



MINI-FOCUS: INFLAMMATION IN CARDIAC INJURY The IL-1b Antibody Gevokizumab Limits Cardiac Remodeling and Coronary Dysfunction in Rats With Heart Failure

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Najah Harouki, Lionel Nicol, Isabelle Remy-Jouet, Jean-Paul Henry, Anaïs Dumesnil, et al.. MINI-FOCUS: INFLAMMATION IN CARDIAC INJURY The IL-1b Antibody Gevokizumab Limits Cardiac Remodeling and Coronary Dysfunction in Rats With Heart Failure. J Am Coll Cardiol Basic Trans Science, 2017, 2 (4), pp.418 - 448. 10.1016/j.jacbts.2017.06.005 . inserm-02296604

HAL Id: inserm-02296604

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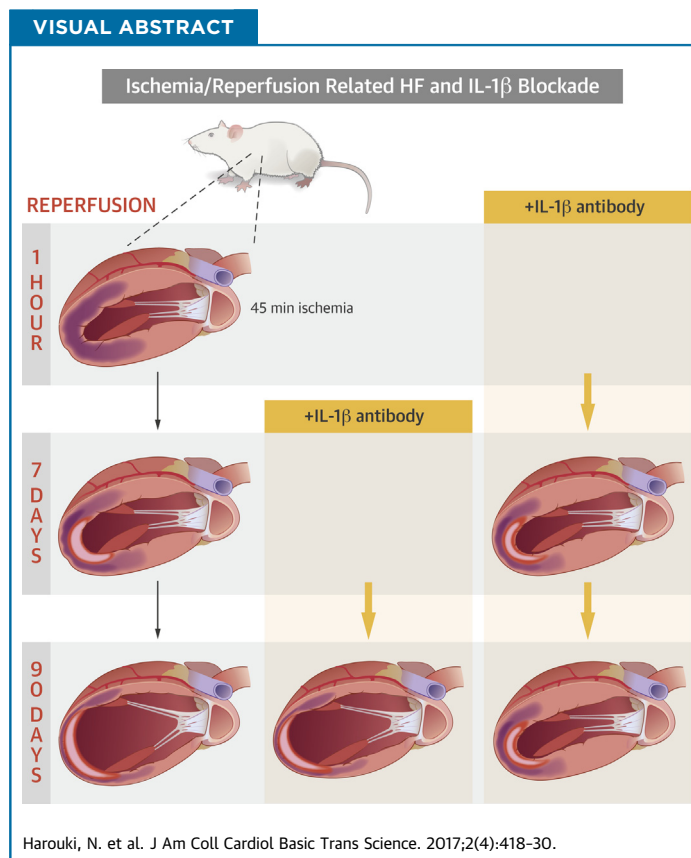
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MINI-FOCUS: INFLAMMATION IN CARDIAC INJURY

The IL-1 β Antibody Gevokizumab Limits Cardiac Remodeling and Coronary Dysfunction in Rats With Heart Failure



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HIGHLIGHTS

- Immediate IL-1 β antibody gevokizumab administration reduces ischemia/reperfusion related infarct size.
- Immediate and late IL-1 β antibody gevokizumab administration improves heart failure related left ventricular remodeling.
- IL-1 β antibody gevokizumab improves heart failure related coronary dysfunction.

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SUMMARY

This study reports preclinical data showing that the interleukin (IL)-1 β modulation is a new promising target in the pathophysiological context of heart failure. Indeed, in nondiabetic Wistar and diabetic Goto-Kakizaki rats with chronic heart failure induced by myocardial infarction, administration of the IL-1 β antibody gevokizumab improves 'surrogate' markers of survival (i.e., left ventricular remodeling, hemodynamics, and function as well as coronary function). However, whether IL-1 β modulation per se or in combination with standard treatments of heart failure improves long-term outcome in human heart failure remains to be determined. (J Am Coll Cardiol Basic Trans Science 2017;2:418–30) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Enhanced interleukin-1 β (IL-1 β) levels are involved in the immediate and long-term consequences of myocardial ischemia/reperfusion (I/R), as suggested by acute as well as chronic increases in IL-1 β plasma levels observed in patients and rodents following myocardial infarction (1,2). Indeed, after the abrupt but transient increase of cardiac the IL-1 β gene expression within the first hour to 1 day after ischemia (3,4), a second and sustained IL-1 β upregulation is observed (5,6). This specific time course of IL-1 β expression may be important in terms of left ventricular (LV) remodeling and/or LV dysfunction as IL-1 β signaling is essential both during (5,7) and beyond the infarct healing period (8). Indeed, IL-1 β plays an orchestrating role in the inflammatory response to myocardial injury, including enhanced synthesis of other proinflammatory mediators, activation of profibrotic pathways (5), and promotion of cytokine-induced cardiomyocyte apoptosis (9) but also exerts direct negative inotropic effects on myocyte contractility (9–11).

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Although the deleterious role of IL-1 β in the acute consequences of cardiac I/R injury has been well established (7,12), the neutralization and modulation of IL-1 β after myocardial infarction in mice has been suggested as a therapeutic target in the prevention of long-term consequences of I/R (i.e., development of heart failure [HF]) (7,13,14). Thus, the aim of this study was to determine the short- and long-term effects of treatment with the IL-1 β modulating antibody gevokizumab (15,16), initiated either 1 h following reperfusion after myocardial ischemia and continued for

7 (early short-term) or 90 (early long-term) days or initiated 7 days following reperfusion after myocardial ischemia and continued for 83 (delayed long-term) days on I/R-induced LV remodeling or dysfunction and coronary dysfunction. Moreover, as several pathologies, notably diabetes, are known to aggravate myocardial I/R injury, we also evaluated Gevokizumab in the setting of type 2 diabetes, using Goto-Kakizaki (GK) rats.

Our results showed that the IL-1 β antibody gevokizumab induces an immediate but sustained improvement of I/R-induced cardiac and coronary dysfunctions in “healthy” as well as diabetic rat models. However, whether IL-1 β modulation may be a therapeutic option for the acute and long-term consequences (i.e., survival of cardiac I/R in humans remains to be determined).

MATERIALS AND METHODS

The investigation conforms to the Guide for the Care and Use of Laboratory Animals (U.S. National Institutes of Health publication 85-23, revised 1996) and was approved by the local ethical committee (CENOMEXA number 54; ref. 0871.01).

ANIMALS AND EXPERIMENTAL DESIGN. This study was performed in either 12-week-old male Wistar (Janvier Labs, Saint Berthevin, France) or GK (Meta-brain, Chilly-Mazarin, France) rats, anesthetized with intraperitoneal administration of ketamine/xylazine (150 and 5 mg $\cdot$ kg⁻¹, respectively), subjected to either sham surgery or transient ischemia followed by reperfusion, the latter being verified visually before closing the chest, as previously described (17),

ABBREVIATIONS AND ACRONYMS

GK = Goto-Kakizaki

I/R = ischemia/reperfusion

IL = interleukin

LV = left ventricle/ventricular

LVEDP = left ventricular
end-diastolic pressure

LVEDPV = left ventricular
end-diastolic pressure-volume
relationship

LVESP = left ventricular
end-systolic pressure

LVEsPVR = left ventricular
end-systolic pressure-volume
relationship

ROS = reactive oxygen species

SOD = superoxide dismutase

provoked by temporary left coronary artery occlusion (Wistar rats: 45 min; GK rats: 20 min), followed by reperfusion for 2, 7, or 90 days.

