Impact of Extracorporeal Circuit Prime Volume Reduction on Whole Blood Sequestration During Acute Normovolemic Hemodilution for Adult Cardiac Surgery Patients

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Abstract: Acute normovolemic hemodilution (ANH) is a blood-conservation method in which whole blood (WBANH) is sequestered into blood collection bags before the commencement of surgery. However, for cardiac surgery, extracorporeal circuit (ECC) priming techniques limit the amount of blood that may be collected prior to the actual initiation of cardiopulmonary bypass (CPB). In this study, computational modeling was used to examine the effect of reducing extracorporeal “pump” prime volume (PPV) on WBANH prior to the CPB. Increments of estimated blood volume (EBV), precardiopulmonary bypass hemoglobin concentration [HbPre-CPB], and PPV volume were manipulated to assess effects on predicted hemoglobin concentration during cardiopulmonary bypass [HbCPB]. Similarly, increments of EBV and preanesthetic hemoglobin concentration [HbPre-Anes] were manipulated to examine the change in WBANH volume. The impact of PPV reduction on the minimum acceptable precardiopulmonary bypass hemoglobin concentration [HbPre-CPB-MA] was then measured by computing PPV, EBV, and the minimum acceptable cardiopulmonary bypass hemoglobin [HbCPB-MA]. Finally, by manipulating EBV and target hemoglobin concentration [HbTarget], the change in [HbPre-CPB] produced by PPV reduction was used to quantify the effect on WBANH volume. The net increase in the [HbCPB] produced by PPV reduction is inversely proportional to EBV. Higher [HbPre-Anes] or lower [HbTarget] facilitates sequestration of larger WBANH volume. Although PPV and [HbPre-CPB-MA] bear a direct relationship, as EBV decreases, proportionally greater increases in [HbPre-CPB-MA] occur. The impact of PPV reduction on precardiopulmonary bypass hemoglobin concentration [HbPre-CPB] is reflected by the “excess hemoglobin” over the minimum hemoglobin threshold (designated as 7 g/dL in this study). For each 100-mL decrement in PPV, “excess hemoglobin” increases from 1% (EBV = 8000 mL) to 2% (EBV = 4000 mL). In turn, increases in “excess hemoglobin” are associated with expansion of WBANH volume. In conclusion, sequential PPV reduction from 2000 mL increases the volume of WBANH that potentially may be sequestered prior to initiation of CPB. Therefore, the combination of PPV reduction with ANH may represent a useful blood conservation approach in adult patients undergoing cardiac surgery with CPB. Keywords: acute normovolemic hemodilution; cardiac surgery, extracorporeal circuit prime, whole blood sequestration.

Acute normovolemic hemodilution (ANH) is an accepted point-of-care blood-conservation technique used to avoid and minimize allogeneic blood transfusion; in certain surgical procedures ANH may also “save” autologous red blood cells (1,2). The standard method of performing ANH requires that whole blood is first collected in bags containing anticoagulant (citrate phosphate dextrose) via a large peripheral vein, central vein or artery, termed “whole blood sequestration (WBS)” (3). This is usually initiated by the anesthesiologist after the induction of anesthesia, prior to the commencement of surgery. As blood is collected, asanguinous fluid (colloid or crystalloid) is simultaneously administered to maintain normovolemia; the actual amount of volume replacement is guided by hemodynamic function but usually ranges approximates 3 mL of crystalloid or 1 mL colloid for each milliliter of sequestered whole blood (3).

Widespread adoption of ANH for cardiac surgery has been impeded by several conflicting studies, which show varying blood conservation effects (4,5). Cited reasons for the divergence of results include variance in actual surgical and anesthetic technique, study design and methodology, heterogeneity of results, and use of adjunctive pharmacologic agents (6). Another important factor that impacts the efficacy of ANH is that hemodilution associated with the extracorporeal circuit (ECC) priming technique limits the amount of blood that may be collected prior to the actual initiation of cardiopulmonary bypass (CPB). During CPB,
perfusionists maintain hemoglobin (Hb) levels at greater than a certain threshold to maintain adequate perfusion and oxygen delivery to the brain, kidney, and other vital organs (7). Therefore, the actual volume of whole blood collected using ANH pre-CPB, ie, whole blood sequestration volume (WBANH), must take into consideration this second-phase hemodilution that occurs after the initiation of CPB and the “minimum” Hb threshold maintained by perfusionists.

