Potential Deleterious Interactions between Certain Chemical Compounds and a Thermoplastic Polyurethane Heat Exchanger Membrane Oxygenator

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Presented at the 56th AmSECT International Meeting, San Diego, California, April 28–May 1, 2018.

Abstract: Extracorporeal membrane oxygenation (ECMO) has become a powerful tool in the race to reverse failure to rescue events. Rapid implementation set the stage for the advent of the 30-day wet-priming storage as a standard practice. A recent alert regarding methylene blue (MB) unidirectional leach from patient’s circulation through the oxygenator thermoplastic polyurethane (TPU) heat-exchanger membrane into the heater–cooler unit (HCU) water bath led us to believe that despite reassurances, the reverse process might be possible. To that effect, we performed a pilot in vitro experiment. We tested three adult ECMO sets (Adult Quadrox iD Oxygenator, Getinge, Doral, FL) probing for the transfer of MB between the water bath of a Sarns Dual Heater Cooler (Terumo Corporation, Ann Arbor, MI) and the circuit stored wet-primed for 30 days. In each test, 1,500 mg of reconstituted MB (HiMedia, Mumbai, India) were added to the 7.5 L of water in the HCU, circulated for 6 hours on which the water lines were disconnected and the setup was stored for 30 days. The primed circuit was tested for MB transfer at days 0, 13, and 30 by means of optical density (OD) at 665 nm and 26.5°C. Transfer of MB from the HCU water bath into the ECMO circuit could be detected as early as day 13 after setup, achieving significant values by day 30 (median OD .019 (.014–.021). Expected OD if no diffusion present: 0. The complete separation of water interfaces between the patient’s circuit and the HCU water bath may prove to be more dogma than fact when certain chemical substances are used in conjunction with TPU membrane oxygenators. Whether the transfer of substances is due to chemical processes or molecular weight needs further evaluation. Meanwhile, the use of chemicals for the cleaning of the HCU should be mindful of potential noxious effects. Keywords: CPB, equipment, extracorporeal membrane oxygenation (ECMO). J Extra Corpor Technol. 2018;50:244–7

Since 2005, the use of extracorporeal membrane oxygenation resuscitation (E-CPR) has gained favor as the primary rescue strategy in intensive care units worldwide (1). Understanding the significance of speed during ECMO implementation as one of the most important predictors of outcome has led to a number of measures aiming to facilitate rapid deployment. Among such measures, wet-primed storage has become the standard of care (2,3).

First-hand clinical experience of thermoplastic polyurethane (TPU) membrane oxygenators crossover issues when methylene blue (MB) was used on vasoplegic patients prompted our investigation. We decided to monitor and possibly establish criteria regarding conditions facilitating reverse diffusion of chemical substances between the water bath of the heater–cooler unit (HCU) and the patient’s circuit.
MATERIALS AND METHODS

Three identical simple closed loop circuits were constructed in a sterile fashion consisting of three-eighth of an inch of polyvinyl chloride tubing and an Adult Quadrox iD Oxygenator (Getinge). A Sarns Dual Heater Cooler (HCU) (Model #11160 Terumo Corporation) was filled with 7.5 L of water and connected to the oxygenators heat exchanger (HE) (Figure 1). The oxygenators were then water-tested using maximum cool setting of the heater-cooler for 5 minutes to verify no leaks were present, and recirculation setting was then selected (4).

Using a Sarns 8000 heart-lung machine roller pump (Terumo Corporation), occlusion was set in the usual fashion and the circuit was primed with 400 mL of plasmalyte and circulated to de-air the circuit and oxygenator. The circuit was then set at a flow of four liter per minute with the HCU in a recirculation mode.

MB (HiMedia) powder was then reconstituted and a 1,500-mg dose was added to the HCU water reservoir during recirculation. Recirculation of both circuits was continued for 6 hours and then discontinued.

The HCU water bath containing the MB was circulated for 6 hours, while the patient’s side closed circuit was also circulated. After 6 hours, both circuit’s circulations were terminated. The water bath circuit was then disconnected from the oxygenator and any remaining water allowed to drain. The patient’s circuit was kept statically primed and quarantined for 30 days.

On day 13 and 30, the circuit was allowed to recirculate at previous settings for 30 minutes without any connection to the HE. The last sample was then drawn from the simulated patient side of the circuit before dismounting the setup.

Samples were drawn from the patient side of the circuit at 1-hour intervals for the first 6 hours, then again on day 13 and finally on day 30. Testing for MB on the patient’s simulated circuit was performed by spectrophotometric measurement of light scattered at 660, 665, and 670 nm in a process known as optical density (OD). A SpectraMax Plus 384 microplate reader (Molecular Devices, LLC., San Jose, CA) was utilized to that purpose.

