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ORIGINAL RESEARCH

Oxygen Delivery and Consumption in Patients Who Are Comatose After Out-of-Hospital Cardiac Arrest Are Affected by Blood Pressure Target

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BACKGROUND: In the management of patients resuscitated from out-of-hospital cardiac arrest, a primary goal is to restore sufficient oxygen delivery (DO_2) to meet demands in oxygen consumption (VO_2).

METHODS AND RESULTS: This post hoc analysis of the BOX (Blood Pressure and Oxygen Targets) study included adult patients who were comatose and experienced out-of-hospital cardiac arrest from a presumed cardiac cause, who were randomized to a mean arterial blood pressure (MAP) target of 63 mm Hg (MAP63) or 77 mm Hg (MAP77) and a Restrictive PaO_2 target of 9 to 10 kPa versus a Liberal target of 13 to 14 kPa in a 2×2 factorial design. A pulmonary artery catheter was inserted following randomization. DO_2 and VO_2 were calculated as: DO_2=cardiac output × arterial oxygen content, and VO_2= cardiac output × arteriovenous oxygen difference. Of 789 patients, 730 (92.5%) were included in this substudy. A total of 362 patients were randomized to MAP77, and 368 to MAP63, 368 to a liberal PaO_2 target, and 362 to a restrictive target. At all prespecified time points, DO_2 in MAP77 was higher compared with MAP63, with a cumulative treatment effect of 203 L (95% CI, 132–274) O_2 after 36 hours. VO_2 was higher in MAP77 after 36 hours, with a cumulative treatment effect of 21.9 L (95% CI, 5.8–38) O_2, compared with the MAP63 group.

CONCLUSIONS: Targeting a MAP of 77 mm Hg resulted in an overall increase in DO_2 and a smaller increase in VO_2 compared with a MAP target of 63 mm Hg. A higher PaO_2 target did not result in any difference in DO_2 or VO_2.

Key Words: blood pressure ■ Fick's principle ■ hemoglobin ■ out-of-hospital cardiac arrest ■ oxygen consumption ■ oxygen delivery ■ oxygen supply

The primary objective of cardiopulmonary resuscitation and critical care for resuscitated patients with out-of-hospital cardiac arrest (OHCA) who remain comatose after return of spontaneous circulation (ROSC) is to provide sufficient oxygen to meet the oxygen demand of the body.[1] Sufficient oxygen delivery (DO_2) to meet the demands in oxygen consumption (VO_2), is often guided by hemodynamic measurements and metabolic stabilization.[2] Subsequently, sufficient DO_2 is achieved through improved ventilation and cardiac output (CO), and thus end-organ perfusion is optimized by mechanical ventilation and the administration of vasoactive drugs.[3,4] If the demand for oxygen is not met, hypoperfusion will continue, potentially

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CLINICAL PERSPECTIVE

What Is New?

- A higher blood pressure target resulted in a significantly higher concentration of hemoglobin.
- Patients with more severe postcardiac arrest syndrome consumed more oxygen than patients with a smaller suspected ischemic insult.

What Are the Clinical Implications?

- Targeting a higher blood pressure target resulted in a significantly higher delivery of oxygen while affecting consumption only to a lesser extent, possibly representing the low deficit between delivery and consumption of oxygen in our cohort of patients with out-of-hospital cardiac arrest.
- Using either a restrictive or liberal target of oxygen pressure had no effect on delivery or consumption of oxygen.

Nonstandard Abbreviations and Acronyms

BOX	Blood Pressure and Oxygen Targets
CaO_2	O_2 content in arterial blood
CO	cardiac output
CPO	cardiac power output
CvO_2	O_2 content in venous blood
DO_2	oxygen delivery
NSE	neuron-specific enolase
OHCA	out-of-hospital cardiac arrest
PCAS	postcardiac arrest syndrome
VO_2	oxygen consumption

worsening ischemic brain injury, which remains the leading cause of death in patients with OHCA.[5,6] The mean arterial blood pressure (MAP) is commonly used as a target for real-time perfusion pressure. We have recently shown that targeting a higher MAP increases CO during the first 36 hours of admission, possibly increasing DO_2 and thus allowing for a higher VO_2.[7] Treating the patient with a higher oxygen target could also result in more oxygen being offered to cells and therefore possibly increase VO_2. Increasing DO_2 is in theory required only if there is a demand for more O_2 delivery and consequently an increase in VO_2. This also requires intact aerobic metabolism and mitochondrial function.

Postcardiac arrest syndrome (PCAS)[8] is known to cause mitochondrial injury.[6,9] Microcirculatory blood flow and uptake of oxygen at the cellular level may be impaired, causing further hypoxic insult despite sufficient DO_2.[10,11] Thus, mitochondrial dysfunction and the concomitant activation of pathogenic mechanisms inhibiting oxidative phosphorylation could affect VO_2 in patients with a greater ischemic insult.[12] Therefore, the ischemic insult that occurs until ROSC, the degree of systemic inflammation, and subsequent neurological injury could all affect VO_2, where knowledge of interactions is lacking. Thus, although augmenting DO_2 is a basic tenet in the treatment of patients with OHCA, the relationship between DO_2 and VO_2 has not yet been investigated in these patients.

Therefore, the aim of this study was to (1) determine whether DO_2 and VO_2 were affected by different MAP and PaO_2 targets and (2) to assess whether VO_2 correlated with inflammation (CRP [C-reactive protein]), and hypoxic injury (NSE [neuron-specific enolase]), and time to ROSC as markers of PCAS severity.

METHODS

Data can be made available upon reasonable request and pending regulatory approval.

Trial Design

The present study was a substudy of the BOX (Blood Pressure and Oxygen Targets) trial and the design and results of the main trial have been described elsewhere.[13,14] In summary, the BOX trial included consecutive patients >18 years of age, with OHCA of presumed cardiac cause, sustained ROSC, and classified as Glasgow Coma Scale score <9 on hospital arrival at 2 tertiary cardiac centers in Denmark. All patients were randomized upon arrival to the intensive care unit to a MAP target of 63 versus 77 mm Hg and a PaO_2 target of 9 to 10 versus 13 to 14 kPa.

