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Effect of Interleukin-1 Blockade on Left Ventricular Systolic Performance and Work: A Post-Hoc Pooled Analysis of Two Clinical Trials

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Abstract

Background—Interleukin-1 (IL-1) blockade appears to improve anaerobic exercise in patients with systolic heart failure through improved left ventricular systolic performance. However, it is unclear whether IL-1 blockade affects left ventricular systolic performance.

Methods—We pooled data from two clinical trials of patients with systolic heart failure who were randomized to IL-1 blockade or placebo. We estimated changes in left ventricular systolic performance (left ventricular ejection fraction [LVEF] and end-systolic elastance [LV_{Ees}]) and pressure-volume area, a surrogate of oxygen consumption, after 14 days of treatment.

Results—LVEF increased from 30% (24–38%) to 36% (29–43%) between baseline and day 14 only in anakinra-treated patients (P=0.03 for within-group change and P=0.02 for between-group change compared to placebo). LV_{Ees} increased from 1.0 mm Hg/mL (0.7–1.5) to 1.3 mm Hg/mL (0.8–1.6) in anakinra-treated patients between baseline and day 14 but not in placebo-treated patients (P=0.03 for within-group change and P=0.08 for between-group change). A change in PVA between baseline and 14 days was not detected in either anakinra or placebo patients.

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Conclusions—In this post-hoc analysis, $LV_{E_{es}}$ and LVEF increased significantly in patients treated with an IL-1 blocker but not in placebo-treated patients. An effect of IL-1 blockade on calculated pressure-volume area was not detected.

Keywords

Interleukin-1; Inflammation; Heart Failure

1. Introduction

Left ventricular (LV) systolic dysfunction is the predominant impairment in half of all patients with heart failure (HF).¹ Interleukin-1 (IL-1) is a pro-inflammatory cytokine that improves LV systolic performance in murine HF as measured by LV fractional shortening and ejection fraction.² Currently available inotropes, such as dopamine, increase oxygen consumption and have been associated with increased mortality.³ Therefore, we sought to determine the effect of IL-1 blockade LV systolic performance and calculated myocardial pressure-volume area, an established surrogate of cardiac oxygen consumption, in patients with systolic HF.

2. Methods

The Virginia Commonwealth University Institutional Review Board approved of the study, which was conducted according to International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to study enrollment.

2.1 Patients

We pooled patients from two separate clinical trials of IL-1 blockade in systolic HF.^{4,5} In one trial, patients received anakinra 100 mg twice daily for 3 days followed by 100 mg once daily for 11 days. In the second trial, anakinra patients received 100 mg daily for 12 weeks, 4 weeks or placebo. This analysis is based upon only the initial 2 weeks of treatment for patients who received 12 weeks of treatment. We pooled patients from each trial who received anakinra and those who received placebo into distinct groups.

2.2 Left Ventricular Performance Measures

We assessed left ventricular ejection fraction (LVEF) and LV end-systolic elastance (E_{es}) as measures of LV systolic performance.^{6,7} LVEF was measured according to Simpson's method as recommended for clinical trials.⁸ Doppler echocardiography was performed by a blinded cardiologist with images recaptured as necessary to achieve acceptable quality. All measurements were subsequently performed by 2 separate operators blinded to group allocations after study completion. The average of the 2 measurements was used for measures differing $\leq 10\%$, whereas those with $>10\%$ were reviewed and discussed to achieve consensus.

LV E_{es} is a load-independent measure of contractility^{7,9} and was estimated as the slope of the LV end-systolic pressure-volume relationship and calculated by dividing LV end-systolic

pressure (ESP) by LV end-systolic volume.⁶ LVESP was estimated as $0.9 \times$ brachial artery systolic blood pressure. Arterial elastance (LV_{Ea}) is a measure of LV afterload and was calculated as LV ESP divided by LV stroke volume.⁶

Systolic blood pressure, stroke volume and heart rate were measured after 5 minutes of rest over a 1-minute period using a non-invasive continuous hemodynamic monitor (NexfinCC, Edwards Lifesciences, Irvine CA) and the averaged value was utilized for LV performance calculations. This monitor calculates brachial artery blood pressure and LV stroke volume based upon fingertip capillary pressure waveforms.¹⁰

Myocardial oxygen consumption and LV pressure-volume area (PVA) have been shown to be linearly related.¹¹ We estimated PVA the sum of stroke work and potential energy, where potential energy is estimated as $\frac{1}{2}$ LV end-systolic volume $\times$ LVESP.^{6,7} LV stroke work was estimated as stroke volume $\times$ LVESP.^{6,7} Myocardial work efficiency was estimated as stroke work divided by pressure-volume area.

