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Analysis of Bicarbonate-Based Purge Solution in Patients With Cardiogenic Shock Supported Via Impella Ventricular Assist Device

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Abstract

Background: The Impella device is a continuous axial flow pump which provides hemodynamic support by expelling blood into the aorta. The manufacturer recommends using dextrose-based heparin containing solutions as the default purge. As an alternative to anticoagulant solutions, a bicarbonate-based purge solution has been proposed with limited data substantiating adequate protection and durability. **Objective:** To assess the impact of a bicarbonate-based purge solution on Impella pump thrombosis and bleeding outcomes. **Methods:** Single-center, retrospective study of cardiogenic shock patients who received an Impella between December 2020 through September 2021. Patients were evaluated based on whether they received bicarbonate-based purge solutions or remained on heparin-based purge solutions. The primary outcome was the rate of Impella pump thrombosis, defined as multiple purge pressures greater than 800 mm Hg. Secondary outcomes included incidence of bleeding defined as a drop in Hgb of at least 2 g/dL along with use of blood products and supratherapeutic anticoagulation defined as an aPTT of greater than 70 seconds. **Results:** Forty-three patients received bicarbonate-based purge solutions and 49 controls received heparin. The incidence of purge thrombosis by purge pressure threshold was similar between the two groups (16.3% vs 12.2%, $P = 0.58$). The rate of bleeding was lower with bicarbonate-based purge (27.9% vs 65.3%, $P < 0.05$) driven by a drop in Hgb of more than 2 g/dL. The rate of supratherapeutic anticoagulation was higher in the heparin arm (65.3% vs 27.9%, $P < 0.05$) **Conclusion and Relevance:** Nonanticoagulant purge alternatives offer the potential to reduce bleeding complications and laboratory monitoring burden while maintaining durability.

Keywords

cardiogenic shock, Impella, mechanical circulatory support, ventricular assist device, anticoagulation

Introduction

Cardiogenic shock is a state that is characterized by decreased cardiac output in the presence of adequate intravascular volume and often occurs as the result of severe left ventricular dysfunction.[1] In response to this shock state, patients may require some combination of vasopressors, inotropes, or mechanical circulatory support. There are several mechanical circulatory support devices available capable of providing temporary support, one of these being Impella. The Impella (Abiomed, Danvers, MA, USA) platform is a continuous, nonpulsatile, axial flow device which is inserted through an arterial access point into the left ventricle (LV) where it provides hemodynamic support and LV unloading by expelling blood from the LV into the aorta.[2] Common complications include hemolysis, device thrombosis, bleeding, aortic valvular damage, and arrhythmias. To prevent device thrombosis formation, Impella uses a countercurrent flow of a purge solution, which prevents blood from reaching the motor and causing platelet activation, pump thrombosis, and mechanical failure.[2-4]

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The manufacturer recommends the use of a dextrose-based solution containing heparin as the default purge solution in addition to systemic intravenous (IV) heparin.[2] Since the rate at which the purge solution is determined autonomously by the Impella device controller, the heparin exposure from this source is variable. Use of two heparin sources may contribute to unpredictable exposure and require meticulous monitoring of systemic heparin to maintain therapeutic anticoagulation. A systemic and heparin purge combination may result in increased risk of bleeding in an already at-risk population. There have also been significant challenges with the usage of direct thrombin inhibitor (DTI)-based purge solutions in patients with heparin induced thrombocytopenia (HIT) including reduced reliability in prevention of pump thrombosis, thus adding to a clear need for heparin-free purge solutions.[5] As an alternative to these anticoagulant containing solutions, a bicarbonate-based purge solution has been proposed. Coupled with the viscosity shielding qualities of dextrose, sodium bicarbonate may theoretically confer motor protection via blood protein stabilization and reduced protein deposition without modulating the coagulation cascade.[6]

Clinical application and outcomes related to the use of bicarbonate-based purge solutions are limited. In a small study of 10 patients who developed HIT and required a change to a bicarbonate-based purge solution, none of the patients experienced pump thrombosis or bleeding events. The authors suggested this solution represented a viable therapeutic option in this population, albeit further investigation would be warranted.[5] Unpublished manufacturer data on the use of bicarbonate containing purge solutions in ex vivo ($n=3$), animal ($n=7$), and in vivo ($n=70$) models have not revealed any indications of deleterious effects on purge pressure or purge flow.[7] A recently published expert consensus recommends that bicarbonate-based purge solutions may be preferred in scenarios when heparin containing solutions are not feasible such as bleeding and HIT, but heparin containing solutions should remain the default purge selection.[3]

Within our institution, a bicarbonate-based purge solution has been utilized as a common primary or secondary purge solution in many patients, including those without direct contraindications for heparin. Given the limited data available for the usage of bicarbonate-based purge solutions, we performed a retrospective analysis of Impella patients, aiming to evaluate the rate of pump thrombosis amongst patients receiving Impella support with exposure to a bicarbonate-based purge solution.