Intervention

Interventions were initiated immediately after randomization. Invasive blood pressure monitoring was achieved with a patient-specific blood pressure module (Hewlett Packard/Philips M1006B Invasive Pressure module) for the duration of invasive blood pressure monitoring in the intensive care unit. These modules had been modified for trial use by adjusting the internal calibration to either report a blood pressure 10% higher than the actual blood pressure or a blood pressure 10% lower than the actual blood pressure, according to randomization. Thus, by targeting a MAP of 70 mm Hg in all patients, half the population would have an actual MAP of 63 mm Hg (MAP63) and the other half would have a MAP of 77 mm Hg (MAP77).[15] The MAP target was reached with fluid administration and catecholamine administration.

Noradrenaline was used in 92.9% of patients in MAP77 and 91.1% of patients in MAP63. Dopamine was used in 49.9% and 40.9% of patients in MAP77 and MAP63, respectively.[14]

Further, all patients underwent device-based fever control, targeting 36 °C during the initial 24 hours and 37 °C the next 12 hours if they remained in coma. Patients were also randomized to the duration of targeted temperature management effective only after 36 hours.[16] The present study is therefore limited to the first 36 hours, where all patients were treated equally regarding targeted temperature management.

All patients received 10 mL/h (1 kcaL/mL) in trophic enteral nutrition in accordance with local protocol and national guidelines.

Ethics

Danish legislation permits immediate inclusion of patients unable to provide consent in trials with delayed proxy consent from a legal representative, most often a relative, and a medical doctor with no relation to the trial. Informed consent from the patient was obtained if the patient regained consciousness.

The main study was registered at ClinicalTrials.gov, identifier: NCT03141099, and was approved by the Danish Regional Committee on Health and Research Ethics and Danish Data Protection Agency.

Data Collection, Measurements, and Calculations

A pulmonary catheter (PAC) was placed shortly after randomization, allowing for sampling of pulmonary artery blood and measuring central hemodynamics. At one research facility, a 7.5F triple lumen Swan-Ganz catheter, incorporating a thermistor and balloon tip manufactured by Edwards Lifesciences of Irvine, CA, USA, was employed. At the other research facility, a Continuous Cardiac Output PAC connected to a Vigilance II monitor, both manufactured by Edwards Lifesciences, was used.

Arterial blood was analyzed for hemoglobin, PaO_2, and arterial blood oxygen saturation. O_2 content in arterial blood (CaO_2) and in venous blood (CvO_2) was calculated using hemoglobin, arterial and pulmonary artery blood oxygen saturation, and PaO_2 and partial pulmonary artery oxygen pressure as shown in the following equation:

$$CaO_2 = \text{hemoglobin (mg/dL)} \times 10 \times 1.36 \times \text{arterial blood oxygen saturation (proportion)} + 0.0225 \times PaO_2 \text{ (kPa)}.$$

The same approach was used to calculate CvO_2:

$$CvO_2 = \text{hemoglobin (mg/dL)} \times 10 \times 1.36 \times \text{pulmonary artery blood oxygen saturation (proportion)} + 0.0225 \times \text{partial pulmonary artery oxygen pressure (kPa)}.$$

Arteriovenous difference was calculated as $CaO_2 - CvO_2$.

DO_2 was calculated as:

$$DO_2 = CaO_2 \times CO.$$

VO_2 was calculated as follows:

$$VO_2 = CO \times CaO_2 - CO \times CvO_2.$$

The rate of energy output of the heart was assessed by the cardiac power output (CPO), which was calculated by including the central venous pressure[17] in the formula:

$$\text{CPO (watt)} = ((\text{MAP} - \text{central venous pressure}) \times CO)/451$$

and the total energy produced by the heart (Joule (J) = Watt × seconds) as the integral/area under the curve (AUC) using the trapezoid method.

The difference in the parameters during the first 36 hours was assessed from PAC insertion and at 6, 12, 24, and 36 hours by both MAP and PaO_2 target intervention. In exploratory analyses the association between cumulated VO_2 during the first 24 hours (before the wakeup call) and time to ROSC, CRP on day 2, NSE on day 2, and survival status at 365 days was assessed.

Statistical Analysis

Baseline characteristics are reported as count (%). Continuous data are reported with median and interquartile range (IQR) (25th percentile to 75th percentile). Pearson's chi-square test, Fisher's exact test, and Mann–Whitney *U* test were used to test for between-group differences.

Hemoglobin, CaO_2, arteriovenous difference, CO, DO_2, VO_2, and CPO were assessed by a linear mixed model including fixed effects for the intervention and time point and a fixed intervention by time point interaction term and with an unstructured covariance pattern to account for repeated measurements on each study participant. Estimated marginal means of the parameters including a 95% CI are reported and used in the figures. The total DO_2, VO_2, and CPO were evaluated as the AUC using the trapezoid method, and missing values in this analysis were handled by a single imputation using the 'missForest' package in R.[18]

Possible interaction between the MAP target and PaO_2 target intervention on VO_2 was tested.

Similarly, VO_2 was assessed as total consumption of oxygen (L) by AUC in the first 24 hours by time to ROSC, CRP, and NSE grouped as ≥median or <median and survival status at 1 year.

In a subgroup analysis, we investigated whether cumulated 24-hour DO_2 was associated with higher risk for 1-year mortality according to time to ROSC grouped as the median for the 2 MAP targets in a logistic regression model categorized by MAP target.

In an additional subgroup analysis, we investigated whether patients with low or high VO_2 would particularly benefitted or harmed by a higher MAP target. Thus, patients were stratified within their respective MAP group as <median (low VO_2) and >median (high VO_2) totaling 4 groups where 1-year mortality was compared.

Pairwise comparisons between the groups of the repeated measurements were adjusted for multiple testing by the Benjamini–Hochberg method, thus mitigating the risk of false positives. Tested factors with a false discovery rate <0.05 were considered statistically significant.

Statistical analysis was performed using R Studio version R version 4.3.2.

