Superoxide Dismutase Plus Catalase Improve Contractile Function in the Canine Model of the “Stunned Myocardium”

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SUMMARY. Fifteen minutes of coronary occlusion followed by reperfusion does not result in myocardial necrosis; however, the contractile function and high energy phosphate content of the previously ischemic myocardium remains depressed or “stunned” for several hours to days after reperfusion. Oxygen-derived free radicals have been implicated in ischemia and reperfusion-induced injury in a variety of tissues. We wished to determine whether administration of free radical scavengers superoxide dismutase plus catalase before and during occlusion, and throughout reperfusion, could attenuate the “stunning” produced by 15 minutes of left anterior descending coronary artery occlusion in anesthetized, open-chest dogs. Segment shortening in the previously ischemic zone recovered to within only ±10% of preinfusion values in the control group during 3 hours of reperfusion, while, in the treated dogs, segment shortening returned to a maximum of 56 ± 16% of preinfusion at 1½ hours post-reperfusion (P < 0.0003 compared to controls). Similarly, superoxide dismutase + catalase-treated dogs exhibited improved wall thickening during reperfusion (+30% to +70% of preinfusion values), compared to controls (0% to +10%). However, this improvement in contractile function in the treated group was not accompanied by increased adenosine triphosphate stores in the previously ischemic zone (31.8 ± 0.8 vs. 28.2 ± 2.2 nmol/mg protein for control vs. treated groups). Infusion of superoxide dismutase + catalase did not influence blood flow during occlusion or reperfusion. However, the treated group did exhibit a significant decrease in blood pressure during reperfusion. Hypotension during reperfusion did not appear to be the cause of the improved contractile function, as administration of sodium nitroprusside (an afterload-reducing agent with no free radical scavenging properties) to an additional group of dogs during reperfusion had no significant effect on segment shortening in the previously ischemic tissue. Thus, treatment with free radical scavengers significantly enhanced function, but did not improve high energy phosphate content, in the stunned myocardium. (Circ Res 58:148-156, 1986)
myocardium following 15 minutes of coronary artery occlusion in the anesthetized, open-chest canine preparation. The effects of SOD + catalase upon regional myocardial blood flow, hemodynamics, and high energy phosphate content were also investigated. As SOD + catalase produced a concomitant reduction in arterial pressure, the question of whether hypotension alone can influence contractile function of the stunned myocardium was further addressed.

**Methods**

**SOD + Catalase Protocol**

Twenty-eight mongrel dogs of either sex (27.2 ± 5.3 kg (mean ± sd)) were anesthetized with an intravenous injection of sodium pentobarbital (30 mg/kg), intubated, and ventilated with room air. After cannulas had been inserted into the external jugular vein (for administration of drugs and fluids) and left common carotid artery (for measurement of heart rate and arterial pressures), a left thoracotomy was performed through the 5th intercostal space. The ribs were retracted, the heart was suspended in a pericardial cradle, and the left atrium was cannulated for infusion of the crystals. After fixation, the hearts were cut into 7-10 transverse slices, parallel to the atrioventricular groove, approximately 5 mm thick. Correct placement of the ultrasonic crystals was confirmed, and the basal surfaces of the heart slices and margins of the area at risk were traced onto acetate sheets. After the right ventricular tissue had been trimmed off, the heart slices were weighed. For measurement of RMBF, tissue samples from both the center of the previously ischemic region and remote normal myocardium were cut and subdivided into epi-, mid-, and endocardial segments. RMBF then was quantified by the method of Domenech et al. (1969). Extent of the area at risk in each tissue slice was assessed by cutting out and trimming off the tracings of the LV and AR and correcting for the weight of the tissue slice. AR weights were summed for each heart and expressed as a percent of the LV (AR/LV).

One pair of crystals, used to measure segment shortening (SS), was inserted through small scalpel incisions into the midmyocardium in the center of the area to become ischemic. These crystals were positioned perpendicular to the major axis of the heart, at a separation of 6-12 mm. An additional pair of crystals for measurement of wall thickening (WT) was also placed into the area to become ischemic: one crystal was inserted via a small diagonal incision to the endocardium, while a larger, disc-shaped crystal was sutured to the epicardium at the point at which the ultrasonic transit time between the pair was the shortest. SS, WT, arterial and LV pressures, and LV dp/dt were monitored continuously during the experiment on a Gould recorder.

