Arterial Limb Microemboli during Cardiopulmonary Bypass: Observations from a Congenital Cardiac Surgery Practice

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Abstract: Gaseous microemboli (GME) are known to be delivered to the arterial circulation of patients during cardiopulmonary bypass (CPB). An increased number of GME delivered during adult CPB has been associated with brain injury and postoperative cognitive dysfunction. The GME load in children exposed to CPB and its consequences are not well characterized. We sought to establish a baseline of arterial limb emboli counts during the conduct of CPB for our population of patients requiring surgery for congenital heart disease. We used the emboli detection and counting (EDAC) device to measure GME activity in 103 consecutive patients for which an EDAC machine was available. Emboli counts for GME <40 μm and >40 μm were quantified and indexed to CPB time (minutes) and body surface area (BSA) to account for the variation in patient size and CPB times. Patients of all sizes had a similar embolic burden when indexed to bypass time and BSA. Furthermore, patients of all sizes saw a three-fold increase in the <40 μm embolic burden and a five-fold increase in the >40 μm embolic burden when regular air was noted in the venous line. The use of kinetic venous-assisted drainage did not significantly increase arterial limb GME. Efforts for early identification and mitigation of venous line air are warranted to minimize GME transmission to congenital cardiac surgery patients during CPB.

Keywords: cardiopulmonary bypass, congenital heart disease, air embolism, gaseous microemboli, adverse events, EDAC.

Although massive air embolism into the cerebral circulation can cause stroke and could be associated with major postoperative complications including death, the relationship between gaseous microemboli (GME) and outcomes has been weakly studied (1). In adults, neurocognitive impairment following cardiac surgery with cardiopulmonary bypass (CPB) has been described as confusion, memory loss, lack of concentration, depression, encephalopathy, or delirium and has been correlated with microemboli delivery during bypass (2). It is clear that GME are delivered to all patients through disposable devices currently in use (3–11) and that oxygenator, venous reservoir, venous filter, and arterial line filter (ALF) design all play an important role in GME clearance during CPB (12). Although there have been several in vitro studies investigating GME in pediatric bypass circuits (3–8), in vivo assessment of GME in pediatric patients has been limited to two small series (9,10). While the relationship between GME and outcomes has been defined for adult CPB (2), no comparable relationship has been described in neonates and children with congenital heart disease (CHD) undergoing cardiac surgery (13). The aim of this prospective observational study was to define the embolic burden to CHD patients undergoing CPB at our center using current disposables and techniques.

CPB EQUIPMENT

We had previously used emboli detection and counting (EDAC) machines (Luna Innovations, Inc., Roanoke, VA) with up to three probes for each bypass case: venous
line, post cardiotomy venous reservoir (CVR), and post ALF. Our experience in transitioning to integrated arterial line filtration was consistent with what other investigators had shown in that the Terumo CAPIOX FX series oxygenators (Terumo Cardiovascular Group, Ann Arbor, MI) with integrated arterial line filtration were comparable with the Terumo CAPIOX RX series oxygenators coupled with an external ALF in regard to GME clearance (14). This gave our practice confidence in transitioning to an oxygenator line which saved circuit prime volume and simplified setup by utilizing integrated arterial line filtration.

Gravity siphon drainage (GSD) was used in all patients with a body surface area (BSA) of <1.2 m² and an anticipated maximum pump flow rate under 3.0 L/min/m² (3.6 L/min). A centrifugal head in the venous line provided kinetic venous-assisted drainage (KVAD) as needed for patients with a BSA ≥1.2 m² and/or an anticipated maximum pump flow rate greater than ≥3.6 L/min. This limit was chosen for our practice based on the desire to eliminate ½³⁰ venous tubing from our circuits and the occasional need to use peripheral cannulation with venous cannula flow-rated less than cannulae placed centrally. Negative pressure in the venous limb of the circuit with KVAD is limited to –40 mmHg in our practice and is measured via a pressure dome connected 8⁰ proximal to centrifugal head inflow and 3.5–4.5⁰ distal the venous cannula(e) connection. Terumo CAPIOX FX oxygenators with integrated 32-μ ALFs and 47-μ venous reservoir filters are used in all patients. Table 1 lists the selection of primary circuit components used in our clinical practice based on an anticipated maximum index pump flow rate of 3.0 L/min/m² during bypass. Circuit components are upsized as needed when maximum anticipated pump flow rates on bypass exceed the 3.0 index standard (i.e., aortopulmonary collaterals, significant aortic insufficiency, and single ventricle physiology) (15).