Independent protocols were performed to study the short- and long-term effects of gevokizumab. A first protocol assessed long-term gevokizumab treatment initiated ($10 \text{ mg} \cdot \text{kg}^{-1}$, intraperitoneally) either 1 h (early long-term) or 7 days (delayed long-term) following reperfusion and continued for 90 or 83 days, respectively, at a dose of $10 \text{ mg} \cdot \text{kg}^{-1}$ subcutaneously once per week. This dosage regimen resulted in an effective “neutralization” of IL1- β between 2 subsequent subcutaneous administrations. A second and a third protocol assessed early short-term gevokizumab treatments initiated 1 h following reperfusion at an intraperitoneal dose of $10 \text{ mg} \cdot \text{kg}^{-1}$ and continued for 2 or 7 days. A fourth protocol assessed the effects of delayed short-term (7-day) gevokizumab treatment initiated in a context of established HF, that is, 83 days following reperfusion at an intraperitoneal dose of $10 \text{ mg} \cdot \text{kg}^{-1}$. All “untreated” control rats received immunoglobulin G (IgG).

MEASURED PARAMETERS. See [Supplemental Methods and Supplemental Figure 1](#).

STATISTICAL ANALYSIS. All results are mean $\pm$ SEM. Left ventricular diastolic/systolic diameters and hemodynamic parameters were assessed as primary endpoints, whereas all other parameters, that is, molecular mechanisms, were assessed as secondary endpoints. Because no data were available for the possible effect of gevokizumab on remodeling and hemodynamics, we made a simulation, using our historical data (18–20) for each parameter obtained in untreated animals to demonstrate statistical significance ($p < 0.05$) with a minimal power of 80%. The minimal expected effect size or difference between untreated and treated was fixed at 10% and 30%, with the coefficient of variation to 25% and 15% for echocardiographic infarct size studies and hemodynamic studies, respectively. For all significant differences concerning primary endpoints, a posteriori powers higher than 80% were also checked.

In order to evaluate the effect of I/R, all parameters obtained in Wistar rats subjected to I/R and sham surgery were compared using Student unpaired 2-tailed t test. Before applying parametric tests, such as Student unpaired 2-tailed t test, the Gaussian distribution of data was assessed by Shapiro-Wilk normality test and Kolmogorov-Smirnov test and graphically by QQplot and normal probability plot.

In order to evaluate the effects of long-term early and delay-initiated gevokizumab, all parameters obtained in placebo, early and delayed long-term

gevokizumab-treated rats were compared using one-way ANOVA followed, in case of significance, by Tukey test for multiple comparisons.

In order to evaluate the effects of short-term (2- or 7-day) gevokizumab treatment, all parameters obtained in IgG placebo, and 2- or 7-day gevokizumab-treated rats were compared by unpaired, 2-tailed Student t test.

Identical statistical analyses were used for the GK protocols. All statistical analysis was conducted using SPSS version 20.0 software (IBM, Armonk, New York) and R Statistic version 3.1.4 (R Foundation for Statistical Computing, Vienna, Austria). Differences were considered significant at a p level of <0.05 .

RESULTS

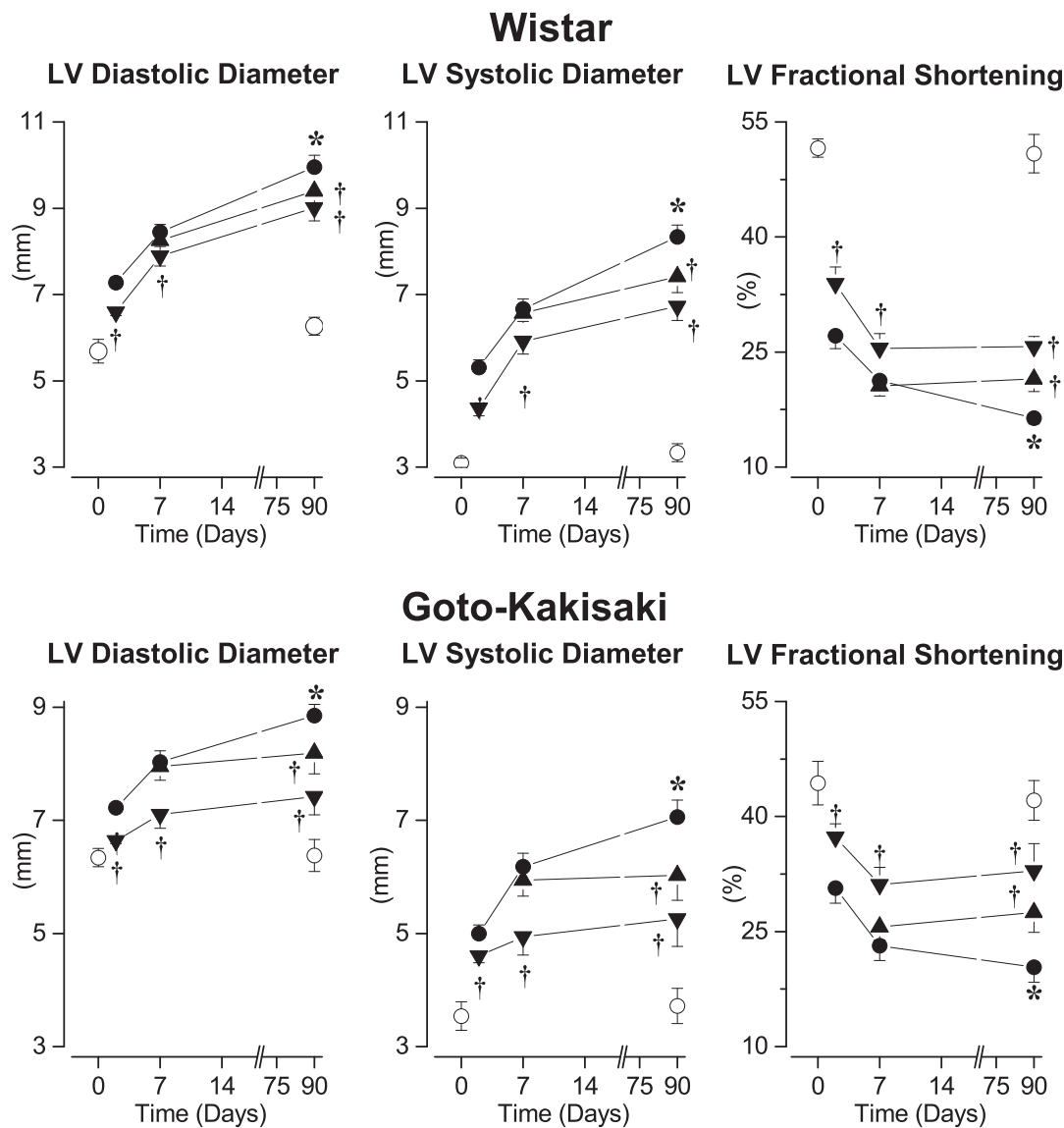
EFFECTS OF EARLY AND DELAYED LONG-TERM GEVOKIZUMAB. LV remodeling and function.