2.3 Statistical Analysis

Summary statistics are provided as number (%) for categorical variables and median (interquartile range [IQR]) for continuous variables. Baseline characteristics were compared between anakinra and placebo groups using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Within-group change was tested with the Wilcoxon Ranked Sum test and between-group change with the Mann-Whitney U test. A P-value < 0.05 was considered statistically significant. Correlations between continuous variables were assessed with Spearman's rho. Statistical analysis was conducted with SPSS 24.0 (IBM, Armonck, NY).

3. Results

3.1 Patient Characteristics

The pooled cohort included 48 patients randomized to anakinra and 32 to placebo. There were no significant between-group differences in clinical characteristics, guideline-directed medications or LV systolic performance measures (Supplemental Table 1 and 2).

3.2 Left Ventricular Systolic Performance

We did not detect a significant change in LVEF or LVE_{es} between baseline and day 14 in the placebo group ($P > 0.22$ for each) (Figure). In the anakinra group, LVEF increased from 30% (24–38%) to 36% (29–43%) between baseline and day 14 ($P = 0.03$ for within-group change and $P = 0.02$ for between-group change compared to placebo) (Figure). LVE_{es} increased from 1.0 mm Hg/mL (0.7–1.5) to 1.3 mm Hg/mL (0.8–1.6) between baseline and day 14 in anakinra-treated patients ($P = 0.03$ for within-group change and $P = 0.08$ for between-group change). A change in PVA between baseline and 14 days was not detected in either anakinra or placebo patients (Supplemental Table 2).

In anakinra-treated patients, the median change in heart rate was -4 beats per minute (-13 to 3 ; $P = 0.01$ for within-group change) and for the placebo arm was 1 beat per minute (-5 to 6 ; $P = 0.97$ for within-group change) ($P = 0.17$ for between-group change). For the anakinra

patients, median LVE_a was 1.56 (1.35–1.99) mm Hg/mL at baseline and 1.56 (1.34–1.94) mm Hg/mL at 14-days (P=0.35). In the placebo arm, median LVE_a was 1.78 (1.47–2.35) mm Hg/mL at baseline and 1.66 (1.50–2.58) mm Hg/mL at 14-days (P=0.33) (P=0.55 for between-group comparison).

4. Discussion

In the present study, we found that the increase in LV systolic performance with IL-1 blockade was not accompanied by a signal for increased myocardial work or oxygen consumption. Considering the adverse effects of catecholaminergic inotropes on myocardial oxygen consumption, the relationship between IL-1 blockade and oxygen consumption in patients with HF is an important concern.

We included two measures of LV systolic performance: LVEF and LVE_{es}. LVEF can be readily measured in routine practice but changes in LVEF may reflect alterations in cardiac load or in contractility. In contrast, LVE_{es} is a load-independent measure of LV contractility.^{7,9} Thus, the fact that both distinct measures suggest that anakinra improves LV systolic performance increases our confidence in the results of this small pilot study.

Resting heart rate significantly declined in anakinra-treated patients. Improvements in LV systolic function in the anakinra arm may have permitted cardiac output to remain sufficient for the body's needs without an elevated heart rate. There was no detectable difference in heart rate in the placebo arm, which may be attributable to our small sample size or short measurement interval. Anakinra did not have an observable effect on LV afterload, measured as LVE_a, which suggests that anakinra's effects on LV systolic performance may be found to be load-independent, pending validation in a larger cohort.

In this analysis, IL-1 blockade as a strategy exhibits a favorable safety profile. Daily subcutaneous administration of anakinra provokes an injection site reaction in many patients and therefore chronic IL-1 blockade with longer-lasting antibodies may be a preferred strategy.

4.1 Distinction Between IL-1 Blockade and Available Inotropes

IL-1 blockade represents a distinct mechanism of action from existing inotropes, which increase myocardial oxygen consumption, promote arrhythmias and are associated with worse survival.³ Pro-arrhythmic effects have not been observed in clinical trials of IL-1 blockade and IL-1 blockade prevented arrhythmias in a preclinical animal model.^{5,12,13} Thus, IL-1 blockade appears to overcome several safety concerns with current positive inotropes. The effects of IL-1 blockade on clinical outcomes remain to be determined, although ongoing clinical trials suggest an improvement in aerobic exercise capacity and a trend towards fewer hospitalizations.⁵