Two EDAC machines were available for up to four operating rooms per day. We aimed to collect emboli data on 100 consecutive congenital cardiac surgery patients for which an EDAC machine was available. For the duration of this observational study, the perfusionist applied an EDAC probe to the arterial limb of the bypass circuit for data collection. The EDAC probe was located distal to the Terumo CAPIOX FX oxygenator and therefore was post oxygenator and post ALF. It is well known that the CVR, membrane oxygenator, and ALF significantly attenuate GME transmission during bypass (3,4,15). Since the aim of our study was to quantify GME transmission to the patient, we used only a single probe in the bypass circuit arterial limb.

### MATERIALS AND METHODS

The Luna Innovations software creates bins of emboli based on their size. These bins run from 0 to 1000 μ in increments as low as 10 μ. All emboli >1000 μ are counted in a single bin. Our embolic data were separated into two bins; <40 μ and >40 μ. The Luna Innovations hardware and software do not have the ability to distinguish gaseous emboli from particulate. We characterized our embolic data as GME given the greater likelihood that emboli detected after the ALF are gaseous as opposed to particulate (16). CPB equipment currently on the market either has integrated arterial line filtration in the 25–40 μ range or it includes external arterial line filtration in the 20–40 μ range (15). The Terumo CAPIOX FX oxygenators have integrated ALFs with a pore size of 32 μ. The 40 μ standard was chosen as a demarcation in line with other published reports using that standard (2,4,7–11) and because the EDAC software cannot bin emboli precisely to the 32 μ pore size that the FX series offers. EDAC data recording was started with the commencement of bypass and stopped at the end of CPB.

CPB was conducted per department standard. Bypass circuits were CO₂ flushed before crystalloid priming with

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**Table 1. Circuit components based on maximum anticipated bypass flow rate.**

<table>
<thead>
<tr>
<th>Maximum Anticipated Pump Flow Rate (L/min)</th>
<th>Circuit Prime Volume (mL)</th>
<th>Oxygenator with Integrated 32 micron ALF</th>
<th>Primary Tubing Pack Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 1.2</td>
<td>215 Terumo CAPIOX FX05 for up to 1.5 L/min</td>
<td>3/16 arterial</td>
<td>3/16 arterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/4 venous</td>
<td>3/16 arterial</td>
</tr>
<tr>
<td>1.2–1.5</td>
<td>230 Terumo CAPIOX FX15–30 for up to 5 L/min with assisted drainage</td>
<td>1/4 arterial</td>
<td>1/4 venous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/8 venous</td>
<td>3/8 venous</td>
</tr>
<tr>
<td>1.8–2.1</td>
<td>560</td>
<td>3/8 venous</td>
<td>3/8 venous</td>
</tr>
<tr>
<td>2.1–3.15</td>
<td>595</td>
<td>3/8 venous</td>
<td>3/8 venous</td>
</tr>
<tr>
<td>3.15–3.6</td>
<td>700</td>
<td>3/8 arterial</td>
<td>3/8 venous</td>
</tr>
<tr>
<td>3.6–4.4</td>
<td>775</td>
<td>3/8 arterial</td>
<td>3/8 venous</td>
</tr>
<tr>
<td>4.4–5</td>
<td>800</td>
<td>3/8 arterial</td>
<td>3/8 venous</td>
</tr>
<tr>
<td>5.0–7.0</td>
<td>980 Terumo CAPIOX FX25 for up to 7 L/min</td>
<td>3/8 arterial</td>
<td>3/8 venous</td>
</tr>
</tbody>
</table>

Plasma-Lye A 7.4 (Baxter Healthcare, Deerfield, IL) and circulated through a ≤5 μ prebypass filter (Sorin Group USA Inc., Arvada, CO). The circuit prime was adjusted for a dilutional hematocrit once on bypass of 25–30% depending on the patient with the aim of a hematocrit of 30–35% for separation from bypass. Reconstituted whole blood (red blood cells with plasma added) was used as needed for patients requiring a blood prime. Sodium bicarbonate and calcium gluconate were added to the prime before it was ventilated. A blood gas sample was analyzed for blood prime circuits to ensure proper pH, blood gas, and electrolyte values. The prime was kept circulating at 30°C–32°C before the arteriovenous loop was divided on the sterile field. No forms of autologous priming of the bypass circuit were used. All patients received 300 U/kg of heparin as a bolus dose with more given as needed for a target activated clotting time (ACT) of ≥480 seconds before instituting and while on bypass. Typical target bypass flow rates while warm were 2.5–3.0 L/min/m² with flow decreasing in step with depth of hypothermia and surgeon preference. Patient blood pressure was managed with adjustments to pump flow rate, phenylephrine, and isoflurane as needed during CPB. Alpha-stat blood gas management was used for patients cooled to >30°C whereas pH-stat management was used for patients cooled to ≤30°C. A level sensor servoregulated to the arterial roller head pump was placed on the venous reservoir for all cases and was set at or above the manufacturer recommended minimum operating volume. A Sorin Xtra (Sorin Group USA Inc.) autotransfusion device was used for processing shed blood and residual pump circuit volume for all cases.

