

Hyperoxia During Extracorporeal Cardiopulmonary Resuscitation for Refractory Cardiac Arrest Is Associated With Severe Circulatory Failure and Increased Mortality

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Abstract

Background: High levels of arterial oxygen pressures (PaO₂) have been associated with increased mortality in extracorporeal cardiopulmonary resuscitation (ECPR), but there is limited information regarding possible mechanisms linking hyperoxia and death in this setting, notably with respect to its hemodynamic consequences. We aimed therefore at evaluating a possible association between PaO₂, circulatory failure and death during ECPR.

Methods: We retrospectively analyzed 44 consecutive cardiac arrest (CA) patients treated with ECPR to determine the association between the mean PaO₂ over the first 24h, arterial blood pressure, vasopressor and intravenous fluid therapies, mortality, and cause of deaths.

Results: Eleven patients (25%) survived to hospital discharge. The main causes of death were refractory circulatory shock (46%) and neurological damage (24%). Compared to survivors, non survivors had significantly higher mean 24h PaO₂ (306±121 mmHg vs 164±53 mmHg, $p < 0.001$), lower mean blood pressure and higher requirements in vasopressors and fluids, but displayed similar pulse pressure during the first 24h (an index of native cardiac recovery). The mean 24h PaO₂ was significantly correlated with hypotension and vasoactive therapies. Patients dying from neurological cause had better preserved blood pressure and lower vasopressor requirements. Patients dying from circulatory failure died after a median of 17h, compared to a median of 58 h for patients dying from a neurological cause (OR 0.95, 95% CI 0.90–0.99, $p = 0.001$).

Conclusion: In conclusion, hyperoxia is associated with increased mortality during ECPR, possibly by promoting circulatory collapse or delayed neurological damage.

Background

Extracorporeal cardiopulmonary resuscitation (ECPR) for refractory out-of-hospital (OHCA) or in-hospital (IHCA) cardiac arrest has gained growing interest over the past years (1, 2). However, recent multicenter registries reported relatively low favorable neurological outcome and survival in heterogeneous cohorts of patients treated with ECPR (3, 4), implying that this strategy should be limited to highly selected patients (4–6). Besides patient selection, improving the quality of post-cardiac arrest care might also be key to improve ECPR outcome. The restoration of systemic oxygenated blood flow after cardiac arrest may trigger reperfusion injury, largely mediated by the generation of oxidants and free radicals (7), whose magnitude may be influenced by the arterial partial pressure of oxygen (PaO₂) during reperfusion (8, 9). In conventional CPR, an association between hyperoxia (defined as supranormal PaO₂ caused by high fractions of inspired oxygen, with a cut-off value of 300 mm Hg frequently used in clinical studies) after return of spontaneous circulation (ROSC) and outcome has been indeed reported in large observational studies (10, 11).

Patients undergoing ECPR may be exposed to significant hyperoxia, given the ease to oxygenate blood through the oxygenator (12), and recent retrospective analyses indicated that hyperoxia during the first 24h of ECPR was associated with reduced survival (13, 14). In a retrospective cohort of 291 ECPR patients, Chang et al. reported that a first PaO₂ value during the first 24h after ECPR initiation between 77 and 220 mm Hg, was significantly associated with neurologically intact survival in comparison to higher values (14). In a retrospective cohort of 66 patients undergoing ECPR for refractory OHCA, Halter et al. reported a significant association between PaO₂ measured at 30 min after ECPR initiation and 28 days mortality. Using a threshold value of PaO₂ of 300 mm Hg to define hyperoxia, the odds ratio for 28 days mortality was 4.07 (13).

Importantly, in the study by Chang et al., the authors reported a significant association between circulatory shock during the first 24h and mortality, whereas Halter et al. reported that most deaths (88%) occurred during the first 48h and were related to multiple organ failure. These findings suggest the hypothesis that early hyperoxia during ECPR may precipitate cardiovascular dysfunction leading to organ failure and death, by exacerbating post-resuscitation disease related to reperfusion injury. To address this hypothesis, we sought to determine the potential association between hyperoxia during the first 24h of ECPR and the severity of hemodynamic failure, as well as its possible association with mortality in a cohort of 44 patients treated with ECPR for refractory IHCA and OHCA. In addition, since hyperoxia-mediated toxicity is largely related to the generation of oxygen free radicals, one can hypothesize that a longer duration of hyperoxia might be associated with a cumulative exposure to such species, hence greater toxicity, as recently shown by Roberts et al. in a prospective study on hyperoxia in cardiac arrest (11). Therefore, instead of relying on a single value of PaO₂, we averaged the values of several PaO₂ measurements during the first 24h of ECPR, in order to take into account the duration of exposure to elevated PaO₂ levels during this period of time.

Methods

Study setting

This study was approved by our ethical committee (Commission Cantonale d’Ethique de la Recherche sur l’Etre Humain/CER-VD-Nr: 2017 – 01184), as a retrospective use of clinical data with waiver of consent (CER-VD-Nr: 2017–011184), and conforms to the STROBE statement for the report of observational studies. All methods were performed in accordance with the relevant guidelines and regulations. The cohort included 44 consecutive patients hospitalized in our 35-bed multidisciplinary ICU for refractory, non-traumatic and non-hypothermic, OHCA and IHCA treated with ECPR from June 2017 to June 2019. During this period, our internal recommendations for starting ECPR were: refractory OHCA or IHCA; no flow < 5min; low flow < 80 min; age < 75y; absence of major co-morbidities; absence of Do Not Resuscitate order. A subset of patients of the current cohort were also included in an unrelated study evaluating automated pupillometry during Veno-Arterial ECMO (VA-ECMO) for various indications (15).