Methods

Design

We conducted a retrospective analysis of all adult patients with cardiogenic shock who were supported with an Impella device from December 1, 2020, to September 30, 2021. The design of this study was approved by the local Institutional Review Board. Given its retrospective nature, the need for informed consent was waived.

We included adults, age 18 years or older, who were admitted to our institution with a diagnosis of cardiogenic shock and receiving mechanical support with an Impella device. Patients were excluded if their duration of Impella support was less than 24 hours. We assigned patients to one of two groups based on the purge solutions utilized during the Impella course. The intervention group included all patients who were exposed to a bicarbonate-based purge solution during their clinical course, while the control group consisted of those who only received the manufacturer standard heparin containing purge solution for their entire course. Of note, pump implantations in procedural areas including the operating room and catheterization laboratory were initiated on heparin-based solutions. Transition to sodium-bicarbonate solutions were determined upon ICU admission based on provider preference. General provider considerations for using sodium bicarbonate purge included but were not limited to bleeding risk, heparin allergy, anticipated procedures, as well as desire to limit duplicate heparin sources in patients receiving systemic anticoagulation with heparin. The standard heparin purge consisted of 25,000 units of heparin in 500 mLs of D5W, for a concentration of 50 units/mL. Though the manufacturer endorses a 25 unit/mL purge solution, our institutional standard remains consistent with manufacturer's recommendation.[2] The bicarbonate-based purge solution consisted of 25 mEq of sodium bicarbonate in 1000 mLs of D5W.

Outcomes

Our primary outcome was the rate of Impella pump thrombosis, defined as (1) more than one purge pressure greater than 800 mm Hg, (2) use of thrombolytics in the purge, or (3) need for Impella pump replacement. The threshold for purge pressure was selected based on expert opinion and previously published case reports of Impella pump thrombosis.[8] Secondary outcomes included bleeding, defined as a decline in hemoglobin by ≥ 2 g/dL within 24 hours and use of blood products. Supratherapeutic anticoagulation, which was defined as an aPTT $>$ 70 seconds. Institutional aPTT reference range is 50–70 seconds. Data were collected on the number of blood products transfused along with frequency of aPTT laboratory collections. Markers of hemolysis including lactate dehydrogenase (LDH) and free hemoglobin (Hgb) were also collected. We performed a subgroup analysis of initial and terminal Impella purge pressures based on Impella runtime of greater than versus less than 14 days. This was predetermined to help provide insight into the long-term durability of the bicarbonate-based purge solution.

