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SHORT COMMUNICATION

Cardiopulmonary exercise testing predicts prognosis in amyloid cardiomyopathy: a systematic review and meta-analysis

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Abstract

Background The clinical value of cardiopulmonary exercise testing (CPET) in cardiac amyloidosis (CA) is uncertain. Due to the growing prevalence of the disease and the current availability of disease-modifying drugs, prognostic stratification is becoming fundamental to optimizing the cost-effectiveness of treatment, patient phenotyping, follow-up, and management. Peak VO_2 and VE/VCO_2 slope are currently the most studied CPET variables in clinical settings, and both demonstrate substantial, independent prognostic value in several cardiovascular diseases. We aim to study the association of peak VO_2 and VE/VCO_2 slope with prognosis in patients with CA.

Methods and results We performed a systematic review and searched for clinical studies performing CPET for prognostication in patients with transthyretin-CA and light-chain-CA. Studies reporting hazard ratio (HR) for mortality and peak VO_2 or VE/VCO_2 slope were further selected for quantitative analysis. HRs were pooled using a random-effect model. Five studies were selected for qualitative and three for quantitative analysis. A total of 233 patients were included in the meta-analysis. Mean peak VO_2 resulted consistently depressed, and VE/VCO_2 slope was increased. Our pooled analysis showed peak VO_2 (pooled HR 0.89, 95% CI 0.84–0.94) and VE/VCO_2 slope (pooled HR 1.04, 95% CI 1.01–1.07) were significantly associated with the risk of death in CA patients, with no significant statistical heterogeneity for both analyses.

Conclusions CPET is a valuable tool for prognostic stratification in CA, identifying patients at increased risk of death. Large prospective clinical trials are needed to confirm this exploratory finding.

Keywords Amyloidosis; CPET; Heart failure; Mortality; VO_2 peak; VE/VCO slope

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Anna Cantone and Matteo Serenelli contributed equally to the present manuscript.

Background

Cardiopulmonary exercise testing (CPET) has been proved to be a good tool in prognostic stratification of chronic heart failure with both reduced (HFrEF) and preserved (HFpEF) ejection fraction[1]; however, a minimal number of investigations has examined the prognostic value of CPET in patients with cardiac amyloidosis (CA). With the increasing knowledge and clinical suspicion toward CA, the growing disease prevalence, and the current availability of disease-modifying drugs, prognostic stratification is becoming fundamental to optimize the cost-effectiveness of treatment, patient follow-up, and management.

Aim

The present paper aims to perform a systematic review and meta-analysis of clinical studies investigating the prognostic role of all-cause mortality of CPET in patients with CA.

Methods

Electronic databases (MEDLINE, Biomed Central, and Cochrane Library) were searched for studies performing CPET for prognostication in patients with CA. The search strategy was elaborated by MS in July 2022. The terms searched were '((cardiopulmonary) OR (CPET)) AND ((cardiac amyloidosis) OR (amyloidosis))'.