In untreated Wistar rats, 2 days after I/R, LV systolic and diastolic diameters were increased resulting in a reduced LV fractional shortening compared with that in sham-operated rats. Further increases in LV systolic and diastolic diameters were observed 7 and 90 days after I/R, resulting in a progressive impairment of LV fractional shortening ([Figure 1](#), upper panel). These effects were associated with an increase in pulmonary weight (sham: $0.89 \pm 0.01 \text{ g}$ vs. I/R: $1.22 \pm 0.03 \text{ g}$; $p < 0.05$) 90 days after I/R. Early gevokizumab, initiated 1 h after I/R, induced rapid and persistent reduction of LV diastolic and systolic diameters after 2, 7, and 90 days, resulting in an improved LV fractional shortening. Similarly, compared to untreated Wistar I/R rats, delayed gevokizumab initiated 7 days after I/R reduced the progressive LV dilation and the impairment of LV fractional shortening ([Figure 1](#), upper panel). Pulmonary weight was not significantly modified by gevokizumab (early: 1.17 ± 0.05 and delayed: 1.15 ± 0.04 , nonsignificant vs. I/R, respectively).

In GK rats, I/R induced progressive LV dilation and impairment of LV fractional shortening, as it did in Wistar rats. Early and delayed long-term gevokizumab limited, as in Wistar rats, LV dilation and impairment of LV fractional shortening ([Figure 1](#), lower panel).

LV hemodynamics. After 90 days, I/R Wistar rats displayed decreases in LV end-systolic pressure (LVESP) as well as in LV end-systolic pressure-volume relationship (LVESPVR) and increases in LV end-diastolic pressure (LVEDP) as well as in LV EDP volume relationship (LVEDPVR) compared with sham-operated animals ([Figure 2](#), upper panel). Early and delayed gevokizumab increased LVESPVR and decreased LVEDP as well as LVEDPVR.

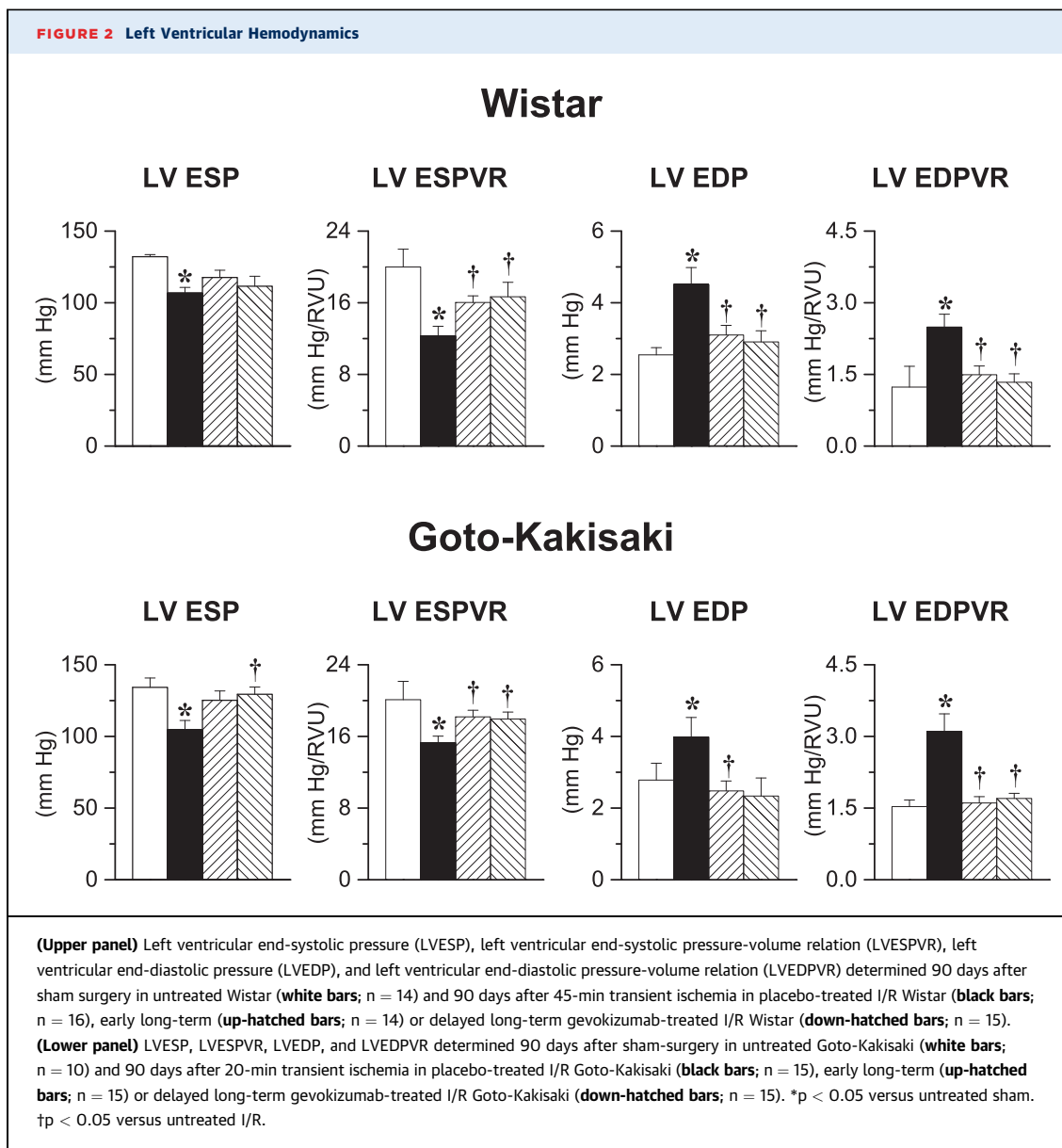
FIGURE 1 Time Course of Left Ventricular Dilatation



(Upper panel) Left ventricular (LV) diastolic, LV systolic diameter, and LV fractional shortening determined, before and 90 days after sham surgery, in untreated Wistar (open circles; n = 10) and 2, 7, and 90 days after 45-min transient ischemia in placebo-treated I/R Wistar (filled circles; n = 15), early long-term (down-triangles; n = 14) or delayed long-term gevokizumab-treated I/R Wistar (up-triangles; n = 15). **(Lower panel)** LV diastolic, LV systolic diameter, and LV fractional shortening determined, before and 90 days after sham surgery in untreated Goto-Kakizaki (open circles; n = 12) and 2, 7, and 90 days after 20-min transient ischemia in placebo-treated I/R Goto-Kakizaki (filled circles; n = 16), early long-term (down-triangles; n = 15) or delayed long-term gevokizumab-treated I/R Goto-Kakizaki (up-triangles; n = 15). *p < 0.05 versus untreated sham. †p < 0.05 versus untreated I/R.

In GK rats, after 90 days, I/R decreased LVESP and LVESPVR but increased LVEDP and LVEDPVR (Figure 2, lower panel). Early and delayed long-term gevokizumab increased LVESP as well as LVESPVR and decreased LVEDP as well as LVEDPVR.

