Intravascular Volume Administration: A Contributing Risk Factor for Intracranial Hemorrhage During Extracorporeal Membrane Oxygenation?
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Intravascular Volume Administration: A Contributing Risk Factor for Intracranial Hemorrhage During Extracorporeal Membrane Oxygenation?

Amerik C. de Mol, MD, Luella C. Gerrits, MD, Arno F. J. van Heijst, MD, PhD, Huub Straatman, MSc, Frans H. J. M. van der Staak, MD, PhD, Kian D. Liem, MD, PhD

Intracranial Hemorrhage (ICH) is the most devastating complication during va-ECMO, but there are no previous data about volume administration and ICH during ECMO.

ABSTRACT

OBJECTIVE. The objective of this study was to determine the relationship between the frequency and total volume of intravascular volume administration and the development of intracranial hemorrhage during venoarterial extracorporeal membrane oxygenation.

METHODS. In a retrospective, matched, case-control study, 24 newborns who developed an intracranial hemorrhage during venoarterial extracorporeal membrane oxygenation treatment were compared with 40 control subjects. Both groups were analyzed for gestational age, gender, race, Apgar scores at 1 and 5 minutes, birth weight, cardiopulmonary resuscitation before venoarterial extracorporeal membrane oxygenation, age at the start of treatment, duration of treatment, worst arterial blood gas sample preceding treatment, activated clotting time values, need for platelet transfusions, mean blood pressure, and the use of inotropics and steroids before the treatment. For both groups, total number and volume of intravascular infusions of normal saline, pasteurized plasma protein solution, erythrocytes, and platelets during the first 24 hours of treatment were determined. Variables were analyzed in their relationship to intracranial hemorrhage by using univariate and multivariate conditional logistic regression.

RESULTS. The only statistically significant difference in patient characteristics between the case patients and control subjects was arterial blood gas values. Newborns who developed intracranial hemorrhage during the treatment received both a statistically significantly higher number and a statistically significantly higher total volume of intravascular volume administrations compared with control patients. After adjustment for pH, PaCO₂, and Pao₂ in the multivariate analysis, we found a significant relation between the development of intracranial hemorrhage and >8 infusions or >300 mL of volume infusion in the first 8 hours and >10 infusions in the first 24 hours of treatment.

CONCLUSIONS. The number and total volume of intravascular volume administration in the first 8 and 24 hours of venoarterial extracorporeal membrane oxygenation treatment are statistically significantly related to the development of intracranial hemorrhage.

Since Bartlett and colleagues in 1976 treated the first newborn successfully with venoarterial extracorporeal membrane oxygenation (va-ECMO), ECMO has become a rescue therapy for neonates with severe but potentially reversible respiratory failure when maximal conventional therapy has failed. Without ECMO, the mortality rate is high. More than 22 000 neonates have been treated with ECMO, 15 000 of whom were treated with va-ECMO, with an overall survival rate of 80%. Although ECMO has increased survival, the occurrence of hemorrhagic and ischemic cerebral lesions, resulting in future neurologic and neurodevelopmental dysfunction, are major complications. Imaging studies revealed intracranial hemorrhage (ICH) or ischemic abnormalities in 10 up to even 52% of the patients. The cause of ICH during va-ECMO treatment is probably multifactorial and might be...
determined by pre-ECMO– as well as ECMO-related
events or conditions.\textsuperscript{10} Optimizing neurologic outcome
remains 1 of the priorities in ECMO research. The pop-
ulation at greatest risk for ICH, however, is not clearly
defined. Hardart et al\textsuperscript{11,12} determined gestational age,
postconceptional age, acidosis, sepsis, coagulopathy, and
treatment with epinephrine as independent factors as-
associated with ICH in neonates who were treated with
ECMO. A study by Dela Cruz et al\textsuperscript{13} demonstrated that
an elevated activated clotting time (ACT) and low plate-
let counts that required transfusion were statistically
associated with an increase in the development of ICH.
Hirthler et al\textsuperscript{14} reviewed that instability of ACT and
platelet count are early predictors of ICH. Finally, lactate
before ECMO treatment was found to be a useful marker
for the development of ICH during ECMO.\textsuperscript{15}