After the initial measurement of SS, WT, heart rate, and arterial pressures under control conditions, dogs received either SOD (5 mg/kg per hour) + catalase (5 mg/kg per hour) dissolved in 500 ml of saline, or saline alone (500 ml). Infusion of the saline or SOD + catalase solution was begun 15 minutes before occlusion, and was maintained at a constant rate of approximately 2.4 ml/min for the duration of the experiment. Measurements of hemodynamics, SS, and WT were repeated at 13 minutes postinfusion, before occlusion.

After a bolus dose of lidocaine (1.5 mg/kg, iv) had been administered, the LAD was occluded using two Schwartz atrumatic vascular clamps. Hemodynamics and function were monitored at 5, 10, and 14 minutes post-occlusion, and microspheres for measurement of RMBF were injected at 10 minutes post-occlusion. Fifteen minutes after occlusion, the LAD was reperfused by releasing the Schwartz’s clamps.

Infusion of the control or drug solution was continued for 3 hours following reperfusion, with measurements of function and hemodynamics repeated at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, and 180 minutes post-reperfusion. A second RMBF measurement was made 2 hours after reperfusion.

Immediately prior to sacrifice at 3 hours post-reperfusion, in vivo transmural needle biopsies were taken from both previously ischemic and normal myocardium, divided into endo- and epicardial segments, and assayed for adenosine triphosphate (ATP) and creatine phosphate (CP) content (Deboer et al., 1980). The LAD then was reoccluded, and monastral blue pigment (1 ml/kg) was injected into the coronary vasculature via the left atrium to delineate the in vivo area at risk (AR). The heart then was arrested with KCl (20–40 mEq), excised, the positions of the crystals were marked, and the heart fixed by immersion in 10% neutral buffered formalin.

After fixation, the hearts were cut into 7–10 transverse slices, parallel to the atrioventricular groove, approximately 5 mm thick. Correct placement of the ultrasonic crystals was confirmed, and the basal surfaces of the heart slices and margins of the area at risk were traced onto acetate sheets. After the right ventricular tissue had been trimmed off, the heart slices were weighed. For measurement of RMBF, tissue samples from both the center of the previously ischemic region and remote normal myocardium were cut and subdivided into epi-, mid-, and endocardial segments. RMBF then was quantified by the method of Domenech et al. (1969). Extent of the area at risk in each tissue slice was assessed by cutting out and weighing the tracings of the LV and AR and correcting for the weight of the tissue slice. AR weights were summed for each heart and expressed as a percent of the LV (AR/LV).
Sodium Nitroprusside Protocol

An additional group of 15 dogs (23.4 ± 4.4 kg) were anesthetized and instrumented as described previously. After isolation of the LAD, ultrasonic crystals for measurement of segment shortening were placed within the midmyocardium in the center of the area to become ischemic. Wall thickening was not assessed in this group of dogs.

After the initial measurement of SS and hemodynamic parameters and administration of a lidocaine bolus, the LAD was occluded for 15 minutes and then reperfused. At 45 minutes post-reperfusion, sodium nitroprusside (0.75–6.5 μg/kg per min, iv) was infused at a dose titrated to reduce systolic and diastolic pressures by approximately 20%, comparable to the hypotension observed in dogs given SOD + catalase.

The infusion was maintained for 30 minutes and then discontinued for 30 minutes; this cycle was repeated a total of 3 times. Heart rate, arterial pressures, and SS were monitored continuously throughout the experiment, and were quantified pre-occlusion, 10 minutes post-occlusion, 15, 30, and 45 minutes post-reperfusion, and at 10-minute intervals throughout infusion/discontinuation of sodium nitroprusside.

Ten minutes after discontinuation of the final nitroprusside challenge, the in vivo area at risk was delineated by injection of monastral blue dye, and the hearts were arrested with KCL, excised, and immersed in formalin. AR/LV was quantified as described previously; however, RMBF, ATP, and CP content were not measured in this segment of the study.

