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Clinical Predictors of Response to Anakinra in Patients with Heart Failure

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Letter to the Editor

Systemic inflammation is often present in patients with heart failure (HF)¹. Interleukin-1 (IL-1) a key pro-inflammatory cytokine regulates cardiac function in acute and chronic inflammatory illnesses². Recent data from two pilot studies showed that treatment with an interleukin-1 blocker, anakinra, improved cardiopulmonary exercise testing (CPX) performance in patients with heart failure - reduced ejection fraction (HFrEF)³ as well as in patients with heart failure - preserved ejection fraction (HFpEF)⁴. HFrEF and HFpEF share a similar burden of symptoms, such as exercise intolerance, but different mechanisms of disease⁵.

The aim of this analysis was to pool data from the 2 pilot studies to explore whether baseline characteristics could serve as predictors of improved CPX performance with anakinra. The analysis included 19 patients, 7 with HFrEF³ and 12 with HFpEF⁴. Inclusion criteria included symptoms of HF (New York Heart Association [NYHA] class II-III) on stable medical therapy without any changes in medications in the prior 3 months, hospital admissions in the prior 12 months, and evidence of impaired left ventricular systolic function (left ventricular ejection fraction [LVEF]<40%) for patients with HFrEF or impaired left ventricular relaxation or elevated left ventricular filling pressures for patients with HFpEF.³⁻⁴ Acute or chronic inflammatory conditions, malignancy, recent surgeries or

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other comorbidities limiting the completion of a maximal CPX were among the exclusion criteria.^{3,4} All patients had a baseline high-sensitivity C-reactive protein (CRP) levels >2 mg/l. All patients underwent a baseline transthoracic Doppler echocardiographic study according to the American Society of Echocardiography recommendations⁶: LVEF was measured using volumetric analysis for two perpendicular apical views, diastolic function was measured as ratio of transmitral early diastolic velocity (E) to the mitral annulus early diastolic velocity at tissue Doppler (E') obtained from an average of the septal and lateral wall measurements, right ventricular function was measured as tricuspidal annulus plane systolic excursion (TAPSE). A CPX was completed according to the American Heart Association recommendations as previously described.⁷ Patients were then treated with anakinra (Kineret™, Swedish Orphan Biovitrum, Stockholm, Sweden); 100 mg subcutaneously daily for 14 days and repeated determination of CRP levels and CPX.³⁻⁴ Patients with HFrEF received open-label treatment, whereas patients with HFpEF had blinded treatment.³⁻⁴

Peak VO_2 and the minute ventilation/carbon dioxide production (VE/VCO_2) slope were pre-specified primary end-points, reflecting 2 important and complementary prognostic indicators in HF.⁸⁻⁹ Additional endpoints included the oxygen uptake efficiency slope (OUES),¹⁰ the Duke activity status index (DASI)¹¹, plasma CRP levels and B-type natriuretic peptide levels.

Data are reported as median and interquartile range for continuous variables to account for potential deviation from a Gaussian distribution. Discrete variables are reported as a number (%). Paired changes in each variable were analyzed using the Wilcoxon test and correlations between variables were measured with the Spearman correlation test (SPSS 21, IBM, NY, USA).

The characteristics of the 19 patients as a whole are reported in Table 1, whereas characteristics of the subgroups are available in the original publications^{3,4}

Treatment with anakinra led to a significant improvement in peak VO_2 (from 14.1 [11.4–16.7] to 15.9 [13.7–17.5] $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P=0.002$), the VE/VCO_2 slope (from 25.6 [22.8–31.1] to 24.9 [22.8–28.2], $P=0.002$), OUES (from 2.1 [1.7–2.4] to 2.2 [1.8–2.5], $P=0.003$), and the DASI (24 [15–31] to 27 [24–37], $P=0.016$).

Anakinra also led to a significant reduction in CRP levels (6.6 [3.6–15.2] to 1.3 [0.5–3.1] mg/l, $P<0.001$), and no significant change in B-type natriuretic peptide (25 [15–112] to 37 [10–57] pg/ml, $P=0.48$). Anakinra had no significant effects on blood pressure, heart rate or body weight (*data not shown*).