Various techniques aimed at reducing the ECC or “pump” prime volume (PPV) have been used, including the use of retrograde autologous prime, avoidance of the cardiomyotomy reservoir, and reduction of arterial and venous circuit tubing volume (8–10). In reducing PPV, because hemodilution is decreased, higher Hb levels [Hb] are achieved during CPB, which in turn lower the probability of transfusing allogeneic blood. However, when ANH is used for cardiac surgery, it is not clear how reducing PPV affects the ANH technique. Intuitively, if PPV is reduced, more whole blood may be sequestered during the pre-CPB phase. In this study, computational modeling of the effect of reducing PPV on ANH technique was performed to quantify the impact of PPV reduction and ascertain whether its use in conjunction with ANH might be really beneficial.

METHODS

Task 1: Interactions of Estimated Blood Volume, Pre-CPB [Hb], and PPV Reduction on Predicted CPB [Hb]

Predicted [Hb] during CPB [HbCPB] was calculated using the following formula; [HbCPB] = [EBV/ (EBV + prime volume)] × [HbPre-CPB], where [HbPre-CPB] = [Hb] prior to commencing CPB and EBV = estimated blood volume. Maintaining [HbPre-CPB] and EBV constant, PPV was reduced in 100-mL decrements from 2000 to 0 mL. Predicted [HbCPB] was calculated at each PPV, and the difference noted, to calculate the impact of PPV reduction. Then, maintaining EBV constant, [HbPre-CPB] was reduced in 0.5 g/dL decrements from 16 to 9 g/dL and [HbPre-CPB] calculated as PPV was reduced. Finally, maintaining [HbPre-CPB] constant, EBV was reduced from 8000 to 4000 mL in 500-mL decrements and [HbPre-CPB] similarly calculated as PPV was reduced.

Task 2: Interactions of Estimated Blood Volume and Preanesthetic [Hb] on Volume of Whole Collected During ANH (WBS Volume)

The WBS volume to be collected during ANH (WBANH) was calculated using the following formula (see Appendix); WBANH = EBV × [HbPre-Anes] – [HbTarget] / HbAvx, where [HbPre-Anes] = preanesthetic [Hb]; [HbTarget] = target Hb for ANH; average Hb [HbAvx] = [HbPre-Anes] + [HbTarget]/2. [HbTarget] of 10, 9.5, and 9 g/dL were selected as ANH end points for separate subroutines because this reflects current clinical practice using ANH in patients undergoing cardiac surgery. Maintaining EBV and [HbTarget] constant, the effect of reducing [HbPre-Anes] on WBANH was assessed by reducing [HbPre-Anes] in 0.5 g/dL decrements from 16 to 9 g/dL. Then, maintaining [HbTarget] constant, EBV was reduced in 500-mL decrements from 8000 to 4000 mL and WBANH similarly calculated at each decreasing [HbPre-Anes] value. Finally, maintaining EBV and [HbPre-Anes] constant, PPV was reduced in 100-mL decrements from 2000 to 0 mL and WBANH calculated at each point. [HbTarget] of 10, 9.5 and 9 g/dL also were selected as ANH end points. Computations were voided when [HbPre-Anes] < [HbTarget].

Task 3: Impact of PPV Reduction on Minimum Acceptable Pre-CPB [Hb]

Seven g/dL was selected as the minimum acceptable [Hb] for CPB, ie, the “minimum [Hb] threshold” ([HbCPB-MA]). The minimum acceptable [Hb] prior to the expected hemodilution on pump ([HbPre-CPB-MA]) was calculated using the following equation; [HbPre-CPB-MA] = (EBV + prime volume) × [HbCPB-MA]/EBV. As PPV was reduced from 2000 to 0 mL in 100-mL decrements, [HbPre-CPB-MA] was recalculated at each decremented point. The effect of PPV reduction was then repeated as EBV was reduced from 8000 to 4000 mL in 500-mL decrements. To characterize the impact of PPV reduction on [HbPre-CPB-MA], at each PPV decrement, the difference in [HbPre-CPB] and [HbTarget] was determined to calculate the “excess Hb” ([ExcHb]) over a minimum Hb threshold of 7 g/dL. [ExcHb] was expressed as a percentage (ExcHb%) for hypothetical [HbTarget] of 9, 9.5, and 10 g/dL. A nomogram was constructed to reflect the range of (ExcHb%) as PPV is reduced for different EBV. Finally, WBANH was corrected by [ExcHb] for EBV and selected PPV. The relative change in WBANH, particularly the expansion of WBANH [WB(exp-ANH)], secondary to PPV reduction was then calculated as [HbPre-Anes] was reduced from 16 to 9 g/dL in 0.5 g/dL decrements.