LV hypertrophy, tissue perfusion, and infarct size. After 90 days, untreated I/R Wistar rats showed major infarct size associated with increased LV weight and collagen density, whereas pulmonary weight was increased (sham: 0.90 ± 0.03 g vs. I/R:

FIGURE 2 Left Ventricular Hemodynamics

0.97 ± 0.01 g; $p < 0.05$) but reduced LV tissue perfusion. Early and delayed gevokizumab initiation decreased LV weight and collagen density by increased tissue perfusion 90 days post I/R, while only early gevokizumab reduced infarct size (Figure 3). Pulmonary weight was not significantly modified by gevokizumab (early: 0.97 ± 0.09 ; delayed: 1.00 ± 0.09 , NS vs. I/R, respectively).

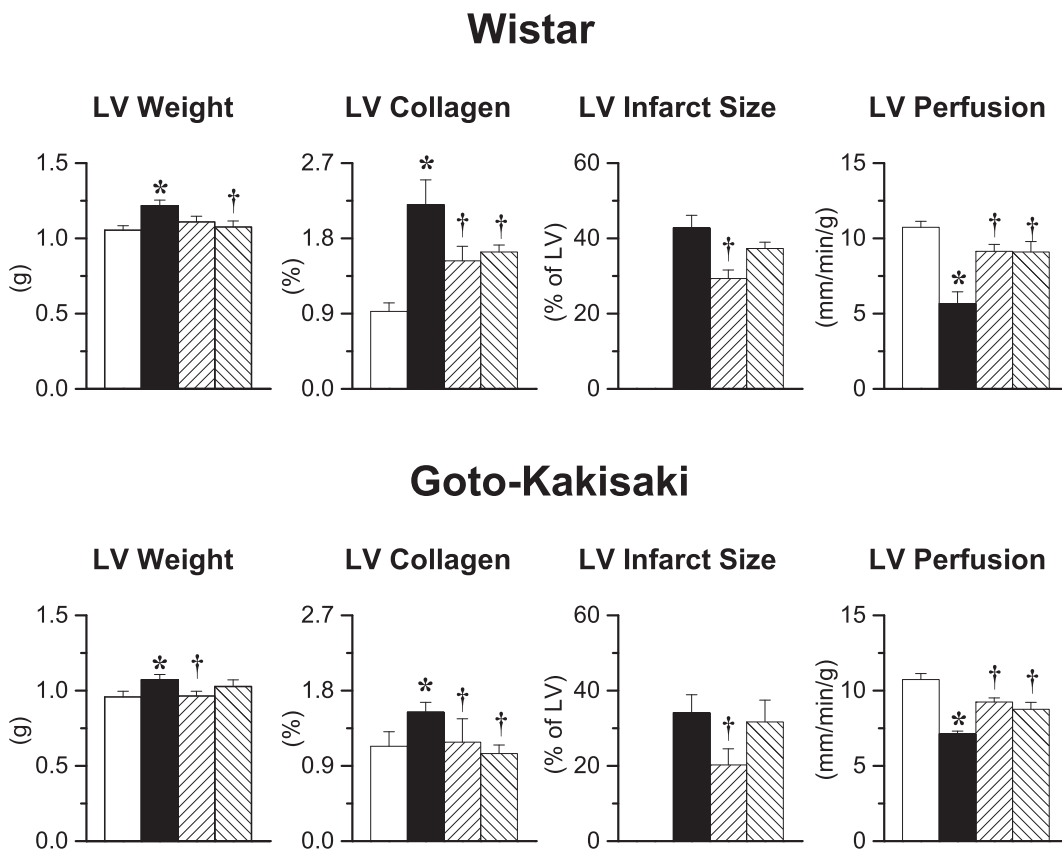
Ischemia/reperfusion induced large infarcts in GK rats, as it did in Wistar rats, which were associated with increased LV weight, collagen density, and reduced tissue perfusion. Again, early and delayed long-term gevokizumab decreased LV weight and

collagen density and increased tissue perfusion, only early gevokizumab reduced infarct size (Figure 3).

Coronary artery relaxation. After 90 days, acetylcholine-induced relaxation of coronary arteries was impaired after I/R. Early and delayed long-term gevokizumab prevented this I/R-induced impaired coronary relaxation. Furthermore, L-NG-nitro-arginine abolished the responses to acetylcholine in all groups, whereas apocynin or superoxide dismutase (SOD) restored acetylcholine-induced relaxation only in coronary arteries from untreated I/R rats (Figure 4).

In sham-operated GK rats, the acetylcholine-induced coronary relaxation was impaired compared

FIGURE 3 Left Ventricular Remodeling



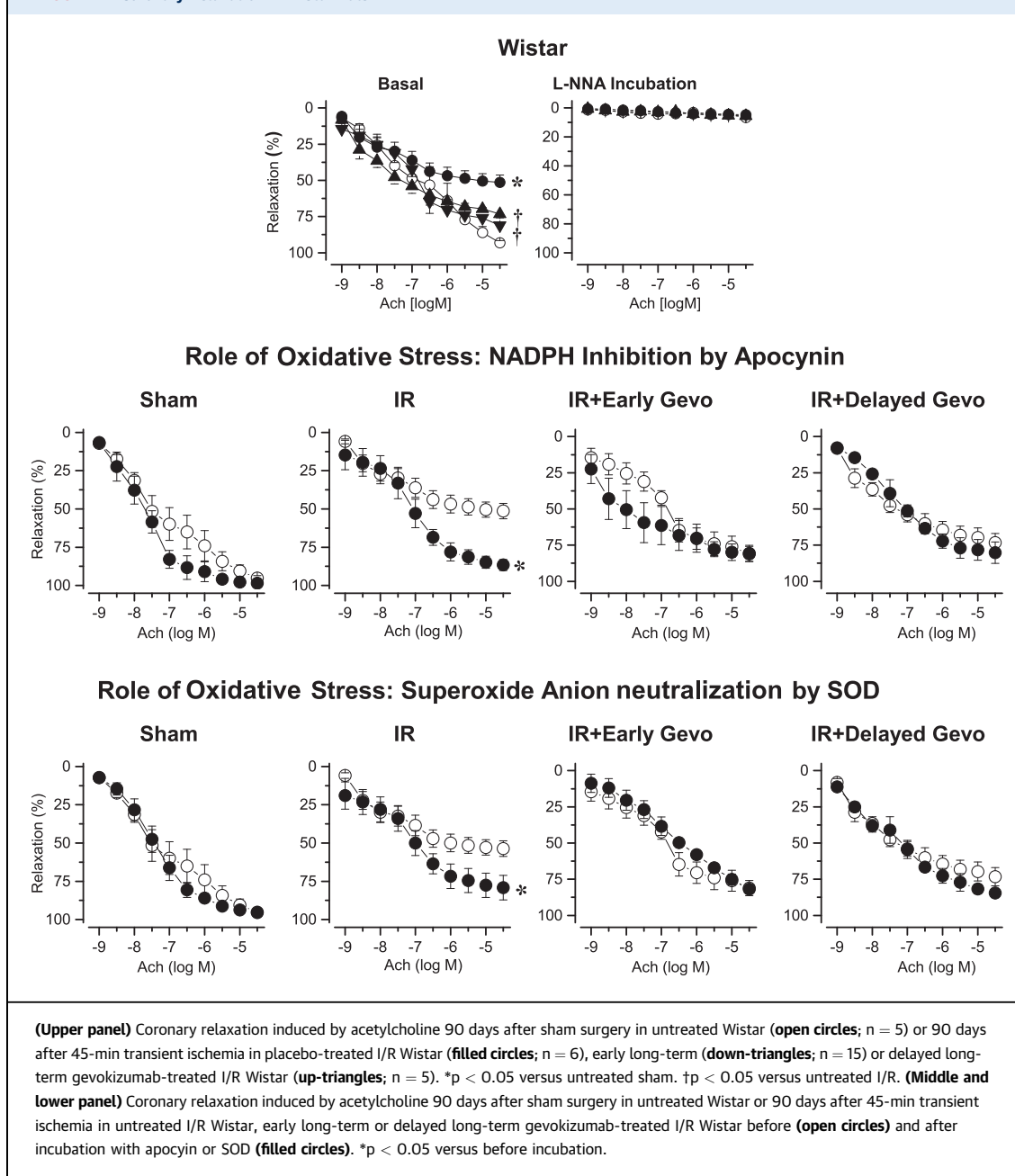
(Upper panel) Left ventricular (LV) weight, collagen density, infarct size, and tissue perfusion in the 'viable' part of the LV determined 90 days after sham surgery in untreated Wistar (white bars; n = 14) and 90 days after 45-min transient ischemia in placebo-treated I/R Wistar (black bars; n = 16), early long-term (up-hatched bars; n = 14) or delayed long-term gevokizumab-treated I/R Wistar (down-hatched bars; n = 15). (Lower panel) LV weight, collagen density, infarct size, and tissue perfusion in the 'viable' part of the LV determined 90 days after sham surgery in untreated Goto-Kakizaki (white bars; n = 10) and 90 days after 20-min transient ischemia in placebo-treated I/R Goto-Kakizaki (black bars; n = 15), early long-term (up-hatched bars; n = 15) or delayed long-term gevokizumab-treated I/R Goto-Kakizaki (down-hatched bars; n = 15). *p < 0.05 versus untreated sham. †p < 0.05 versus untreated I/R.

