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# *Efficacy of Acute Normovolemic Hemodilution Assessed as a Function of Fraction of Blood Volume Lost*

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***Background:*** **It has been recommended that intraoperative acute normovolemic hemodilution (ANH) be considered for patients expected to experience surgical blood loss of 20% or more of their blood volume. Previous mathematical analyses have not evaluated the potential efficacy of ANH in terms of fraction of blood volume lost. Since decrease of oxygen-carrying capacity is a function of erythrocyte loss relative to blood volume, the purpose of this analysis was to provide an assessment of ANH applicable to all blood volumes and to determine whether this recommendation is appropriate.**

***Methods:*** **Equations were developed to describe the fractional blood volume loss (blood volume loss/blood volume; $V_{Rem}/V_{Bld}$) required to reduce hematocrit below a "trigger" hematocrit with maintenance of isovolemia. This is also the minimum fractional blood volume loss required for initial erythrocyte savings by any conservation technique. Equations were also developed to describe the fractional surgical blood volume loss for which ANH will obviate the need for transfusion of erythrocytes from any source other than those removed by ANH, and the fractional surgical blood volume loss required for ANH to save a defined volume of erythrocytes.**

***Results:*** **Acute normovolemic hemodilution can extend the allowable fractional surgical blood loss before erythrocyte transfusion is required. The $V_{Rem}/V_{Bld}$ required to initiate erythrocyte savings is approximately 0.5–0.9. The efficacy of ANH in terms of erythrocytes saved cannot be expressed as a function of the fractional blood volume lost alone. To save 1 unit of erythrocytes requires a fractional surgical blood loss of approximately 0.7–1.2 for the usual surgical patient when the transfusion trigger hematocrit is 0.18–0.21.**

***Conclusions:*** **This analysis suggests that surgical blood loss should be 0.50 or more for ANH to begin to "save" erythrocytes and 0.70 or more of the patient's blood volume for ANH to save 1 unit erythrocytes, for the usual surgical patient with an initial hematocrit of 0.32–0.36 and a transfusion "trigger" hematocrit (the value at which transfusion is initiated) of 0.18–0.21.**

SEVERAL mathematical analyses and clinical studies have failed to resolve the controversy regarding the efficacy of presurgical acute normovolemic hemodilution (ANH). Mathematical analyses have shown that the efficacy of the technique increases with (1) greater initial hematocrit; and (2) lesser "trigger" hematocrit (the hematocrit at which erythrocytes are to be transfused; the "transfusion trigger"); and that a minimum surgical blood loss is required for ANH to have any efficacy.[1,2]

Clinical studies, however, have had difficulty demonstrating efficacy for ANH.[3] The results of clinical studies may disagree because of the definition of "efficacy" or the varied clinical conditions regarding the above factors. Therefore, meta-analyses[3] are of limited value in attempting to resolve the controversy. Nevertheless, two relatively recent publications have recommended that intraoperative isovolemic hemodilution be considered for patients expected to have surgical blood loss of more than 20% of their blood volume.[4,5]

Previous mathematical analyses have examined the efficacy of ANH as a function of the absolute volume of blood lost, initial and trigger hematocrits, and the patient's blood volume.[1,2] There has been no formal analysis of the above suggestion. Decrease of oxygen-carrying capacity depends on blood loss relative to the total blood volume. Previous mathematical examinations of ANH have provided separate analyses of examples of patients with differing blood volumes. This analysis sought to provide a more comprehensive assessment, by examining the efficacy of ANH as a function of the fraction of blood volume lost, and thereby to determine whether the recent suggestions regarding implementation of ANH are appropriate.

## Methods and Results

To determine the "efficacy" of acute normovolemic hemodilution in terms of fraction of blood volume lost during surgery, two separate, but related, issues require consideration:

1. when not using ANH: a determination of the limits of the fraction of blood volume loss when no erythrocyte conservation technique has been used and for which no transfusion of erythrocytes is required (*i.e.*, when the hematocrit or hemoglobin concentration determined as the value requiring transfusion [the "transfusion trigger"] is not reached);
2. when using ANH: a determination of the volume of erythrocytes saved and the additional (more than that when ANH is not used) fraction of blood volume loss permitted (without the need for erythrocytes from sources other than those withdrawn by ANH).