Microsoft®Excel 2002 and GraphPad Prism® 2.01 were used for all computational and graphical functions.

RESULTS

Task 1: Interactions of Estimated Blood Volume, Pre-CPB [Hb], and PPV Reduction on Predicted CPB [Hb]

For an EBV of 8000 mL, as PPV is reduced from 2000 mL, the decrease in [HbCPB] secondary to hemodilution is reduced from 20% to 11.1% and 5.9% for PPVs of 1000 and 500 mL, respectively (Figure 1). This represents a net increase in the [HbCPB], ie, at each 100-mL decrement, the respective increase in [HbCPB] approximates 1%; this change is independent of [HbPre-CPB]. For example, decreasing PPV to 1600 mL in a subject with an EBV of 8000 mL and a [HbPre-CPB] of 16 g/dL produces a [HbCPB] of...
13.3 g/dL or a reduction of 16.9%. However, when PPV is decreased to 500 mL, [Hb CPB] is 15.1 g/dL, or a reduction of only 5.9%.

The increment in [Hb CPB] produced by PPV reduction is inversely proportional to EBV (Figure 2). For example, when PPV is reduced from 2000 to 1000 mL in a subject with an EBV of 7500 mL, the decrement in [Hb CPB] secondary to hemodilution is reduced from 21.1 to 11.8%. In contrast, for a subject with an EBV of 4500 mL, this is reduced from 30.8 to 18.2%. In other words, for an EBV of 7500 and 4500 mL, a 50% reduction in PPV is associated with a 9.3 and 12.6% increase in [Hb CPB], respectively.

Task 2: Interactions of Estimated Blood Volume, Subject Weight and Preanesthetic [Hb] on Volume of Whole Collected During ANH (WBS Volume)

[Hb Pre-Anes] and [Hb Target] directly influence WBAIH in that higher [Hb Pre-Anes] and/or a lower [Hb Target] facilitate the collection of larger WBAIH (Figure 3). For example, assuming a [Hb Target] of 9 g/dL and an EBV of 6000 mL, a [Hb Pre-Anes] of 15.5 g/dL will facilitate the collection of 3184 mL whole blood. In contrast, a [Hb Pre-Anes] of 12 g/dL will facilitate the collection of only 1714 mL, respectively. EBV is directly proportional to WBAIH, ie, as EBV is reduced; the volume of WBAIH also decreases (Figure 4). For example, a [Hb Pre-Anes] of 13 g/dL in a subject with an EBV of 8000 mL will facilitate collection of 2910 mL WB. In contrast, for an EBV of 6000 mL, the WBAIH decreases to 2180 mL.

Task 3: Impact of PPV Reduction on Minimum Acceptable Pre-CPB [Hb]

In Figure 5, a nomogram is depicted in which the predicted change in [Hb Pre-CPB] is plotted as PPV is reduced for varying EBV and a [Hb Target] of 9 g/dL. The nomogram demonstrates that the effect of PPV reduction in elevating [Hb Pre-CPB] is directly proportional to EBV. Initially, subjects with lower EBV will require a higher [Hb Pre-CPB-MA]. However, as PPV reduces, the differences in [Hb Pre-CPB-MA] across varying EBV become smaller. For example, subjects with EBVs of 8000, 6000, and 4000 mL and a PPV of 2000 mL require [Hb Pre-CPB-MA] of 8.7, 9.3, and 10.5 g/dL respectively, to prevent [Hb CPB] falling to less than 7 g/dL. When PPV is reduced to 700 mL,
respective [HbPre-CPB-MA] are 7.6, 7.8, and 8.2 g/dL. Figure 5 further demonstrates that PPV reduction of 800 mL or more produces a positive net gain in [HbPre-CPB], irrespective of subject weight or EBV (relative to a [Hb Target] of 9 g/dL).