with that in sham-operated Wistar rats, and this response was further impaired 90 days after I/R (Figure 5). Early and delayed long-term gevokizumab supra-normalized, acetylcholine induced coronary vasorelaxation, whereas the effects of L-NNA, apocynin, and SOD were similar to those observed in coronary arteries of Wistar rats.

LV oxidative stress. Ninety days post I/R, the levels of reactive oxygen species (ROS) increased in Wistar rats (sham: 15.0 ± 0.9 AU/mg prot; untreated I/R: 18.2 ± 1.0 AU/mg prot; $p < 0.05$). Early and delayed long-term gevokizumab reduced cardiac ROS levels (early: 12.8 ± 0.6 AU/mg prot; delayed: 13.4 ± 0.8 AU/mg prot; both $p < 0.05$ vs. untreated I/R).

EARLY SHORT-TERM EFFECTS OF GEVOKIZUMAB. LV remodeling and hemodynamics. Reductions in LV systolic and diastolic diameters and resulting increase in LV fractional shortening after 2 and 7 days of gevokizumab treatment (Figure 1) were associated with increased LVESP and LVESPVR and decreased LVEDP as well as LVEDPVR (Table 1). Simultaneously, 2-day gevokizumab initiated 1 h after I/R in Wistar rats reduced the surface of the necrotic area, whereas the area at risk was not modified.

Similarly, in GK rats, reductions in LV systolic and diastolic diameters and resulting increase in LV fractional shortening after 2 days of gevokizumab (Figure 1) were associated with increased LVESPVR

FIGURE 4 Coronary Relaxation in Wistar Rats

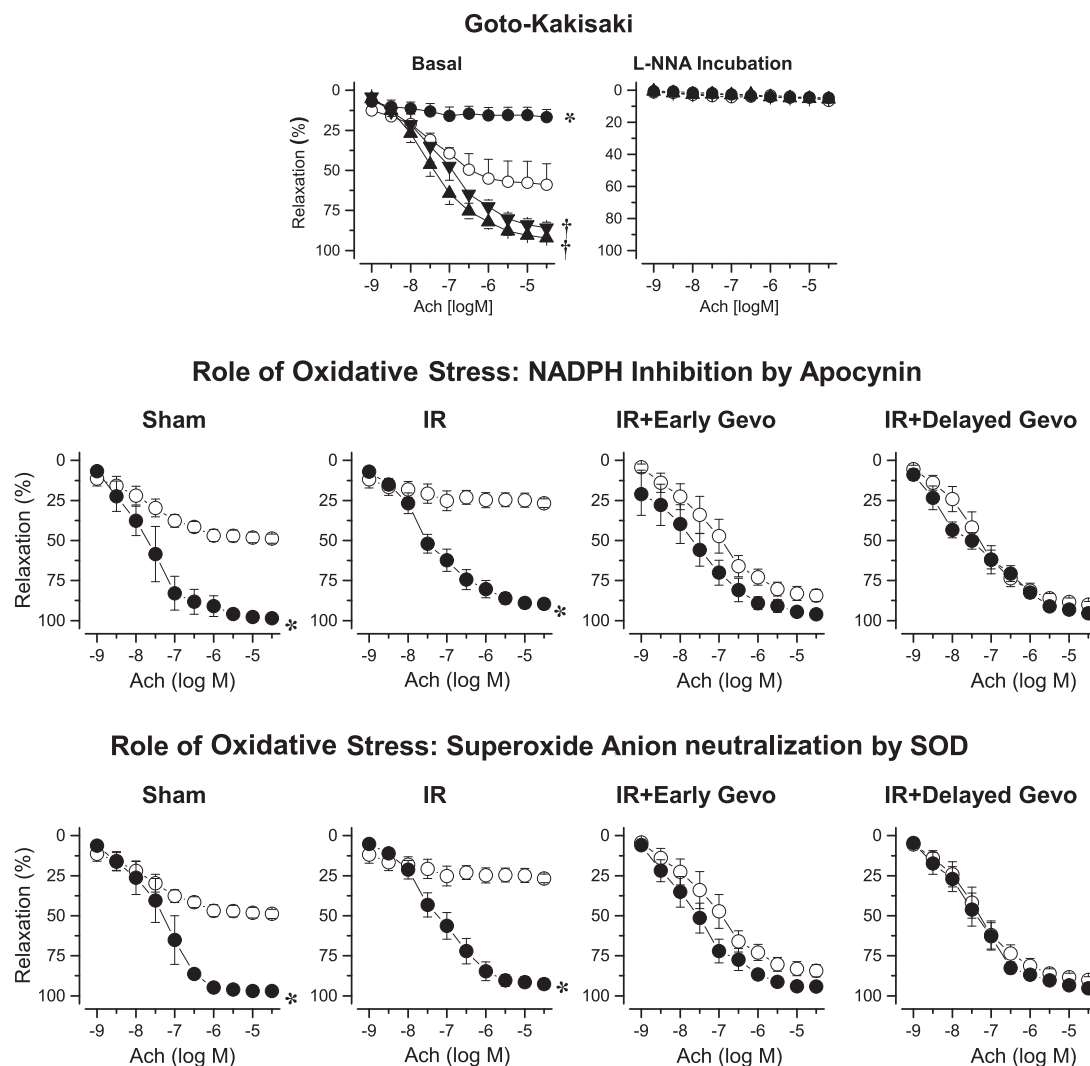
and decreased LVEDP, as well as LVEDPVR. Similar to Wistar rats, the 2-day gevokizumab treatment in GK rats reduced the necrotic area, whereas the area at risk was not modified (Table 2).