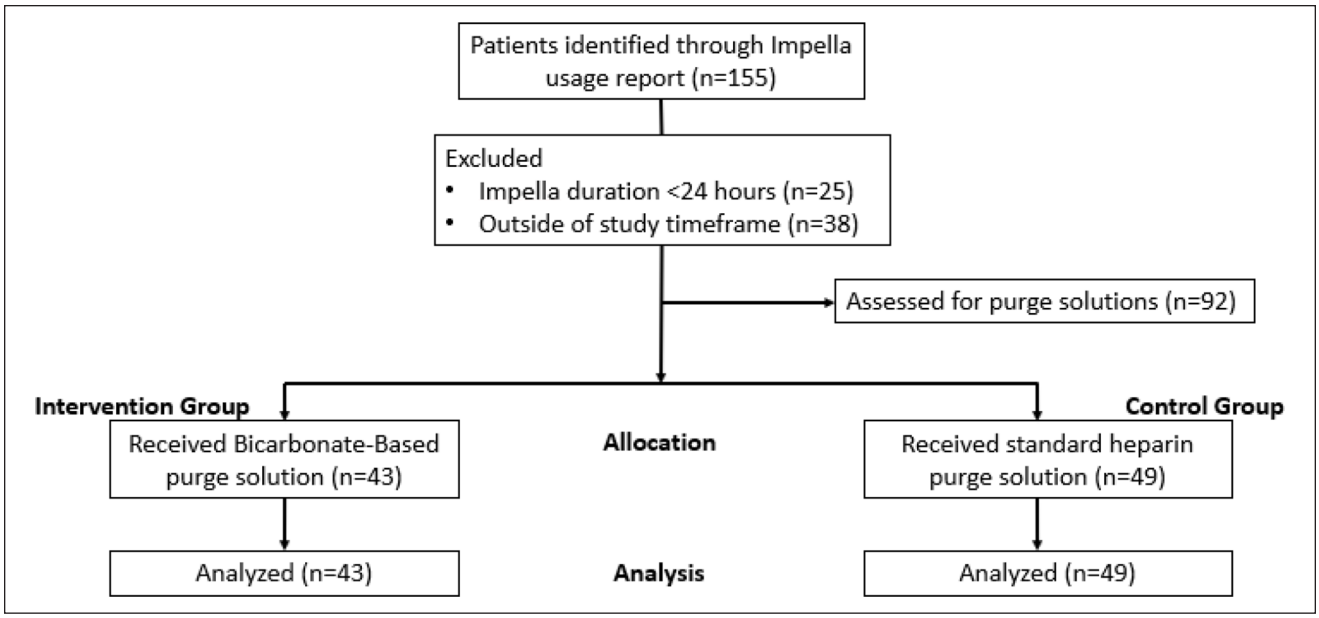

Figure 1. Screening of patient population.

Statistics

Given the paucity of published literature assessing the differences between these purge solutions, we were unable to perform a power or sample size calculation. Therefore, we opted to use our institutional Impella case load as a guide, and targeted enrollment of 40 patients in each group. Categorical data were assessed using Chi-squared tests and nonparametric continuous variables were assessed using Mann–Whitney *U* test. Data collection was performed by the lead author, who was not blinded to group assignments due to the need to determine bicarbonate purge solution start time in those patients. The data analyst was blinded to the treatment assignments. Data analysis was performed utilizing SPSS software.

Results

Patient Population

A total of 155 unique patients who received Impella support were identified. Twenty-five received Impella support for less than 24 hours and were excluded, along with 38 patients who did not receive Impella support during the study timeframe. The final population consisted of 92 patients, with 43 patients who received bicarbonate-based purge solutions and 49 who only received standard purge solutions (Figure 1). Relevant baseline characteristics can be found in Table 1. There was significant heterogeneity amongst the initial Impella device utilized, with the control group having a predominance of Impella CP and the bicarbonate-based group having a predominance of Impella 5.5 ($P < 0.05$). While there were numerically more patients in the bicarbonate-based purge solution group with positive heparin antibodies or serotonin release assays than the control population, the majority of the population did not have direct contraindications to receiving heparin. Furthermore, the duration of Impella support was significantly longer in the bicarbonate-based group, with a median duration of 11.3 days as compared with 4.8 days in the control group ($P < 0.05$). The patients in the bicarbonate population transitioned from heparin purge solutions after 1 day of Impella support on average and were maintained on bicarbonate-based purge solutions for a median of 7 days.

Primary Outcome

Details for the primary and secondary outcomes can be found in Table 2. Thrombosis outcomes occurred in 12 patients among the bicarbonate-based purge solution group and 10 patients in heparin control group ($P = 0.4$). The most common thrombosis outcome was multiple purge pressures greater than 800 mm Hg, which occurred at similar rate in each group (16.3% vs 12.2%, *P*-value = 0.58). Of note, there were 6 total patients who received fibrinolytics. Three of these events occurred while patients were receiving bicarbonate-based purge solutions. The remaining three of these events occurred in patients with a heparin containing purge solution prior to their transition to a bicarbonate-based purge solution. Because of the occurrence during heparin usage and prior to bicarbonate exposure, these three were included as thrombosis events for the heparin population, giving a total of three occurrences of fibrinolytic usage in

Table 1. Baseline Characteristics.