RESULTS

In total, 789 patients were included in the BOX trial, of whom 730 (92.5%) had a PAC placed and were included in this study (flow chart, Figure S1). The median time from randomization to PAC insertion was 1.3 hours (IQR: 0.5–2.3 hours).

Table 1 summarizes the clinical and baseline characteristics of the included patients. The study population mainly comprises men (n=591, 81%) with predominantly witnessed cardiac arrest (n=618, 85%) with a shockable rhythm (n=653, 89%). Overall, the MAP77 (n=362), MAP63 (n=368), Restrictive (n=362), and Liberal (n=368) groups were well balanced in comorbidities and clinical factors regarding the cardiac arrest.

Oxygen Delivery and Consumption

Out of 5 possible measures (admission, 6, 12, 24, 36 hours), the mean±SD number of available DO_2 measurements was 4.05 (1.35), and for VO_2 this number was 3.50 (1.44). Missing data on VO_2 and DO_2 are shown by time since PAC insertion in Figure S2.

The underlying elements of DO_2: CO (previously published[7]) and CaO_2 increased during the initial 36 hours from PAC insertion in MAP77. Specifically, regarding

Table 1. Clinical and Baseline Characteristics of Patients Randomized to MAP77 or MAP63 and PaO_2 of 9–10 or 13–14 kPa

Characteristic	MAP		Oxygen	
	MAP77, N=362	MAP63, N=368	Liberal, N=368	Restrictive, N=362
Male sex, no. (%)	291 (80%)	300 (82%)	293 (80%)	298 (82%)
Age, y, median (IQR)	64 (55, 73)	65 (53, 72)	65 (55, 73)	63 (53, 72)
Diabetes, no. (%)	46 (13%)	55 (15%)	53 (14%)	48 (13%)
Heart failure, no. (%)	60 (17%)	65 (18%)	75 (20%)	50 (14%)
Hypertension, no. (%)	161 (44%)	173 (47%)	174 (47%)	160 (44%)
Chronic obstructive pulmonary disease, no. (%)	30 (8.3%)	27 (7.4%)	30 (8.2%)	27 (7.5%)
Ischemic heart disease, no. (%)	85 (23%)	72 (20%)	76 (21%)	81 (22%)
Witnessed cardiac arrest, no. (%)	310 (86%)	308 (84%)	313 (85%)	305 (84%)
Initial rhythm shockable, no. (%)	329 (91%)	324 (88%)	330 (90%)	323 (89%)
Time to return of spontaneous circulation, median (IQR)	20 (12–27)	17 (11–25)	18 (12–25)	19 (12–26)
Left ventricular ejection fraction at admission, median (IQR)	35 (25–45)	35 (25–45)	35 (20–45)	35 (25–50)
Lactate at admission, median (IQR)	5.0 (2.9–8.1)	4.7 (2.8–7.3)	5.0 (2.8–7.9)	4.7 (2.8–7.7)
pH at admission, median (IQR)	7.24 (7.15–7.29)	7.24 (7.17–7.30)	7.24 (7.16–7.30)	7.24 (7.16–7.29)
Po_2 at admission, median (IQR)	10 (7–20)	11 (7–19)	11 (7–20)	10 (7–19)
Pco_2 at admission, median (IQR)	6.20 (5.50–7.20)	6.30 (5.70–7.40)	6.30 (5.60–7.40)	6.30 (5.60–7.20)
Acute coronary angiography, no. (%)	336 (93%)	333 (90%)	338 (92%)	331 (91%)
Acute percutaneous coronary intervention, no. (%)	156 (43%)	148 (40%)	144 (39%)	160 (44%)
ST-segment–elevation myocardial infarction, no. (%)	154 (43%)	165 (45%)	158 (43%)	161 (44%)
Hemoglobin at admission, median (IQR)	8.80 (8.10–9.50)	8.90 (8.10–9.50)	8.90 (8.08–9.50)	8.90 (8.20–9.50)

IQR indicates interquartile range; and MAP, mean arterial blood pressure.

CaO_2, the MAP77 group saw a significant increase in the concentration of hemoglobin, when compared with MAP63. The greatest difference in hemoglobin was seen after 6 hours: MAP77: 8.48 mmoL/L (95% CI, 8.37–8.60 mmoL/L) versus MAP63: 8.16 mmoL/L (95% CI, 8.05–8.27 mmoL/L), false discovery rate corrected *P* value=0.0004 (Figure 1).

MAP77 received a median of 6009 (IQR: 4726–7495) mL of fluids during the initial 36 hours after PAC insertion, whereas MAP63 received a median of only 5526 (IQR: 4408–6744) mL, *P*<0.0001. There was no difference in fluid administration between PaO_2 targets, *P*=0.77. Receiving more or less than MAP target-specific median volume of fluids was not associated with DO_2 or VO_2 in the first 36 hours (both *P*>0.05).

Temporal changes in DO_2 and VO_2 during the initial 36 hours after PAC insertion by randomization are shown in Table 2 and Figures 2 and 3, respectively, including between-group false discovery rate-corrected comparisons. In all groups, DO_2 and VO_2 increased throughout the initial 36 hours from PAC insertion.

In the first 36 hours after PAC insertion, cumulated DO_2 in the MAP77 group was 203 L (95% CI, 132–274 L O_2) or 12.8% (95% CI, 8.1–17.7) higher than in the MAP63 group, with 1785 L O_2 (95% CI, 1735–1835 L O_2) versus 1582 L O_2 (95% CI, 1532–1632 L O_2) in the MAP77 and MAP63 groups, respectively, *P*<0.0001 (Figure 2, Table 3). The MAP77 group had a higher DO_2 compared with MAP63 at all time points (all false discovery rate corrected between-groups *P* value <0.05, Table 2).