Analysis and Statistics

Values of heart rate and systolic and diastolic blood pressures at each sample time were obtained from a mean of five continuous cardiac cycles. Measurements of WT and SS were timed using LV dP/dt. End-diastolic and end-systolic lengths (EDL, ESL) and wall thicknesses (EDWT, ESWT) were defined as the onset of the rapid rise in LV dP/dt and the peak negative dP/dt, respectively (Lange et al., 1984). ESL, EDL, EDWT, and ESWT were measured from three well-separated cardiac cycles for each sample period, and were averaged. Percent SS during the sample periods was then calculated from the formula:

\[ \% \text{ SS} = \frac{(\text{EDL} - \text{ESL})}{\text{EDL}} \times 100 \]

and, similarly, % WT was determined using:

\[ \% \text{ WT} = \frac{(\text{ESWT} - \text{EDWT})}{\text{EDWT}} \times 100. \]

These values were then presented in two ways: (1) normalized to the pre-occlusion measurements of %SS and %WT (Lange et al., 1984), and (2) normalized to the most negative value of %SS and %WT measured during occlusion (i.e., Δ %SS).

In the SOD + catalase protocol, RMBF, ATP, and CP content, and AR/LV between the treated and control groups, were compared by paired t-test. Hemodynamics and function for the control and treated groups were compared by repeat measures analysis. Contrasts between the two groups then were performed for preinfusion values (for hemodynamic variables only), and at 30, 90, and 180 minutes post-reperfusion (for both hemodynamics and function). Bonferroni’s correction for multiple comparisons was applied to the P-values. All data are presented as mean ± SEM, and values were considered to differ significantly if P < 0.05.

Results

SOD + Catalase Protocol

Of the 28 dogs entered into the study, two were excluded because of development of persistent arrhythmias upon cannulation of the left atrium and infusion of saline. In addition, six dogs died of ventricular fibrillation, five within the first 10 minutes of LAD occlusion and one immediately upon reperfusion. Thus, 20 dogs—eight treated and 12 controls—remained.

Area at Risk

Area at risk of infarction was 23.3 ± 1.0% of the LV for the controls, and 23.1 ± 1.6% for the SOD + catalase-treated group (P = NS), indicating that infusion of oxygen-derived free radical scavengers did not significantly influence in vivo area at risk in this model.

Blood Flow

RMBF in the center of the area at risk was reduced to 0.12 ± 0.03, 0.25 ± 0.08, and 0.59 ± 0.17 ml/min per g of tissue in the subendo-, mid-, and subepicardium of the saline controls, respectively. Flow in the treated dogs did not differ significantly during occlusion from that of controls [0.14 ± 0.06, 0.37 ± 0.14, 0.81 ± 0.31 (Fig. 2)]. No difference in RMBF during occlusion was observed between the treated and control groups in normal myocardium perfused by the circumflex bed. At 2 hours post-reperfusion, infusion of SOD + catalase did not significantly affect flow in either the previously ischemic area or normal myocardium (Fig. 2). These results indicate that treatment with SOD + catalase did not significantly alter RMBF during occlusion or after 2 hours of reperfusion.

Segment Shortening

Infusion of either SOD + catalase or saline solution did not significantly influence segment shortening during the initial 15 minutes prior to LAD occlusion. In 17 of the 20 animals in the study, segment shortening was replaced by paradoxical systolic bulging in the ischemic region during occlusion (Fig. 3). The remaining three dogs (all controls) demonstrated a marked reduction in segment shortening during LAD occlusion. Mean %SS for the treated group was −74.5 ± 13.4%, −69.8 ± 14.1%, and −98.5 ± 3.8% of the preinfusion value at 5, 10, and 14 minutes post-occlusion, while the control dogs exhibited a mean %SS of −45.3 ± 15.0%, −45.2 ± 17.5%, and −54.7 ± 15.0% of the preinfusion value at comparable times during occlusion (Fig. 3). These data suggest that the severity of ischemia, assessed by regional function, was as bad
if not worse in the treated group as compared to the controls.