In Figure 6, the effect of PPV on (ExcHb%) is shown. PPV produces an approximate 1% increase in the (ExcHb%), for each 100-mL decrement in PPV, whereas (ExcHb%) is inversely proportional to [Hb Target]. For example, in a subject with a PPV of 1000 and [Hb Target] of 10 g/dL, (ExcHb%) over the [HbPre-CPB-MA] is 12.5%. Reducing the [HbTarget] to 9 g/dL increases the (ExcHb%) to 23.6%. In Figure 7, the interaction of PPV, EBV and (ExcHb%) associated with a [HbCPB-MA] of 7 g/dL is shown. (ExcHb%) is estimated with respect to the calculated ([HbPre-CPB-MA]). For each 100-mL decrement in PPV, the increment in (ExcHb%) is inversely proportional to the EBV. For example, PPV reduction produces an approximate 1, 1.1, 1.3, 1.6, and 2% increase in (ExcHb%) for EBVs of 8000, 7000, 6000, 5000, and 4000 mL, respectively. The (ExcHb%) over a specific [HbPre-CPB-MA] produced by PPV reduction, represents the potential additional volume of whole blood that may be collected with ANH, that is, the expansion of WBANH. Therefore, expansion of WBANH may be calculated if [HbPre-Anes], [HbTarget], EBV, PPV, and (ExcHb%) are known.

In Figures 8A and B, the expansion of WBANH is shown for a subject with an EBV of 8000 mL and [HbTarget] of 9 and 10 g/dL, respectively ([HbPre-Anes] decreases from 16 to 9 g/dL from right-to-left). Sequential PPV reduction is associated with proportionally greater expansion of WBANH volume. For example, a [HbPre-Anes] of 14.5 g/dL and [HbTarget] of 9 g/dL facilitates the collection of 3478 mL of WBANH – PPV reduction of 1000-mL increases WBANH by 435 mL (12.5%). In contrast, a [HbTarget] of 10 g/dL facilitates collection of 2,939 mL of WBANH – PPV reduction of 1000-mL increases WBANH by 690 mL (23.5%).

**DISCUSSION**

This computational model demonstrates that sequential PPV reduction prior to the initiation of CPB is associated with incremental increases in WBANH. In addition, PPV reduction reduces the magnitude of hemodilution after the initiation of CPB, particularly in subjects with smaller EBV (Figure 5). Because EBV and WBANH manifest a direct relationship, PPV reduction would therefore offset the limitations on WBANH created by small subject size. Furthermore, for a predetermined [Hb CPB], as PPV reduces, the extrapolated [HbPre-CPB] increases. In this study, relating the impact of PPV reduction to changes in the [HbPre-CPB] and (ExcHb%) was designed to create a measurable effect that could be used to calculate changes in the estimated WBANH. As expected, the increase in [HbCPB] produced by PPV reduction correlates with the increase in (ExcHb%), ie, from 1% (EBV = 8000 mL) to 2% (EBV = 4000 mL) per 100-mL decrement in PPV. However, for a predetermined [HbPre-CPB], although the extrapolated (ExcHb%) increases as PPV is reduced, the actual blood conservation effect is not significant until a positive net gain occurs, as shown in Figures 5 and 7 (positive net gain occurs when PPV reduction > 800 mL for a [HbTarget] of 9 g/dL).

Recent studies suggest that ANH efficacy may be influenced by the actual volume of sequestered whole blood. Rosengart et al. advocate “maximal” intraoperative autologous blood collection as part of their blood conservation paradigm for patients undergoing cardiac surgery (11). Matot et al. report in patients undergoing major liver
resection that whole blood sequestration of 2000 mL was associated with a 10% allogeneic transfusion rate compared with 36% in controls (12). Casati et al. used low-volume ANH, i.e., 5–8 mL/kg (1–2 units) in their study of adult cardiac surgery patients, reporting no difference between patients undergoing ANH vs. controls (4). These reports suggest that variances in ANH technique may influence efficacy and contribute to the divergence of results associated with ANH and cardiac surgery. Indeed, a comprehensive meta-analysis of the effect of ANH on perioperative blood conservation by Bryson et al. cited methodological problems and excessive data heterogeneity in the sample of eligible studies (6). Therefore, any modality, technique or maneuver that potentially increases the volume of WBANH might enhance ANH efficacy.

