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Change in Myocardial Contractility in Response to Treatment with Norepinephrine in Septic Shock

To the Editor:

Noradrenaline is actually the first-choice vasoactive agent for septic patients who do not reach an adequate blood pressure after the early volume replacement (1). Current guidelines recommend the administration of an initial bolus of fluids and the early beginning of vasoactive medications, as an excessive fluid administration can increase mortality owing to the accumulation of fluids in the third space with worsening tissue perfusion. On the other side, because of the arterial vasoconstriction induced by noradrenaline, with consequent increased afterload, caution has been recommended for its administration in patients with systolic dysfunction. Moreover, concerns have been raised about possible negative effects on the immune function (2, 3).

The aim of this prospective observational study was to investigate the effect of the early administration of norepinephrine on cardiac performance in patients with septic shock, by means of a parameter relatively independent to loading conditions. Some of the results of these studies have been previously reported in the form of an abstract (4).

Methods

This is a preliminary report of a prospective observational study, performed in Emergency Department and a High-Dependency Unit located within the Emergency Department of the Careggi University Hospital, from January 2019 to January 2020. The study was approved by the Comitato Etico Area Vasta Centro (Registration number N° 11565_oss) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). All patients gave their informed consent to enter the study.

We included patients with a diagnosis of sepsis, who had already undergone the first fluid bolus, according to current guidelines, and needed the administration of vasopressors to maintain a mean arterial pressure ≥ 65 mm Hg. The diagnosis of sepsis was based on Sepsis-3 criteria.

Author Contributions: Conception and design of the work: F.I. and V.P. Acquisition and analysis of data for the work: I.T., E.C., A.D.P., A.M., M.M., and A.G. Drafting the work and revising it critically for important intellectual content: F.I., V.P., I.T., and R.P. All authors gave their final approval of the version submitted for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1. Echocardiographic Parameters before Starting Norepinephrine Infusion (T0), When the Patient Reached the Target Pressure (T-fin), and after 1 Hour (T-1h)

	T0	T-fin	T-1h
Vital signs			
HR, beats/min	93 ± 25	87 ± 24	94 ± 25
SBP, mm Hg	73 ± 10	106 ± 15*	106 ± 16*
MBP, mm Hg	53 ± 6	75 ± 11*	71 ± 10*
DBP, mm Hg	40 ± 7	56 ± 12*	54 ± 9*
RR, breaths/min	22 ± 8	22 ± 6	21 ± 6
SO ₂ , %	97 ± 4	97 ± 3	97 ± 4
GCS	14.6 ± 0.8	14.6 ± 0.8	14.6 ± 0.8
Lactate level, mEq/L	2.4 ± 1.4	2.2 ± 1.5	1.6 ± 0.8*
Echocardiographic parameters			
LV systolic function			
EDV, ml	52 ± 20	55 ± 23	51 ± 24
ESV, ml	27 ± 15	25 ± 16	21 ± 16
SV, ml	25 ± 12	29 ± 10	30 ± 13*
LV GLS, %	-12.5 ± 2.8	-14.1 ± 3.8*	-15.8 ± 4.8*
LV EF, %	49 ± 17	57 ± 15*	57 ± 15*
TDI S wave, cm/s	9 ± 4	10 ± 4	12 ± 4
RV systolic function			
TAPSE, mm	15 ± 5	17 ± 6*	18 ± 6*
LV diastolic function			
Mitral E wave, m/s	0.62 ± 0.22	0.72 ± 0.26*	0.77 ± 0.26
Mitral A wave, m/s	0.88 ± 0.32	0.88 ± 0.38	0.88 ± 0.34
TDI E' wave, cm/s	16 ± 2	10 ± 0	17 ± 19
E/e'	7.4 ± 3.0	7.7 ± 3.8	6.1 ± 5.0

Definition of abbreviations: DBP = diastolic blood pressure; EDV = end-diastolic volume; E/e' = ratio between mitral E wave and tissue Doppler e' wave; ESV = end-systolic volume; GCS = Glasgow Coma Scale; HR = heart rate; LV EF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain; MBP = mean blood pressure; RR = respiratory rate; RV = right ventricular; SBP = systolic blood pressure; SO₂ = O₂ saturation; SV = stroke volume; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging.

**P* < 0.05 versus T0.

Before starting the norepinephrine infusion (T0), a comprehensive transthoracic echocardiographic examination was performed. Norepinephrine was initially infused at a dosage of 0.1 µg/kg/min and was increased by the same value every 5' until a mean arterial pressure ≥65 mm Hg was obtained. The echocardiographic examination was repeated every 10 minutes, when the patient reached the target pressure (T-fin), and after 1 hour (T-1h).

Left (LV) and right (RV) ventricular systolic function was assessed based on current guidelines, as already described (5–7). We defined LV systolic dysfunction as LV global longitudinal strain (GLS) greater than or equal to -14% and RV systolic dysfunction as tricuspid annular plane systolic excursion (TAPSE) < 16 mm (8). Data about reproducibility of LV GLS and TAPSE have been previously reported (5, 6).