The cumulated VO_2 was also higher with a total of 21.9 L (95% CI, 5.8–38 L O_2) or 4.9% (95% CI, 1.2–8.6) more O_2 consumed in the MAP77 group in the first 36 hours compared with patients with the MAP63 target, *P*=0.0078 (total VO_2: MAP77: 473 L O_2 [95% CI, 462–485 L O_2] versus MAP63: 451 L O_2 [95% CI, 440–463 L O_2]) (Table 3). The increased VO_2 was driven by a higher CO but only an initial lower arteriovenous oxygen difference (ie, less oxygen was extracted from the blood per mL) in MAP77 compared with MAP63 (Figure S3). Looking at individual time points, the VO_2 was not statistically significantly higher in the MAP77 group compared with MAP63 at any time point following correction for multiple testing (Table 2 and Figure 3).

The total DO_2 and VO_2 during ther first 36 hours were also similar between the Restrictive and Liberal oxygen target group (total DO_2, Liberal: 1677 L O_2 [95% CI, 1626–1728 L O_2] versus Restrictive: 1688 [95% CI, 1637–1739 L O_2]), not significant, and total VO_2: Liberal: 455 (95% CI, 444–467 L O_2) versus Restrictive: 469 L O_2 (95% CI, 458–481 L O_2), not significant.

Possible interactions between the 2 interventions on accumulated DO_2 and VO_2 were investigated by linear regression through possible change in the point estimate and by the *P* value of the interaction term. The *P* value of the interaction term MAP target × PaO_2 target for AUC DO_2 was 0.90, for AUC VO_2 *P*=0.30, and for AUC CPO *P*=0.60.

Cardiac Power Output and Energy Exerted by the Heart

CPO increased over time for all groups and was significantly higher in the MAP77 compared with MAP63

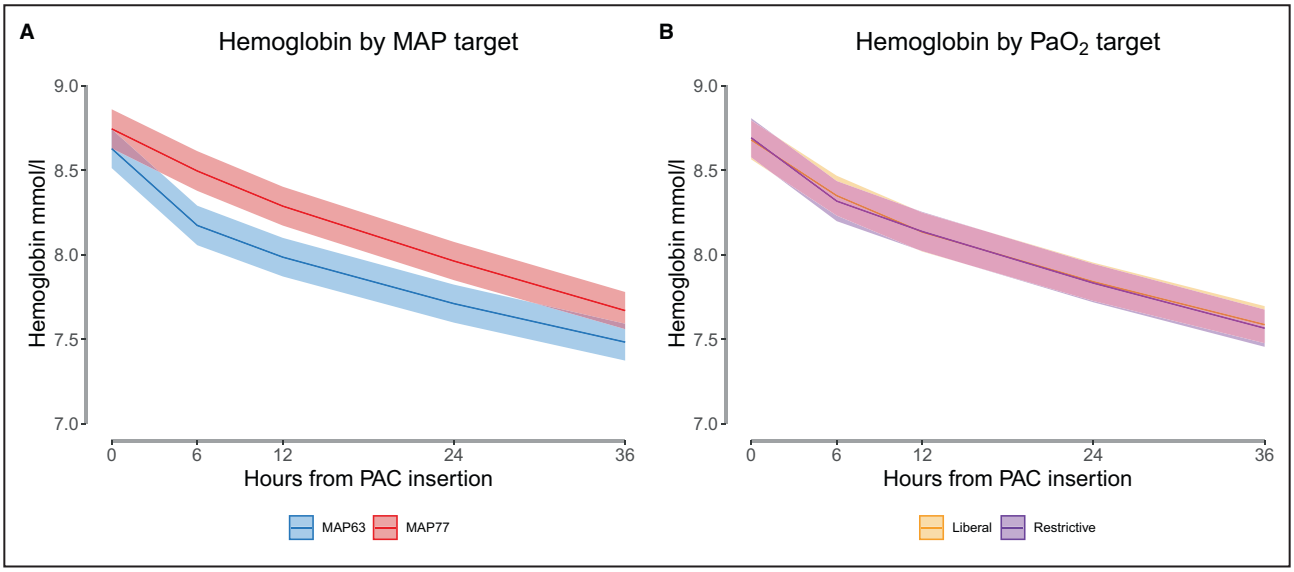

Figure 1. Temporal changes in hemoglobin concentration in patients with OHCA (n=730) randomized to (A) a mean arterial blood pressure target of 63 mm Hg (MAP63) or 77 mm Hg (MAP77) and (B) a PaO_2 target of 9-10 vs 13-14 kPa.
Line indicates estimated marginal means with 95% CI. Means were calculated from a linear regression mixed model analysis. MAP indicates mean arterial blood pressure; OHCA, out-of-hospital cardiac arrest; and PAC, pulmonary artery catheter.

Table 2. Temporal Changes in Oxygen Delivery and Consumption in n=730 Patients With OHCA by Randomization During the Initial 36 Hours

MAP intervention	PAC insertion	6 hours	12 hours	24 hours	36 hours	Oxygen intervention	PAC insertion	6 hours	12 hours	24 hours	36 hours
Oxygen delivery, mLO_2/min						Oxygen delivery, mLO_2/min					
MAP63	619 (590–649)	622 (595–649)	690 (662–718)	755 (725–784)	915 (875–954)	Liberal	641 (611–671)	674 (646–701)	735 (707–764)	816 (786–847)	937 (898–976)
MAP77	705 (675–735)	733 (706–760)	786 (758–814)	863 (834–893)	991 (952–1029)	Restrictive	683 (653–713)	681 (654–709)	741 (712–769)	801 (771–832)	968 (929–1008)
Difference	85 (43–127)	111 (73–149)	96 (57–136)	109 (67–151)	76 (21–131)	Difference	43 (0–85)	8 (–32–47)	5 (–35–46)	–15 (–58–28)	31 (–25–86)
Adjust *P* difference	<0.001	<0.001	<0.001	<0.001	0.007	Adjust *P* difference	0.25	0.80	0.80	0.80	0.69
Oxygen consumption, mLO_2/min						Oxygen consumption, mLO_2/min					
MAP63	197 (187–208)	197 (190–205)	203 (195–210)	209 (201–217)	236 (225–247)	Liberal	194 (183–205)	199 (191–206)	202 (194–210)	214 (206–222)	239 (228–249)
MAP77	204 (193–214)	212 (204–219)	209 (201–217)	222 (214–230)	251 (240–262)	Restrictive	207 (196–217)	211 (203–219)	210 (202–218)	217 (209–225)	249 (238–259)
Difference	6 (–8–21)	14 (3–25)	6 (–5–17)	13 (2–24)	15 (0–30)	Difference	13 (–2–28)	12 (1–23)	8 (–3–19)	4 (–8–15)	10 (–5–25)
Adjust *P* difference	0.4	0.06	0.32	0.06	0.08	Adjust *P* difference	0.24	0.19	0.24	0.52	0.24