LV oxidative stress. Two days post I/R, cardiac ROS levels were not modified either in untreated rats (sham: 2.47 ± 0.38 AU/mg prot; untreated: I/R: 2.10 ± 0.15 AU/mg prot) or in gevokizumab-treated rats (2.36 ± 0.11 AU/mg prot). However, the

increased LV ROS levels observed 7 days after I/R (sham: 1.53 ± 0.21 AU/mg prot; I/R: 2.23 ± 0.19 AU/mg prot; $p < 0.05$) were reduced by 7-day gevokizumab treatment (1.84 ± 0.16 AU/mg prot; $p < 0.05$ vs. I/R).

Furthermore, cardiac glutathione peroxidase, catalase, and CuZn SOD enzymatic activities were not modified 2 days post I/R, but mitochondrial SOD activity was reduced in untreated I/R rats compared

FIGURE 5 Coronary Relaxation in Gotokakisaki Rats



(Upper panel) Coronary relaxation induced by acetylcholine 90 days after sham surgery in untreated Goto-Kakisaki (open circles; $n = 5$) or 90 days after 20-min transient ischemia in placebo-treated I/R Goto-Kakisaki (filled circles; $n = 8$), early long-term (down-triangles; $n = 6$) or delayed long-term gevokizumab-treated I/R Goto-Kakisaki (up-triangles; $n = 6$). * $p < 0.05$ versus untreated sham. $\dagger p < 0.05$ versus placebo-treated I/R. **(Middle and lower panels)** Coronary relaxation induced by acetylcholine 90 days after sham-surgery in IgG-treated Goto-Kakisaki or 90 days after 20-min transient ischemia in placebo-treated I/R Goto-Kakisaki, early long-term or delayed long-term gevokizumab-treated I/R Goto-Kakisaki before (open circles) and after incubation with apocynin or SOD (filled circles). * $p < 0.05$ versus before incubation.

with that in sham-operated animals. Two-day gevokizumab reduced catalase activity and tended to normalize mitochondrial SOD (Table 3).

Cardiac inflammation. Two days post I/R, lymphocytes and leukocytes accumulated in the infarcted area, while activated caspase-1 activity increased and gevokizumab reduced lymphocyte and leukocyte accumulation as well as caspase-1 activity (Table 2).

SHORT-TERM EFFECTS OF GEVOKIZUMAB IN WELL-ESTABLISHED HEART FAILURE. Short-term gevokizumab initiated 83 days post I/R reduced LV systolic diameter but did not modify LV diastolic diameter, resulting in improved LV fractional shortening. This was associated with a marked increase in LVESP and LVESPVR, although the latter did not reach statistical significance. Furthermore, LVEDP and LVEDPVR were decreased. Moreover, neither LV

TABLE 1 Infarct Size and Hemodynamics in 2- or 7-Day Gevokizumab Treatments in Wistar Rats

	Time	Sham Treatment	Ischemia/Reperfusion	
			Untreated	Gevokizumab Treated
LV weight, g	D ₀₋₂	-	0.79 $\pm$ 0.07	0.66 $\pm$ 0.04
	D ₀₋₇	0.65 $\pm$ 0.02	0.64 $\pm$ 0.02	0.66 $\pm$ 0.03
Area at risk, % of LV	D ₀₋₂	-	45.2 $\pm$ 3.4	45.6 $\pm$ 1.9
Necrotic area, % of LV	D ₀₋₂	-	25.9 $\pm$ 2.7	8.5 $\pm$ 0.3 [†]
Infarct size, % of LV	D ₀₋₇	-	42.9 $\pm$ 2.6	34.0 $\pm$ 2.9 [†]
LV ESP, mm Hg	D ₀₋₂	-	84.6 $\pm$ 5.5	100.4 $\pm$ 6.8 [†]
	D ₀₋₇	130.1 $\pm$ 1.6	101.9 $\pm$ 7.0*	119.6 $\pm$ 5.1 [†]
LV ESRP, mm Hg/RVU	D ₀₋₂	-	14.4 $\pm$ 0.8	16.8 $\pm$ 0.5 [†]
	D ₀₋₇	24.1 $\pm$ 0.64	12.3 $\pm$ 1.2*	15.5 $\pm$ 0.9 [†]
LV EDP, mm Hg	D ₀₋₂	-	2.68 $\pm$ 0.53	1.96 $\pm$ 0.19 [†]
	D ₀₋₇	1.87 $\pm$ 0.59	4.09 $\pm$ 0.57*	3.19 $\pm$ 0.59
LV EDPVR, mm Hg/RVU	D ₀₋₂	-	1.81 $\pm$ 0.15	1.43 $\pm$ 0.09 [†]
	D ₀₋₇	0.89 $\pm$ 0.11	2.10 $\pm$ 0.22*	1.66 $\pm$ 0.16 [†]

Values are mean $\pm$ SD. *p < 0.05 versus sham. [†]p < 0.05 versus untreated I/R. n = 4 to 17 per group.

D₀₋₂ = 2-day treatment initiated 1 h after I/R; D₀₋₇ = 7-day treatment initiated 1 h after I/R; LV EDP = left ventricular end-diastolic pressure; LV EDPVR = left ventricular end-diastolic pressure-volume relationship; LV ESP = left ventricular end-systolic pressure; LV ESPVR = left ventricular end-systolic pressure-volume relationship; LV = left ventricular; RVU = relative volume units.

weight nor collagen accumulation were modified by short-term gevokizumab initiated in a context of established HF, but myocardial tissue perfusion of the “viable” part of the LV was increased (Table 4). At the vascular level, short-term gevokizumab also restored the HF-induced impairment of coronary relaxation.

DISCUSSION

Our results, obtained in a rat model of HF induced by cardiac I/R, showed that neutralization of IL-1 β by the IL-1 β antibody gevokizumab is associated not only with immediate but also sustained long-term improvement of cardiac and vascular functions involving multiple direct and indirect mechanisms,

such as reduction of IL-1 β 's direct negative inotropic effects, LV oxidative stress, and LV tissue inflammation and/or reduction of infarct size.