Previous analyses have examined these issues as a function of the absolute volume of blood lost during surgery, but not as a fraction of the blood volume shed. Therefore, earlier analyses were applicable only for the specific examples of blood volume evaluated. For the

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current analysis, mathematical expressions rather than computerized iterations were developed in terms of the fractional rather than absolute volume of blood loss. For these analyses, the following assumptions were made:

1. Isovolemia is maintained for all conditions.
2. Blood loss (when ANH is not used) or ANH proceeds until the trigger hematocrit is reached. Thereafter, when ANH is used, as blood loss continues, the trigger hematocrit and normovolemia are maintained by infusion of erythrocytes collected by ANH and asanguineous fluid. This approach maximizes the additional blood loss permitted when ANH is used. Other approaches, such as performing ANH to a hematocrit greater than the transfusion trigger followed by surgical blood loss to the transfusion trigger results in lesser erythrocyte conservation and lesser additional permitted blood loss (see below).

### *Limits of Blood Loss without Use of Any Erythrocyte Conservation Technique*

When small portions of a fluid are repeatedly replaced by equal volumes of fluid not containing a specific constituent (*e.g.*, erythrocytes), with maintenance of constant fluid volume and with perfect mixing, the decreasing concentration of that constituent can be described mathematically. Transforming the solution of the differential equation describing isovolemic loss of erythrocytes without their replacement[6] from

$$V_{Rem} = V_{Bld}[\ln(H_o/H_t)] \qquad (1)$$

to

$$V_{Rem}/V_{Bld} = \ln(H_o/H_t) \qquad (2)$$

where $V_{Rem}$ = volume of blood shed surgically or removed by ANH
$V_{Bld}$ = blood volume
$H_o$ = initial hematocrit (or hemoglobin concentration)
$H_t$ = final (or trigger) hematocrit or hemoglobin concentration

indicates that the blood loss expressed as a fraction of the blood volume, $V_{Rem}/V_{Bld}$, and not the absolute volume lost, determines the resultant hematocrit ($H_t$) for any given initial hematocrit ($H_o$). This is the standard logarithmic dilution equation. The solution of equation 2 for a range of initial and trigger hemoglobin concentrations provides the limit of the fractional surgical blood volume loss that can be sustained without use of any erythrocyte conservation strategy or without administration of erythrocytes from any source ("allowable surgical blood loss"). Therefore, this also indicates the maximum allowable surgical blood loss without the use of ANH, or any other erythrocyte conservation strategy.

The maximal fractional surgical blood volume loss, $V_{Rem}/V_{Bld}$, that can be sustained without any conservation strategy or transfusion of any erythrocytes from any source is shown in figure 1 for a wide range of $H_o$ and $H_t$. $V_{Rem}/V_{Bld}$ thus represents the minimal fractional surgical blood volume loss that must be sustained before any savings of erythrocytes by ANH is needed. Note that this figure is true for any blood volume. The lower the trigger hematocrit, the greater the fractional surgical blood volume loss required to initiate any savings. For the usual surgical patient, with an $H_o$ of 0.35–0.45 and an $H_t$ of 0.18–0.21, 0.51–0.92 of the blood volume must be lost before any erythrocyte conservation strategy, including ANH, is necessary. If surgical blood loss is less than $V_{Rem}/V_{Bld}$ when ANH is used, ANH will not have permitted an increased allowable blood loss, but it may result in a higher final hematocrit, depending on the strategy of reinfusion of withdrawn blood.

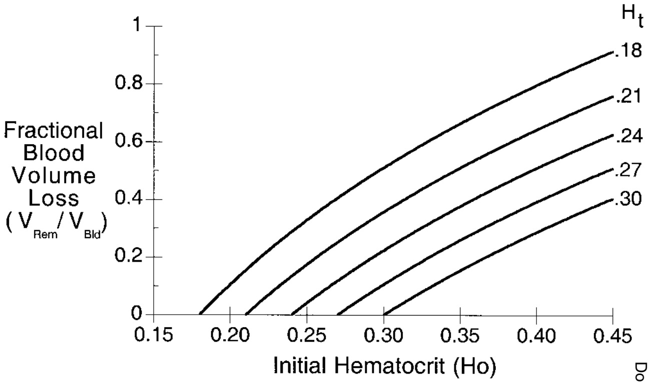

**Fig. 1. Graphic representation of equation 2. Each curve delineates the maximal fraction of blood volume loss ($V_{Rem}/V_{Bld}$), which does not require erythrocyte transfusion or an erythrocyte conservation strategy to maintain a trigger hematocrit ($H_t$) for a given initial hematocrit ($H_o$). Therefore, $V_{Rem}/V_{Bld}$ is also the minimal fractional blood loss required to initiate erythrocyte savings by acute normovolemic hemodilution.**