Especially during the first days of ECMO, intravascular
volume administration is regularly required. One reason
is the occurrence of bladderbox alarms, as a sign of
inadequate venous drainage from the right atrium to
maintain the required flow of the ECMO system, which
is aimed to realize adequate oxygenation of the patient.
In a reaction, volume administration is often given when
other causes of bladderbox alarms are ruled out. Next to
this anemia or thrombocytopenia are reasons to add
volume with blood products. From our clinical experi-
ence, we had the impression that neonates who required
frequent volume administration during the first days of
the va-ECMO treatment developed ICH more fre-
quently. The objective of this study was to investigate
whether there is a relationship between intravascular
volume administration and the occurrence of ICH in the
neonate during treatment with va-ECMO.

METHODS
From September 1989 through November 2005, 236 new-
borns (64% boys, 36% girls) were treated with va-ECMO
at the Radboud University Nijmegen Medical Centre.
Overall survival rate was 77%, and ICH occurred in 25
(11%) patients. All patients with ICH were analyzed to
participate in a matched case-control study. One patient
was excluded because of congenital abnormality of the
heart, so 24 patients with ICH were included in the study.
ICH was diagnosed by cerebral ultrasound, performed daily
during the ECMO treatment (n[r] = 18), by computed
tomography (CT), or by MRI in the period directly after
decannulation (n = 6). The 24 newborns who developed
ICH related to va-ECMO treatment (case patients) were
matched with 40 patients who did not develop ICH (con-
trol subjects). Each pair of 1 case patient and 1 or 2 control
subjects was matched for diagnosis, gestational age (±1
week), and birth weight (±500 g). For statistical reasons,
we aimed for 2 control subjects for each case patient. When
>2 possible candidates were available, the patients whose
dates of birth were closest to that of the case patient were
selected as control subjects. Newborns were excluded from
the study when there were congenital abnormalities
other than congenital diaphragmatic hernia; a second
ECMO treatment, ICH before the initiation of ECMO; or
coaugulation disorders as screened for by the determination
of prothrombin time, activated partial thromboplastin
time, and platelet count. Cerebral ultrasound, none of
them showing ICH, was performed for all patients, case
patients and control subjects, before the ECMO treatment.
Before the initiation of ECMO, informed consent from the
parents was obtained, and all case patients and control
subjects met institutional criteria for ECMO treatment,
which did not change during the study period. All patients
were treated with va-ECMO. The ECMO circuit itself con-
sisted of a custom-packed ¼-in flexible polyvinylchloride
tubing (Baxter, Uden, Netherlands) with a silicone reser-
voir, the bladderbox (Seabrook Medical System, Værløse,
Denmark), a 0.6-m² membrane oxygenator (Scimed Life
Systems, Minneapolis, MN), a heat exchanger (Cincinnati
Sub Zero, Cincinnati, OH), and a roller pump (Polystan
A/S, Copenhagen, Denmark).

A loading dose of heparin was given before cannulation
to achieve an ACT of >300 seconds. After this, hepariniza-
tion was checked every hour by measurement of the ACT
aiming for values between 200 and 220 seconds (Hemo-
chron). During the course of ECMO, plasma transfusions
were given to maintain a platelet count >80 000/mm³.
Erythrocyte transfusions were given to maintain a hemo-
globin level >8.0 mmol/L and a hematocrit value >0.40
L/L. Hemoglobin level and platelet count were determined
every 4 hours. Normal saline (NaCl 0.9%) and pasteurized
plasma protein solution (albumin 3.8%) were used to re-
store the ECMO flow after bladderbox alarms caused by
insufficient blood drainage from the right atrium.