Although extensive research has clearly established that the inflammatory response is one of the major determinants involved in I/R-induced adverse cardiac remodeling or dysfunction, most clinical trials evaluating anti-inflammatory or immune modulatory drugs in HF, such as the anti-tumor necrosis factor (TNF)- α antibody etanercept (21) and colchicine (22) have been disappointing. However, IL-1 β neutralization could be a new treatment of HF because in our study chronic neutralization of IL-1 β by the IL-1 β anti-body gevokizumab limits the progression of HF, shown by the limitation of LV dilation and LV dysfunction and improved LV hemodynamics. Our results, obtained in rats, which are similar to those obtained in mice (8), clearly show that IL-1 β neutralization is beneficial beyond the “acute” phase of myocardial infarction, where IL-1 β neutralization by the antibody anakinra/IL-1 trap has already shown improvement in LV function and remodeling in acute experimental (7,23,24) and human myocardial infarction (25-27).

Concerning the pathways involved in the improvement of cardiac function, our results clearly show that multiple direct and indirect mechanisms act in concert. First, reduction of IL-1 β 's direct negative inotropic properties (10,28) will lead to an immediate and sustained improvement of LV function, as illustrated by the increase of LV end-systolic pressure-volume relationship after 2, 7, and 90 days of gevokizumab treatment. Indeed, such direct mechanism of IL- β antagonism has already been suggested in mice (8,13), and gevokizumab may thus oppose the impaired Ca²⁺ handling in HF (29) by limiting IL-1 β -induced Ca²⁺ leakage from sarcoplasmic reticulum (11). Second, reduction of IL-1 β -induced production of ROS (30), resulting in a reduced LV oxidative stress, as illustrated by the reduction of LV ROS observed after 7 or 90 days of gevokizumab treatment, should be beneficial. Indeed, it may reduce oxidative stress-induced production of local vasoconstrictors, such as endothelin (31), which is implicated in the deterioration of LV function and/or remodeling (32,33). Moreover, although this has not been assessed in our study, the reduction of ROS by gevokizumab per se will diminish oxidative stress-induced modifications of sarcoplasmic reticulum Ca²⁺-ATPase protein structure and its activity, resulting in abnormal Ca²⁺ handling and impaired excitation-contraction coupling (34,35). Third, the reduction of myocardial oxidative stress by gevokizumab may induce indirect long-term effects

TABLE 2 Effect of 2-Day Gevokizumab Treatment in Goto-Kakisaki Rats

	Ischemia/Reperfusion	
	Untreated	Gevokizumab Treated
LV weight, g	0.90 $\pm$ 0.02	0.86 $\pm$ 0.01
Area at risk, % of LV	43.4 $\pm$ 3.0	45.2 $\pm$ 4.9
Infarct size, % of LV	16.6 $\pm$ 1.8	7.6 $\pm$ 1.9*
LV ESP, mm Hg	93.9 $\pm$ 6.8	90.0 $\pm$ 5.2
LV ESPVR, mm Hg/RVU	12.5 $\pm$ 1.0	16.4 $\pm$ 1.0*
LV EDP, mm Hg	2.06 $\pm$ 0.31	1.27 $\pm$ 0.15*
LV EDPVR, mm Hg/RVU	2.15 $\pm$ 0.21	1.44 $\pm$ 0.17*

Values are mean $\pm$ SD. *p < 0.05 versus untreated I/R. n = 10 to 15 per group.

Abbreviations as in Table 1.

interfering with LV diastolic function. Indeed, oxidative stress induces cardiac remodeling, such as accumulation of interstitial collagen (36,37). Hence, reduction of oxidative stress by IL-1 β neutralization may partly explain the reduction of LV collagen density observed after long-term gevokizumab administration. This reduced fibrosis will contribute to the improvement of LV diastolic function, as LV collagen accumulation provokes LV diastolic dysfunction. However, the exact role of the modifications in myocardial collagen remains to be elucidated because the 7-day gevokizumab initiated in established HF, that is, after 83 days after I/R, still improves LV diastolic function without any modification of LV collagen accumulation, probably involving, as discussed above, immediate effects on inotropism/calcium handling. Fourth, the reduction in LV ROS levels should, theoretically, improve LV nitric oxide (NO) bioavailability. This could contribute to the improvement of LV diastolic dysfunction observed after both short- and long-term gevokizumab administration, because reduced myocardial NO bioavailability increases myocyte resting tension and impairs LV function (38–41), while an increase in NO bioavailability and production, such as that induced through administration of the eNOS cofactor tetrahydrobiopterin (42) or NO donors (43) or eNOS enhancers (44) reduces LV diastolic dysfunction.

In addition to the beneficial effects of gevokizumab on LV function and structure, our results show for the first time that neutralization of IL-1 β by gevokizumab also prevents HF-related coronary dysfunction, illustrated by the complete normalization of coronary endothelium-dependent relaxation. This normalization of coronary relaxation by gevokizumab may be the direct consequence of the prevention of I/R-induced vascular (endothelial) oxidative stress and the subsequent increase in vascular NO bioavailability, as illustrated by the fact that the normalized coronary relaxation in gevokizumab-treated animals is abolished by the NO synthase inhibitor L-NNA.

The restoration of coronary relaxation observed in gevokizumab-treated animals could indirectly contribute to the improvement of LV function. Indeed, the restoration of coronary relaxation by gevokizumab probably contributes to the improved myocardial tissue perfusion, as observed after gevokizumab, which will prevent LV tissue hypoxia. Moreover, as hypoxia induces production of ROS through enhanced pro-oxidant systems such as NADPH oxidase (45–47), imbalanced eNOS-to-iNOS ratio (48), and/or hypoxia-induced production of local cytokines, including

TABLE 3 Cellular Effects of 2-Day Gevokizumab Treatment in Wistar Rats With I/R

	Sham Treated	Ischemia/Reperfusion	
		Untreated	Gevokizumab Treated
Glutathione peroxidase activity, $\mu\text{mol/min/mg prot}$	219 $\pm$ 9	175 $\pm$ 21	168 $\pm$ 15
Catalase activity, $\mu\text{mol/min/mg prot}$	13.4 $\pm$ 1.1	16.39 $\pm$ 1.8	10.8 $\pm$ 1.1†
Mitochondrial SOD activity, U SOD Mn/mg prot	7.2 $\pm$ 0.9	2.8 $\pm$ 0.7*	4.9 $\pm$ 0.8
Cytosolic SOD activity, U SOD CuZn/mg prot	4.5 $\pm$ 1.1	3.7 $\pm$ 0.7	4.4 $\pm$ 1.2
Total lymphocytes, nb/field	11.7 $\pm$ 2.1	44. $\pm$ 6.9*	38.9 $\pm$ 8.1
Lymphocytes in infarct area, nb/field	2.9 $\pm$ 0.5	26.9 $\pm$ 4.4*	22.1 $\pm$ 5.1
Total leukocytes, nb/field	56.3 $\pm$ 15.5	241.2 $\pm$ 23.2*	115.3 $\pm$ 41.2†
Leucocytes in infarct area, nb/field	13.5 $\pm$ 3.6	89.4 $\pm$ 12.0*	31.8 $\pm$ 11.9†
Cleaved caspase-1 in infarct area, nb/field	0.00 $\pm$ 0.00	0.75 $\pm$ 0.25*	0.30 $\pm$ 0.10†

Values are mean $\pm$ SD. *p < 0.05 versus sham. †p < 0.05 versus untreated I/R. n = 6 TO 10 per group. nb = 9 per group; SOD = superoxide dismutase.