Estimated marginal means (95% CI), *P* values are false discovery rate corrected; a *P* value of <0.05 is considered statistically significant.
MAP indicates mean arterial blood pressure; OHCA, out-of-hospital cardiac arrest; and PAC, pulmonary artery catheter.

at all time points (Figure 4). The total energy output by the heart during the initial 36 hours was 27% (95% CI, 22–32) higher in MAP77 compared with MAP63 (93.4 kJ [95% CI, 91.1–95.8 kJ]) versus 73.6 kJ (95% CI, 71.2–75.9 kJ). A liberal or restrictive PaO_2 target did not affect CPO or energy output by the heart.

The Relationship Between VO_2 and DO_2 and Time to ROSC, CRP, and NSE in the First 24 Hours

The median time to ROSC was 18 minutes (IQR 12–26). The median CRP at day 2 was 165 mg/L (IQR: 114–222) (n=50) and the median NSE at day 2 was 18 ng/mL (IQR: 11–35) (n=606).

No difference in DO_2 was found according to time to ROSC > median. Patients with NSE > median had a higher DO_2 than patients with NSE < median. No significant differences in DO_2 were observed between patients stratified according to above or below median CRP (Table 4). Temporal changes in VO_2 by time to ROSC, CRP, and NSE are shown in Figure 5. VO_2 was highest in patients with a longer time to ROSC, high CRP, and higher NSE levels. In patients with time to ROSC > median, a total disparity of 30.4 (95% CI, 14.2–46.5) L O_2 was observed when compared with patients with time to ROSC < median. After the initial 24 hours, patients with high NSE consumed a total of 33.4 L O_2 (95% CI, 15.7–51.1) more than patients with low NSE. During the same timeframe, patients with CRP > median exhibited a higher VO_2, with a difference of 27.7 L O_2 (95% CI, 7–30), when compared with < median CRP. A trend with lower VO_2 was observed in patients with high CRP and NSE who died at or before day 2 and thus did not have available CRP and NSE levels (Figure S4).

Survival

Survival assessed at 365 days from OHCA was not associated with DO_2 or VO_2 in the first 24 hours (Figures S5, S6).

In patients with time to ROSC < median, increasing DO_2 was associated with a better prognosis (*P*=0.03) (Figure S7). This association was not observed in patients with a longer time to ROSC (*P*>0.05).

In the subgroup analysis of patients stratified into low and high VO_2 within their respective MAP group, we found no association between augmenting DO_2 (higher MAP target) and a low/high VO_2.

DISCUSSION

In this substudy of the BOX trial, we investigated the effect of blood pressure and oxygen targets on DO_2 and VO_2 in survivors of OHCA who were comatose.

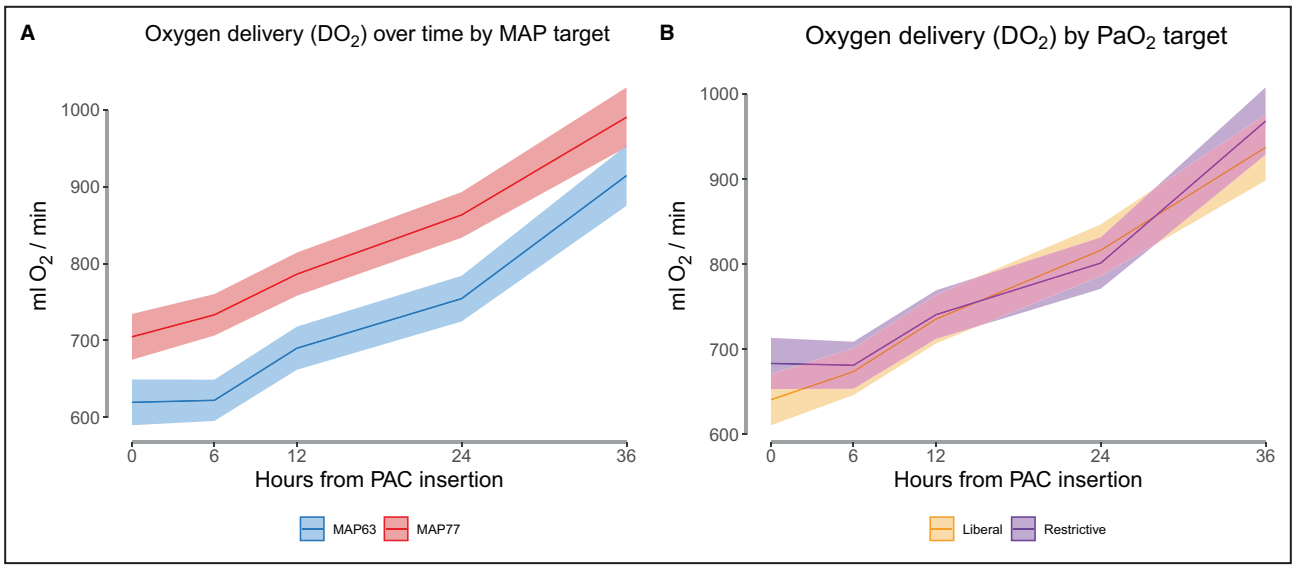

Figure 2. Temporal changes in oxygen delivery in patients with OHCA (n=730) randomized to (A) a mean arterial blood pressure target of 63 mm Hg (MAP63) or 77 mm Hg (MAP77) and (B) a PaO_2 target of 9–10 vs 13–14 kPa.
Line indicates estimated marginal means with 95% CI. Means were calculated from a linear regression mixed model analysis. MAP indicates mean arterial blood pressure; OHCA, out-of-hospital cardiac arrest; and PAC, pulmonary artery catheter.