Treatment strategy

The insertion of venous and arterial femoral cannulas was performed in the hospital by a cardiac surgeon. Initial VA-ECMO settings included a sweep fraction of oxygen (F_{sO_2}) of 100% and a pump setting for a target blood flow of 40–60 ml/kg, using the Maquet Cardiohelp ECLS system®. Sweep gas flow was adapted to maintain normal $PaCO_2$. Systemic anticoagulation (intravenous heparin) initiated at the end of surgery was maintained to achieve an anti-Xa activity of 0.3–0.5. A coronary angiography was performed at the discretion of the in charge physicians. Noradrenaline (NA) and Adrenaline (Adre) were given to maintain mean blood pressure (BP) \geq 65 mm Hg. Intravenous (IV) fluids were administered to maintain the target blood flow. Mechanical ventilation was performed with a tidal volume of 6 ml/kg, rate of 10–15/min and PEEP of 6–10 cm H_2O . Both FiO_2 and FsO_2 were set by default at 100% on ECPR initiation. Following these initial settings, decisions to reduce FiO_2 or/and FsO_2 were entirely at the discretion of the treating physicians, without specific recommendation. Sedation was maintained with Propofol (2–4 mg/kg/h) or Midazolam (0.05–0.15 mg/h). Targeted temperature management at 35–36°C for 24h was implemented in all patients. Criteria for discontinuing VA-ECMO were the absence of cardiac function recovery, intractable circulatory shock, or evidence of severe neurological injury. Criteria for weaning of VA-ECMO included a mean BP > 65 mm Hg, left ventricle ejection fraction > 20% and aortic velocity time integral (VTI) > 10 cm on transthoracic echocardiography, under minimal vasopressor/inotropic support and ECMO flow.

Data collection

Demographic variables included age, sex, location of CA (OHCA, IHCA), initial rhythm, duration of no flow and low flow (total duration of CPR before ECMO initiation), SAPS 2 score, ICU and hospital length of stay, duration of ECMO treatment, proportion of patients undergoing coronary angiography and angioplasty (PTCA), as well as the causes of death.

Hemodynamic variables included: (A) Arterial blood pressure (BP, obtained via an arterial catheter in all but 3 patients), using a mean value computed from the average of all measurements performed each 2 hour during the first 24h (or until death if it occurred before 24h). (b) Pulse pressure (systolic minus diastolic blood pressure), determined during the first 24h as an indirect indicator of native cardiac output recovery (16), which was averaged from values obtained at 2, 6, 12 and 24h (or until death if it occurred before 24h). (C) The amount of catecholamines, fluids, packed red blood cells and fresh frozen plasma administered (first 72 h).

Blood gas data were obtained from an indwelling intra-arterial catheter, whose position was recorded (right radial, left radial or femoral). The values of PaO_2 measured at 5 different times of ECPR (first 15 minutes, 2h, 6h, 12h and 24h) were averaged as the mean 24h PaO_2 (in patients dying before 24h, mean PaO_2 was computed from values obtained during the time spent under ECPR until death). Arterial blood lactate was determined in the first arterial blood sampling (first 15 minutes of ECPR).

Data analysis

Continuous variables are expressed as means \pm SD, or medians and interquartile ranges (IQR), and categorical data as absolute numbers and percentages. All comparisons were done using the Wilcoxon's rank sum test for continuous variables and the chi-square test for categorical variables. We determined which variables were associated with survival using univariate logistic regression analysis for continuous variables and contingency analysis with Pearson's test for categorical variables. To evaluate the association of hyperoxia with mortality, multivariable logistic regression was applied, using mean PaO₂, age, low flow and no flow duration, shockable rhythm, as well as the duration of ECMO as the co-variables, and hospital mortality as the response binomial variable. Odds ratios with 95% CI were calculated, and Wald statistics was used to assess the significance of each variable. Furthermore, due to the relatively low number of events in our cohort and the inherent risk of overestimating regression coefficients (17), we complemented this analysis by running several logistic regressions using only mean PaO₂ and a second co-variable at a time (including co-variable with a p value < 0.2 in the multivariable logistic regression: no flow, low flow, and shockable rhythm). To control for possible type I error, we introduced a Bonferroni adjustment for assessing significance in these 3 models (thus, a p value of 0.05/3 = 0.016 was used as the significance limit in these analyses). To determine a possible association between PaO₂ and circulatory failure, we performed bivariate analyses and simple linear regressions between mean PaO₂ and mean blood pressure and between mean PaO₂ and the amount of vasopressive catecholamines administered, with calculation of the Pearson r coefficient. To determine the influence of the arterial catheter position on PaO₂, PaO₂ values obtained in the different catheter positions were compared using Wilcoxon rank test. The JMP software, version 15, was used for all the analyses, and a p value < 0.05 was considered statistically significant.

Results

The characteristics of patients and differences between survivors and non survivors are shown in Table 1. No patient in our cohort displayed ROSC before ECMO initiation. For the whole cohort, in-hospital survival was 25% (11pts), including OHCA: 7/27 = 26% and IHCA: 4/17 = 24% (p = 0.86). Survivors had lower SAPS 2 scores, longer LOS and ECPR duration. There were no differences in terms of location of CA, initial rhythm, no flow duration and PaCO₂ levels, whereas low flow duration, first arterial lactate and intravenous fluids administration were significantly higher in non survivors.

In two patients dying early after ECPR initiation, arterial blood samples were not obtained. Non-survivors had significantly higher mean PaO₂ during the first 24h (Table 1 and Fig. 1). At each time point, the values of PaO₂ in non-survivors vs survivors were: ECMO initiation: 444 \pm 107 vs 352 \pm 136 mm Hg (p = 0.03); 2h: 287 \pm 175 vs 164 \pm 108 mm Hg (p = 0.07); 6h: 253 \pm 148 vs 125 \pm 78 mm Hg (p = 0.02); 12h: 161 \pm 111 vs 85 \pm 22 mm Hg (p = 0.004); 24h: 121 \pm 44 vs 94 \pm 21 mm Hg (p = 0.02). At the respective time-points, the number of measurements were 11 in survivors and 31, 27, 27, 22 and 18 in non-survivors. Non-survivors also displayed lower mean blood pressure during the first 24h, and received significantly more vasopressive catecholamines (Table 1 and Fig. 2A and B). Pulse pressure during the first 24h was not different between non-survivors and survivors (Table 1 and Fig. 2C). The mean PaO₂ value during the first

24h displayed a significant negative correlation with mean blood pressure (Fig. 2D) and positive correlation with total amount of vasopressors (NA + Adre, in $\mu\text{g}/\text{kg}/\text{min}$ during the first 3 days, Fig. 2E).