Cerebral ultrasound imaging through the anterior
fontanel (Philips HDI-3000, Ultrasound, Inc, Bothell,
WA) was performed daily to check for ICH. Images were
interpreted by the neonatologist and the pediatric neu-
rologist. After decannulation, CT or MRI was performed
on all patients and analyzed by the neuroradiologists.

To check the matching procedure and possible differ-
ences between the case patients and the control subjects,
both groups were analyzed for gestational age, gender,
race, Apgar scores at 1 and 5 minutes, birth weight, car-
diopulmonary resuscitation (CPR) before ECMO, age at
the start of ECMO, duration of ECMO treatment, survival,
worst arterial blood gas sample in the 6 hours preceding
ECMO, number and volume of required thrombocyte
transfusions, ACT value after the loading dose at the start of
ECMO, mean of ACT and mean blood pressure values as
well as the coefficient of variation for ACT and mean blood
pressure during the first 8 and 24 hours of ECMO, and the
use of inotropics (dopamine, dobutamine, epinephrine,
norepinephrine) and steroids before the start of ECMO.

To investigate the relationship between intravascular
volume administration and the occurrence of ICH, we
analyzed the number and volume of intravascular infu-
sions of normal saline, pasteurized plasma protein solu-
tion, erythrocytes, and platelets during the first 8 and 24
hours of ECMO treatment. Data were collected from the
international Extracorporeal Life Support Organization
forms, patient files, and patient medical checklists in
which physiologic parameters, laboratory results, and
ACT values were written down every hour and all vol-
ume administrations are registered.

Statistical analysis was performed by using SPSS 13.0
(IBM Inc, Chicago, IL). Patient characteristics were an-
alized by Student’s t tests for comparison of means (P < .05) and χ² tests (P < .05) for dichotomized characteristics. Univariate and multivariate testing of variables in their relation to ICH was performed by use of conditional logistic regression. For several variables, the cutoff points for which dichotomization of the variable leads to a statistically significant odds ratio (OR) at univariate analysis were determined by stepwise changing the segregation value for dichotomization. Steps were 0.1 for pH, 5 mm Hg for PaCO₂ and PaO₂, 100 mL for the volume of infusions, and 1 for the number of infusions. Variables that were found to have a significant relationship with the development of ICH in the univariate analysis were further used in the multivariate conditional logistic regression. ORs and 95% confidence intervals (CIs) were determined. Because CPR, gestational age, and age at the start of ECMO are generally considered to be important in their relation to ICH, we performed a univariate as well as a multivariate analysis for these terms. In the latter, the outcome for volume administration was corrected for each separate parameter, CPR, gestational age, and age at the start of ECMO.

RESULTS

All 24 newborns who developed an ICH during va-ECMO treatment could be matched with 1 or 2 control patients with the same primary diagnosis. Primary diagnoses for the case patients in this study were as follows: congenital diaphragmatic hernia in 8 (33%), sepsis in 8 (33%), meconium aspiration syndrome in 5 (21%), and primary pulmonary hypertension in 3 (13%). The other matching parameters used (gestational age and birth weight) were not significantly different between the case patients and control subjects (Table 1). Maximum time span between a case patient and his or her control subject(s) was 8 months. In this study, we found the following types of ICH: parenchymal in 10 (42%), intraventricular in 9 (38%), subependymal in 3 (13%), petechial in 1 (4%), and in the posterior fossa in 1 (4%). Of these 24 cases of ICH, 18 were diagnosed by cerebral ultrasound during va-ECMO and 6 were diagnosed by either CT or MRI after decannulation. Of the 18 cases of ICH on cerebral ultrasound, 8 (44%) were demonstrated within 24 hours after the start of va-ECMO and 14 (78%) within 72 hours. Also, for other than the matching variables, we found no statistically significant differences in patient characteristics, except for pH and survival (Table 1). Next to these characteristics, we found no significant differences in ACT values, platelet requirements, blood pressures, the use of inotropics and steroids, or race of the patients.

