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Comparison of the cardiovascular effects of two novel superoxide dismutase mimetics, SC-55858 and SC-54417, in conscious dogs

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Abstract

The hemodynamic actions and left ventricular mechanical effects of two new superoxide dismutase mimetics, SC-55858 [Manganese (II) dichloro (2*R*,3*R*,8*R*,9*R*-bis-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)] ($n = 10$) and SC-55417 [Manganese (II) dichloro (trans-2,3-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)] ($n = 8$), were studied in chronically instrumented dogs in the conscious state and after 30 min equilibration at 0.033, 0.067, 0.233, and 0.667 $\mu M \cdot kg^{-1} \cdot min^{-1}$ SC-55858 or SC-54417 (total doses of 1, 2, 7, and 20 $\mu M \cdot kg^{-1}$). SC-55858 and SC-54417 increased heart rate and decreased mean arterial pressure and left ventricular systolic and end-diastolic pressures. SC-55858 decreased preload recruitable stroke work slope and $+dP/dt_{max}$ and increased the time constant of isovolumic relaxation, consistent with a direct negative inotropic and lusitropic effect. In contrast, SC-54417 did not depress left ventricular systolic and diastolic function. Decreases in mean arterial pressure caused by SC-55858 may be secondary to negative inotropic effects and reduction in cardiac preload. In contrast, SC-54417 does not depress myocardial contractility but also reduces arterial pressure via venodilation.

Keywords: Ventricular function; Preload recruitable stroke work; Diastolic function; Isovolumic relaxation; Superoxide dismutase; SC-55858; SC-54417

1. Introduction

The production of oxygen-derived free radicals by damaged vascular endothelium and infiltrating polymorphonuclear leukocytes has been identified as an important cause of reperfusion-induced myocardial damage after acute ischemia (Braunwald and Kloner, 1985). Exogenous superoxide dismutase administered prior to or during an ischemic insult may reduce myocardial infarct size (Hatori et al., 1992; Jolly et al., 1984; Omar and McCord, 1991) and enhance the functional recovery of stunned myocardium (Burton, 1985; Gross et al., 1986), presumably by attenuating the deleterious effects of oxygen-derived free radicals (Bolli et al., 1988; Zweier, 1988; Zweier et al., 1987). However, recognition of the potential biophysical limitations of superoxide dismutase (inability to traverse cell membranes and access subendothelial and intracellular locations because of the large molecular size (Black et al., 1994; Omar and McCord, 1991)) has stimulated the development of low molecular weight, membrane-permeable superoxide dismutase mimetics. These agents are iron-, copper-, or manganese-chelated macrocyclic ligand complexes which have been shown to exhibit free radical scavenging activity similar to superoxide dismutase in vitro (McCord and Fridovich, 1969; Nagano et al., 1989; Rabinowitch et al., 1987; Riley and Weiss, 1994). More recently, the manganese-based SOD mimetic SC-52608 was shown to protect against ischemia-reperfusion damage (Kilgore et al., 1994) and reduced myocardial infarct size (Black et al., 1994), in contrast to an inactive analog, SC-54385. Two novel manganese-containing superoxide dismutase mimetics (Fig. 1), SC-55858 [Manganese (II) dichloro (2*R*,3*R*,8*R*,9*R*-bis-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)] and SC-55417 [Manganese (II) dichloro (*trans*-2,3-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)], are structurally related to SC-52608 and have been shown to produce greater catalytic activity (as assessed with a stopped-flow kinetic assay) against

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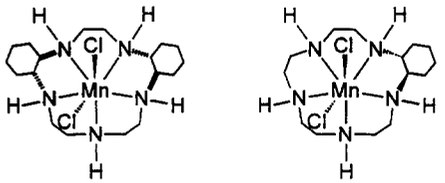

Fig. 1. Chemical structures of superoxide dismutase mimetics SC-55858 and SC-54417.

oxygen-derived free radicals than SC-52608 (unpublished observations, G.D. Searle). The hemodynamic and functional effects of SC-55858 and SC-54417 in the intact cardiovascular system are unknown. Thus, the present investigation was undertaken to characterize the systemic hemodynamic actions and left ventricular systolic and diastolic mechanical effects of SC-55858 and SC-54417 in conscious, chronically instrumented dogs.