4.2 Limitations

This proof-of-concept analysis has certain limitations. It was a post-hoc analysis conducted using non-invasive cardiac measurements in which we assumed a linear slope of the end-systolic pressure-volume relationship and a volume-axis intercept (V_0) = 0. We did not alter

loading conditions and measured only a single point on the end-systolic pressure-volume relationship. We assessed LV systolic function at rest but not during exercise. Hemodynamic measurements were averaged over a short (1-minute) interval and, despite best efforts to minimize variability by resting the patient and eliminating distractions, we may have introduced unnecessary variability into our measurements. We combined results from clinical trials with different designs and had a small sample size. Although pressure-volume area is an established surrogate of oxygen consumption, we did not measure invasively pressure-volume area but rather calculated an estimate. These results improve our understanding of IL-1 blockade in patients with HF and may inform the design of the larger outcomes trials necessary to determine the clinical efficacy of IL-1 blockade.

5. Conclusions

In summary, we found that IL-1 blockade improved LV systolic performance. We did not detect an effect of IL-1 blockade on myocardial pressure-volume area. IL-1 blockade's effects on systolic performance appear to be distinct from classic inotropes and therefore this strategy may have an improved safety profile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006; 355:251–259. [PubMed: 16855265]
2. Toldo S, Mezzaroma E, Bressi E, Marchetti C, Carbone S, Sonnino C, Van Tassell BW, Abbate A. Interleukin-1 β blockade improves left ventricular systolic/diastolic function and restores contractility reserve in severe ischemic cardiomyopathy in the mouse. *J Cardiovasc Pharmacol*. 2014; 64:1–6. [PubMed: 25006675]
3. Francis GS, Bartos JA, Adaya S. Inotropes. *J Am Coll Cardiol*. 2014; 63:2069–2078. [PubMed: 24530672]
4. Van Tassell BW, Abouzaki NA, Oddi Erdle C, Carbone S, Trankle CR, Melchior RD, Turlington JS, Thurber CJ, Christopher S, Dixon DL, Fronk DT, Thomas CS, Rose SW, Buckley LF, Dinarello CA, Biondi-Zoccai G, Abbate A. Interleukin-1 blockade in acute decompensated heart failure: a randomized, double-blinded, placebo-controlled pilot study. *J Cardiovasc Pharmacol*. 2016; 67:544–551. [PubMed: 26906034]
5. Van Tassell BW, Canada J, Carbone S, Trankle C, Buckley L, Oddi Erdle C, Abouzaki NA, Dixon D, Kadariya D, Christopher S, Schatz A, Regan J, Viscusi M, Del Buono M, Melchior R, Mankad P, Lu J, Sculthorpe R, Biondi-Zoccai G, Lesnefsky E, Arena R, Abbate A. Interleukin-1 Blockade in Recently Decompensated Systolic Heart Failure: Results from the REcently Decompensated Heart failure Anakinra Response Trial (REDHART). *Circ Hear Fail*. 2017; 10:e004373.
6. Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. *J Appl Physiol*. 2008; 105:1342–1351. [PubMed: 18617626]
7. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *AJP Hear Circ Physiol*. 2005; 289:H501–H512.
8. Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, Weissman NJ. American Society of Echocardiography

recommendations for use of echocardiography in clinical trials. *J Am Soc Echocardiogr.* 2004; 17:1086–1119. [PubMed: 15452478]

9. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res.* 1973; 32:314–322. [PubMed: 4691336]
10. Chen G, Meng L, Alexander B, Tran NP, Kain ZN, Cannesson M. Comparison of noninvasive cardiac output measurements using the Nexfin monitoring device and the esophageal Doppler. *J Clin Anesth.* 2012; 24:275–283. [PubMed: 22608581]
11. Suga H. Total mechanical energy of a ventricle model and cardiac oxygen consumption. *Am J Physiol.* 1979; 236:H498–505. [PubMed: 426086]
12. 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]
13. Monnerat G, Alarcón ML, Vasconcellos LR, Hochman-Mendez C, Brasil G, Bassani RA, Casis O, Malan D, Travassos LH, Sepúlveda M, Burgos JI, Vila-Petroff M, Dutra FF, Bozza MT, Paiva CN, Carvalho AB, Bonomo A, Fleischmann BK, De Carvalho ACC, Medei E. Macrophage-dependent IL-1 β production induces cardiac arrhythmias in diabetic mice. *Nat Commun.* 2016; 7:13344. [PubMed: 27882934]

Figure. Effect of IL-1 Blockade of Left Ventricular Systolic Performance

IL-1 blockade improves measures of LV systolic performance.

E_{es} = end-systolic elastance; LV = left ventricle