Characteristic	Heparin ($n = 49$)	Bicarbonate ($n = 43$)	*P*-value
Age, years; median (IQR)	61 (50–68)	59 (50–66)	0.415
Sex, male; *n* (%)	42 (85.7)	33 (76.7)	0.269
Positive Heparin AB, *n* (%)	5 (10.2)	11 (25.6)	0.117
Positive SRA, *n* (%)	1 (2.0)	3 (7.0)	0.1
Initial Impella, *n* (%)			<0.05
2.5	1 (2.0)	0	
CP	32 (65.3)	11 (25.6)	
5.5	10 (20.4)	31 (72.1)	
RP	1 (2.0)	0	
CP + RP	4 (8.2)	1 (2.3)	
5.5 + RP	1 (2.0)	0	
Impella run time, days; median (IQR)			
Overall	4.8 (3.0–7.7)	11.3 (6.8–20.7)	<0.05
Pre-Bicarb	N/A	0.9 (0.6–5.9)	n/a
Post-Bicarb	N/A	6.6 (4.4–11.0)	n/a
Time on Bicarb, %, median (IQR)	N/A	80 (38–94)	n/a

Abbreviations: AB, antibody; IQR, interquartile range; SRA, serotonin release assay.

Table 2. Thrombosis Outcomes.

Outcome	Heparin ($n = 49$)	Bicarbonate ($n = 43$)	*P*-value
Multiple PP >800 mm Hg, *n* (%)	6 (12.2)	7 (16.3)	$P = 0.58$
Thrombolytics in Purge, *n* (%)	3 (6.1)	3 (7.0)	NS
Impella Replacement, *n* (%)	1 (2.0)	2 (4.7)	$p = 0.60$

Abbreviation: PP, purge pressure.

each group. Three patients required Impella pump replacement; the difference between the two groups was not statistically significant (4.7% vs 2%, *P*-value = 0.60).

Amongst patients who experienced a primary outcome, key data points can be found in Figure 2. The nadir, peak, and median purge pressures were found to be similar amongst these patients. Lactate dehydrogenase (LDH) and free hemoglobin (Hgb) were used as surrogates of hemolysis. Of the two major markers of hemolysis, peak free Hgb was significantly higher in the heparin control patients while peak LDH was similar between the groups.

Secondary Outcomes

Data related to the secondary outcomes can be found in Table 3. Bleeding events occurred more frequently in the heparin control patients compared with the bicarbonate-based purge solution group, noted by a higher rate of Hgb decline by >2 g/dL within 24 hours (27.9% vs 65.3%, *P*-value < 0.05). Blood products were administered at similar rates per patient in both groups, except for the rate of platelet transfusions which were significantly higher in the heparin control patients (median units per patient: 2 vs 4, *P*-value = 0.02).

While there was a larger absolute number of aPTTs measured in the bicarbonate-based purge solution group, the median number of aPTTs checked per patient per day of care did not differ between the groups. Given the similar number of daily aPTTs measured per patient, the difference in absolute number of aPTTs checked is likely due to increased duration of care in the bicarbonate-based purge solution group. There was a numerically higher rate of supratherapeutic aPTTs in the heparin control patients compared to the bicarbonate-based purge solution group, with 29% of aPTTs being > 70 seconds in the control group compared with 19% in the bicarbonate-based purge solution group, but this did not meet statistical significance (*P*-value = 0.62).

Subgroup Analysis

Results for the subgroup analysis can be found in Table 4. In total, 9 patients in the bicarbonate-based purge solution group were maintained on Impella with that purge solution for a 14-day course along with 3 patients in the heparin control group. For patients with an Impella duration less than 14 days, change in purge pressure from the beginning to end of the Impella course was an increase of 6 mm Hg in the