2. Materials and methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. All conformed to the Guiding Principles in the Care and Use of Animals of the American Physiologic Society and were in accordance with the Guide for the Care and Use of Laboratory Animals [DHEW (DHHS) publication no. (NIH) 85-23, revised 1985].

2.1. Surgical preparation

The surgical implantation of instruments has been previously described in detail (Pagel et al., 1995). Briefly, under general anesthesia and using aseptic techniques, conditioned mongrel dogs underwent a left thoracotomy for placement of instruments for measurement of aortic, left atrial, and intrathoracic pressures (heparin-filled catheters), subendocardial segment length (ultrasonic crystals), and cardiac output (ascending thoracic aortic ultrasonic flow transducer). A high fidelity, miniature micromanometer was positioned in the left ventricular apex for measurement of continuous left ventricular pressure and the peak rate of increase and decrease of left ventricular pressure ($+dP/dt_{max}$ and $-dP/dt_{min}$, respectively). A hydraulic vascular occluder was placed around the inferior vena cava for abrupt alteration of left ventricular preload. All instrumentation was firmly secured, tunneled between the scapulae, and exteriorized via several small incisions. The pericardium was left open, the chest wall closed in layers, and the pneumothorax evacuated by a chest tube.

All dogs received systemic analgesics (fentanyl-droperidol) as needed after surgery. Dogs were allowed to recover a minimum of 7 days prior to experimentation during which time all were treated with intramuscular antibiotics [cephalothin (40 $mg \cdot kg^{-1}$) and gentamicin (4.5 $mg \cdot kg^{-1}$)] and trained to stand quietly in an animal sling during hemodynamic monitoring. Segment length signals were monitored by ultrasonic amplifiers (Crystal Biotech, Hopkinton, MA). End-systolic and end-diastolic segment length were measured at $-dP/dt_{min}$ and immediately prior to the onset of left ventricular isovolumic contraction, respectively. Percent segment shortening was determined using the equation: [percent segment shortening = (end-diastolic length − end-systolic length) · 100 · end-diastolic $length^{-1}$. All hemodynamic data were recorded on a polygraph and digitized via a computer interfaced with an analog to digital computer for subsequent analysis of left ventricular pressure-segment length waveforms and diagrams.

2.2. Experimental protocol

Dogs were assigned to receive SC-55858 or SC-54417 in a random fashion on separate experimental days (Fig. 1). Each dog was fasted overnight, and fluid deficits were replaced before experimentation with 500 ml 0.9% saline. After the instrumentation was calibrated, baseline systemic hemodynamics were recorded. Left ventricular pressure, intrathoracic pressure, and segment length waveforms were also recorded for later off-line analysis of diastolic function. Regional myocardial contractility was evaluated using a series of left ventricular pressure-segment length diagrams generated by abrupt constriction of the inferior vena cava (Pagel et al., 1995). Left ventricular pressure-segment length diagrams were rejected if heart rate increased more than 10% above baseline levels during the occlusion. In this case, pressure-length diagrams were repeated after steady-state hemodynamics had been reestablished. Respiratory variation in left ventricular pressure in the conscious state was later reduced by electronically subtracting the continuous intrathoracic pressure waveform from the left ventricular pressure waveform via the digital oscilloscope. (Pagel et al., 1995) Inferior vena caval occlusion was released immediately after recording of pressure-length diagrams. The slope of the regional preload recruitable stroke work relationship was used to determine myocardial contractility as previously described. (Glower et al., 1985; Pagel et al., 1995) Left ventricular diastolic function was evaluated with a time constant of isovolumic relaxation determined using the derivative method, maximum segment lengthening velocity during rapid ventricular filling calculated by differentiation of the segment length wave form, and a regional chamber stiffness constant derived using a simple monoexponential equation relating segment length to left ventricular pressure (Pagel et al., 1995).