At dichotomization, we found the following statistically significant values in the univariate conditional logistic regression for the worst arterial blood gas samples in the 6 hours preceding the ECMO treatment in relation to the development of ICH: pH ≤7.3, PaCO₂ ≥45 mm Hg, and PaO₂ ≤50 mm Hg (Table 2). These parameters were further used in the multivariate conditional logistic regression.

Single infusions of intravascular volume administration ranged from 20 to 50 mL. In Fig 1, it is shown that the newborns who developed ICH during the treatment with va-ECMO had received both a statistically significantly higher number and a statistically significantly

### Table 1: Patient Characteristics of Newborns With ICH (Case Patients) and Newborns Without ICH (Control Subjects) During ECMO Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case Patients</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 24)</td>
<td>(n = 40)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.3 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td>.79</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38 ± 3</td>
<td>39 ± 2</td>
<td>.64</td>
</tr>
<tr>
<td>Age at start of ECMO, h</td>
<td>35 ± 30</td>
<td>53 ± 64</td>
<td>.20</td>
</tr>
<tr>
<td>Duration of ECMO, h</td>
<td>155 ± 76</td>
<td>171 ± 83</td>
<td>.43</td>
</tr>
<tr>
<td>Apgar at 1 min, median</td>
<td>6.0 ± 2.6</td>
<td>6.1 ± 2.5</td>
<td>.94</td>
</tr>
<tr>
<td>Apgar at 5 min, median</td>
<td>7.0 ± 2.0</td>
<td>7.1 ± 2.1</td>
<td>.82</td>
</tr>
<tr>
<td>pH</td>
<td>7.23 ± 0.15</td>
<td>7.33 ± 0.15</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>45.8 ± 13.9</td>
<td>42.7 ± 16.7</td>
<td>.46</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>48.1 ± 29.6</td>
<td>53.7 ± 19.1</td>
<td>.36</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>11/17/7</td>
<td>—</td>
<td>.03</td>
</tr>
<tr>
<td>CPR before ECMO</td>
<td>3/24/32/40</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>11/12/34/24</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>No. of platelet T24</td>
<td>2.1 ± 1.2</td>
<td>1.6 ± 1.2</td>
<td>.64</td>
</tr>
<tr>
<td>Volume of platelet T24, mL</td>
<td>85 ± 48</td>
<td>67 ± 48</td>
<td>.18</td>
</tr>
<tr>
<td>Loading ACT</td>
<td>399 ± 136</td>
<td>397 ± 161</td>
<td>.96</td>
</tr>
<tr>
<td>ACT, first 8 h</td>
<td>276 ± 35</td>
<td>266 ± 54</td>
<td>.42</td>
</tr>
<tr>
<td>ACT, first 24 h</td>
<td>258 ± 34</td>
<td>246 ± 34</td>
<td>.19</td>
</tr>
<tr>
<td>CV ACT, first 8 h</td>
<td>0.17 ± 0.09</td>
<td>0.15 ± 0.09</td>
<td>.41</td>
</tr>
<tr>
<td>CV ACT, first 24 h</td>
<td>0.15 ± 0.07</td>
<td>0.15 ± 0.10</td>
<td>.75</td>
</tr>
<tr>
<td>Mean MAP, first 8 h</td>
<td>53 ± 10</td>
<td>56 ± 7</td>
<td>.24</td>
</tr>
<tr>
<td>Mean MAP, first 24 h</td>
<td>52 ± 8</td>
<td>53 ± 7</td>
<td>.63</td>
</tr>
<tr>
<td>CV MAP, first 8 h</td>
<td>0.13 ± 0.06</td>
<td>0.14 ± 0.06</td>
<td>.60</td>
</tr>
<tr>
<td>CV MAP, first 24 h</td>
<td>0.13 ± 0.07</td>
<td>0.15 ± 0.06</td>
<td>.42</td>
</tr>
<tr>
<td>Use of steroids</td>
<td>3/24/5/40</td>
<td>—</td>
<td>.82</td>
</tr>
<tr>
<td>Use of inotropics</td>
<td>21/24/38/40</td>
<td>—</td>
<td>.31</td>
</tr>
</tbody>
</table>

