodarone	12 (26)	5 (24)	7 (28)	1.000
Furosemide	26 (57)	10 (48)	16 (64)	0.372
Anticoagulation therapy	28 (61)	11 (52)	17 (68)	0.367
Outcomes				
MACE	17 (37)	2 (10)	15 (60)	**0.0004**

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. Bold type represents statistical significance. Statistical significance was set at p<0.05. ATTR: transthyretin amyloidosis; BMI: body mass index; NYHA: New York Heart Association classification; IVS: interventricular septum thickness; LV: left ventricle; LVEF: left ventricular ejection fraction; E/e′: early diastolic transmitral velocity to early mitral annulus diastolic velocity ratio; CPET: cardiopulmonary exercise testing; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; V'_{O_2}: oxygen uptake; RER: respiratory exchange ratio; V'_E: minute ventilation; V'_{CO_2}: pulmonary carbon dioxide output; V_T: tidal volume; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro B-type natriuretic peptide; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; MACE: composite of all-cause death or heart failure-related hospitalisation. [#]: ATTR biomarker staging (n=30): stage I: NT-proBNP ⩽3000 ng L^{-1} and eGFR ⩾45 mL min^{-1}; stage III: NT-proBNP >3000 ng·L^{-1} and eGFR <45 mL·min^{-1}; stage II: the remainder (see [5]).

Participant follow-up was carried out prospectively from the time of spirometry and cardiopulmonary testing until death or heart failure-related hospitalisation or censoring on 15 June 2021. The primary end-point during follow-up was the composite of heart failure-related hospitalisation or all-cause death (major adverse cardiac event: MACE), determined either by exhaustive review of medical files or phone calls to referent doctors and patients.

Mean±SD and median (interquartile range) were reported for quantitative variables. Categorical variables were presented as absolute value (percentage). Tests used for group comparisons were Wilcoxon–Mann–Whitney test, Chi-squared test and Fisher's exact test. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), with statistical significance set at $p<0.05$.

We included 46 cardiac amyloidosis patients: five (11%) nonmutated ATTR amyloidosis and 41 (89%) variant ATTR amyloidosis (29 ATTR-V122I (p.Val142Ile); eight ATTR-I107 V (p.Ile127Val); two ATTR-V30M (p.Val50Met); one ATTR-Phe64Leu (p.Phe84Leu); one ATTR-Glu89Gln (p.Glu89Gln)). Main patient characteristics are reported in table 1. Major adverse cardiac events were observed in 17 (37%) patients. 25 (54%) patients presented with a restrictive spirometry pattern ($FEV_1/FVC \geqslant 0.70$ and FVC <80% pred).

Despite similar cardiovascular function impairment, ECG abnormalities and medication, lung-restricted cardiac amyloidosis patients displayed lower peak V'_{O_2} and higher minute ventilation (V'_E) carbon dioxide production (V'_{CO_2}) slope when compared to patients with normal spirometry. Hyperventilation, as evidenced by increased peak exercise ventilatory equivalents (*i.e.* V'_E/V'_{O_2} and V'_E/V'_{CO_2}) also seemed to be more severe in cardiac amyloidosis patients with lung restriction. In the latter, ventilatory pattern was characterised by a more severe rapid shallow breathing pattern illustrated by a higher respiratory frequency. Furthermore, patients with a restrictive spirometry pattern presented with worse NYHA (New York Heart Association) stages, higher ATTR biomarker staging scores and worst outcome (MACE).

This study investigated pulmonary spirometry pattern and CPET response of patients with proven ATTRwt and ATTRv cardiac amyloidosis. The most common genotype in our study was ATTR-V122I (p.Val142Ile), which is consistent with the recruitment of a majority of Afro-Caribbean patients. Novel findings are two-fold. Firstly, our study suggests that restrictive spirometry pattern is a common feature in ATTR cardiac amyloidosis patients. Secondly, we found that patients with pulmonary restriction presented with reduced peak V'_{O_2} and poor outcome, defined as either all-cause death or heart failure related hospitalisation.

Our results seem to be in line with previous studies describing reduced peak V'_{O_2} as predictive of mortality in cardiac amyloidosis patients [6–8]. Analysis of CPET-derived parameters further suggests that decreases in peak V'_{O_2} might not be exclusively explained by low inotropic reserve and restrictive filling pattern, as previously reported in cardiac amyloidosis patients [13]. A modestly reduced baseline left ventricular ejection fraction, a normal peak V'_{O_2}/Watt slope, a slightly decreased peak oxygen pulse (surrogate of stroke volume) and the absence of periodic breathing (so-called oscillatory ventilation) argued against major myocardial dysfunction in our series. Nevertheless, study participants had increased $V'_E V'_{CO_2}$ slope, which is a well-established prognostic marker in chronic heart failure [14]. As such, factors governing the rise of $V'_E V'_{CO_2}$ slope are not limited to impaired cardiac function. Indeed, $V'_E V'_{CO_2}$ slope contains information on how lung function (gas exchange impairment and ventilatory constraints) might affect cardiopulmonary response to exercise [15]. A higher $V'_E V'_{CO_2}$ slope in cardiac amyloidosis patients with lung restriction might be attributed, at least in part, to a higher degree of hyperventilation, along with a more severe tachypnoeic breathing pattern indicating inadequate pulmonary response to submaximal exercise.

The present study only included patients referred for known cardiac amyloidosis and able to perform exercise, potentially generating selection bias. It is also to be noted that arterial carbon dioxide partial pressure was not determined, rendering impossible the calculation of physiologic dead space and limiting the full interpretation of $V'_E V'_{CO_2}$ slope rise during exercise. In addition, tidal flow–volume loops were not performed, which may be critical to evaluate pulmonary mechanical constraints in the context of restrictive spirometry pattern. Lastly, the absence of plethysmography did not allow the assessment of functional residual capacity and total lung capacity. As such, lung restrictive pattern could not be fully characterised in our patient series.

Cardiac amyloidosis is a rare disease, even when considering recruitment of patients in expert centres. In this pioneering study, we have evaluated the functional profile of patients by combining spirometry and

CPET. We highlight that poor outcome does not forcibly concur solely with major cardiac impairment, but rather with mixed cardiac and pulmonary dysfunction. Moreover, our results suggest that cardiac amyloidosis patients with a restrictive spirometry pattern might have poorer aerobic capacity and worst outcome, when compared with cardiac amyloidosis patients with normal spirometry. Further studies are required to investigate the prognostic value of spirometry and CPET and their contribution towards improved risk stratification.

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The data that support the findings of this study are available from the corresponding author (R. Neviere), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of the corresponding author.

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