Statistical analyses were conducted using IBM SPSS software package (version 26). Data in tables are mean values ± SD, median and interquartile range, or counts and percentage. For continuous variables, the null hypothesis was tested using the Student's *t* test for independent groups; Fisher exact test was used to compare counts in cross tables. The ANOVA was used to test the presence of significant differences in the trends of the parameters of interest. Two-tailed *P* < 0.05 was used to reject null hypotheses.

Results

The study population included 16 patients, mean age 74 ± 14 years, 44% male sex, Sequential Organ Failure Assessment score 5.5 (interquartile range, 4–7.8) at admission. The most frequent previous medical

conditions were arterial hypertension (50%), coronary artery disease (38%), and neoplasia (31%). The sepsis source was pulmonary in 31% of patients and the urinary tract in 38%. Five patients had a known history of LV systolic dysfunction, and, in one patient, an RV systolic dysfunction coexisted. The Day 7 mortality rate was 12% (*n* = 2) and reached 38% (*n* = 6) by the Day 28 endpoint.

Patients received a median fluid bolus of 27 ml/kg (interquartile range, 13–31) and they reached the pressure target at a mean dosage of noradrenaline of 0.44 ± 0.18 µg/kg/min. From T0 to T-fin, as expected, we observed a significant increase of systolic blood pressure, mean blood pressure, and diastolic blood pressure; mitral E wave increased significantly, compatible with an increased LV preload (Table 1). LV ejection fraction, LV GLS, and TAPSE, respectively indices of LV and RV systolic function, significantly improved (Table 1). We did not observe significant changes of the diastolic function, expressed by the E/e' ratio. At T-1h, the improvement of these parameters was maintained (*P* < 0.05 compared with baseline), without significant differences between T-fin and T-1h values. Lactate levels improved during the infusion, and the change became significant after 1 hour (Table 1).

At baseline, the prevalence of systolic dysfunction was 81% (*n* = 13), and, excluding those with a known history of LV and/or RV systolic dysfunction, it is presumably a relevant component of patients with sepsis-induced myocardial dysfunction. Four patients showed an isolated LV systolic dysfunction, 1 patient an isolated RV dysfunction, and 8 patients a biventricular dysfunction. The trend of LV ejection fraction, LV GLS, and TAPSE were similar regardless of the presence of baseline LV and/or RV systolic dysfunction (Figures 1A–1C).