In this study, an initial PPV volume of 2000 mL and a “minimum” Hb threshold of 7 g/dL were selected, because these are customarily used by practicing perfusionists (7). HbTarget of 10, 9.5, and 9 g/dL were selected as ANH end points, which reflects current clinical practice (1–4). Pre-CPB Hb differs from the preanesthetic Hb [HbPre-Anes] because the latter excludes the effect of intravenous fluids administered by the anesthesiologist prior to initiating CPB. Therefore, [HbPre-Anes] was used for calculation of WBANH. PPV reduction may be achieved using many different methods including retrograde autologous prime, avoidance of the cardiotomy reservoir, and reduction of

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**Figure 5.** Nomogram depicting the predicted change in [HbPre-CPB] as PPV is reduced. EBV from 4000 to 8000 is plotted for a target [Hb] of 9 g/dL. [HbPre-CPB], precardiopulmonary bypass hemoglobin concentration; PPV, pump prime volume; EBV, estimated blood volume.

**Figure 6.** Demonstration of the excess Hb (%) over [HbPre-CPB-MA] of 7 g/dL for target [Hb] of 9, 9.5, and 10 g/dL as PPV is reduced. Excess Hb (%), percent excess hemoglobin; [HbPre-CPB-MA], minimum-acceptable precardiopulmonary bypass hemoglobin concentration.

**Figure 7.** The effect of EBV on excess Hb (%) for [HbPre-CPB-MA] of 9 g/dL and minimum-acceptable cardiopulmonary bypass hemoglobin concentration [HbCPB-MA] of 7 g/dL. EBV ranges from 4000 to 8000 mL. EBV, estimated blood volume; Excess Hb (%), percent excess hemoglobin concentration; [HbPre-CPB-MA], minimum-acceptable precardiopulmonary bypass hemoglobin concentration; [HbCPB-MA], minimum-acceptable cardiopulmonary bypass hemoglobin concentration.
ECC component volume. Cardiomyotomy-less CPB, described by Lilly et al. (9), removes the cardiotomy suction reservoir from the ECC. Retrograde autologous priming is performed by draining blood from the aortic cannula into the ECC in conjunction with displacement of pump prime crystalloid (8). Balachandran et al. performed a unique modification to this approach by draining autologous blood into the ECC via the venous circuit as well (13).

Reduction of the volume of individual components of the ECC has been evaluated in customized and condensed systems in which prime volume is reduced to less than 1000 mL. These include the MAST system (14), the CORx® System (15), and Rousou’s “primeless pump” (16).

In summary, this computational model examined the impact of PPV reduction on ANH performed for adult patients undergoing cardiac surgery with CPB. Sequential PPV reduction from a volume of 2000 mL produces progressive expansion of whole blood sequestration volume, prior to initiation of CPB. Although this model requires confirmation in a prospective clinical or ex vivo simulation study, combining PPV reduction with ANH may represent another practical approach to conservation of allogeneic blood for adult patients undergoing cardiac surgery with CPB.

APPENDIX

The formula used for calculation of WBANH, ie, $WB_{ANH} = EBV \times \frac{[Hb_{Pre-Anes}] - [Hb_{Target}]}{Hb_{Ave}} \times \frac{[Hb_{Pre-Anes}]}{Hb_{Ave}}$, where $[Hb_{Pre-Anes}] = \text{pre-anesthetic [Hb]}$; $[Hb_{Target}] = \text{target Hb for ANH}$; average Hb $[Hb_{Ave}] = \frac{[Hb_{Pre-Anes}] + [Hb_{Target}]}{2}$, as described by Gross (17), is derived from the differential equation; $WB_{ANH} = EBV \times \ln\left(\frac{[Hb_{Pre-Anes}]}{[Hb_{Target}]}\right)$, where $\ln$ = natural logarithm function. This approach differs from the linear formulation, $WB_{ANH} = EBV \times \frac{[Hb_{Pre-Anes}] - [Hb_{Pre-CPB}]}{[Hb_{Pre-Anes}]}$, where $[Hb_{Pre-CPB}] = \text{pre-CPB [Hb]}$, that may be applied when WBANH is collected “en masse” directly from the ECC, post heparinization.

REFERENCES