During the 3 hours of reperfusion, the 12 control dogs demonstrated a mean %SS ranging within approximately ±10% of the preinfusion value (1.9 ± 16.0%, −3.9 ± 16.1%, and −10.1 ± 14.1% at 30 minutes, 1½ hours, and 3 hours, respectively). In spite of the severe systolic bulging demonstrated by the treated dogs during occlusion, %SS in the SOD + catalase-treated group returned to 56 ± 16% of the preinfusion value at 1½ hours post-reperfusion, and leveled off to 19.8 ± 14.6% at 3 hours post-reperfusion (Fig. 3). At both 1½ and 3 hours post-reperfusion, %SS for the SOD + catalase-treated dogs was significantly greater (P < 0.0003 and P < 0.047, respectively) than that of controls.

When segment shortening data was normalized to the most negative value during occlusion for each dog (i.e., to compensate for variations in the degree of passive bulging during occlusion among the animals), the saline control group showed a Δ%SS of +39.7 ± 11.7% at 30 minutes, +46.5 ± 11.1% at 1½ hours, and +40.3 ± 9.1% at 3 hours post-reperfusion. Dogs treated with SOD + catalase had a Δ%SS of +103.2 ± 16.0%, +140.5 ± 21.8%, and +104.2 ± 16.7%, respectively. Differences between the two groups were significant (P < 0.0003) at all three time periods (Fig. 4).
Wall Thickening

Fifteen minutes of SOD + catalase or saline infusion did not alter pre-occlusion wall thickening in the soon-to-be ischemic tissue. Upon occlusion, both treated and control dogs demonstrated passive thinning, rather than active thickening, during systole (Fig. 5). As was the case with %SS, animals infused with SOD + catalase demonstrated greater values of %WT during reperfusion (+42.8 ± 10.7%, +71.0 ± 15.3%, and +39.6 ± 14.0% at ½, 1½, and 3 hours) than did the controls (+0.2 ± 12.1%, +6.0 ± 12.8%, and +2.4 ± 13.1%, respectively). Differences between the two groups proved significant at 30 minutes and 1½ hours post-reperfusion (P < 0.0027 and P < 0.0003), but not at the end of the reperfusion phase [P < 0.0546 (Fig. 5)].

When the baseline for wall thickening was taken as the most negative value during occlusion, SOD + catalase-treated dogs exhibited Δ %WT of +78.2 ± 19.1%, +102.9 ± 20.1%, and +81.5 ± 20.7% at ½, 1½, and 3 hours post-reperfusion. In contrast, the saline controls improved by only +27.0 ± 5.7%, +33.0 ± 9.1%, and +29.5 ± 11.2% (Fig. 6). Differences in Δ %WT between the treated and control dogs were significant at 30 minutes, 1½, and 3 hours post-reperfusion (P < 0.0069, P < 0.0003, and P < 0.0408).

Hemodynamics

Heart rate measured preinfusion did not differ significantly between the two groups of dogs, and was not influenced significantly, during the course of the experiment, by infusion of SOD + catalase (Fig. 7). Both systolic and diastolic blood pressures were slightly lower prior to infusion in the treated group. Systolic and diastolic pressures were reduced significantly during reperfusion in dogs treated with SOD + catalase [P < 0.0004 at 30 minutes, 1½ hours, and 3 hours post-reperfusion (Fig. 7). However, there was no change in arterial pressures in the control group during the course of the experiment.

High Energy Phosphates

ATP content in normal myocardium averaged 35 nmol/mg protein in both control and treated groups. In the area previously ischemic, ATP concentration remained somewhat depressed, particularly in the endocardium (i.e., approximately 80% of control) after 3 hours of reperfusion. However, there was no difference in ATP content between control dogs and those infused with SOD + catalase (Fig. 8).

Mean CP concentration was 52 nmol/mg protein in normal myocardium. Following 3 hours of reperfusion, CP content in the previously ischemic tissue had returned to (or slightly above) normal, and was not influenced by treatment with SOD + catalase (Fig. 9).

Sodium Nitroprusside Protocol

Of the 15 dogs entered into this part of the study, two were excluded because no area at risk or evidence of post-ischemic stunning could be detected. Data from one other animal could not be validly analyzed due to electrical interference in the segment shortening signal, and an additional six animals succumbed to ventricular fibrillation (five during occlusion and one immediately upon reperfusion). Results for the remaining six dogs are presented below.