To our knowledge, this is the largest clinical study investigating DO_2 and VO_2 in patients resuscitated from OHCA. Patients randomized to a *high* blood pressure (MAP77 mm Hg) exhibited a higher DO_2, through both an increased CO and a higher concentration of hemoglobin. A higher VO_2 was also observed in patients targeting a MAP of 77 mm Hg, compared with patients randomized to a MAP target of 63 mm Hg. Patients treated with a liberal PaO_2 target had a similar DO_2 and VO_2 compared with a restrictive PaO_2 target.

Interventions aiming to optimize cerebral blood flow (augmenting MAP[14]) or hypercapnia (TAME[19] [Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest]) or increasing arterial oxygen content (BOX[13]) have not improved outcomes. Though the present study investigated systemic DO_2 in contrast

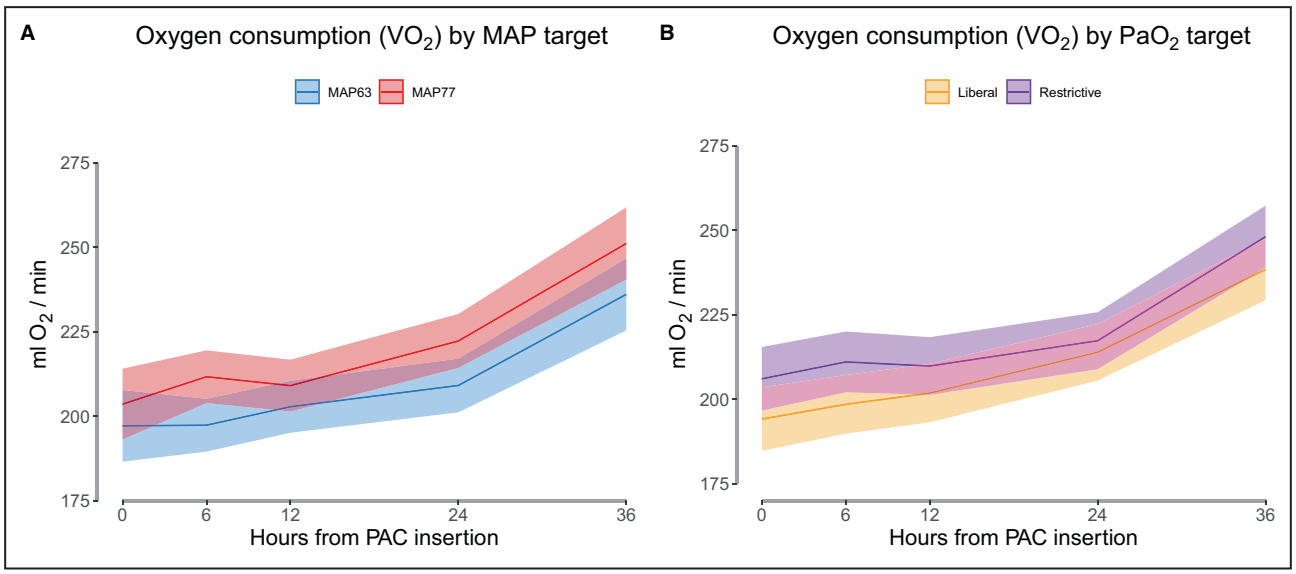

Figure 3. Temporal changes in oxygen consumption in patients with OHCA (n=730) randomized to (A) a mean arterial blood pressure target of 63 mm Hg (MAP63) or 77 mm Hg (MAP77) and (B) a PaO_2 target of 9–10 vs 13–14 kPa.
Line indicates estimated marginal means with 95% CI. Means were calculated from a linear regression mixed model analysis. MAP indicates mean arterial blood pressure; OHCA, out-of-hospital cardiac arrest; and PAC, pulmonary artery catheter.

Table 3. Total Oxygen Consumption and Delivery in Patients Resuscitated After OHCA (n=730) by MAP and PaO_2 Targets in the First 36 Hours

	Oxygen delivery, L	Oxygen consumption, L
MAP63	1582 (1532–1632)	451 (440–463)
MAP77	1785 (1735–1835)	473 (462–485)
Difference	203 (132–274)	21.9 (5.8–38)
P difference	<0.0001	0.0078
Restrictive	1688 (1532–1632)	469 (458–481)
Liberal	1677 (1626–1728)	455 (444–467)
Difference	10.6 (–61.9–83)	14.2 (–1.9–30.4)
P difference	0.77	0.084

Unadjusted group-specific mean (95% CI) total oxygen consumption and delivery first 36 hours. No interaction was found between the interventions.

MAP indicates mean arterial blood pressure; and OHCA, out-of-hospital cardiac arrest.

Table 4. Total Oxygen Consumption and Delivery by CRP, NSE, and Time to ROSC in Patients (n=730) Resuscitated After OHCA

	Oxygen delivery, L	Oxygen consumption, L
CRP < median	1690 (1635–1744)	450 (438–462)
CRP > median	1726 (1672–1780)	478 (466–490)
Difference	36.6 (–40.1–113)	27.7 (10.7–44.6)
P difference	0.35	0.0014
NSE < median	1623 (1567–1679)	444 (432–457)
NSE > median	1722 (1666–1777)	478 (465–490)
Difference	98.8 (20–178)	33.4 (15.7–51.1)
P difference	0.014	0.0002
Time to ROSC < median	1648 (1596–1701)	447 (435–458)
Time to ROSC > median	1721 (1670–1773)	477 (466–489)
Difference	72.7 (–0.57–146)	30.4 (14.2–46.5)
P difference	0.051	0.0002

Mean (95% CI) total oxygen consumption and delivery first 24 hours. CRP indicates C-reactive protein at day 2; NSE, neuron-specific enolase at 48 hours; OHCA, out-of-hospital cardiac arrest; and ROSC, return of spontaneous circulation.

to cerebral DO_2, most patients had a DO_2 during the study period above a critical DO_2 level[20] with a "low" MAP target of 63 mm Hg and a restrictive PaO_2 target. Thus, augmenting oxygen delivery in patients experiencing OHCA might provide only minor benefits.