RESULTS

Samples taken at 1-hour intervals for the first 6 hours were negative for the diffusion of MB into the patient’s circulation. A minimal insinuation of retrograde transfer of the dye was detected by OD, on samples taken on day 13 (only taken on tests #1 and #2). All samples taken on day 30 on all three circuits (nine samples total) were significantly positive by OD (Table 1) and the blue-tinged changes in the patient circulation side of the setup were easily observable to the naked eye (Figures 2 and 3).

DISCUSSION

As early as 1961, Cooley and Beall described a case report for an early form of emergency cardiopulmonary support, and in 1975, Mattox and Beall presented the first series of patients treated with portable cardiopulmonary bypass. Both cases related to moribund adult patients diagnosed with pulmonary thromboembolism (5,6). Nearly three decades passed before Barlett and his group described a more systematic use of ECMO support in adult patients (7). It was not until the development of disposable membrane oxygenators, clear priming techniques and battery-operated pumps that the use of ECMO support became more widely available.

Table 1. OD measurements on day 0, 13, and 30 for each of the three circuits tested.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample</th>
<th>Day 0 (OD Value)</th>
<th>Day 13th (OD Value)</th>
<th>Day 30th (OD Value)</th>
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</thead>
<tbody>
<tr>
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<td>1</td>
<td>0</td>
<td>np</td>
<td>.020</td>
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<td>0</td>
<td>np</td>
<td>.016</td>
<td></td>
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<tr>
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<td>3</td>
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np, not performed.
Early experiences and common sense, more than evidence-based research, dictated that faster ECMO implementation would likely provide better outcomes. After working out the technical aspects of bedside cannulation, focus shifted to the immediate use of the ECMO circuit setup by means of nearby storage of already primed circuits.

As early as 1990, research was primarily focused on the safety of wet-primed stored circuits, initially for short periods (e.g., 48 hours) while progressively moving the self-declared “expiration deadline” to 6 days, 2 weeks, until finally achieving the current 30 days accepted standard (8–10). Since then, the tendency has been to adopt this off-label mode in many centers, keeping wet-primed circuits in storage for rapid deployment for up to 30 days.

According to Extracorporeal Life Support Organization, the number of ECMO centers and patients had been steadily growing worldwide since 2005, reaching slightly more than 9,000 patients treated with ECMO in 2018 (11). Although the global E-CPR trend as a rescue mechanism may be approaching stabilization, as financial barriers are lowered in low- and middle-income countries, we are likely to see further increments in the use of this technology.

Patient safety studies related to wet-prime storage and the progressive increase in the number of hours deemed safe to fulfill this practice have dealt with the potential risk of bacterial contamination or the likelihood of plasticizers exposure (12–16). Very limited information is available regarding the possibility of patient circuit contamination with chemical compounds gaining access through an, until now, unimaginable port of entry, the TPU membrane of the HE portion of the oxygenator.

Breach of TPU membrane integrity was first publicly reported through an adverse event report issued by the Food and Drug Administration on August 2014 (17). The manufacturer of this particular oxygenator recommended that MB not be used on vasoplegic patients on prolonged ECMO support because of the passage of MB through the TPU membrane onto the HCU water bath, purportedly in a unidirectional mode.

The adsorption of MB onto polyether polyurethanes (manufactured as a foam) has been well documented as a process based on particle diffusion and spontaneously occurring at room temperature (18).

Although several polycyclic chemicals have also been documented to interact with TPUs, this interaction seems to be limited to temperatures higher than those used during ECMO support (19).
Although it is very likely that the retrograde diffusion phenomenon is limited to a purely chemically reaction among specific chemical groups, one should not discard the possibility that low molecular weight (e.g., MB = 319.851 g/mol and hydrogen peroxide = 34.0147 g/mol) may also play a role in the facilitation of transmembrane diffusion.

Knowing that the oxygenator’s TPU membrane allows, under certain conditions, for retrograde diffusion of chemical compounds, such as MB and hydrogen peroxide, into a patient’s circulation should prompt us to question our long held dogma regarding unbreachable separation of the HCU water bath from the patient’s circulation (20).

We should also question which other chemical compounds currently recommended in the cleaning of the HCU water basin may be able to interact with the TPU membrane and if testing of such substances should now be compulsory (21,22).

CONCLUSION

The complete separation of water interfaces between the blood circuit and the HCU water bath may prove to be more dogma than fact when certain chemical substances are used in conjunction with TPU membrane oxygenators.

Whether the transfer of substances is due to chemical processes or molecular weight needs further evaluation. Meanwhile, the use of chemicals for the cleaning of the HCU should be mindful of potential noxious effects.

REFERENCES