Table 1. Characteristics of patients

Variable	All pts (n=44)	Dead (n=33)	Alive (n=11)	p value
Age (years), mean (SD)	52 (14)	54 (12)	48 (19)	0.456
Male sex, n (%)	31 (70)	24 (73)	7 (63)	0.567
SAPS 2, mean (SD)	83 (13)	85 (14)	76 (6)	0.003
ICU LOS (days), median (IQR)	2.6 (18.8)	1.5 (4.3)	22.9 (28.8)	<0.001
HOSP LOS, (days), median (IQR)	2.8 (27.3)	1.6 (4.2)	51.4 (38.0)	<0.001
ECMO Weaning, n (%)	15 (34)	4 (12)	11 (100)	<0.001
Survival (Hospital), n (%)	11 (25)	0 (0)	11 (100)	
ECMO duration (hours), median (IQR)	43 (106)	28 (106)	81 (74)	0.024
Location of CA				0.858
OHCA, n (%)	27 (61)	20 (65)	7 (63)	
IHCA, n (%)	17 (39)	13 (35)	4 (37)	
Initial rhythm				0.141
VF, n (%)	23 (52)	16 (49)	7 (64)	
PEA, n (%)	14 (32)	11 (33)	3 (27)	
Asystole, n (%)	6 (14)	6 (18)	0 (0)	
Unknown, n (%)	1 (2)	0 (0)	1 (9)	
Shockable Rhythm	23 (52)	16 (48)	7 (64)	0.214
No flow (minutes), mean (SD)	1.2 (2.0)	1.1 (2.0)	1.5 (2.2)	0.572
Low flow (minutes), mean (SD)	68 (23)	73 (22)	51 (18)	0.005
Mean PaO ₂ (first 24h, mm Hg), mean (SD)	269 (124)	306 (121)	164 (53)	0.001
Mean PaCO ₂ (first 24h, mm Hg), mean (SD)	37 (6)	36 (7)	38 (3)	0.525
First lactate (mmol/L), mean (SD)	13.4 (5.9)	14.9 (5.8)	9.4 (4.1)	0.004
Mean BP (first 24h), mean (SD)	67 (12)	64 (12)	75 (5)	0.007
Pulse Pressure (first 24h), mean (SD)	20 (13)	18 (12)	25 (13)	0.149
Coronarography, n (%)	22 (50)	16 (48)	6 (54)	0.728
PTCA, n (%)	17 (39)	11 (33)	6 (54)	0.211
NA ($\mu\text{g}/\text{kg}/\text{min}$, first 72h), median (IQR)	0.25 (0.44)	0.37 (0.54)	0.12 (0.13)	0.006
ADRE, ($\mu\text{g}/\text{kg}/\text{min}$, first 72h), median (IQR)	0.02 (0.13)	0.06 (0.20)	0.00 (0.04)	0.043
Total catecholamines (NA+ADRE, first 72h)	0.36 (0.73)	0.54 (0.67)	0.12 (0.16)	0.002
Cristalloid (ml/kg/h, first 72h), mean (SD)	6.0 (9.8)	7.3 (11.2)	2.4 (0.8)	0.023
Packed RBC (n, first 72h), mean (SD)	5.2 (4.7)	5.5 (4.8)	4.4 (4.4)	0.449
FFP (n, first 72h), mean (SD)	2.4 (3.0)	2.6 (3.1)	1.6 (2.7)	0.294

Variables associated with in-hospital mortality at the 5% level in univariate analysis (Table 2) included the duration of low flow, mean PaO₂, the first arterial lactate concentration, the amounts of catecholamines and IV fluids administered, as well as mean blood pressure during the first 24h. Table 3 shows the results of the multiple logistic regression analyses which indicate that mean PaO₂ was the only co-variate showing a p value < 0.05 for the association with mortality. The results of the logistic regressions including only 2 co-variates (mean PaO₂ and low flow; mean PaO₂ and no flow; mean PaO₂ and initial rhythm), also show an association between mean PaO₂ and mortality following Bonferroni correction.

Table 2. Variables associated with in-hospital mortality (univariate analysis)

Variable	OR [95% CI]	p value
Age	1.03 [0.98-1.09]	0.244
Localization of CA (OHCA vs IHCA)	0.88 [0.20-3.54]	0.858
Initial rhythm (VF vs non VF)	0.40 [0.08-1.73]	0.226
SAPS II	1.06 [0.99-1.15]	0.052
No flow duration	0.91 [0.66-1.26]	0.580
Low flow duration	1.06 [1.02-1.11]	0.003
Lactate at ECMO initiation	1.22 [1.06-1.46]	0.005
Mean PaO ₂ first 24h on ECMO	1.03 [1.01-1.06]	< 0.001
Mean PaCO ₂ first 24h on ECMO	0.95 [0.82-1.08]	0.462
Mean BP (first 24h)	0.84 [0.72-0.98]	0.001
Pulse Pressure (first 24h)	0.96 [0.90-1.01]	0.129
Total catecholamines (NA+ADRE)	4.51 [1.70-15.68]	0.012
Total Cristalloid	1.67 [0.96-2.89]	0.005
Catheter position (right RA vs other)	2.10 [0.53-9.54]	0.297
Coronarography	0.78 [0.32-5.23]	0.728
PTCA	0.42 [0.10-1.67]	0.217
Packed RBC	1.06 [0.91-1.26]	0.459
FFP	1.14 [0.87-1.49]	0.322

Univariate analysis of variables associated with in-hospital mortality. Data are shown as p values and Odds Ratio (OR) with 95% confidence interval (CI). Abbreviations. ADRE: Adrenaline; CA: Cardiac Arrest; ECMO: Extra-Corporeal Membrane Oxygenation; FFP: Fresh Frozen Plasma; IHCA: In-Hospital Cardiac Arrest; NA: Noradrenaline; OHCA: Out-of-Hospital Cardiac Arrest; PTCA: Percutaneous Transluminal Coronary Angioplasty; RA: Radial Artery; RBC: Red Blood Cells; SAPS: Simplified Acute Physiology Score; VF: Ventricular Fibrillation.