Baseline LVEF was linearly correlated with peak VO_2 ($R=+0.52$, $P=0.024$) but not with the VE/VCO_2 slope or OUES (both $P>0.2$). Reduced LVEF predicted greater improvement peak VO_2 with treatment ($R=-0.47$, $P=0.044$), but not in the VE/VCO_2 slope or OUES. Values of E/E' ratio or TAPSE did not correlate with baseline CPX variables or changes following anakinra treatment.

On the other hand, the greater baseline impairment in peak VO_2 (i.e. lower value), the VE/VCO_2 slope (i.e. higher value), and OUES (i.e. lower value), the greater the improvement seen with anakinra treatment in each of these variables (Figure 1). Baseline CRP or BNP levels failed to predict changes in peak VO_2 , the VE/VCO_2 slope or OUES.

In summary, the data pooled from two pilot studies confirm the improvement in CPX performance with anakinra across the spectrum of HFrEF and HFpEF, with improvements in peak VO_2 , ($+1.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), the VE/VCO_2 slope (-0.7) and the OUES ($+0.1$) that are considered clinically relevant,^{8–10} and an associated improvement in perceived functional capacity (DASI questionnaire $+3$).¹¹

Inflammatory biomarkers, such as CRP, predict cardiac dysfunction and risk.^{12–14} The current study shows a significant reduction in CRP levels with anakinra. In this pooled analysis, we explored whether baseline characteristics, such as CRP, could serve as predictors of improved performance. We set forth 4 hypotheses. First, we proposed that inflammation (CRP levels) would predict improvement. However, in this analysis of all patients with $\text{CRP} > 2.0 \text{ mg/l}$, this was not the case. Second, we hypothesized that the degree of LV systolic or diastolic dysfunction or RV systolic dysfunction would identify a group of subjects with greater improvement with treatment. While this was in part true for LVEF, the strength of the relationship and statistical significance were marginal and limited to peak VO_2 . Third, we analyzed whether the effects of anakinra were most evident in those subjects with more severe baseline impairment.¹⁵ In our data, peak VO_2 , the VE/VCO_2 slope and OUES prior to treatment strongly predicted the improvement in each of the 3 variables, with greater improvement seen with anakinra in patients with worse baseline CPX performance. The superior prognostic value of exercise parameters should not come as a surprise considering that majority of symptoms in HF are provoked by exertion and are absent at rest, and these parameters are equally valuable in HFrEF and HFpEF.¹⁶ Fourth, we explored whether baseline BNP levels, used to stratify patients with HF,¹⁷ would predict improvement, but found no association between BNP levels and changes in CPX variables.

References

1. Parish RC, Evans JD. Inflammation in chronic heart failure. *Ann Pharmacother*. 2008; 42:1002–1016. [PubMed: 18477736]
2. Van Tassell BW, Toldo S, Mezzaroma E, Abbate A. Targeting interleukin-1 in heart disease. *Circulation*. 2013; 128:1910–1923. [PubMed: 24146121]
3. Van Tassell BW, Arena RA, Toldo S, Mezzaroma E, Azam T, Seropian IM, Shah K, Canada J, Voelkel NF, Dinarello CA, Abbate A. Enhanced interleukin-1 activity contributes to exercise intolerance in patients with systolic heart failure. *PLoS One*. 2012; 7:e33438. [PubMed: 22438931]
4. Van Tassell BW, Arena R, Canada J, Biondi-Zoccai GG, Oddi C, Abouzaki NA, Jahangiri A, Melchior RD, Dewilde C, Falcao RA, Kontos MC, Shah KB, Voelkel NF, Dinarello CA, Abbate A. Effects of Interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure with preserved ejection fraction (from the D-HART pilot study). *Am J Cardiol*. 2013 (in press).
5. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011; 32:670–679. [PubMed: 21138935]
6. Gardin J, Adams D, Douglas P, Feigenbaum H, Forst D, Fraser A, Grayburn P, Katz A, Keller A, Kerber R, Khandheria B, Klein A, Lang R, Pierard L, Quinones M, Schnittger I. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American

Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. *J Am Soc Echocardiography*. 2002; 15:275–290.

7. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV. American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010; 122:191–225. [PubMed: 20585013]
8. Cahalin LP, Chase P, Arena R, Myers J, Bensimhon D, Peberdy MA, Ashley E, West E, Forman DE, Pinkstaff S, Lavie CJ, Guazzi M. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. *Heart Fail Rev*. 2013; 18:79–94. [PubMed: 22733204]
9. Arena R, Humphrey R, Peberdy MA. Relationship between the Minnesota Living With Heart Failure Questionnaire and key ventilatory expired gas measures during exercise testing in patients with heart failure. *J Cardiopulm Rehabil*. 2002; 22:273–277. [PubMed: 12202848]
10. Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJ, Piepoli MF, Francis DP. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J*. 2006; 27:684–690. [PubMed: 16338939]
11. Parissis JT, Nikolaou M, Birmipa D, Farmakis D, Paraskevaidis I, Bistola V, Katsoulas T, Filippatos G, Kremastinos DT. Clinical and prognostic value of Duke's Activity Status Index along with plasma B-type natriuretic peptide levels in chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2009; 103:73–75. [PubMed: 19101233]
12. Lamblin N, Mouquet F, HEnnache B, Dagorn J, Susen S, Bauters C, de Groote P. High-sensitivity C-reactive protein: potential adjunct for risk stratification in patients with stable congestive heart failure. *Eur Heart J*. 2005; 26:2245–2250. [PubMed: 16183690]
13. McMurray JJ, Kjekshus J, Gullestad L, Dunselman P, Hjalmarson A, Wedel H, Lindberg M, Waagstein F, Grande P, Hradec J, Kamenský G, Korewicki J, Kuusi T, Mach F, Ranjith N, Wikstrand J. CORONA Study Group. Effects of statin therapy according to plasma high-sensitivity C-reactive protein concentration in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): a retrospective analysis. *Circulation*. 2009; 120:2188–2196. [PubMed: 19917888]
14. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1 β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J*. 2011; 162:597–605. [PubMed: 21982649]
15. Guazzi M, Arena R. The impact of pharmacotherapy on the cardiopulmonary exercise test response in patients with heart failure: a mini review. *Curr Vasc Pharmacol*. 2009; 7:557–569. [PubMed: 19485908]
16. Guazzi M, Labate V, Cahalin LP, Arena R. Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure with reduced and preserved ejection fraction. *Eur J Prev Cardiol*. 2013 online first.
17. Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol*. 2007; 50:2357–2368. [PubMed: 18154959]

Figure 1.

Baseline cardiopulmonary exercise test (CPX) variables such as peak oxygen consumption (peak VO_2) and ventilatory efficiency (VE/VCO_2 slope and OUES) predict improvement with anakinra.

Table 1

Clinical characteristics.

Number of patients	19
Age (years)	59 [55–63]
Gender (males)	4 (21%)
Race/ethnicity	
Caucasians	5 (26%)
African Americans	13 (68%)
Hispanic	1 (5%)
New York Heart Association class	2 [2–3]
Left ventricular ejection fraction	57 [30–63]
LVEF<50%	7 (37%)
Diastolic function	
E' (cm/s)	6 [5–8]
E/E'	11[10–20]
B-type natriuretic peptide (pg/ml)	25 [15–112]
C-reactive protein (mg/l)	7 [4–15]
Diabetes mellitus	11 (58%)
Hypertension	18 (95%)
Hypercholesterolemia	16 (84%)
Obesity (Body Mass Index>30)	16 (84%)
Body Mass Index	37 [33– 43]
Weight (Kg)	97 [86–118]
Ischemic heart disease	5 (26%)
Concomitant medications	
ACE-inhibitors or ARB	17 (89%)
Beta-adrenergic blockers	17 (89%)
Aldosterone blocker	5 (26%)
Statins	14 (79%)

Abbreviations: ACE= Angiotensin-converting enzyme; ARB= Angiotensin Receptor Blocker; LVEF = Left Ventricular Ejection Fraction