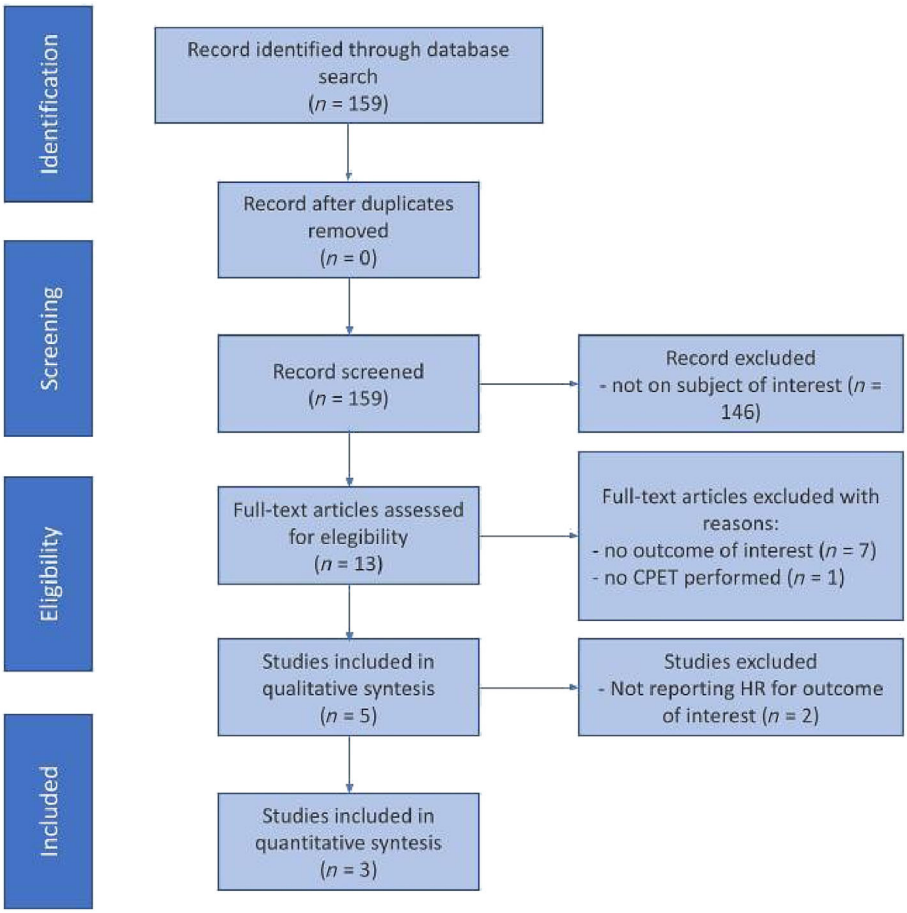
This was supplemented by searching the reference lists of key reviews and all potentially relevant studies. The protocol has been registered in Open Science Framework (OSF) with the following DOI: 10.17605/OSF.IO/HU9AF.

Only papers published in English and in peer-reviewed journals were selected. The inclusion criteria for the qualitative analysis were (i) observational or clinical studies performing CPET in patients with transthyretin (TTR) CA and/or light-chain (AL) CA and (ii) relating peak VO_2 and/or VE/VCO_2 slope to survival. The exclusion criteria were (i) duplicated reports, (ii) duplicate of the sample population, (iii) case reports/series, (iv) reviews, and (v) lack of outcome of interest. Two independent reviewers (M. S. and A. C.) analysed the records and decided which deserved full-text analysis. In case of disagreement between the reviewers, a third independent reviewer (R. P.) was involved in discussing the disagreement and taking the final decision. Furthermore, the reviewers independently analysed the references of all the evaluated articles for a further articles search. Studies reporting hazard ratio (HR) for mortality and peak VO_2 and/or VE/VCO_2 slope were further selected for quantitative analysis. Effect sizes were pooled using the natural logarithms (ln) of the HR with a random effect model (restricted maximum-likelihood estimator). Between-study heterogeneity was examined using the I^2 statistic. Two unblinded reviewers (M. S. and A. C.) independently evaluated the quality of the included studies using the MINORS criteria for non-comparative studies.[2]

Results

The database search yielded 159 records. After the first evaluation of the title and abstract, 146 papers were excluded because they were out of the field of interest, whereas 13 were analysed as full text (*Figure 1*). After careful analysis, eight full

Figure 1 Outline of the search strategy. The images show the outline of the search strategy with the PRISMA flow-chart.



articles were excluded for specific reasons, five studies were selected for qualitative analysis,[3–7] and three studies were included in the quantitative analysis (*Figure 1*).[4–6] No investigation was excluded based on the quality assessment analysis, and all studies obtained a score of 15.

A total of 233 patients were included in the meta-analysis. In all three studies peak VO_2 was measured on a breath-by-breath analysis, with peak oxygen uptake defined as the highest oxygen uptake measured at the end of the exercise period. The main characteristics of these studies and populations are reported in *Table 1*.

In the overall population, 127 (55%) patients had TTR-CA, and 106 (45%) patients had AL-CA. The mean peak VO_2 in each trial was depressed, ranging from a mean of 14.5 ± 4.5 mL/kg/min to a mean of 15.2 ± 10 mL/kg/min, while the VE/VCO_2 slope ranged from a mean of 30 ± 3% to a mean of 41.3 ± 9.7% (*Table 1*).