SC-55858 and SC-54417 (G.D. Searle, St. Louis, MO, USA) were freshly prepared immediately prior to administration on the day of the experiment. Preliminary studies indicate that the catalytic activity (k_{cat}) of SC-55858 and

Table 1
Hemodynamic effects of SC-55858 in conscious dogs

	N	Conscious control	SC-55858 dose ($\mu M \cdot kg^{-1}$)			
			1	2	7	20
HR (bpm)	10	92 ± 3	107 ± 5	115 ± 6 [a]	143 ± 10 [a,b,c]	176 ± 11 [a,b,c,d]
SBP (mm Hg)	10	124 ± 3	118 ± 4	117 ± 3	117 ± 5	91 ± 4 [a,b,c,d]
DBP (mm Hg)	10	93 ± 4	90 ± 3	90 ± 3	94 ± 4	77 ± 4 [a,b,c,d]
MBP (mm Hg)	10	103 ± 3	101 ± 5	101 ± 3	100 ± 4	81 ± 4 [a,b,c,d]
LVSP (mm Hg)	10	124 ± 4	120 ± 4	118 ± 3	111 ± 5 [a]	91 ± 4 [a,b,c,d]
LVEDP (mm Hg)	10	10 ± 2	9 ± 1	9 ± 2	7 ± 2	5 ± 1 [a,b,c]
EDL (mm)	10	17.8 ± 1.0	17.8 ± 0.9	17.7 ± 0.8	17.2 ± 0.8	16.6 ± 0.9 [a,b,c]
ESL (mm)	10	14.6 ± 0.9	14.7 ± 0.8	14.7 ± 0.8	14.9 ± 0.7	14.5 ± 0.8
SS (%)	10	18.2 ± 2.3	17.4 ± 2.4	17.0 ± 2.1	13.3 ± 2.5 *	12.5 ± 2.4 [a,b,c]
CO ($l \cdot m^{-1}$)	9	2.2 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	2.0 ± 0.2
SVR ($dyn \cdot s \cdot cm^{-5}$)	9	3960 ± 310	3490 ± 230	3510 ± 370	3820 ± 370	3480 ± 280
SV (ml)	9	24 ± 2	23 ± 2	21 ± 2	17 ± 2 [a,b]	12 ± 2 [a,b,c]

Data are means ± S.E.M. [a] Significantly ($P < 0.05$) different from control. [b] Significantly ($P < 0.05$) different from 1 $\mu M \cdot kg^{-1}$ SC-55858. [c] Significantly ($P < 0.05$) different from 2 $\mu M \cdot kg^{-1}$ SC-55858. [d] Significantly ($P < 0.05$) different from 7 $\mu M \cdot kg^{-1}$ SC-55858. Abbreviations: HR = heart rate; SBP, DBP, and MBP = systolic, diastolic, and mean aortic blood pressures, respectively; LVSP and LVEDP = left ventricular systolic and end diastolic pressure, respectively; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance.