Table 3. Variables associated with in-hospital mortality (multivariable analysis)

Variable	Odds ratio	95 % CI	p value
Age	1.04	0.92-1.17	0.55
No Flow duration	0.01	0.01-1.38	0.09
Low flow duration	1.26	0.99-1.59	0.06
ECMO duration	1.01	0.99-1.03	0.25
Shockable rhythm	0.01	0.01-3.29	0.12
Localization (IH vs OH)	0.05	0.01-7.32	0.24
Mean PaO ₂	1.07	1.01-1.13	0.03

Models with 2 co-variables

Variable	Odds ratio	95 % CI	p value
Mean PaO ₂	1.04	1.02 – 1.08	0.009
No flow	0.62	0.31- 1.07	0.121

Mean PaO ₂	0.37	1.01 - 1.06	0.011
Low flow	1.03	0.98 -1.11	0.232

Mean PaO ₂	0.32	1.01-1.06	0.013
Shockable rhythm	0.42	0.06 -2.86	0.383

CI: Confidence Interval. Odds ratio for continuous variables are calculated for one unit change for each variable (1 y for age, 1 minute for no flow and low flow duration, 1h for ECMO duration, 1 mmHg for mean PaO₂)

The two main causes of death were profound circulatory shock (n = 15, 46% of patients) and neurological injury (severe anoxic encephalopathy or major stroke, n = 8, 24% of patients). Other causes of death included hemorrhagic shock (n = 3). Multiple organ failure (n = 4), septic shock (n = 2) and technical issue (n = 1). Comparisons between patients dying from circulatory or neurological causes are shown in Fig. 3. Low flow was not statistically different in the two groups (Fig. 3A). Patients dying from circulatory cause had significantly higher initial lactate (Fig. 3B) and shorter ICU LOS (Fig. 3C). The mean PaO₂ during the first 24h was not different (p = 0.1 between both groups, Fig. 3D). Patients with neurological death had significantly higher mean BP during the first 24h (Fig. 3E) and received significantly less vasopressive catecholamines (Fig. 3F).

Mean PaO₂ measured via a right arterial catheter was not different from that measured from a left radial catheter, but was lower than that measured via a femoral catheter, and mean PaO₂ measured from a left radial catheter was not different from that measured via a femoral catheter (Fig. 4A). When comparing mean PaO₂ between survivors and non survivors according to the catheter position, values were significantly lower in survivors for each position of the arterial catheter (Fig. 4B).

Discussion

The restoration of systemic oxygenated blood flow after a prolonged period of hypoxia may trigger widespread reperfusion injury. A key mechanism of reperfusion injury is the generation of oxidants and free radicals (18), whose flux increases in proportion with the local PO_2 (19–21), implying an increased risk of oxidant-mediated damage at higher PO_2 during reperfusion (22). In the setting of ECPR, the risk of hyperoxia is particularly elevated, due to the ease of oxygenating blood through the membrane oxygenator (5, 12), and a few retrospective studies have indeed reported a negative impact of hyperoxia on survival after ECPR (13, 14, 23). In our study, non survivors displayed a higher mean 24h PaO_2 , lower mean blood pressure, higher needs in vasopressors, and profound circulatory shock was the primary cause of death in a majority of non survivors. Taken together, these findings suggest that severe vascular failure with refractory circulatory shock may represent an important mechanism of hyperoxia toxicity during ECPR.

Hyperoxia results in an increased vascular generation of superoxide ($O_2^{\cdot-}$), which reacts rapidly with nitric oxide (NO) to form peroxynitrite, that can trigger significant vascular contractile failure through a number of processes (24–26). In addition, oxidants such as peroxynitrite promote the expression of multiple inflammatory cytokines and mediators (27–30), which also reduce vascular tone and may precipitate hypotension. These effects may contribute to foster a sepsis-like state, characterized by an irreversible loss of vascular contractility and refractory hypotension with negative prognostic impact after prolonged resuscitation and ECPR, as recently reported by Jouffroy et al. (31). Obviously, the formation of peroxynitrite and other oxidants, together with the generation of inflammatory mediators, at different levels of PaO_2 during ECPR, should be evaluated in future investigations to explore these mechanisms.

A critical aspect in the interpretation of arterial blood gases during peripheral VA-ECMO is the localization of arterial blood sampling and right radial artery sampling is recommended (32), owing to the risk of upper body hypoxia in case of cardiac recovery and impaired pulmonary gas exchange (33). Accordingly, we found that PaO_2 was lower when measured from a right radial artery than from a femoral artery, while it did not differ from values obtained from the left radial artery. One could therefore argue that the lower PaO_2 in survivors might reflect an earlier recovery of native cardiac function, but this appears unlikely in view of the similar values of pulse pressure, an indirect, real-time measure of native cardiac output during extracorporeal support (34), in survivors and non survivors.

The two main causes of death were early circulatory failure and delayed neurological damage. Patients dying from either cause had similar durations of low flow and mean PaO_2 , but initial lactate levels were lower in patients dying from neurological damage, pointing to less profound systemic anoxia. These patients also had higher mean blood pressure and required significantly less vasopressors. Overall, these findings suggest that patients with more severe anoxia (higher lactate levels) might develop more severe reperfusion injury under hyperoxic conditions, leading to predominantly vascular failure and early deaths, whereas those with less severe anoxia would survive the early stage and develop delayed hyperoxic neurological damage. This hypothesis should require validation in larger cohorts of patients treated with ECPR for refractory cardiac arrest.

We did not find significant association between the initial rhythm and survival, which differs from the notion that survival under ECPR is better in patients with an initial shockable rhythm (35). This discrepancy most likely reflects the small sample size in our study. Only 52 % of patients had an initial shockable rhythm, and among those with a non-shockable rhythm, all patients with asystole died, whereas 3 out of 14 patients (21%) with pulseless electrical activity (PEA) survived to hospital discharge. Interestingly, these 3 patients had the lowest mean PaO₂ (152, 162 and 184 mmHg, respectively) among the 14 PEA patient, which may suggest that the avoidance of hyperoxia during ECPR could be critical to determine outcome in PEA patients undergoing ECPR.

Besides PaO₂, survival in our cohort was significantly associated with the duration of low flow in univariate analysis, in line with previous investigations (36–38). However, this association was not observed in a multivariable analysis evaluating several co-variables commonly associated with poor outcome after CA and ECPR, such as no flow, low flow, initial rhythm, localization of CA (IHCA vs OHCA) and age, together with mean 24h PaO₂. We also included the duration of ECMO as a co-variate, given that the initial sweep gas oxygen fraction was set at 100%, which could have favored persisting hyperoxia in these patients. With the exception of mean PaO₂, none of these variables displayed a significant association with mortality. Although these findings may suggest a particularly negative prognostic implication of hyperoxia in ECPR, they warrant cautious interpretation. Owing to the relatively small sample size in our study, the results of multivariate analysis may be subject to some bias related to an overestimation of regression coefficients (17). For this reason, we performed additional analyses using only one co-variate with mean PaO₂, including no flow, low flow and initial rhythm, which confirmed the association of mean PaO₂ with mortality. In addition, due to the retrospective nature of our study, the association of PaO₂ with mortality could represent a surrogate for the sickness of patients. Physicians would indeed be inclined to maintain high levels of administered O₂ to the most severely affected patients, and hyperoxia would therefore be a side effect of such management.