Area at Risk

AR/LV averaged 20.1 ± 1.5% in the six dogs treated with sodium nitroprusside, a value which
does not differ significantly from those of the SOD + catalase or saline control groups.

**Hemodynamics**

Both systolic and diastolic pressures were reduced by approximately 20% during infusion of nitroprusside (Fig. 10); thus, the magnitude of the induced hypotension was comparable to that observed in dogs treated with SOD + catalase (Fig. 7). At these doses, nitroprusside infusion was not accompanied by reflex tachycardia (Fig. 10)—heart rates in these dogs remained similar to those in the SOD + catalase and saline control groups (Fig. 7).

**Segment Shortening**

All six dogs demonstrated paradoxical systolic bulging in the ischemic zone during occlusion. When segment shortening for each dog was normalized to the value measured during occlusion, Δ %SS averaged +55.5 ± 8.5%, and +58.4 ± 7.3%, and +56.5...
± 9.4% during the three periods of nitroprusside infusion, and +48.1 ± 9.4%, +44.4 ± 10.0%, and +47.2 ± 10.8% while the infusion was discontinued (Fig. 11). Values of Δ %SS both with and without nitroprusside infusion do not differ from those of the saline control group illustrated in Figure 4, and are clearly less than the maximum Δ %SS of +140% observed in animals treated with SOD + catalase. Thus, although values of Δ %SS fluctuated very slightly upon infusion and discontinuation of the afterload-reducing agent, infusion of sodium nitroprusside did not significantly improve the contractile function of the stunned myocardium.

**Discussion**

Oxygen-derived free radicals (O₂⁻, ·OH) and H₂O₂ are unstable, highly reactive, and cytotoxic variations of the oxygen molecule. These reactive oxygen species have been implicated in ischemia and reperfusion-mediated injury of a variety of tissues, including the brain, intestine, lung, kidney, and heart (Parks et al., 1982; McCord, 1984; Jolly et al., 1984; Burton et al., 1984). Free radicals are produced in vivo by both mitochondria and phagocytes; however, their rate of production is greatly accelerated upon reoxygenation of ischemic tissue (McCord et al., 1984).

Free radical scavengers such as superoxide dismutase and catalase are the enzymatic defenses against these cytotoxic agents. SOD acts by catalyzing the dismutation of O₂⁻ to H₂O₂ and O₂, while catalase accelerates the conversion of H₂O₂ to H₂O and O₂ (Fig. 1; Fridovich, 1978; Jolly et al., 1984). However, during reperfusion of ischemic tissue, not only is the rate of free radical production increased, but the damage is exacerbated by the washout of enzymes, including endogenous supplies of SOD and catalase, from the previously ischemic tissue (McCord, 1984). Thus, reoxygenated tissue becomes even more susceptible to free radical mediated injury.

A large body of evidence has been presented to indicate that myocardial necrosis resulting from ischemia followed by reperfusion may be attributed to the formation of oxygen-derived free radicals. Using a canine model of myocardial infarction, Chambers et al. (1983) found that administration of either SOD or allopurinol (a xanthine oxidase inhibitor) during 1 hour of LAD occlusion and 4 hours of reperfusion significantly reduced infarct size, compared to nontreated controls. Similar results were obtained by Jolly et al. (1984): SOD + catalase significantly reduced the extent of necrosis produced by 90 minutes of circumflex occlusion followed by 22½ hours of reperfusion. Similar results have been obtained with isolated, perfused hearts subjected to global ischemia followed by reperfusion: administration of free radical scavengers SOD, catalase, allopurinol, and/or mannitol improved subcellular and mechanical function, and qualitative morphology of the hearts (Guarnieri et al., 1980; Schlafer et al., 1982a, 1982b; Stewart et al., 1983; Casale et al., 1983; Gauduell and Duvelleroy, 1984). It should be noted that in both the in vivo and in vitro models, the protection afforded by the scavengers was significant only when administered prior to and at the onset of reperfusion, and was not significant when given during reperfusion alone (Casale et al., 1983; Gardner et al., 1983; Gauduell and Duvelleroy, 1984; Jolly et al., 1984). Direct proof of the toxic effects of the O₂⁻ and ·OH radicals on developed tension and myocardial ultrastructure has been demonstrated in isolated, perfused rabbit septa (Burton et al., 1984). These studies indicate that O₂⁻ and ·OH radicals are capable of producing functional and structural alterations in the myocardium, and treatment with free radical scavengers can, at least in part, ameliorate this damage.