SC-54417 are 12.0 and $9.09 \cdot 10^7 \cdot M^{-1} \cdot s^{-1}$, respectively, as determined with a stopped flow kinetic assay in vitro (unpublished findings, G.D. Searle, St. Louis, MO, USA). These catalytic activities exceed the k_{cat} of SC-52608 ($4.13 \cdot 10^7 \cdot M^{-1} \cdot s^{-1}$), an agent that has been shown to reduce myocardial injury during ischemia and reperfusion in vivo (Kilgore et al., 1994; Black et al., 1994). The plasma half-lives of SC-55858 and SC-54417 are 350 and 8.4 min, respectively (unpublished findings, G.D. Searle, St. Louis, MO, USA). Both SC-55858 and SC-54417 are metabolized by the liver and excreted by the liver and kidney. Each drug was dissolved in 0.9% saline and buffered to pH 7.5 with 1 N NaOH. Doses of 1, 2, 7, and 20 $\mu M \cdot kg^{-1}$ of SC-55858 and SC-55417 (cumulative doses of 1, 3, 10, and 30 $\mu M \cdot kg^{-1}$) were administered in escalating order over 30 min via intravenous infusions (0.033, 0.067, 0.233, and 0.667 $\mu M \cdot kg^{-1} \cdot min^{-1}$) on separate experimental days. Hemodynamics were recorded and left ventricular pressure-segment length waveforms and diagrams were acquired in the manner described above after 30 min equilibration at each infusion rate of SC-55858 and SC-54417. Dogs recovered for at least 2 days prior to subsequent experimentation.

2.3. Statistical analysis

Statistical analysis of the data within and between groups was performed by multiple analysis of variance with repeated measures, followed by use of Student's *t*-test with Bonferroni's correction for multiplicity. Changes were considered to be statistically significant when the probability (P) value was < 0.05. All data are expressed as means ± S.E.M.

3. Results

No differences in baseline systemic hemodynamics and indices of left ventricular systolic and diastolic function

Table 2
Effects of SC-55858 on left ventricular function in conscious dogs

	Conscious control	SC-55858 dose ($\mu M \cdot kg^{-1}$)			
		1	2	7	20
M_w (mm Hg)	114 ± 10	106 ± 7	85 ± 6	77 ± 10 [a]	60 ± 9 [a,b,c]
L_w (mm)	13.4 ± 1.2	13.8 ± 1.0	13.8 ± 1.1	13.5 ± 0.7	14.7 ± 1.3
$+dP/dt_{max}$ (mm Hg · s^{-1})	2476 ± 184	2691 ± 207	2409 ± 180	2283 ± 190	1655 ± 113 [a,b,c,d]
$-dP/dt_{min}$ (mm Hg · s^{-1})	−2494 ± 134	−2566 ± 149	−2454 ± 126	−2268 ± 109	−1676 ± 78 [a,b,c,d]
τ (ms)	35 ± 1	34 ± 2	34 ± 2	34 ± 2	38 ± 2 [a,b,c,d]
K_p (mm^{-1})	0.32 ± 0.04	0.36 ± 0.05	0.32 ± 0.05	0.28 ± 0.05	0.22 ± 0.04
dL/dt_{max} (mm · s^{-1})	61 ± 9	65 ± 11	76 ± 9	67 ± 8	76 ± 12

Data are means ± S.E.M.; $n = 10$. [a] Significantly ($P < 0.05$) different from control. [b] Significantly ($P < 0.05$) different from 1 $\mu M \cdot kg^{-1}$ SC-55858. [c] Significantly ($P < 0.05$) different from 2 $\mu M \cdot kg^{-1}$ SC-55858. [d] Significantly ($P < 0.05$) different from 7 $\mu M \cdot kg^{-1}$ SC-55858. Abbreviations: M_w and L_w = preload recruitable stroke work slope and length intercept, respectively; τ = time constant of isovolumic relaxation; K_p = regional chamber stiffness constant.