Our study has several limitations. First, we must acknowledge the usual limitations related to the retrospective design of our study (39) and to its relatively small sample size. Second, although we established an association between hyperoxia and mortality, as well with refractory circulatory failure, such associations do not necessarily mean a causal relationship. Third, the absence of internal recommendations for the management of arterial oxygen levels during ECPR may have favored the development of hyperoxia, which could have been avoided with a dedicated clinical protocol. Fourth, we did not measure circulating mediators related to oxidative stress and inflammation, which could have given important insights on the effects of hyperoxic reperfusion during ECPR. Such measurements will be the matter of additional future investigations.

Conclusions

In conclusion, although we acknowledge several important limitations, our study shows that, in patients undergoing ECPR for refractory cardiac arrest, a high PaO₂ during the first 24 h of support is associated

with worse outcome, possibly by promoting severe vascular failure and refractory circulatory shock. PaO₂ should therefore be strictly controlled during the first 24h of ECPR, via blood sampling from the right radial artery. Future studies should evaluate the impact of different PaO₂ levels during ECPR on biomarkers of oxidative stress and inflammation, to provide further insights into possible mechanisms of hemodynamic collapse in this setting.

Declarations

Ethics approval, consent to participate and consent for publication

Ethical Committee Name: Commission Cantonale d'Ethique de la Recherche sur l'Être Humain (CER-VD). Retrospective use of clinical data with waiver of consent (Approval number: CER-VD-Nr: 2017-01184).

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

JB: Data acquisition and analysis; Interpretation of data; Writing: original draft

MR: Data acquisition and analysis; Interpretation of data; Writing: review and editing

ZL: Data acquisition and analysis; Interpretation of data; Writing: review and editing

AR: Data acquisition and analysis; Interpretation of data; Writing: review and editing

PT: Data acquisition and analysis; Interpretation of data; Writing: review and editing

MO: Conception and design of the work; Project administration; Interpretation of data; Writing: review and editing

MK: Conception and design of the work; Project administration; Interpretation of data; Writing: review and editing

LL: Conception and design of the work; Project administration; Data acquisition and analysis; interpretation of data; Writing: original draft

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References

1. Fagnoul D, Combes A, De Backer D. Extracorporeal cardiopulmonary resuscitation. *Curr Opin Crit Care*. 2014;20(3):259–65.
2. Patricio D, Peluso L, Brasseur A, Lheureux O, Belliato M, Vincent JL, et al. Comparison of extracorporeal and conventional cardiopulmonary resuscitation: a retrospective propensity score matched study. *Crit Care*. 2019;23(1):27.
3. Bougouin W, Dumas F, Lamhaut L, Marijon E, Carli P, Combes A, et al. Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a registry study. *Eur Heart J*. 2020;41(21):1961–71.
4. Lunz D, Calabro L, Belliato M, Contri E, Broman LM, Scandroglio AM, et al. Extracorporeal membrane oxygenation for refractory cardiac arrest: a retrospective multicenter study. *Intensive Care Med*. 2020;46(5):973–82.
5. Dennis M, Lal S, Forrest P, Nichol A, Lamhaut L, Totaro RJ, et al. In-Depth Extracorporeal Cardiopulmonary Resuscitation in Adult Out-of-Hospital Cardiac Arrest. *J Am Heart Assoc*. 2020;9(10):e016521.
6. MacLaren G, Masoumi A, Brodie D. ECPR for out-of-hospital cardiac arrest: more evidence is needed. *Crit Care*. 2020;24(1):7.
7. Inoue A, Hifumi T, Sakamoto T, Kuroda Y. Extracorporeal Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest in Adult Patients. *J Am Heart Assoc*. 2020;9(7):e015291.
8. McKenzie NF, Dobb GJ. Oxygen After Cardiac Arrest: Enough Is Enough? *Circulation*. 2018;137(20):2125–7.
9. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest - A systematic review and meta-analysis of animal trials. *Resuscitation*. 2012;83(4):417–22.
10. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303(21):2165–71.
11. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Pierce L, Donnino M, et al. Association Between Early Hyperoxia Exposure After Resuscitation From Cardiac Arrest and Neurological Disability: Prospective Multicenter Protocol-Directed Cohort Study. *Circulation*. 2018;137(20):2114–24.

12. Hutin A, Abu-Habsa M, Burns B, Bernard S, Bellezzo J, Shinar Z, et al. Early ECPR for out-of-hospital cardiac arrest: Best practice in 2018. *Resuscitation*. 2018;130:44–8.
13. Halter M, Jouffroy R, Saade A, Philippe P, Carli P, Vivien B. Association between hyperoxemia and mortality in patients treated by eCPR after out-of-hospital cardiac arrest. *Am J Emerg Med*. 2020;38(5):900–5.
14. Chang WT, Wang CH, Lai CH, Yu HY, Chou NK, Wang CH, et al. Optimal Arterial Blood Oxygen Tension in the Early Postresuscitation Phase of Extracorporeal Cardiopulmonary Resuscitation: A 15-Year Retrospective Observational Study. *Crit Care Med*. 2019;47(11):1549–56.
15. Miroz JP, Ben-Hamouda N, Bernini A, Romagnosi F, Bongiovanni F, Roumy A, et al. Neurological Pupil index for Early Prognostication After Venous Arterial Extracorporeal Membrane Oxygenation. *Chest*. 2020;157(5):1167–74.
16. Mourad M, Eliet J, Zeroual N, Saour M, Sentenac P, Manna F, et al. Pulse pressure and end-tidal carbon dioxide for monitoring low native cardiac output during veno-arterial ECLS: a prospective observational study. *Crit Care*. 2020;24(1):569.
17. Steyerberg EW, Eijkemans MJ, Habbema JD. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. *J Clin Epidemiol*. 1999;52(10):935–42.
18. Johnson NJ, Carlbom DJ, Gaieski DF. Ventilator Management and Respiratory Care After Cardiac Arrest: Oxygenation, Ventilation, Infection, and Injury. *Chest*. 2018;153(6):1466–77.
19. Fridovich I. Quantitative aspects of the production of superoxide anion radical by milk xanthine oxidase. *J Biol Chem*. 1970;245(16):4053–7.
20. Di Maria CA, Bogoyevitch MA, McKittrick DJ, Arnolda LF, Hool LC, Arthur PG. Changes in oxygen tension affect cardiac mitochondrial respiration rate via changes in the rate of mitochondrial hydrogen peroxide production. *J Mol Cell Cardiol*. 2009;47(1):49–56.
21. Carnesecchi S, Deffert C, Pagano A, Garrido-Urbani S, Metrailler-Ruchonnet I, Schappi M, et al. NADPH oxidase-1 plays a crucial role in hyperoxia-induced acute lung injury in mice. *Am J Respir Crit Care Med*. 2009;180(10):972–81.
22. Llitjos JF, Cariou A. Hyperoxia in post-cardiac arrest: friend or foe? *J Thorac Dis*. 2018;10(Suppl 33):3908-S10.
23. Munshi L, Kiss A, Cypel M, Keshavjee S, Ferguson ND, Fan E. Oxygen Thresholds and Mortality During Extracorporeal Life Support in Adult Patients. *Crit Care Med*. 2017;45(12):1997–2005.
24. Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. *Physiol Rev*. 2007;87(1):315–424.
25. Liaudet L, Rosenblatt-Velin N, Pacher P. Role of peroxynitrite in the cardiovascular dysfunction of septic shock. *Curr Vasc Pharmacol*. 2013;11(2):196–207.
26. Liaudet L, Soriano FG, Szabo E, Virag L, Mabley JG, Salzman AL, et al. Protection against hemorrhagic shock in mice genetically deficient in poly(ADP-ribose)polymerase. *Proc Natl Acad Sci U S A*. 2000;97(18):10203–8.

27. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2014;18(6):711.
28. Nagato AC, Bezerra FS, Lanzetti M, Lopes AA, Silva MA, Porto LC, et al. Time course of inflammation, oxidative stress and tissue damage induced by hyperoxia in mouse lungs. *Int J Exp Pathol*. 2012;93(4):269–78.
29. Helmerhorst HJF, Schouten LRA, Wagenaar GTM, Juffermans NP, Roelofs J, Schultz MJ, et al. Hyperoxia provokes a time- and dose-dependent inflammatory response in mechanically ventilated mice, irrespective of tidal volumes. *Intensive Care Med Exp*. 2017;5(1):27.
30. Lugin J, Rosenblatt-Velin N, Parapanov R, Liaudet L. The role of oxidative stress during inflammatory processes. *Biol Chem*. 2014;395(2):203–30.
31. Jouffroy R, Guyard A, Philippe P, Carli P, Vivien B. Effect of Mean Blood Pressure During Extracorporeal Life Support on Outcome After Out-of-Hospital Cardiac Arrest. *Turk J Anaesthesiol Reanim*. 2019;47(2):134–41.
32. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial Extracorporeal Membrane Oxygenation for Cardiogenic Shock and Cardiac Arrest. *Circ Heart Fail*. 2018;11(9):e004905.
33. Roumy A, Liaudet L, Rusca M, Marcucci C, Kirsch M. Pulmonary complications associated with venoarterial extra-corporeal membrane oxygenation: a comprehensive review. *Crit Care*. 2020;24(1):212.
34. Rilinger J, Riefler AM, Bemtgen X, Jackel M, Zotzmann V, Biever PM, et al. Impact of pulse pressure on clinical outcome in extracorporeal cardiopulmonary resuscitation (eCPR) patients. *Clin Res Cardiol*. 2021: in press.
35. De Charriere A, Assouline B, Scheen M, Mentha N, Banfi C, Bendjelid K, et al. ECMO in Cardiac Arrest: A Narrative Review of the Literature. *J Clin Med*. 2021;10(3).
36. Otani T, Sawano H, Natsukawa T, Nakashima T, Oku H, Gon C, et al. Low-flow time is associated with a favorable neurological outcome in out-of-hospital cardiac arrest patients resuscitated with extracorporeal cardiopulmonary resuscitation. *J Crit Care*. 2018;48:15–20.
37. Wengenmayer T, Rombach S, Ramshorn F, Biever P, Bode C, Duerschmied D, et al. Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). *Crit Care*. 2017;21(1):157.
38. Yu HY, Wang CH, Chi NH, Huang SC, Chou HW, Chou NK, et al. Effect of interplay between age and low-flow duration on neurologic outcomes of extracorporeal cardiopulmonary resuscitation. *Intensive Care Med*. 2019;45(1):44–54.
39. Tofthagen C. Threats to validity in retrospective studies. *J Adv Pract Oncol*. 2012;3(3):181–3.