No interventions were made on bypass based on real-time EDAC data. Studies were saved for off-line analysis. Twelve studies were excluded from analysis because of significant electrical interference causing false-positive emboli detection. False-positive emboli detection caused by electromagnetic interference was defined as apparent emboli activity on the EDAC monitor during setup without flow through the bypass circuit.

Data Analysis

Emboli counts for GME < 40 μ and >40 μ were quantified and indexed to CPB time (minutes) since there was a wide range of time spent on bypass (interquartile range [IQR]: 92–158 minutes). We divided our population into two groups based on BSA <1.2 m² and ≥1.2 m² since it is our practice to use KVAD for patients in the larger BSA group. Indexed GME counts were compared relative to patient weight, patient BSA, oxygenator size, use of an aortic cross-clamp, whether maximum pump flow rate exceeded 80% or 90% of the oxygenator’s rated flow, type of drainage used (GSD vs. KVAD), target patient temperature on bypass, and whether venous line air was regular. We defined “regular venous line air” as venous air visible to the perfusionist occurring longer than 5 minutes. This time threshold allowed the surgeon to attempt to alleviate the cause of venous line air.

Statistical Analysis

Categorical variables are expressed as number and percentage. We used the Shapiro–Wilk test to assess continuous variables for normality. Data are presented as median and IQR or mean and SD. Groups were compared using the Student t test or Wilcoxon rank sum test for continuous variables and the Chi-square test for categorical variables. A p value <.05 was considered statistically significant for all tests. Statistical analyses were performed using STATA version 14.0 for Mac OS (StataCorp, College Station, TX).

RESULTS

We included 103 patients (median weight: 9.4 kg; IQR: 5.1–31.3) from October 2014 to April 2015. Of these patients, 79 were included in the group with BSA < 1.2 m² and 24 were included in the group with BSA ≥ 1.2 m². Demographic and CPB characteristics are described in Table 2.

Figure 1A shows that GME < 40 μ/min/BSA were comparable in patients with a BSA < 1.2 m² (1411; range: 380–3566) and patients with a BSA ≥ 1.2 m² (1194; range: 86–1937) when no regular air was present in the venous line. Also shown is that the regular air in the venous line significantly increases the embolic burden for all patients in both groups seeing a three-fold increase in GME < 40 μ/min/BSA under those conditions (GME < 40 μ/min/BSA; BSA < 1.2 m²—no air: 1411 to air: 4416 and BSA ≥ 1.2 m²—no air: 1194 to air: 3520). Figure 1B shows the embolic load for GME > 40 μ/min/BSA was comparable in patients with a BSA < 1.2 m² (18; range: 2–63) and patients with a BSA ≥ 1.2 m² (15; range: 2–33) when no regular air was present in the venous line. There was a five-fold increase in the embolic burden for emboli >40 μ/min/BSA with regular air in the venous line (GME > 40 μ/min/BSA; BSA < 1.2 m²—no air: 18 to air: 87 and BSA ≥ 1.2 m²—no air: 15 to air: 85). Although KVAD was mainly used in patients with BSA ≥1.2 m², no difference in the number of GME < 40 μ/min (Figure 1A) and GME > 40 μ/min (Figure 1B) was observed between the two groups after adjustment for BSA, with p = .707 and .816, respectively. Higher <40 μ/min GME counts were also associated with increased >40 μ/min GME counts (Figure 2).

DISCUSSION

A microbubble is defined as an air bubble <1000 μ in diameter (17). Capillaries are generally considered to be 4–9 μ and GME greater than or equal to these dimensions
may occlude the microvascular bed producing ischemia and activating an endothelial based inflammatory response (18). Even though most GME > 40 μ are removed from CPB circuits with current venous and ALFs (14), those <40 μ have the ability to coalesce upon exiting the ALF and can later become lodged within capillaries (19). These lodged microbubbles then transform from a sphere to a cylindrical shape in the vessel increasing dissolution time by at least 50% (20). This dissolution time may further increase since GME do not only exist as gas bubbles in whole blood, but they may be encapsulated with proteins, lipids, platelets, and white blood cells (21). Longer dissolution times increase the risk of watershed ischemic injury.

Our study of 103 congenital cardiac surgical patients is the largest to date characterizing arterial limb GME delivery

Data are expressed in median and interquartile range, mean and SD, or number and percentage.
during CPB in this heterogeneous population. We examined numerous factors and found that the presence of venous line air was associated with a significant increase in GME of all sizes. Furthermore, after adjustment for BSA, the use of KVAD independent of venous air was not associated with increased GME.