The pooled HR for a 1-unit increase of peak VO_2 was 0.89 (95% CI 0.84–0.94), with no heterogeneity (I^2 0.0%, P = 0.66) (*Figure 2A*).

The pooled HR for a 1-unit increase in VE/VCO_2 slope was 1.04 (95% CI 1.01–1.07), with a low statistical heterogeneity (I^2 30.3%, P-value = 0.238) (*Figure 2B*).

Discussion and conclusion

This meta-analysis highlights the predictive value of CPET in patients with CA. In the selected studies, peak VO_2 and VE/VCO_2 slope were altered both in ATTR-CA and AL-CA patients.

A low peak VO_2 was linked to a poor prognosis, and specifically to an 11% increased risk of death for each 1-unit decrease in VO_2 peak. This is probably linked to the decreased stroke volume, chronotropic incompetence, and muscular deconditioning seen in patients with CA.

On the other hand, a high VE/VCO_2 slope, a marker of ventilatory inefficiency (attributed to autonomic dysfunction, excessive sympathoexcitation, and a high physiological dead space (VD/VT) ratio during exercise), was also associated with a worse outcome.[8,9]

In the attempt to overcome the limitation of the small sample size of each study, our pooled analysis showed that both peak VO_2 and VE/VCO_2 slope were significantly associated with the risk of death in CA patients, and interestingly, the statistical heterogeneity was not significant and very low for each analysis.

Furthermore, in all the selected studies, a low peak VO_2 remained an independent predictor of worse outcomes, even after adjustment for clinically relevant covariates.

We believe that our findings have several meaningful clinical implications; once demonstrated the correlation between peak VO_2 and VE/VCO_2 slope with mortality, these parameters can become tools to better stratify patients' prognosis.

Specific cutoff values of CPET parameters or classification methods regarding functional impairment of CA patients could allow the identification of patients who may benefit from disease-modifying treatment or require only symptomatic treatment.[10] Incorporating CPET into the clinical manage-

Table 1 Main characteristics of the studies included in the meta-analysis

Study	Pt. No.	Median/mean follow-up time	Male gender, *n* (%)	NYHA II; III, *N* (%)	ATTR-CA, *n* (%)	AL-CA, *n* (%)
Nicol et al. 2020	150	20 (IQR 8–38) months	109 (69%)	58 (39%); 43 (29%)	59 (39%)	91 (61%)
Hein et al. 2018	27	38.2 (SD ± 41.1) months	19 (70%)	8 (30%); 14 (52%)	12 (44%)	15 (56%)
Yunis et al. 2019	56	35.0(range 10.8–89.5) months	56 (100%)	21 (37%); 25 (45%)	56 (100%)	0 (0%)

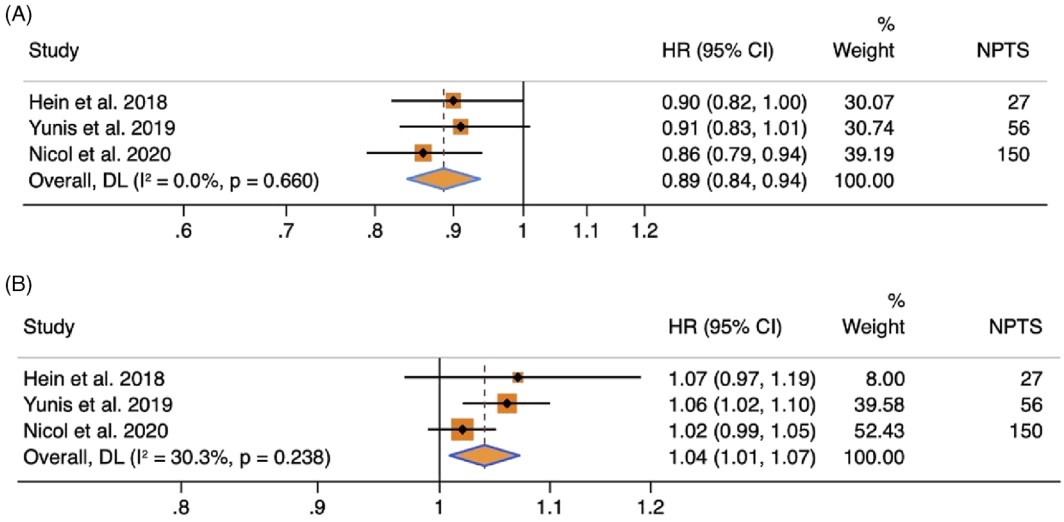
Pt means patients; ATTR-CA means transthyretin cardiac amyloidosis; AL-CA means light chain cardiac amyloidosis; VO2 means oxygen uptake; VCO2 means carbon dioxide output; CPET means cardiopulmonary exercise test. Central Illustration: VO_2 means oxygen uptake, VCO_2 means carbon dioxide output.