Figures

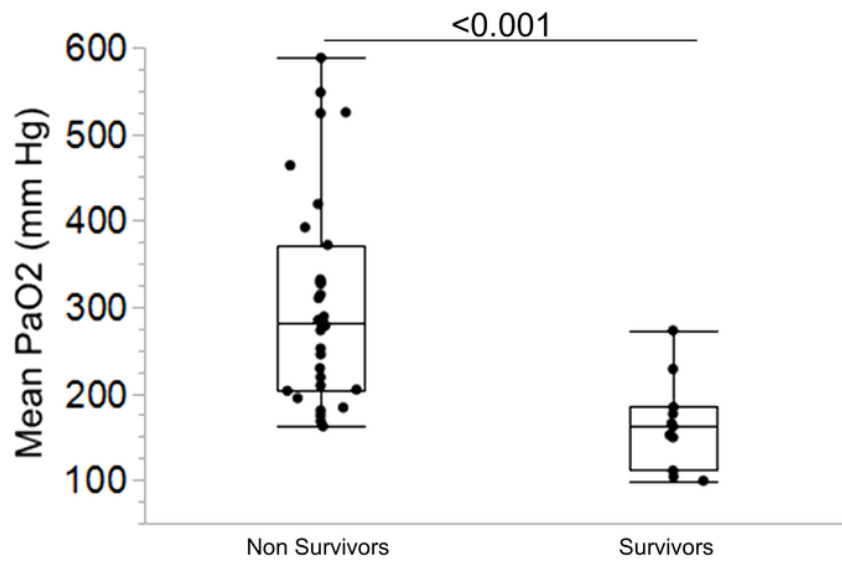


Figure 1

Comparison of mean 24h PaO2 in survivors and non survivors

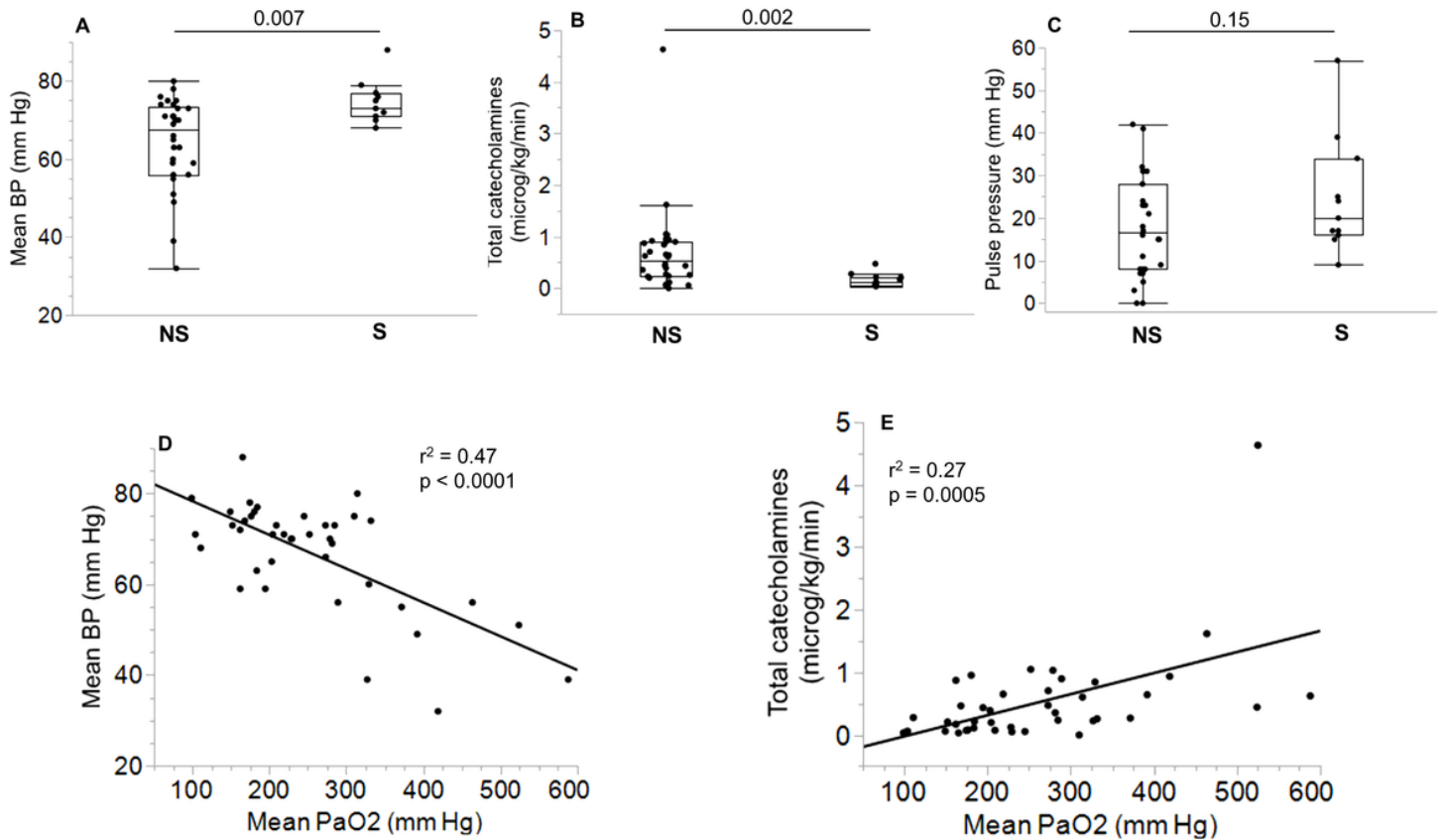


Figure 2

Comparison of hemodynamic variables and vasopressor therapy in survivors and non survivors during ECPR and correlations with mean PaO₂. A. Mean blood pressure during the first 24h of ECPR; B. Total catecholamines administered during the first 72h of ECPR; C. Pulse pressure (systolic minus diastolic blood pressure) during the first 24h of ECPR; D, E: Simple linear regressions showing correlations between mean PaO₂ and mean blood pressure (D) and catecholamine therapy (E) during ECPR. Box plots show median, 1st and 3rd quartiles, whiskers indicate minimal and maximal values. NS: Non Survivors; S: Survivors