The increase in VO_2 during the first 36 hours, regardless of treatment targets observed in this study, follows the pattern described in other smaller studies of patients with OHCA.[21,22] The changes observed likely reflect that cellular and mitochondrial uptake of oxygen are initially impaired, thus reducing oxidative phosphorylation and leading to a lower VO_2.[10,23] Furthermore, DO_2 was also observed to increase throughout the initial 36 hours, possibly relating to the initial stunning of the heart and later improvement.[24] The sudden increase after 24 hours likely also reflects a relation to the wakeup call, thus increasing

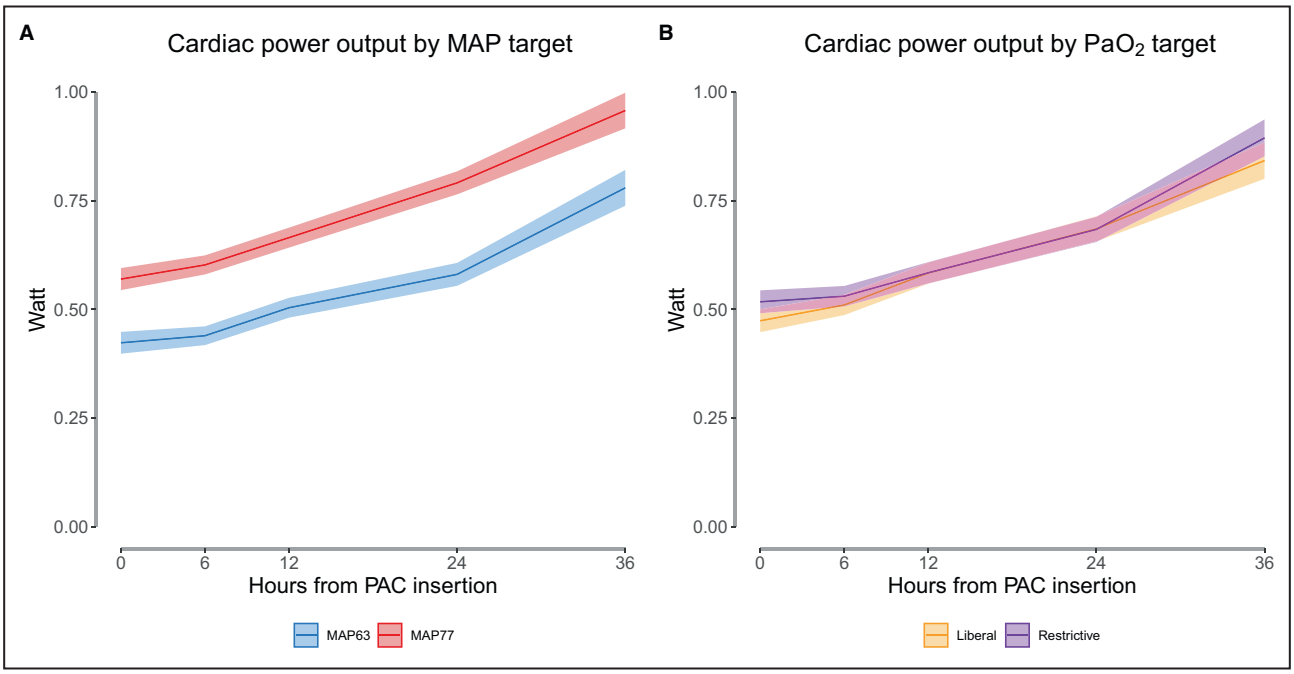

Figure 4. Temporal changes in cardiac power output in OHCA patients with OHCA (n=730) during the initial 36 hours after PAC insertion randomized to (A) a blood pressure target of 63 or 77 mm Hg and (B) a PaO_2 of 9-10 versus 13-14 kPa

Line indicates estimated marginal means with 95% CIs. Means were calculated from a linear regression mixed model analysis. MAP indicates mean arterial blood pressure; OHCA, out-of-hospital cardiac arrest; and PAC, pulmonary artery catheter.

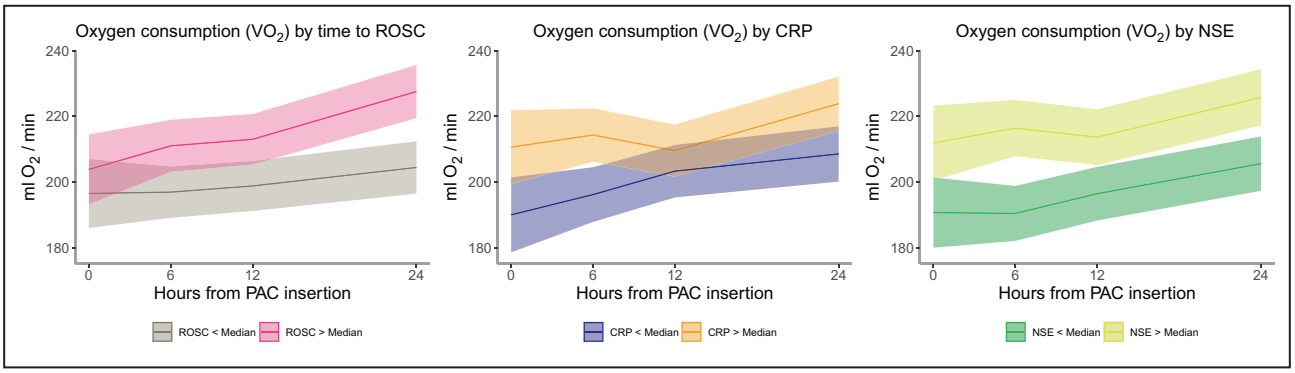

Figure 5. Temporal changes in oxygen consumption in patients with OHCA (n=730) with (A) time to ROSC, (B) CRP, and (C) NSE above or below median.

