Inhaled but not intravenous milrinone prevents pulmonary endothelial dysfunction after cardiopulmonary bypass

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Objective: Cardiopulmonary bypass triggers a systemic inflammatory response that alters pulmonary endothelial function, which can contribute to pulmonary hypertension. Milrinone is a type III phosphodiesterase inhibitor. The objective of this study was to compare the effects of inhaled and intravenous milrinone on the pulmonary endothelium–dependent relaxations and hemodynamic and oxygenation parameters after cardiopulmonary bypass in a porcine model.

Methods: Five groups of Landrace swine were compared: (1) control group, no cardiopulmonary bypass; (2) bypass group, 90 minutes of normothermic bypass and 60 minutes of reperfusion; (3) inhaled milrinone group, bypass preceded by a 1.8-mg bolus of inhaled milrinone followed by a continuous milrinone nebulization; (4) intravenous milrinone group, bypass preceded by 2 mg of intravenous milrinone; and (5) inhaled NaCl group, bypass preceded by inhaled saline solution. After sacrifice, pulmonary arterial endothelium–dependent relaxations to acetylcholine and bradykinin were studied in organ chambers.

Results: Inhaled milrinone caused less hypotension ($P < .05$), a lesser decrease in peripheral vascular resistances ($P < .01$), and a lower heart rate ($P < .05$) than intravenous milrinone. Inhaled milrinone prevented the alterations in relaxations of pulmonary arteries to acetylcholine caused by cardiopulmonary bypass, and relaxations to bradykinin were improved in the inhaled milrinone group ($P < .05$) compared with the cardiopulmonary bypass and control groups.

Conclusions: Inhaled milrinone prevents the occurrence of the pulmonary endothelial dysfunction seen after cardiopulmonary bypass. The hemodynamic and oxygenation profiles obtained with inhaled milrinone are safer than with intravenous milrinone. These strategies might be useful in preventing pulmonary hypertension after cardiac surgery.

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Cardiopulmonary bypass (CPB) induces a systemic inflammatory response that affects all organ systems. The physiologic alterations after CPB were recognized early after the development of CPB in the 1950s. The postpump syndrome is characterized by an increase in pulmonary capillary permeability, leading to decreased oxygenation, increased alveolar-arterial oxygen gradient, decreased pulmonary compliance, and an increased pulmonary vascular resistance.[1,2] Among the most important repercussions of the inflammatory cascade are those on the pulmonary vasculature. During CPB, blood flow is diverted from the right atrium to the CPB pump, goes through an oxygenator membrane, and is pumped back into the aorta, and thus the lungs are minimally perfused during CPB. At separation from CPB, the lungs are reperfused and experience ischemia-reperfusion injury caused by exposure to large amounts of free radicals. Because of the contact of the blood elements with the nonphysiologic surface of the bypass circuit, neutrophils and platelets are activated and contribute to pulmonary damage, which triggers endothelial dysfunction after CPB.[3,4] After CPB, the damage to

TABLE 1. Hemodynamic data throughout the experiment

		Before Rx	SEM	After Rx	SEM	15 min on CPB	SEM	45 min on CPB	SEM
MAP	CPB	59.8	2.2	—	—	68	7	66	5.8
	Inhaled milrinone	72.8	5.2	60.1	4.1	74.1	5.7	68.6	3.8
	Inhaled NaCl	79	12.6	71	10.4	78.6	10.2	74.6	9.4
	IV milrinone	79.6	5.1	55	3.6	71	11	74.6	10.8
CI	CPB	4.8	1	—	—	4.6	0.3	4.5	0.3
	Inhaled milrinone	3.6	0.3	3.2	0.4	3.9	0.3	4.0	0.3
	Inhaled NaCl	4.0	0.1	3.9	0.2	4.3	0.5	4.4	0.4
	IV milrinone	2.9	0.2	3.5	0.8	4.5	0.2	4.5	0.2
HR	CPB	95.2	6.3	—	—	89	10.5**	95.4	9.5***
	Inhaled milrinone	76.3	3.2	75	4.7	62.2	3.5$$$	66	3.9$$$
	Inhaled NaCl	86	13	71	3	92	2	92	7
	IV milrinone	80.1	8.7	96	19.5	106.3	4.9	117.7	6.2
W	CPB	7.3	1.1	—	—	—	—	—	—
	Inhaled milrinone	5.2	1	10.5	0.7	—	—	—	—
	Inhaled NaCl	6.6	0.7	6	1	—	—	—	—
	IV milrinone	5	0	3.3	0.3	—	—	—	—
mPAP	CPB	12	1.2	—	—	—	—	—	—
	Inhaled milrinone	10.5	1	4	0.3	—	—	—	—
	Inhaled NaCl	11.6	2.3	11.3	1.2	—	—	—	—
	IV milrinone	18.3	7.4	20	3.2	—	—	—	—
CVP	CPB	4	0.9	—	—	—	—	—	—
	Inhaled milrinone	4.2	1.1	2.8	1.2	—	—	—	—
	Inhaled NaCl	5	1.5	6	3	—	—	—	—
	IV milrinone	1.7	0.3	1	0	—	—	—	—
A-aDo_2	CPB	100	14	—	—	218	36	188	13
	Inhaled milrinone	134	20	—	—	178	12	181	16
	Inhaled NaCl	156	40.8	—	—	216	27.5	183	23
	IV milrinone	162	17	—	—	174	1	168	4

Rx, Experimental drug; *CPB*, mean cardiopulmonary bypass; *MAP*, mean arterial pressure; *IV*, intravenous; *CI*, cardiac index; *HR*, heart rate; *W*, wedge pressure; *mPAP*, pulmonary artery pressure; *CVP*, central venous pressure; *A-aDo_2*, alveolar-arterial oxygen gradient. $*P < .05$ versus inhaled milrinone. $**P < .01$ versus inhaled milrinone. $***P < .001$ versus inhaled milrinone. $\$P < .05$ versus intravenous milrinone. $\$\$\$P < .001$ versus intravenous milrinone. $\&\&P < .01$ versus CPB. $\$P < .05$ versus NaCl. $\$\$P < .011$ versus NaCl. $\$\$\$P < .001$ versus NaCl.

the pulmonary endothelium can lead to pulmonary hypertension (PH), leading to an increase in right ventricular work. Right ventricular dysfunction after CPB carries a poor prognosis, with a perioperative mortality ranging from 44% to 86%.[5]

The endothelium has an important role in regulating the vascular tone by releasing several vasorelaxing substances, such as nitric oxide (NO) and prostacyclin (PGI_2), and vasoconstrictors, such as endothelin and thromboxanes. The ability to induce vasorelaxation can be decreased when endothelial dysfunction is present.[6] Several pharmacologic agents have been used to limit the increase in pulmonary vascular resistance and PH after cardiac surgery, including intravenous nitroglycerin, intravenous milrinone, inhaled NO, and inhaled PGI_2.

Milrinone, a phosphodiesterase III inhibitor that increases intracellular levels of cyclic adenosine monophosphate (cAMP), induces positive cardiac inotropy and systemic vasorelaxation. When administered intravenously, milrinone decreases systemic vascular resistances, causing hypotension, which can be hazardous in the hours after cardiac surgery. The use of inhaled milrinone has recently been described by Haraldsson and colleagues[7] to avoid the systemic hypotension associated with intravenous milrinone. They observed a de-