Table 1 (continued)

Study	Median/mean age	Median/mean peak VO_2 (mL/kg/min)	Median/mean VE/VCO_2 slope	%Predicted peak VO_2	RER	CPET protocol
Nicol et al. 2020	70 (IQR 64–78)	13.0 (IQR 10.0–16.9)	37 (IQR 33–45)	56%	1.17 (IQR 1.11–1.28)	Bicycle ergometer, 10 W/min workload increments
Hein et al. 2018	59 (SD ± 3)	15.2 (SD ± 10)	30 (SD ± 3)	63%	1.0 (SD ± 0.1)	Bicycle ergometer, modified Bruce protocol with 2 W/10 s increments
Yunis et al. 2019	74.8 (SD ± 6.2)	13.49 (SD ± 4.46)	41.3 (SD ± 9.7)	NA	1.14 (SD ± 0.12)	Treadmill ergometer with standard Bruce protocol

Pt means patients; ATTR-CA means transthyretin cardiac amyloidosis; AL-CA means light chain cardiac amyloidosis; VO2 means oxygen uptake; VCO2 means carbon dioxide output; CPET means cardiopulmonary exercise test. Central Illustration: VO_2 means oxygen uptake, VCO_2 means carbon dioxide output.

Figure 2 Risk of mortality according to peak VO_2 (A) and VE/VCO_2 slope (B). The figure shows the pooled mortality hazard ration for 1-unit increase in VO_2 peak (panel A) and VE/VCO_2 slope (B).



ment of CA patients could lead to more personalized and effective treatment plans; by monitoring changes in peak VO_2 and VE/VCO_2 slope over time, clinicians can assess the efficacy of treatment and adjust management strategies accordingly. Furthermore, identifying patients with a high mortality risk could prompt more aggressive treatment approaches or enrolment in clinical trials.

In addition to providing valuable prognostic information,[11] using CPET in CA patients could have therapeutic implications for promoting physical activity and exercise. Regular exercise has been shown to improve peak VO_2, reduce the risk of hospitalization, and improve quality of life in patients with heart failure; by assessing a patient's functional capacity through CPET, clinicians can design personalized exercise programs that are safe and effective, improving outcomes and quality of life.

Limitations of the study include firstly, CA patients are often elderly and may have co-morbidities that could potentially confound exercise performance; however, we found a strong correlation between patient performance and the endpoint, and the populations across the various studies had similar age and co-morbidity prevalence, which enhanced the population homogeneity and contributed to the low statistical heterogeneity observed in the pooled analysis. Secondly, the unavailability of separate HR for CPET in patients with AL and TTR-CA made it difficult to draw separate conclusions for the two aetiologies; however, CPET parameters were interestingly balanced and similar in these two populations. Lastly, the studies included in our meta-analysis did not report data on cardiovascular mortality, which may be an important outcome in CA patients. These limitations should be considered when interpreting the results of our meta-analysis, and further studies are needed to address these gaps in knowledge.

In conclusion, it is evident how CPET, beyond helping the physicians understand the mechanisms that lead to exercise limitations, can identify CA patients with worse prognosis by providing data on functional status, with possible use as a tool to guide the clinical and therapeutic management of these patients. While these findings are promising, due to the limitations of the present analysis, large prospective clinical trials are required to confirm this exploratory finding and better investigate the role of VO_2 peak and VE/VCO_2 slope in the specific setting of TTR-CA and AL-CA.

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