The larger the initial hematocrit, $H_o$, the larger the fractional surgical blood volume loss must be for any $H_t$ in order for ANH to conserve erythrocytes. For example, increasing $H_o$ from 0.35 to 0.45, the $V_{Rem}/V_{Bld}$ required for ANH to initiate conservation of erythrocytes increases from 0.51 to 0.76 for an $H_t$ of 0.21 and from 0.67 to 0.92 for an $H_t$ of 0.18 (fig. 1).

### *Use of Acute Normovolemic Hemodilution*

The above examples and figure 1 describe the point when ANH begins to conserve erythrocytes. ANH has a range ("window") of surgical blood loss in which it can conserve erythrocytes: blood loss between $V_{Rem}/V_{Bld}$ and $V_{LOSSmax}/V_{Bld}$ (see below). Surgical blood loss less than the "window" (less than $V_{Rem}/V_{Bld}$) does not require transfusion of erythrocytes from any source. Blood loss within the "window" allows for ANH to extend permissible surgical blood loss without resorting to other sources of erythrocytes to maintain the selected hematocrit ($H_t$). However, the $V_{Rem}/V_{Bld}$ for erythrocyte conservation by ANH is finite. It is limited by the volume of erythrocytes removed by ANH. Blood loss more than the window

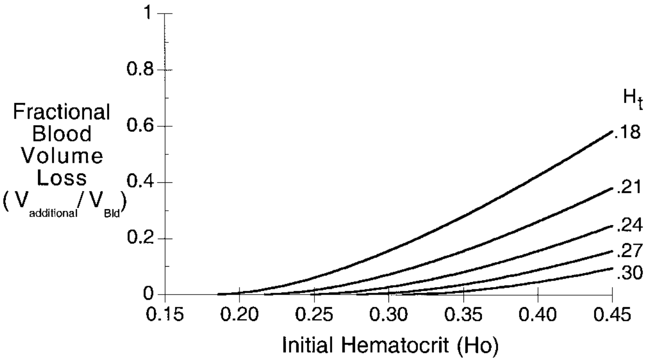

**Fig. 2. Graphic representation of equation 10. Each curve delineates the fractional additional blood volume loss ($V_{additional}/V_{Bld}$), allowed by the use of hemodilution, as a function of initial hematocrit ($H_o$) and trigger hematocrit ($H_t$).**

($V_{LOSSmax}/V_{Bld}$; see below) exceeds the maximum ability of ANH to extend permissible surgical blood loss.

To determine the maximum allowable fractional surgical blood volume loss permitted after performing ANH without transfusion of erythrocytes other than those collected by ANH, the equations below were developed. In these equations, it is assumed that ANH proceeds until $H_t$ is reached. Other strategies may also be used clinically; however, this assumption allows for the maximum increase in allowable blood loss by ANH (see below).

Let $V_{LOSSmax}$ equal the maximum volume of surgical blood loss permitted after performance of ANH.

Let $Rbc_{LOSSmax}$ equal the maximum volume of erythrocytes permitted to be lost surgically after performance of ANH (erythrocytes lost while the hematocrit is maintained at $H_t$ by transfusion of the erythrocytes collected by ANH and asanguineous fluid to maintain isovolemia). Then,

$$Rbc_{LOSSmax} = (V_{LOSSmax})(H_t) \qquad (3)$$

Therefore,

$$V_{LOSSmax} = Rbc_{LOSSmax}/H_t \qquad (4)$$

Let $Rbc_{ANHrem}$ equal the amount of erythrocytes removed (collected) by ANH.