IL-1 β , the increased LV tissue perfusion observed with gevokizumab might rupture the vicious circles of IL-1 β -induced ROS production (30) and/or IL-1 β -induced IL-1 β release, as well as ROS-induced IL-1 β release and/or ROS-induced ROS production but also IL-1 β induced activation of the renin-angiotensin system (49).

Finally, the reduction of infarct size observed after early but not delayed gevokizumab contributes to the improvement of LV function. This might be related to the reduced activation of the IL-1 β pathway as suggested by the reduction of (activated) caspase-1

TABLE 4 Hemodynamics of 7-Day Gevokizumab in Wistar Rats With CHF

	Chronic Heart Failure	
	Untreated	Gevokizumab Treated
LV diastolic diameter, mm	9.74 $\pm$ 0.24	9.61 $\pm$ 0.46
LV systolic diameter, mm	8.20 $\pm$ 0.19	7.18 $\pm$ 0.36*
LV fractional shortening, %	15.8 $\pm$ 0.7	25.3 $\pm$ 1.1*
LV ESP, mm Hg	108.0 $\pm$ 9.7	126.8 $\pm$ 2.9*
LV ESPVR, mm Hg/RVU	12.2 $\pm$ 1.0	14.3 $\pm$ 0.5
LV EDP, mm Hg	4.40 $\pm$ 0.58	2.43 $\pm$ 0.16*
LV EDPVR, mm Hg/RVU	2.45 $\pm$.21	1.96 $\pm$ 0.10*
LV Weight, g	1.20 $\pm$ 0.04	1.19 $\pm$ 0.08
LV collagen density, %	3.15 $\pm$ 0.44	3.01 $\pm$ 0.52
LV infarct size, %	39.2 $\pm$ 8.8	40.1 $\pm$ 6.1
Myocardial perfusion, ml/min/100 g	7.92 $\pm$ 0.16	8.57 $\pm$ 0.18*
Coronary relaxation, %		
Basal	37.1 $\pm$ 5.9	78.0 $\pm$ 9.0*
Apocin incubation	80.4 $\pm$ 13.4	87.2 $\pm$ 7.1
SOD incubation	81.0 $\pm$ 6.9	82.8 $\pm$ 8.7

Values are mean $\pm$ SD. *p < 0.05 versus untreated I/R. Abbreviations as in Table 1.

activity in our experiments, as already reported with the human recombinant IL-1 β receptor antagonist anakinra (23). However, it cannot be excluded that the caspase-1 pathway is reduced because infarct size is reduced, as IL-1 β blockade in a severe ischemic myocardial infarction does not reduce inflammatory activation (5). Furthermore, other pathways, such as enhanced NO bioavailability due to reduced oxidative stress may be involved in the reduction of infarct size (50). Although not determined, reduced IL-1 β -induced production of ROS during the infarct healing period, that is, the first 7 days after I/R, will reduce LV oxidative stress and increase NO bioavailability, which are both clearly observed after 7 and 90 days in our experiments. However, whether a reduction of infarct size occurs in humans is currently unknown. Although a reduction of infarct size per se will have a beneficial effect, gevokizumab also exerts beneficial effects in terms of cardiovascular function even when started after completion of the infarct healing. It is thus tempting to state that treatment should be initiated as early as possible and continued beyond the infarct healing period but might also be initiated after infarct healing. This is clinically important because it suggests that a number of patients may benefit from gevokizumab or other IL-1 β antagonism rather than being reserved for patients with acute myocardial infarction treated with early primary percutaneous coronary intervention (12,51). However, it must be stressed that, in this experimental study, the duration of the ischemic period is longer in nondiabetic animals in order to reproduce similar I/R injury since diabetes renders prone to I/R injury. However, in the clinical setting diabetic patients will have similar time of ischemia to nondiabetic patients, which could limit the efficacy of gevokizumab in humans. These critical points need to be evaluated in humans.

It must be stressed that several pathologies, such as diabetes, render the heart more prone to I/R injury, which may be related in part to the modest but significant increase in IL-1 β concentrations observed in humans with diabetes (52). Thus, we also evaluated the efficiency of gevokizumab in I/R injury in a model of diabetes (i.e., GK rats). In this pathological context, gevokizumab's short- and long-term cardiac effects, that is, improved LV hemodynamics and function, reduced LV remodeling, and so forth, are similar to those observed in Wistar rats. However, at the vascular level, gevokizumab restores the coronary endothelial-dependent relaxation beyond the relaxation observed in the untreated GK group and reaches even the value

of the relaxation of coronary artery from Wistar rats. This suggests that, in diabetes, increased IL-1 β levels per se reduce endothelium-dependent vasorelaxation.

Surprisingly, in GK rats, gevokizumab improves cardiovascular function and structure independently from possible metabolic modifications, as all metabolic parameters, especially glucose and insulin tolerance are not statistically significantly modified by gevokizumab. Whether this is related to the dosage regimen used in our study remains to be investigated, as short-term anakinra therapy improves insulin sensitivity in patients with type 1 diabetes (53).

STUDY LIMITATIONS. Although this study did not evaluate long-term survival, our results suggest that gevokizumab may improve long-term survival after I/R. Indeed, as the magnitude of infarct size is correlated with the relative risk of death (54), the reduction of infarct size observed when gevokizumab treatment is initiated “immediately” after I/R should be associated with an increase in long-term survival. Furthermore, although intermediate “surrogate” markers of survival (i.e., LV dilation) are improved by long-term gevokizumab, other major determinants of survival in this model of HF (i.e., reductions in arterial blood pressure and heart rate) (32,55), are not observed in gevokizumab-treated animals. Thus, the effect of IL-1 β modulation per se or in combination with standard treatments of HF on long-term survival after I/R remains to be determined.

CONCLUSIONS

The IL-1 β antibody gevokizumab limits the progression of HF due to cardiac I/R. The improvement of cardiac and coronary functions involves immediate effects (i.e., reduction of IL-1 β -related negative inotropic effects, improved myocardial perfusion, reduced oxidative stress, reduced infarct size, and so forth, and long-term effects such as modifications in the myocardial structure, all independent from the pathological metabolic status). Furthermore, the fact that, in I/R GK diabetic rats, gevokizumab's improvement of coronary endothelium-dependent relaxation reaches relaxation of coronary arteries from nondiabetic Wistar suggests a possible role for not only secondary but also primary protection in diabetes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Heart failure is a clinical syndrome characterized by dyspnea, fatigue, and poor exercise capacity and has become a major health problem because, despite medical treatment, its incidence continues to increase. We report pre-clinical data showing that IL-1 β modulation is a new, promising target in the pathophysiological context of HF. Indeed, the IL-1 β antibody gevokizumab improves

intermediate “surrogate” markers of survival, that is, left ventricular remodeling and function and coronary function.

TRANSLATIONAL OUTLOOK: However, whether IL-1 β modulation per se or in combination with standard treatments for HF improves long-term outcome in human HF remains to be determined.

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KEY WORDS cardiovascular function, heart failure, IL-1 β , ischemia/reperfusion

APPENDIX For an expanded Methods section and a supplemental figure, please see the online version of this article.