Table 3
Hemodynamic effects of SC-54417 in conscious dogs

	N	Conscious control	SC-54417 dose ($\mu M \cdot kg^{-1}$)			
			1	2	7	20
HR (bpm)	8	91 ± 5	100 ± 6	107 ± 6 [a]	124 ± 7 [a,b,c]	170 ± 5 [a,b,c,d]
SBP (mm Hg)	8	127 ± 5	122 ± 5	120 ± 6	114 ± 6 [a]	101 ± 5 [a,b]
DBP (mm Hg)	8	95 ± 2	93 ± 5	88 ± 5	89 ± 6	85 ± 5
MBP (mm Hg)	8	108 ± 4	105 ± 5	102 ± 6	97 ± 6	90 ± 5
LVSP (mm Hg)	8	130 ± 5	121 ± 6	119 ± 7	113 ± 6 [a]	101 ± 6 [a,b]
LVEDP (mm Hg)	8	9 ± 2	8 ± 1	7 ± 2	6 ± 1	4 ± 1 [a,b]
EDL (mm)	8	18.3 ± 1.4	18.2 ± 1.4	18.0 ± 1.4	17.4 ± 1.4 [a,b]	15.9 ± 1.2 [a,b,c]
ESL (mm)	8	14.7 ± 1.2	14.9 ± 1.1	14.7 ± 1.1	14.5 ± 1.1	13.6 ± 1.1 [a,b,c]
SS (%)	8	19.4 ± 2.5	17.8 ± 1.9	17.8 ± 2.1	16.2 ± 1.6	14.5 ± 2.5 [a]
CO ($l \cdot m^{-1}$)	7	2.4 ± 0.1	2.6 ± 0.3	2.5 ± 0.2	2.6 ± 0.3	2.7 ± 0.2
SVR ($dyn \cdot s \cdot cm^{-5}$)	7	3760 ± 260	3520 ± 420	3530 ± 510	3450 ± 600	2920 ± 350
SV (ml)	7	27 ± 1	27 ± 3	24 ± 2	21 ± 2 [a]	16 ± 1 [a,b,c]

Data are means ± S.E.M. [a] Significantly ($P < 0.05$) different from control. [b] Significantly ($P < 0.05$) different from 1 $\mu M \cdot kg^{-1}$ SC-54417. [c] Significantly ($P < 0.05$) different from 2 $\mu M \cdot kg^{-1}$ SC-54417. [d] Significantly ($P < 0.05$) different from 7 $\mu M \cdot kg^{-1}$ SC-54417. Abbreviations: HR = heart rate; SBP, DBP, and MBP = systolic, diastolic, and mean aortic blood pressures, respectively; LVSP and LVEDP = left ventricular systolic and end diastolic pressure, respectively; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance.

were observed between experimental groups. The cardiovascular and mechanical actions of SC-55858 are summarized in Tables 1 and 2, respectively. SC-55858 caused significant ($P < 0.05$), dose-related increases in heart rate and decreases in mean arterial pressure, and left ventricular systolic and end-diastolic pressures, and end-diastolic segment length. No changes in cardiac output and systemic vascular resistance occurred with the administration of SC-55858. Stroke volume declined concomitant with increases in heart rate. SC-55858 caused dose-related decreases in myocardial contractility as indicated by the preload recruitable stroke work slope (M_w: 114 ± 10 during control to 60 ± 9 mmHg at 20 $\mu M \cdot kg^{-1}$). Declines in left ventricular $+dP/dt_{max}$ and percentage segment shortening were also observed with SC-55858, consistent with depression of contractile function. A modest, but significant, increase in the time constant of isovolumic relaxation was observed at the highest cumulative dose of SC-55858 (35 ± 1 during control to 38 ± 2 ms at 20 $\mu M \cdot kg^{-1}$), indicating that a delay in isovolumic relaxation had occurred concomitant with depression of inotropic state despite a simultaneous increase in heart rate. No changes in regional chamber stiffness and the rate of early ventricular filling.

