## The role of epinephrine infusion on mortality in critically ill patients A meta-analysis of randomized controlled trials.

Dott. ALESSANDRO BELLETTI (1), Dott. PIERFRANCESCO DE DOMENICO (1), Dott. ADAM NAGY (1), Dott.ssa VALENTINA CAMARDA (1), Dott.ssa GINEVRA ORTOLANI (1), Dott.ssa MARIANNA SARTORELLI (1), Dott.ssa FEDERICA MORSELLI (1), Dott. MATTEO MARZAROLI (1), Dott.ssa GAIA RECCA (1), Prof. GIOVANNI LANDONI (1), Prof. ALBERTO ZANGRILLO (1)

(1) IRCCS San Raffaele Scientific Institute, Via Olgettina, 60, Milano, Mi, Italia.

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**Introduction** Epinephrine is frequently used as inotropic agent in critically ill patients requiring hemodynamic support, especially in patients with low cardiac output. However, data from observational trials suggest that epinephrine use is associated with a worse outcome as compared with other vasoactive drugs.

**Methods** We perfomed a systematic literature review and meta-analysis of RCTs to investigate the effect of epinephrine administration on outcome of critically ill patients. Two independent investigators searched PubMed, EMBASE and Cochrane central register. Inclusion criteria were: administration of epinephrine as intravenous continuous infusion, patients admitted to an ICU or undergoing major surgery, and randomized controlled trials. Exclusion criteria were: epinephrine administration as repeated boluses (e.g. during cardiopulmonary resuscitation), administration of epinephrine as local infiltration, non-human studies, lack of data for outcome of interest, study published as abstract only, and overlapping population. We calculated individual and pooled risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (CI). We computed mean difference (MD) or standardized mean difference (SMD) with corresponding 95% CI for continuous variables. The primary outcome was mortality at the longest follow-up available. Secondary outcomes included receipt of renal-replacement therapy (RRT), myocardial ischemia, arrhythmias, and length of ICU stay.

**Results** A total of 1,754 studies were assessed at a title/abstract level, with a total of 13 studies (1,323 patients) finally included in the meta-analysis. We found no difference in all-cause mortality at the longest follow-up available (198/612 [32.4%] in the epinephrine group versus 222/711 [31.2%] in the control group, RR = 0.95; 95% CI 0.82 to 1.10; p = 0.46, l<sup>2</sup> = 0%). No differences in the need for RRT, incidence of myocardial ischemia, incidence of arrhythmias, and length of ICU stay were observed.

**Conclusions** Continuous intravenous administration of epinephrine as inotropic/vasopressor agent is not associated with a worse outcome in critically ill patients.

	Epinephrine		Control		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Annane_2007	84	161	85	169	38.8%	1.04 [0.84, 1.28]	
Levy_1997	9	15	8	15	3.7%	1.13 [0.60, 2.11]	
Levy_2011	5	15	4	15	1.9%	1.25 [0.41, 3.77]	
Levy_2018	14	27	11	30	4.9%	1.41 [0.78, 2.56]	
Mahmoud_2012	16	30	15	30	7.0%	1.07 [0.65, 1.74]	
Myburgh_2008	41	139	46	138	21.6%	0.88 [0.62, 1.25]	
Ramaswamy_2016	14	29	18	31	8.1%	0.83 [0.51, 1.35]	
Ryu_2012	1	33	3	63	1.0%	0.64 [0.07, 5.88]	•
Salgado_2015	1	39	1	42	0.5%	1.08 [0.07, 16.63]	· · · · · · · · · · · · · · · · · · ·
Seguin_2002	4	11	5	11	2.3%	0.80 [0.29, 2.21]	
Seguin_2006	4	10	3	12	1.3%	1.60 [0.46, 5.53]	
Ventura_2014	4	57	13	63	5.8%	0.34 [0.12, 0.98]	
Wilson_1999	1	46	10	92	3.1%	0.20 [0.03, 1.52]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		612		711	100.0%	0.95 [0.82, 1.10]	•
Total events	198		222				
Heterogeneity: Chi² = 10.42, df = 12 (P = 0.58); l² = 0%							
Test for overall effect: $Z = 0.73$ (P = 0.46)						U.1 U.2 U.5 I Z 5 IU	
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