The erythrocytes removed by ANH equals the blood volume times the difference in the patient's hematocrit before and after erythrocyte removal:

$$Rbc_{ANHrem} = V_{Bld}(H_o - H_t) \qquad (5)$$

In as much as the amount of erythrocytes removed by ANH ($R_{ANH}$) equals the total amount available to maintain $H_t$ during surgical blood loss after ANH, the amount of erythrocytes removed during ANH equals the maximal amount of erythrocytes that can be lost during surgery ($Rbc_{LOSSmax}$), without resorting to sources other than erythrocytes removed by ANH for erythrocyte transfusion:

$$Rbc_{ANHrem} = Rbc_{LOSSmax} \qquad (6)$$

Substituting equations 3 and 5:

$$V_{Bld}(H_o - H_t) = (V_{LOSSmax})(H_t) \qquad (7)$$

which reduces to:

$$V_{LOSSmax}/V_{Bld} = (H_o - H_t)/H_t \qquad (8)$$

This represents the maximal fractional surgical blood volume loss that can be allowed when ANH is used, by determining the degree to which the initial hematocrit ($H_o$) can be diluted to reach the trigger hematocrit ($H_t$).

Equation 8 is depicted graphically in figure 3. Each curve represents the upper limit of the ability of ANH to conserve erythrocytes for a range of $H_o$ at $H_t$ of 0.18–0.30. The limits (window of ability) for ANH to conserve erythrocytes is defined by equations 2 and 8 and is depicted in figure 4 for a range of $H_o$ and two values of $H_t$, 0.21 and 0.30. Figure 2 shows the additional fractional surgical blood volume loss ($V_{additional}/V_{Bld}$) that ANH can allow beyond that permitted without the use of any erythrocyte-saving strategy (equation 10; see below). For example, with an $H_o$ of 0.35 and an $H_t$ of 0.21, $V_{additional}/V_{Bld}$ is 0.16; for an $H_t$ of 0.30 with the same $H_o$, $V_{additional}/V_{Bld}$ is only 0.012. For a patient with a blood volume of 5 l, these values of $V_{additional}/V_{Bld}$ represent 800 and 60 ml, respectively.

Equations 2 and 8 and figures 1–4 define the range of $V_{Rem}/V_{Bld}$ for which ANH can be efficacious but do not quantify the savings of erythrocytes. Quantification of erythrocyte savings is necessary to determine the ability of ANH to reduce or obviate transfusion of erythrocytes from sources other than those collected by ANH. To determine the volume of erythrocytes saved by the use of ANH at additional fractional blood volume loss beyond $V_{Rem}/V_{Bld}$ (the maximum loss requiring no conservation strategy or transfusion), the following equations were developed:

Let $Rbc_{Saved}$ equal the volume of erythrocytes saved by the use of ANH.

Let $V_{additional}$ equal the additional allowable blood loss beyond $V_{Rem}/V_{Bld}$ by the use of ANH.

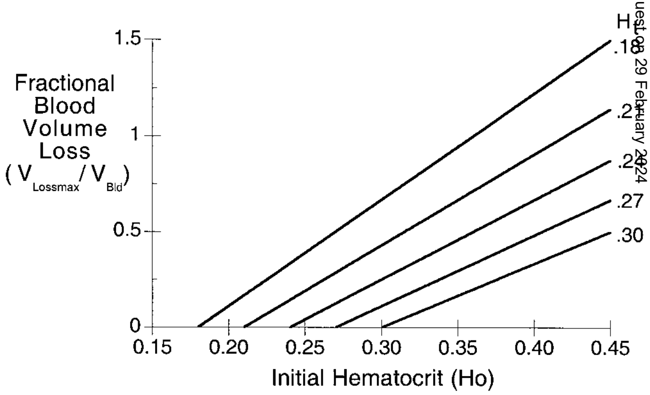

**Fig. 3. Graphic representation of equation 8. Each curve delineates the maximal fraction of blood volume loss, ($V_{LOSSmax}/V_{Bld}$), for which the trigger hematocrit ($H_t$) can be maintained when acute normovolemic hemodilution is used, with a given initial hematocrit ($H_o$).**

