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Poster presentation

Myocyte-specific overexpression of NOS3 prevents endotoxin-induced myocardial dysfunction in mice

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Endotoxemia can cause profound myocardial dysfunction contributing to hypotension and shock. Overproduction of nitric oxide (NO) has been implicated as a cause of the myocardial dysfunction of sepsis. Here, we tested the hypothesis that myocyte-specific overexpression of NO synthase 3 (NOS3) can prevent cardiac dysfunction in endotoxin-challenged mice.

Echocardiographic measurements were obtained before and 4 and 7 h after intraperitoneal challenge with endotoxin (*Escherichia coli* 0111:B4 lipopolysaccaride 50 mg/kg) in wild-type C57BL6 mice (WT) and WT mice with myocyte-specific overexpression of NOS3 (TG), using a 13-MHz ultrasound probe (Sequoia, Acuson, Mountain View, CA). Invasive measurements of LV pressure and volume were obtained with a 1.4F pressure-volume catheter (SPR-839, Millar Instruments, Houston TX) (7 h after challenge with endotoxin or saline).

At baseline, WT and TG mice had comparable measures of LV function. However, as assessed by echocardiography, the endotoxin-induced decrease in LV fractional shortening was attenuated in TG mice (from 54 ± 1 to 40 ± 1%) as compared to WT mice (from 56 ± 1 to 31 ± 2%). Invasive hemodynamics revealed that, compared to saline-challenged mice, dP/dt_{max} and cardiac output (CO) were markedly impaired in WT but not in TG 7 h after endotoxin challenge (Table 1).

Myocyte-specific overexpression of NOS3 prevented endotoxin-induced reduction of minimally load-independent measures of LV function, including maximal power divided by end-diastolic volume (PMX_{EDV}), dP/dt_{max} divided by instantaneous pressure ($dP/dt_{max}/IP$) and LV end-systolic elastance (Ees).

These results suggest that myocyte-specific overexpression of NOS3 confers protection against endotoxin-induced myocardial dysfunction.

Table 1: Cardiac function at baseline and 7 h after endotoxin-challenge in WT and TG mice

		dP/dt_{max} (mmHg/s)	CO (mL/min)	PMX_{EDV} (mmHg/s)	$dP/dt_{max}/IP$ (s^{-1})	Ees (mmHg/μL)
WT	baseline	15124 ± 1087	14.5 ± 1.9	50 ± 3	287 ± 12	11 ± 2
	7h endotoxin	10024 ± 609*	6.1 ± 0.9*	31 ± 5*	161 ± 18*	3 ± 1*
TG	baseline	14562 ± 1491	15.6 ± 2.7	43 ± 2	255 ± 16	11 ± 4
	7h endotoxin	15354 ± 495#	15.7 ± 0.7#	52 ± 5	228 ± 9	12 ± 2#

*P < 0.05 vs baseline, #P < 0.05 vs WT