The majority of CPB circuits currently in use with arterial line filtration are designed to prevent GME > 40 μ from being transmitted to the patient. It has been demonstrated that GME up to 40 μ are regularly delivered to CPB patients (7,9,10,22). GME larger than the ALF pore size may still be transmitted due to device imperfections and increased bypass system pressure contorting air emboli and forcing them through pores smaller than their overall size (23). GME delivered post ALF are also known to increase with manipulation of the heart at the surgical field (11,24), commencement of bypass (9,10,24), cross-clamp removal (9,24), venous line air entrainment (10,24,25), higher pump flow rates and circuit pressures (3,7,8), administration of medications to the circuit (24,26), use of a left ventricular vent with return to the CVR (25,26), the use of augmented venous return with higher negative pressures increasing GME counts (7,8,10), lower perfusate temperatures (7,27), and the use of pulsatile perfusion (7,8).

It has been documented that a primary source of post arterial filter GME is venous air entrainment (9,28). Clark et al. (9) demonstrated that increased venous air was associated with more and larger GME delivered post arterial filter and with more GME in the first 2 minutes of bypass and just before and after cross-clamp removal. The high GME count in the first 2 minutes of bypass was related to incomplete de-airing of the venous cannula, a common source of venous line air. The authors felt that the GME increase before cross-clamp removal was related to de-airing of the right heart with closure of the right atriotomy.

We also examined the use of KVAD vs. GSD. Vacuum-assisted venous drainage (VAVD) exerts additional negative pressure on the venous tubing when GSD is already in use. This increase in negative pressure can be associated with increased venous line air and a subsequent increase in arterial line GME (6–8,10,29). The same effect can be expected with KVAD since it may also increase venous line air. In addition, KVAD has been shown to increase venous line GME by churning the air–blood mixture creating an increased number of smaller air emboli and forming an emulsion, which is not as readily removed within the CVR, oxygenator bundle, and ALF (30). Our study did not allow assessment of VAVD in regard to generation of GME relative to the KVAD and GSD techniques. However, when GME counts were normalized for BSA, the use of KVAD was not associated with an increased embolic load over that seen with GSD. This would imply that the effect of regular air in the venous line dwarfs the effect of KVAD in the generation of GME (Figure 1).

Higher <40 μ/min GME counts were also significantly related to increased >40 μ/min GME counts (Figure 2). An in vivo study of adult cardiac surgical patients concluded that the arterial load of smaller GME was positively correlated with the arterial load of larger GME (24). Our findings are consistent with that study.

Emboli detection devices currently in use significantly underestimate GME volume and numbers (5). Particularly worrisome is that this underestimation may be as high as 97% at circuit flow rates greater than 6 L/min(5). In relation to the size of the GME being counted, the EDAC has been shown to underestimate average bubble diameters at all flows by 38% as well (5). Considering that GME are likely underestimated with current monitoring devices and that increased GME load is associated with adverse neurologic outcomes in adult patients (1,2,17), we believe that GME should be minimized to the greatest extent possible in all patients during CPB.

Our study presents some major limitations. The choice of a GME cutoff of 40 μ can be considered arbitrary; however, this cutoff was based on the threshold defined in the available literature. The primary objective of our study was to describe the GME burden in CHD patients undergoing cardiac surgery; our study was not designed to assess the relationship between the burden of microemboli and clinical outcomes. Further large studies will be needed to assess the relationships between total GME burden, GME size, and outcomes in CHD patients undergoing cardiac surgery.

Second, KVAD was used in patients with a BSA ≥ 1.2 m² in our study. Since BSA and the KVAD could both influence the GME count, we elected to adjust for BSA in addition to the duration of CPB. Although the use of KVAD was not associated with any increase in GME count after adjustment for BSA, it is not certain that the use of KVAD in patients with comparable BSA would not increase the GME count. Further studies are needed to assess the effect of KVAD compared with GSD on GME count when used in the same population.

In addition, this study was not designed to assess the burden of GME at different time points during the surgery. The method of indexing GME counts to CPB time could underestimate patient risk to increased GME counts with longer stable bypass periods masking the effect of interventions known to significantly increase GME counts.

Finally, the strong relationship between visible venous line air and increased GME counts offers an opportunity to address a modifiable factor without changing CPB equipment. Many of the other factors known to increase GME delivered to the patient are less easily addressed or modifiable (aortic cross-clamping, use of a left ventricular vent, requisite pump flow rate, etc.). Other authors have documented a decrease in GME transmission with changes to their disposables including the use of smaller pore sizes in both arterial line and venous filters (31). This would
appear to be an obvious next step to reduce arterial limb GME delivery during CPB. Perfusionists continuously monitor venous return and air in the venous line and relay important changes to the surgeon. This intervention requires no change to the disposables in use. Regular venous line air should be readily addressed. The data we present support efforts to mitigate venous line air to minimize GME transmission to congenital cardiac surgery patients requiring CPB.

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