### Table 2: ORs and CIs for the Relation Between pH, PaCO₂, PaO₂, and the Number and Total Volume of Intravascular Infusion in the First 8 and 24 Hours of ECMO Treatment and the Development of ICH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate Analysis, OR (95% CI)</th>
<th>Multivariate Analysis, OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH ≤7.3 worst arterial gas</td>
<td>4.5 (1.4–14.0)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>PaCO₂ ≥45 mm Hg worst arterial gas</td>
<td>3.3 (1.0–10.9)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>PaO₂ ≤50 mm Hg worst arterial gas</td>
<td>5.3 (1.5–19.0)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Every 100 ml of volume, first 8 h</td>
<td>1.5 (1.1–2.2)</td>
<td>1.6 (1.0–2.6)</td>
<td>.06</td>
</tr>
<tr>
<td>≥300 ml, first 8 h</td>
<td>6.3 (1.4–29.1)</td>
<td>10.0 (1.9–83.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Every single infusion, first 8 h</td>
<td>1.2 (1.0–1.5)</td>
<td>1.3 (1.0–1.6)</td>
<td>.04</td>
</tr>
<tr>
<td>≥8 infusions, first 8 h</td>
<td>13.6 (1.7–106.3)</td>
<td>26.0 (1.6–430.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Every 100 ml of volume, first 24 h</td>
<td>1.1 (1.1–2.2)</td>
<td>1.6 (1.0–2.4)</td>
<td>.04</td>
</tr>
<tr>
<td>≥400 ml, first 24 h</td>
<td>5.7 (1.3–25.6)</td>
<td>6.4 (0.5–77.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Every single infusion, first 24 h</td>
<td>1.1 (1.0–1.3)</td>
<td>1.2 (1.0–1.4)</td>
<td>.04</td>
</tr>
<tr>
<td>≥10 infusions, first 24 h</td>
<td>3.6 (1.1–11.2)</td>
<td>8.5 (1.2–59.2)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Results are given for the univariate analysis (adjustment for pH, PaCO₂, and PaO₂ mentioned) for the first 8 and 24 hours of the treatment with va-ECMO. NS indicates not statistically significant.
higher total volume of intravascular volume administrations during the first 8 and 24 hours of the treatment with va-ECMO, compared with the matched control patients. Statistically, there was a significant increase in the risk for ICH for every extra infusion in the first 8 and 24 hours of treatment with va-ECMO. This was also true for every 100 mL of extra volume administration in the first 8 and 24 hours (Table 2). After dichotomization and adjustment for pH, Paco2, and Pao2 in the multivariate conditional regression, we found the following conditions to be significantly related to the development of ICH during the va-ECMO treatment: 8 infusions or >300 mL of intravascular infusion in the first 8 hours of va-ECMO and >10 infusions in the first 24 hours of va-ECMO. An overview of ORs and 95% CIs for the univariate and multivariate analysis is shown in Table 2.

In the univariate analysis, CPR, gestational age, and age at the start of ECMO did not seem to be significant risk factors for the development of ICH. ORs and CIs were 2.0 (0.4–9.0), 0.4 (0.1–1.4), and 1.0 (0.9–1.0), respectively. When these terms were used in a straight multivariate conditional regression, data found for volume administration, as shown in Table 2, were still statistically significant.