The hemodynamic effects and actions of SC-54417 on cardiac performance are summarized in Tables 3 and 4, respectively. SC-54417 caused hemodynamic effects (Table 3) that were similar to those produced by SC-55858. In contrast to the findings with SC-55858, no changes in preload recruitable stroke work slope and $+dP/dt_{max}$ occurred with the administration of SC-54417 (Table 4), indicating that myocardial contractility was preserved with this drug. Dose-related declines in the time constant of isovolumic relaxation were observed (37 ± 2 during control to 31 ± 2 ms at 20 $\mu M \cdot kg^{-1}$), consistent with shortening of the isovolumic relaxation phase of diastole. A significant decrease in regional chamber stiffness occurred at the highest dose of SC-54417, suggesting that this drug

Table 4
Effects of SC-54417 on left ventricular function in conscious dogs

	Conscious control	SC-54417 dose ($\mu M \cdot kg^{-1}$)			
		1	2	7	20
M_w (mm Hg)	116 ± 13	108 ± 18	88 ± 14	90 ± 15	93 ± 10
L_w (mm)	14.1 ± 1.1	13.8 ± 1.1	13.2 ± 0.9	13.4 ± 0.8	14.4 ± 1.2
$+dP/dt_{max}$ ($mm\ Hg \cdot s^{-1}$)	2491 ± 190	2602 ± 221	2436 ± 177	2479 ± 210	2625 ± 219
$-dP/dt_{min}$ ($mm\ Hg \cdot s^{-1}$)	−2508 ± 98	−2599 ± 111	−2494 ± 87	−2430 ± 72	−2314 ± 80
τ (ms)	37 ± 2	35 ± 1	34 ± 2	33 ± 1 [a]	31 ± 2 [a,b,c]
K_p (mm^{-1})	0.40 ± 0.09	0.39 ± 0.09	0.31 ± 0.05	0.27 ± 0.07	0.24 ± 0.04 [a]
dL/dt_{max} ($mm \cdot s^{-1}$)	63 ± 10	70 ± 13	67 ± 11	65 ± 10	67 ± 10

Data are means ± S.E.M.; $n = 8$. [a] Significantly ($P < 0.05$) different from control. [b] Significantly ($P < 0.05$) different from 1 $\mu M \cdot kg^{-1}$ SC-54417. [c] Significantly ($P < 0.05$) different from 2 $\mu M \cdot kg^{-1}$ SC-54417. Abbreviations: M_w and L_w = preload recruitable stroke work slope and length intercept, respectively; τ = time constant of isovolumic relaxation; K_p = regional chamber stiffness constant.

reduced regional chamber stiffness concomitant with declines in left ventricular end-diastolic pressure. No changes in maximum segment lengthening velocity were observed.

4. Discussion

The results of this investigation indicate that two novel manganese-containing superoxide dismutase mimetics, SC-55858 and SC-54417, cause important cardiovascular actions. SC-55858 and SC-54417 increased heart rate at cumulative doses greater than or equal to 3 $\mu M \cdot kg^{-1}$ in conscious dogs. These findings probably resulted from a combination of direct positive chronotropic effects and carotid baroreceptor reflex activation because increases in heart rate occurred concomitant with reductions in preload (as assessed with left ventricular end-diastolic pressure and end-diastolic segment length), left ventricular systolic pressure, and mean arterial pressure at the higher doses of each drug. The mechanism by which these agents reduce preload and produce hypotension is unclear, however, potentiation of the effects of nitric oxide by a reduction of superoxide anion-induced inactivation of this endogenous dilator of vascular smooth muscle has been proposed (Gryglewski et al., 1986). Although this mechanism may explain the venodilation observed with SC-55858 and SC-54417, systemic vascular resistance remained unchanged with both drugs, indicating that alterations in arterial vascular tone and left ventricular afterload did not substantially contribute to the reductions in mean arterial pressure produced by these new superoxide dismutase mimetics. The relative stability of the manganese in SC-55858 and SC-54417 is unknown at present. Thus, the possibility that these drugs reduce preload and produce hypotension as a result of manganese release from the chelate cannot be completely excluded from the analysis.