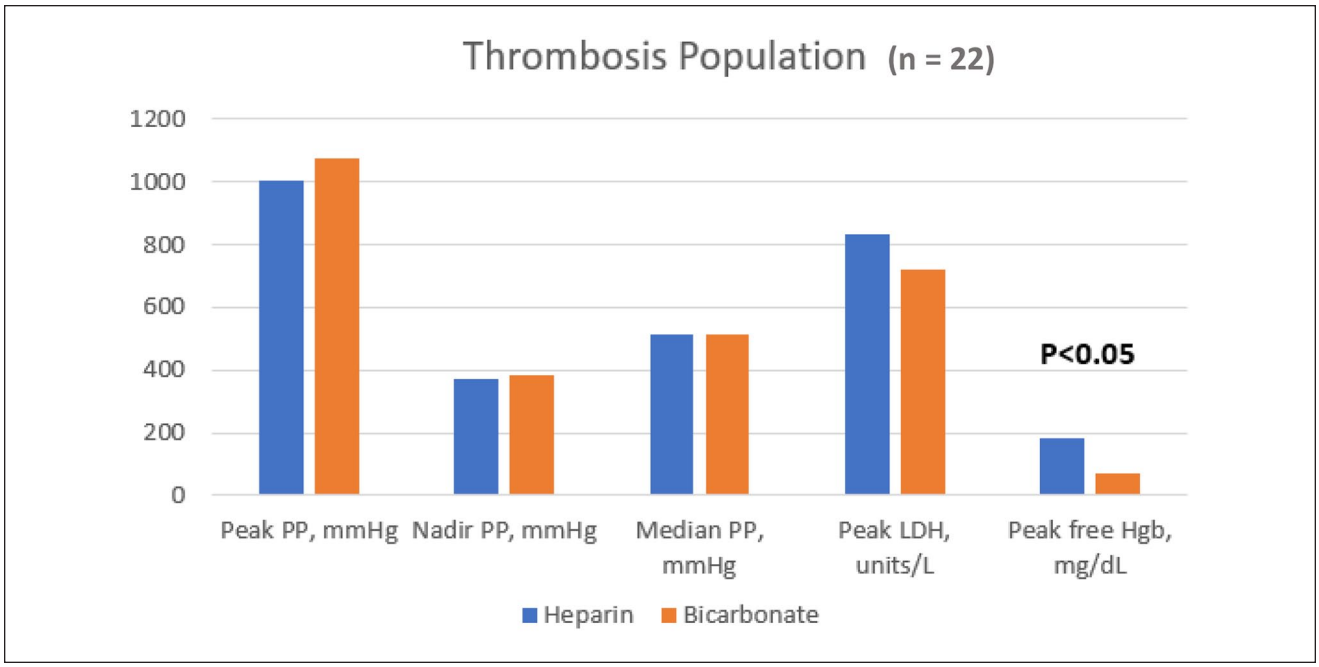

Figure 2. Thrombosis population key characteristics.

Table 3. Secondary Outcomes.

Secondary outcomes	Heparin ($n = 49$)	Bicarbonate ($n = 43$)	*P*-value
Bleeding, *n* (%)	32 (65.3)	12 (27.9)	$P < 0.05$
PRBC Transfusion per pt., *n*, median (IQR)	7 (2.5-14)	5 (3-11)	$P = 0.37$
Platelet Transfusion per pt., *n*, median (IQR)	4 (2-10)	2 (1-5)	$P = 0.02$
FFP Transfusion per pt., *n*, median (IQR)	2.5 (1-7.8)	2.5 (1-4)	$P = 0.50$
Cryoprecipitate Transfusion per pt., *n*, median (IQR)	2 (2-7.5)	2 (1-3)	$P = 0.47$
aPTTs collected, *n*	1732	2063	$P < 0.05$
aPTTs collected per pt., *n*, median (IQR)	19 (8.3-35.5)	49 (25-60)	$P < 0.05$
aPTTs collected per pt. per day, *n*, median	3.4	3.1	$P = 0.68$
Supratherapeutic Anticoagulation, *n* (%)	502 (29.0)	392 (19.0)	$P = 0.62$

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; PRBC, packed red blood cells.

Table 4. Subgroup Analysis.

Temporal Change in Median Purge Pressure (mm Hg)		Heparin	Bicarbonate	*P*-value
Less than 14 days	Beginning Purge Pressure	483	502	$P = 0.539$
	Ending Purge Pressure	477	508	
Greater than 14 days	Beginning Purge Pressure	487	528	$P = 0.121$
	Ending Purge Pressure	537	515	

bicarbonate-based purge solution group and a decline of 6 mm Hg in heparin control group. For the patients with greater than 14-day Impella duration, the change in purge pressure from beginning to end of Impella course declined by 13 mm Hg in the bicarbonate group and increased by 50 mm Hg in the heparin control group. Given that there were no statistical differences between either subgroup, this possibly indicates adequate stability of the Impella device even after prolonged use of bicarbonate-based purge solutions.

Discussion

Our study demonstrated that bicarbonate-based purge solutions can be utilized safely amongst a broad patient population

who may not necessarily have contraindications to the use of heparin. We identified that there were similar rates of each of the thrombosis outcomes between the two populations, further supporting the safe utilization of bicarbonate-based purge solutions. While the efficacy between the two solutions appears comparable, there were multiple safety outcomes that were improved in the bicarbonate-based purge solution group. These include incidence of supratherapeutic anticoagulation, peak hemolysis markers, hemoglobin decline, and number of units of platelets transfused.