Line indicates estimated marginal means with 95% CI. Means were calculated from a linear regression mixed model analysis. CRP indicates C-reactive protein; NSE, neuron-specific enolase; OHCA, out-of-hospital cardiac arrest; and ROSC, return of spontaneous circulation.

the metabolic rate. Targeted temperature management and degree of sedation have been suggested to affect VO_2 by reducing shivering and thus the metabolic rate.[21,25] In the present study, all patients underwent targeted temperature management at 36 °C and were sedated for the first 24 hours.

Although higher MAP was associated with higher DO_2, these findings suggest that VO_2 was not increased to the same degree. The increase in the offer of oxygen on the microvascular scale after severe cellular damage may be disrupted by reduced uptake and diverted flow of oxygen.[26,27] It also remains possible that the cells might be offered more oxygen than needed. The consequence of increasing DO_2 by increasing MAP is likely increased cardiac workload, resulting in increased myocardial oxygen consumption. Indeed, as an indicator hereof, we found a 27% higher energy output by the heart in patients targeting a higher MAP (Figure 4). In healthy individuals' hearts, ≈25% of consumed oxygen is converted to external work, and 1 mL O_2 consumed provides roughly 20 J.[28] This would indicate that by increasing the MAP target from 63 to 77 mm Hg, patients exerted 21.900 mL O_2 × 20 J/mL=446 kJ more in the first 36 hours, of which the heart used around 18% (19.9 kJ [difference in external work between MAP groups] × 4)/446 kJ), thereby lessening the effect of the additional DO_2. This is only a rough calculation as the actual myocardial oxygen consumption is unknown and the efficiency is very likely affected in patients with PCAS. One could argue that this is a waste of energy supply at the cost of strain on the heart.

When assessing DO_2 by the PaO_2 target, the supply of oxygen to cells was not enhanced, despite a higher PaO_2. This may be because the hemoglobin molecule is saturated with oxygen and the physically dissolved oxygen in the blood remains just a negligible part of CaO_2.

Our study showed that patients randomized to MAP77 had a significantly higher concentration of hemoglobin compared with the MAP63 group. Noradrenaline, in some cases followed by low-dose dopamine, was the vasopressor and inotropic drug used to achieve a higher MAP in this trial,[14] and the effect on hemoglobin concentration is seen shortly after the intervention is initiated, indicating that treatment with noradrenaline affects hemoglobin concentration. This effect was seen despite MAP77 having received significantly more fluid than MAP63. Veins carry alpha receptors, allowing for noradrenaline-mediated venous constriction.[29] Vasoconstriction on the venous side reduces overall blood volume, possibly providing a higher concentration of hemoglobin.[30] Activation of the sympathetic nerves is known to contract the spleen.[31,32] Because the splenic blood reservoir has a higher concentration of hemoglobin, this autotransfusion could also be a part of the explanation of hemoconcentration in patients treated to a higher MAP target.[33,34]

We observed an association with several markers of more severe PCAS, such as a large ischemic insult (time to ROSC), a higher degree of inflammation (CRP) and neurological injury (NSE), and oxygen consumption in the first 24 hours. We chose 24 hours as it was before the wakeup call, thus ensuring that all patients were still under sedation and CRP and NSE were evaluated on day 2 due to delayed kinetics[35] and high predictive value, respectively.[36] The ischemic insult that occurs before and during no-flow and low-flow periods of cardiopulmonary resuscitation and the ensuing reperfusion of hypoxic tissue causes brain injury.[5] Further, the combination of hypotension and hypoxia, often seen in patients resuscitated from OHCA, has been associated with a larger degree of neurological injury.[37] Although we observed an association between cerebral injury and VO_2, the present

study measured systemic consumption of oxygen and not cerebral specific consumption of oxygen. The importance of the dissolved oxygen in the blood and its effect on the brain is uncertain and not investigated in this study. However, although securing sufficient delivery of oxygen to the brain has obvious positive implications, interventions regarding PaO_2 and MAP targets were investigated in the original BOX trial where results on neurological injury were neutral. Though a higher DO_2 was not associated with overall mortality, a subgroup analysis found an association between improved outcome and higher DO_2 in patients with shorter duration of the cardiac arrest. This observation likely reflects that the outcome in those patients with an expected smaller brain injury is more dependent on hemodynamic stability when compared with patients with a larger neurological injury.

Fewer observations were available in patients dying before 24 hours, which could introduce bias and possibly overestimate VO_2 in patients who would have presented with high NSE or CRP levels at day 2 if alive. We did observe higher VO_2 in patients with a longer time to ROSC, likely indicating that the relatively few patients in a very unstable circulatory condition have lower VO_2, but in the majority of patients, a larger ischemic insult does not associate with a lower VO_2 in this cohort. This points to the complexity of using VO_2 to guide therapy and as a prognostic tool in cohorts of patients with OHCA.

LIMITATIONS

Calculations of VO_2 were done using Fick's principle, which is based on hemodynamic assumptions. Indirect calorimetry, although time consuming, measures VO_2 directly and would be considered a more accurate approach when compared with the mathematical approximation that is Fick's principle. Though this is the largest and most comprehensive analysis of VO_2 in postcardiac arrest care, missingness was likely not random and the sensitivity analyses indicated that the results might not apply to patients who die within the first 1 to 2 days. NSE was used as a surrogate marker of neurological injury as it is recommended for neuroprognostication in the latest guidelines; however, other markers or modalities, such as electroencephalography or neurofilament light chain, could have provided a more comprehensive assessment of the neurological injury. The study included patients with OHCA of presumed cardiac cause and the proportion of bystander cardiopulmonary resuscitation was high, possibly limiting the generalizability.

CONCLUSIONS

Targeting a higher MAP resulted in a significant increase in hemoglobin and systemic oxygen delivery, whereas consumption of oxygen was only increased to a lesser extent. Targeting either a low or high PaO_2 did not lead to an increased delivery or consumption of oxygen. Patients with more severe PCAS had higher VO_2.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S7

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