The present results are consistent with the observations of Black et al. (1994) who examined the effects of SC-52608 (an active, manganese-containing superoxide dismutase mimetic closely related to SC-55858 and SC-54417) and SC-54385 (an inactive structural analog) on myocardial infarct size. These investigators (Black et al., 1994) reported increases in heart rate and decreases in mean arterial pressure after an intravenous bolus of SC-52608 (11.7 $\mu M \cdot kg^{-1}$). Kilgore et al. (1994) also reported declines in left ventricular peak systolic, end-diastolic, and coronary perfusion pressures in the presence 20 μM SC-52608 in Langendorff-perfused, isolated rabbit hearts. The findings of Black et al. (1994) and Kilgore et al. (1994) indirectly imply that higher doses of active superoxide dismutase mimetics may preserve myocardium at risk for ischemia-reperfusion injury despite the presence of an increase in heart rate or a decrease in coronary perfusion pressure. A preliminary study (unpublished findings, G.D. Searle) has demonstrated that SC-55858 and SC-54417 (5 $\mu M \cdot kg^{-1}$) reduce infarct size in response to a 75 min coronary occlusion and 4.5 hs reperfusion in anesthetized cats, suggesting that the doses of SC-55858 and SC-54417 required to exert myocardial protective actions may be less than the doses associated with hemodynamic effects reported in the present investigation. However, this hypothesis remains to be tested in a conscious, intact animal, an experimental model which provides distinct advantages over anesthetized, open-chest preparations in the study of ischemia-reperfusion pathology. (Triana et al., 1991)

The present results demonstrate that SC-55858, but not SC-54417, affects left ventricular systolic and diastolic function in conscious dogs. SC-55858 caused dose-dependent reductions in the slope of the preload recruitable stroke work relationship, a relatively heart rate- and load-independent index of myocardial contractility in vivo (Glower et al., 1985). SC-55858 decreased contractility approximately $45 \pm 8\%$ at the 30 $\mu M \cdot kg^{-1}$ cumulative dose. This depression of contractility was also indicated by declines in $+dP/dt_{max}$ and percent segment shortening, heart rate- and load-dependent isovolumic and ejection phases indices of left ventricular systolic function (Kass et al., 1987). The negative inotropic effects of SC-55858 may have contributed to decreases in mean arterial and left ventricular systolic pressure observed during administration of higher doses of this agent. SC-55858 also caused increases in the time constant of left ventricular pressure decay and decreases in the magnitude of $-dP/dt_{min}$ concomitant with depression of contractility, indicating that SC-55858 was also modestly affecting left ventricular diastolic function by altering the time course of isovolumic relaxation. These effects occurred despite SC-55858-induced increases in heart rate, a hemodynamic change which would be expected to lead to decrease in the time constant of isovolumic relaxation (Gilbert and Glantz, 1989). No changes in maximum segment lengthening velocity or regional chamber stiffness were observed with SC-55858, however, providing evidence that this novel superoxide dismutase mimetic does not alter the rate of rapid ventricular filling or regional chamber compliance. The negative inotropic and lusitropic effects of SC-55858 may exert beneficial effects during ischemia via reductions in myocardial oxygen demand but may also exacerbate preexisting left ventricular dysfunction. In contrast to the findings with SC-55858, SC-54417 preserved preload recruitable stroke work slope and $+dP/dt_{max}$ at the highest dose, indicating that this agent does not affect myocardial contractility. Significant decreases in the time constant of isovolumic relaxation and regional chamber stiffness were observed at the highest cumulative dose of SC-54417 associated with increases in heart rate and declines in left ventricular end-diastolic pressure, respectively.

In summary, the new manganese-based superoxide dismutase mimetics SC-55858 and SC-54417 cause tachycardia at doses greater than 10 $\mu M \cdot kg^{-1}$ in conscious, chronically instrumented dogs. These agents produce venodilation and decrease arterial pressure at higher doses but

do not affect cardiac output and systemic vascular resistance. SC-55858, but not SC-54417, also depresses left ventricular systolic and diastolic function. Whether the hemodynamic effects and actions of SC-55858 and SC-54417 on left ventricular function will contribute to the efficacy of these agents in the setting of myocardial ischemia-reperfusion injury requires further study.

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