DISCUSSION

Because ICH is one of the most devastating complications of ECMO, it is of ongoing importance to identify patients who are most at risk and eliminate risk factors as much as possible. This matched case-control study is the first to describe a statistically significant relationship between the total number and volume of intravascular volume infusions and the development of ICH during the treatment with va-ECMO. We found that neonates who received >8 infusions or >300 mL of volume infusion during the first 8 hours or >10 infusions during the first 24 hours of va-ECMO were statistically significant more at risk to develop an ICH. We stress that this relationship does not have to be necessarily causal. A hypothetical explanation, however, might be found in disturbances of cerebral hemodynamics caused by the infusions of intravascular volume administration and/or the often preceding bladderbox alarms with consecutive acute interruption of the roller pump resulting in interruption of blood flow to the patient. In normal, healthy situations, cerebral autoregulation maintains the cerebral blood flow over a wide range of cerebral perfusion pressures with a contraregulation response occurring with a delay of 2 seconds after sudden changes in blood pressure. It has been shown, however, that autoregulation is disturbed in severely ill term infants;16–19 Additionally studies of newborn lambs showed that prolonged hypoxia and/or the ECMO treatment itself will significantly disturb the autoregulation20–23; therefore, frequent interruption of the roller pump, followed by infusion of intravascular volume administration, may result in frequent fluctuations in cerebral blood flow, a known risk factor for ICH. Besides this, possible disturbances in cerebral blood flow at bladderbox alarms might be too acute to be compensated for by the autoregulation system, even if not disturbed. The combination of most bladderbox alarms and intravascular volume infusion in the first 24 hours and disturbed autoregulation may be a part of the explanation of why most ICHs occur in the first few days of the ECMO treatment; however, another explanation of the relationship found in this study might be that the pathologic process that leads to ICH also causes the inadequate venous drainage to the ECMO circuit, which in turn leads to the need for volume administration.

Birth weight and gestational age were not significantly different between the ICH group and the group without ICH, which suggests that the matching procedure was successfully performed. The significant relationship between pH, Paco2, and Pao2 and ICH found in this study confirms the findings of previous studies.12,13,15 Confirmation of acidosis by using lactate as other variable was not possible, because this was not always routinely determined.

In contradiction to the study of Dela Cruz et al,13 ACT levels, analyzed for the first 8 and 24 hours between case patients and control subjects, were not significantly different. Instability of ACT during the ECMO treatment was described by Hirthler et al14 but not further confirmed in this study, neither by the mean ACT nor by the coefficient of variation of the ACT. Because the exact time of ICH occurrence is not known, instability of ACT could be a risk factor as well as a consequence of the ICH. This could also be the question for possible differences in platelet counts. In all our patients, case patients and

FIGURE 1
Total number and volume of intravascular volume infusions in the first 8 and 24 hours between patients with and without ICH during the treatment with ECMO. a P = .03; b P = .005; c P = .04.
control subjects, platelet counts were kept strictly above 80 000/mm³. Platelet requirement was slightly higher in the group of patients who developed an ICH, which seems to fit with the previous studies described. In our study, however, this was not statistically significant. We did not find a statistically significant difference in the use of epinephrine, as was found in the study by Hardart et al, or in the use of other inotropic medication or steroids before the ECMO treatment used to treat hypotension.

Although any confounding factor is not completely excluded, we think that this matched case-control study shows an important relationship between intravascular volume administration and the development of ICH. The results of this study can be translated to clinical practice. Any newborn who is treated with va-ECMO and requires high amounts or number of intravascular volume administration should alert the ECMO team. Because of the increased chance of ICH, more frequent neurologic assessment and cerebral ultrasounds are recommended to detect any ICH in an early stage and if possible avoid extension of the hemorrhage.

Additional prospective studies, as currently initiated in our ECMO center, are required to analyze the mechanisms by which volume administration and/or the often preceding bladderbox alarms are related to the development of ICH. Knowledge of these mechanisms may be useful for the development of strategies to reduce the risk for ICH during the va-ECMO treatment, such as how to react on bladderbox alarms and whether it might be indicated to be cautious with intravascular volume administration.

CONCLUSIONS
To our knowledge, this is the first study to show a statistically significant relationship between the total amount and number of intravascular volume administration and the development of ICH during va-ECMO treatment. Additional studies are needed to investigate the pathophysiologic mechanisms of this relationship.

REFERENCES
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