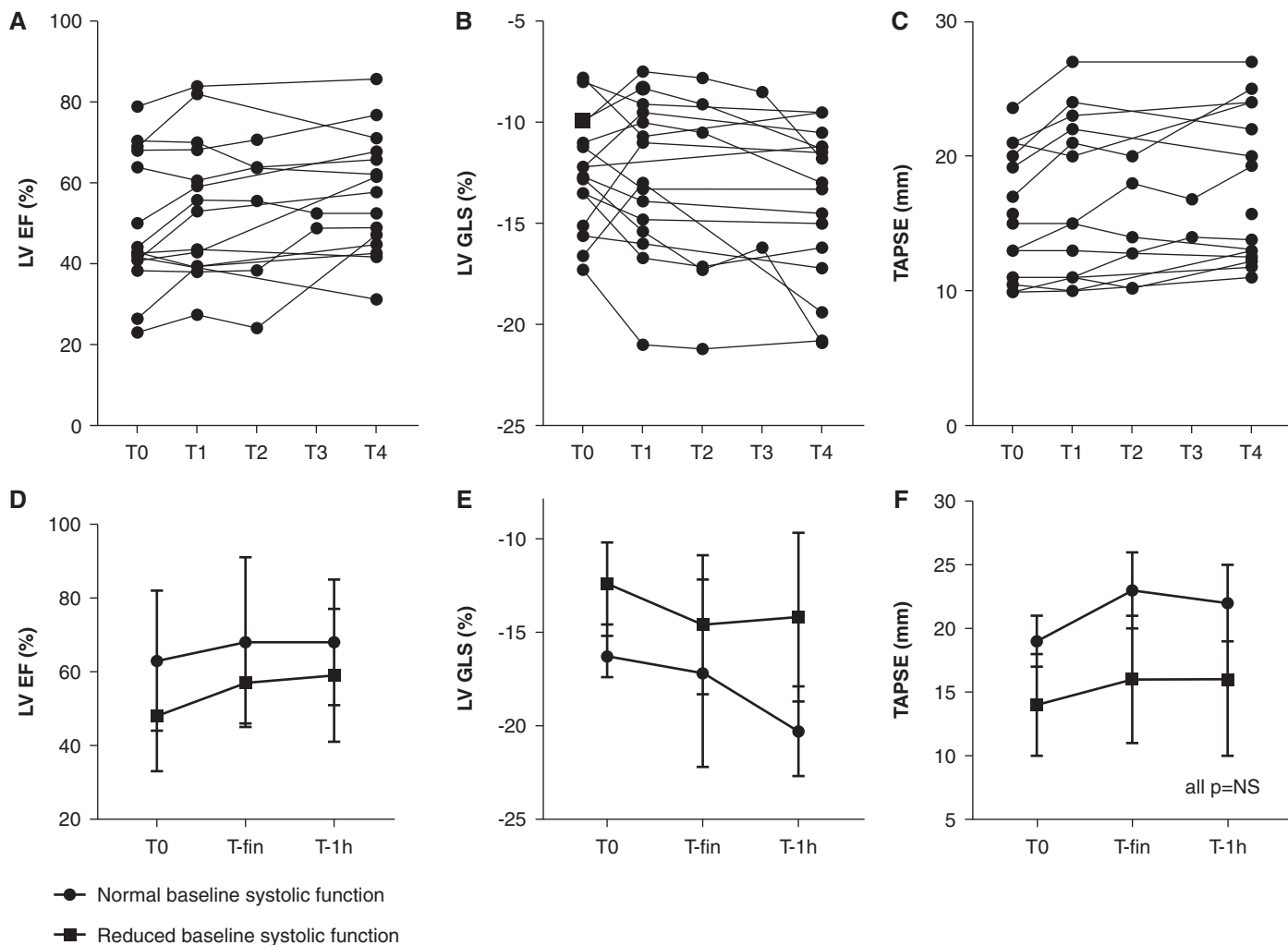


Figure 1. Trend of LV EF, LV GLS, and TAPSE in (A–C) individual patients and in (D–F) patients with and without baseline systolic dysfunction. LV EF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain; NS = nonsignificant; T0 = before starting norepinephrine infusion; T-1h = after 1 hour; TAPSE = tricuspid annular plane systolic excursion; T-fin = when the patient reached the target pressure.

Discussion

In a preliminary series of patients with septic shock, the early administration of norepinephrine determined a persistent improvement in left and right ventricular systolic function, which was also confirmed in patients with abnormal systolic dysfunction. The significant reduction of lactate levels confirmed the amelioration of tissue perfusion, obtained with the treatment.

Noradrenaline is a vasoactive agent, with a predominant α_1 and a concomitant β_1 effect. The net effects are venous and arterial vasoconstriction and increased myocardial contractility (9, 10). An increased afterload coexists and has been advocated as a contraindication to the early administration of noradrenaline in patients with baseline LV dysfunction.

We included only naive patients to the infusion of noradrenaline, who had completed their initial volume replacement. During the early stages of the infusion of noradrenaline, we observed a significant and

persistent increase in LV and RV function as the prominent effect, in agreement with previous reports (11). Compared with baseline, the concomitant better preload and the possible increased coronary flow due to higher diastolic pressure contributed to this improvement. However, the significant reduction of LV GLS documented the presence of an improved myocardial contractility, relatively independent to loading conditions. Previous works reported an improvement of hemodynamic parameters and cardiac output during the infusion of increasing dosages of noradrenaline (12, 13). The novelty of the present study is the demonstration that in a group of patients previously noradrenaline naive, the treatment did not negatively affect cardiac function as one could expect from a vasoconstrictor agent, especially in the presence of poor cardiac performance. The increased preload contributed to this result, but noradrenaline positively impacted myocardial contractility, as evidenced by the improvement of LV GLS, a relatively load-independent parameter. ■

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Adverse Health Effects in People with and without Preexisting Respiratory Conditions during Bushfire Smoke Exposure in the 2019/2020 Australian Summer

To the Editor:

Australia had unprecedented bushfires affecting multiple states in the summer of 2019/2020. Prolonged exposure to bushfire smoke over December 2019 and January 2020 is estimated to have resulted in over 400 excess deaths and over 3,000 additional hospitalizations (1). Some evidence has suggested that people with asthma are at higher risk for adverse health effects after bushfire or wildfire smoke exposure (2–5), although others suggest individuals with asthma are more inclined to take protective measures (6). We aimed to understand the impact of the 2019/2020 bushfire season on the health and behavior of people with and without preexisting respiratory conditions in affected Australian states.

A cross-sectional study was conducted to compare health effects of the 2019/2020 bushfires in people with and without respiratory conditions. Respiratory conditions were defined as self-reported asthma, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, bronchiectasis, and any other chronic lung conditions. Participants 18 years or over with and without respiratory conditions were recruited from postcodes affected by bushfire smoke in the summer of 2019/2020 in six states (New South Wales, Victoria, South Australia, Tasmania, Australian Capital Territory, and Queensland) in Australia during August 2020. *A priori* power analysis was conducted using large sample approximation in G*Power 3.1.9.7 (7). To detect at least 20% difference in risk of adverse health effects after smoke exposure among people with and without respiratory conditions (i.e., odds ratio of 1.2), the sample size necessary to achieve in a two-sided test with $\alpha = 0.05$ and power of 80% is 961.

A market research company, Dynata, distributed the survey link by email to a randomly selected sample of their panel members in the affected areas in selected states. We aimed to recruit 500 people with preexisting (self-reported) respiratory conditions and 500 without preexisting respiratory conditions, on the basis of responses to the survey. Surveys were deidentified and no identifying information was provided or collected. Eligible participants were asked to provide informed consent before completing the survey. The survey was launched on August 3, 2020, and closed on August 21, 2020. The study

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