During coronary artery occlusion, active contraction of the myocardium is almost immediately replaced by passive systolic bulging and wall thinning in the area of ischemia (Heyndrickx et al., 1975; Heyndrickx et al., 1978). For occlusions lasting less than 20 minutes, followed by reperfusion, ischemic damage to the myocytes is reversible and the cells do not become necrotic (Jennings, 1969; Lange et al., 1984). However, the structural, functional, and metabolic properties of the previously ischemic tissue have been shown to remain depressed—or "stunned"—for prolonged periods of time following reperfusion (Heyndrickx et al., 1975; Weiner et al., 1976; Heyndrickx et al., 1978; Deboer et al., 1980; Braunwald and Kloner, 1982; Lange et al., 1984; Kloner et al., 1984). In the present study, measurements of function, biochemistry and RMBF for the control group during the 3 hours of reperfusion indicate that the previously ischemic myocardium was "stunned," and are in good agreement with
previous findings; %SS and %WT remained markedly depressed throughout reperfusion (as was observed by Lange et al., 1984). ATP content was approximately 20% below normal at 2 hours post-reperfusion, while CP concentration was restored to control values following 2 hours of reflow (as shown by Deboer et al., 1980, Lange et al., 1984b, and Heyndrickx et al., 1978, respectively).

The phenomenon of the stunned myocardium has been well-documented; yet, the explanation for its occurrence remains pending. As the recovery of function has been observed to parallel the restoration of the ATP pool, it has been suggested that these two factors may be causally related (Braunwald and Kloner, 1982). Increased concentrations of intracellular calcium have also been implicated as a possible explanation for "stunning" (Braunwald and Kloner, 1982). Our current results indicate that treatment with SOD + catalase significantly improves function in the previously ischemic myocardium, implying that O$_2^-$ and ·OH ions contribute to stunning during reperfusion. As illustrated in Figure 1, free radical formation upon reperfusion is closely related to the degradation of ATP and influx of Ca$^{++}$ during hypoxia. In fact, it has been postulated that oxygen-derived free radicals contribute to ischemia-induced damage of sarcoplasmic reticulum, and thereby directly affect Ca$^{++}$ transport (Hess et al., 1981). Thus, it seems possible that all three factors interact and contribute to depressed function during reperfusion.

It is interesting to note that improvement in SS and WT in the SOD + catalase-treated group was effected without a significant change in stores of ATP in the previously ischemic region. This dissociation in recovery of function vs. failure of recovery of ATP concentration suggests that the stunned myocardium is not solely a consequence of a reduced supply of high energy phosphates. However, it should be stressed that normal function was not fully restored in the SOD + catalase-treated group (%SS and %WT returned to a maximum of +60% and +70% of control, respectively), implying that other as yet undefined factors also contribute to the phenomenon of stunning. Improved function also was not accompanied by a decrease in ATP concentration in the treated dogs—that is, the enhanced SS and WT did not appear to drain further the high energy phosphate pool.

Both SOD and catalase are highly specific in their roles of O$_2^-$ and ·OH scavengers (McCord et al., 1984); thus, reduction in infarct size and/or improvement in function upon treatment with these agents has been attributed directly to their enzymatic action. However, in the present study, animals infused with SOD + catalase demonstrated significant reductions in arterial blood pressure during reperfusion. No such response was observed in the saline control group. It is possible that the improved function observed during reperfusion in the present study may be due in part to the concomitant reduction in afterload, rather than the elimination of free radicals alone. To address this question, the timing and magnitude of the hemodynamic changes observed with SOD + catalase were mimicked by infusion of sodium nitroprusside, an afterload-reducing agent with no free radical scavenging ability. Hypotension produced by sodium nitroprusside during reperfusion was clearly not accompanied by a similar improvement in contractile function as occurred in the SOD + catalase group. These findings support our conclusion that the salutory effects of SOD + catalase on contractile function of the stunned myocardium are due to their free radical scavenging action, and not a consequence of afterload reduction.


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