Though the exact mechanism of sodium bicarbonate-based purge solutions is largely unknown, proposed mechanisms can be extrapolated from the broad biochemical and ionic properties of bicarbonate solutions. The mechanism of the standard heparin containing purge solution is thought to be threefold: (1) the natural anticoagulant effects of heparin preventing clotting via factor IIa and factor Xa inhibition, (2) the increased viscosity provided by dextrose alters blood rheology effectively shielding and diverting blood away from the motor housing and toward the aorta, and (3) the negative charge of heparin molecules providing a protective barrier against negatively charged proteins in the blood.[3,4] Heparin's anticoagulant properties are partially conferred by heparin's negative charge and its binding capacity with thrombin's positively charged amino acid residues. Sodium bicarbonate may adopt similar hemostatic interactions. In addition, sodium bicarbonate is known to chelate calcium, an important cofactor in the coagulation cascade.[9] Calcium chelation may interfere with fibrin production and decrease thrombosis.[6] The quasi-anticoagulant action of bicarbonate may be countered by an increased pH of the Impella motor housing. Rising alkalinity is known to stabilize platelet activation.[10] Calcium chelation and alkaline induced platelet stabilization are borrowed medical concepts from catheter lock solutions and upper gastrointestinal bleeding, respectively, which seek to inform the use of bicarbonate Impella purge solutions. Given the low concentration of bicarbonate utilized in the purge solution (25 mEq in 1000 mL D5W), this alkalinity is unlikely to cause systemic metabolic derangement.

Our study has worthwhile limitations. First, due to its retrospective design, we were unable to adjust for various confounders, such as comorbid conditions, severity of illness, indication for Impella, and allocation to heparin or sodium bicarbonate purge solutions. Selection bias in the form of perceived bleeding risks against heparin purges have the potential to influence results. Due to the limitations of retrospective data collection, we were unable to adhere to ISHLT pump thrombosis definitions.[11] We did, however, create a thrombosis endpoint which we believe was consistent with expert opinion and published literature.[8] Furthermore, adherence to ISTH bleeding definitions were narrowed to account only for a fall in hemoglobin and supplemented with blood product utilization to enhance detection of bleeding differences between groups.[12] Other bleeding parameters utilized as part of the full ISTH definition were not consistently documented. In addition, our institutional default heparin purge uses the higher concentration option of 50 units/mL rather than the 25 unit/mL alternative. Though both are endorsed by the manufacturer, the use of a higher concentration heparin purge could have influenced bleeding outcomes. Another data point we were unable to retrieve retrospectively were yellow luer lock failures on the purge sidearm which have been documented as a concern with the use of bicarbonate-based purge solutions over long periods of time. Due to our inability to collect for this outcome, we performed a 14-day subgroup analysis, which demonstrated the extended use of bicarbonate-based purge solutions was still associated with pump stability. As a result of differences in physician practices at our institution, there were significant differences in baseline Impella device utilized, with a predominance of Impella CP devices in the heparin control group. Contrasting flow profiles between the Impella CP and 5.5 can be considered a potential confounder for durability and hemolysis-related outcomes. Lastly, due to the manufacturer's recommendations at the time of patient management, all patients did receive heparin containing solutions for varying amounts of time until a decision was made to convert to bicarbonate-based purge solutions.

Strengths of our trial include the size of our patient population. Previously reported experiences with bicarbonate-based purge solutions have been limited to lower sample sizes. These populations also exclusively included patients with heparin intolerance or contraindication. Given our low frequency of positive heparin antibodies and serotonin release assays, many of the patients included in our study may have been able to tolerate heparin. We believe we are the first to report outcomes related to bicarbonate-based purge solution in comparison to a heparin-based control population as a primary, default purge solution.

Conclusion and Relevance

In summary, we believe our analysis indicates that bicarbonate-based purge solutions are a viable option for the management of patients on Impella and may help reduce the incidence of bleeding and supratherapeutic anticoagulation. Further prospective research may be necessary to determine superiority[12] of either solution, bicarbonate-, or heparin-based, as the primary solution for Impella management; as well as further investigation amongst the use of bicarbonate-based purge solutions in lower flow pumps such as the Impella CP.

Declaration of Conflicting Interests

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