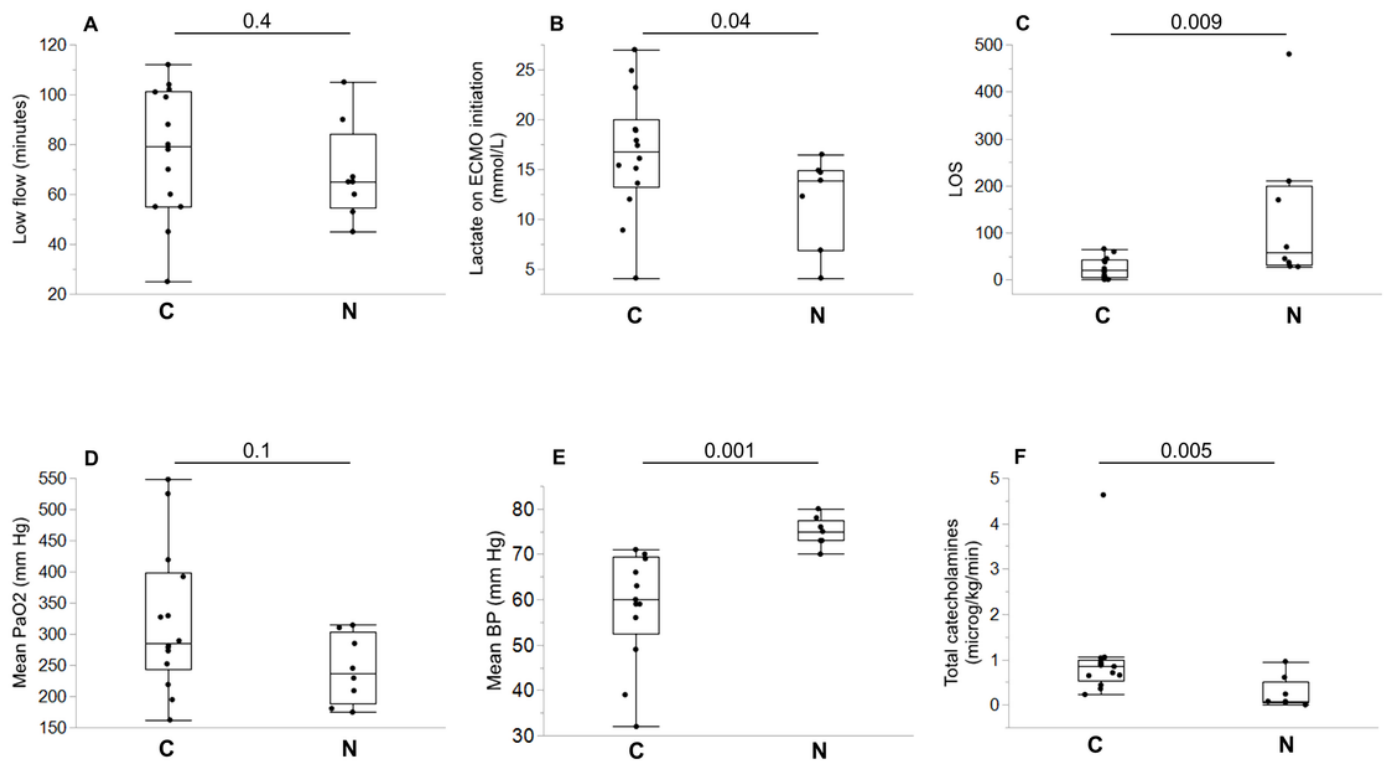


Figure 3

Characteristics of patients dying from circulatory or neurological cause during ECPR. A. Duration of low flow; B. First value of arterial lactate after ECPR initiation; C. Length of stay (LOS) in the ICU; D. Mean PaO₂ during the first 24h of ECPR; E. Mean blood pressure during the first 24 h of ECPR; F. Total catecholamines administered during the first 72h of ECPR. On the X-axis, C means death from circulatory failure and N means death from neurological causes. Box plots show median, 1st and 3rd quartiles, whiskers indicate minimal and maximal values.

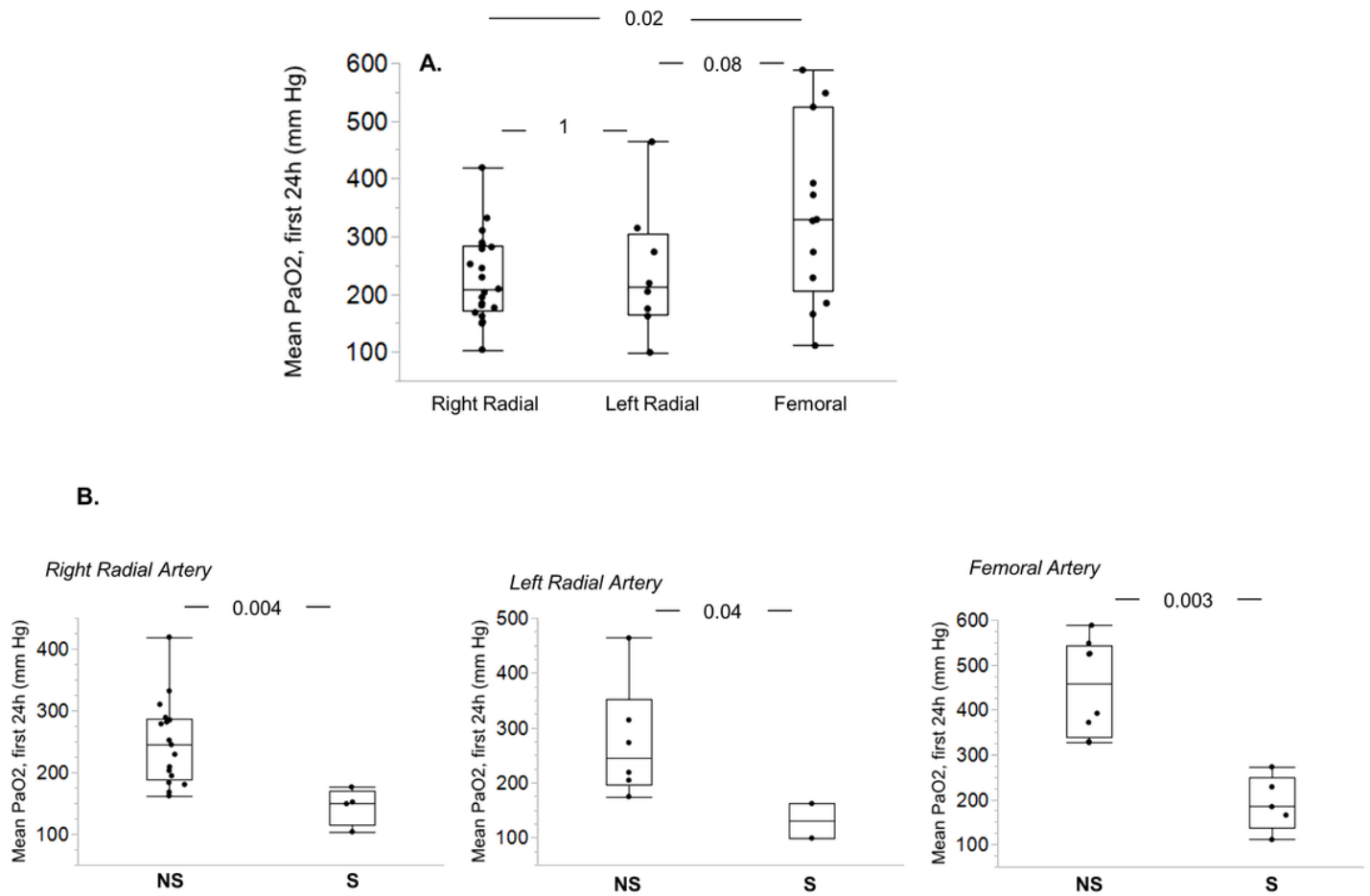


Figure 4

Mean PaO₂ values according to the site of arterial blood sampling. A: Mean PaO₂ during the first 24h of ECPR according to the position of the arterial catheter in the whole cohort; B: Mean PaO₂ values in survivors and non survivors according to the site of blood sampling (right radial, left radial or femoral artery). Box plots show median, 1st and 3rd quartiles, whiskers indicate minimal and maximal values. NS: Non Survivors; S: Survivors

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytable1Studydataset.xlsx](#)