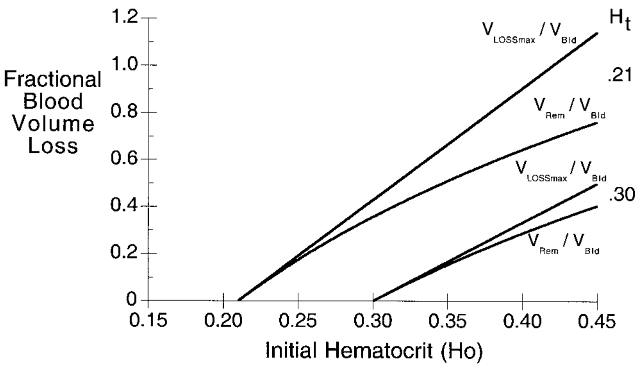

**Fig. 4. The range ("window") of fractional blood volume loss (area between the maximum allowable fractional blood volume loss without [$V_{Rem}/V_{Bld}$], and with acute normovolemic hemodilution [$V_{LOSSmax}/V_{Bld}$]), where acute normovolemic hemodilution can obviate erythrocyte transfusion that otherwise would have been necessary to maintain the trigger hematocrits ($H_t$) of 0.21 and 0.30 had acute normovolemic hemodilution not been used, for initial hematocrit ($H_o$), as defined by equations 2 and 8.**

The volume of erythrocytes saved, $Rbc_{Saved}$, equals the additional allowable blood loss beyond $V_{Rem}/V_{Bld}$ by the use of ANH ($V_{additional}$) multiplied by the trigger hematocrit ($H_t$):

$$Rbc_{Saved} = (V_{additional})(H_t) \tag{9}$$

The additional allowable blood loss equals the maximal allowable blood loss with the use of ANH ($V_{LOSSmax}$) less the maximal allowable blood loss without the use of ANH ($V_{Rem}$):

$$V_{additional} = V_{LOSSmax} - V_{Rem} \tag{10}$$

Substituting equations 1 and 10 into equation 9:

$$Rbc_{Saved} = \{V_{LOSSmax} - [V_{Bld}][\ln(H_o/H_t)]\}\{H_t\} \tag{11}$$

Therefore,

$$Rbc_{Saved}/H_t = V_{LOSSmax} - (V_{Bld})(\ln H_o/H_t) \tag{12}$$

and

$$V_{LOSSmax}/V_{Bld} = [(Rbc_{Saved})/(H_t)(V_{Bld})] + \ln(H_o/H_t) \tag{13}$$

The term $V_{LOSSmax}/V_{Bld}$ is the total fractional blood volume loss required to save the volume of erythrocytes represented by $Rbc_{Saved}$. Note that this cannot be expressed without the inclusion of blood volume as an independent variable: The term $V_{Bld}$ on the right side of the equation cannot be eliminated. Therefore, the erythrocytes saved are a function of blood volume as well as fractional blood volume loss and not the latter alone. Furthermore, this equation is valid only up to the maximal amount of additional fractional blood volume loss permitted by ANH, as defined by equation 8. Blood loss beyond that point exceeds the ability of ANH to conserve additional erythrocytes.

$V_{LOSSmax}/V_{Bld}$ may be calculated, for values of $H_o$, $H_t$, $Rbc_{Saved}$, and $V_{Bld}$, by use of equation 13. The total fractional blood volume loss that must be incurred to produce erythrocyte savings of 180 ml (1 unit) is shown in figure 5 for blood volumes of 3.5 l (an average female patient) and of 5.0 l (an average male patient)[7,8] for a range of $H_o$ (0.15–0.45) and $H_t$ (0.18–0.30). Absence of a depicted curve for a specific $H_t$ and $H_o$ within these ranges indicates that savings of 180 ml of erythrocytes by ANH are not possible for that set of conditions. For example, for ANH to save 1 unit erythrocytes with an $H_o$ of 0.45 and an $H_t$ of 0.21 requires a surgical blood loss equal to 0.92 of the blood volume of an average male patient and 1.01 of the blood volume of an average female patient. However, it is not possible to achieve a similar degree of savings with the same $H_t$, if $H_o$ is less than 0.36 for a typical male patient or less than 0.39 for a typical female patient. The minimum $H_o$ and $V_{LOSSmax}/V_{Bld}$ for a range of $H_t$ required to save 180 ml of erythrocytes is shown in table 1. Savings of 1 unit erythrocytes with a blood volume of 5.0 l requires a minimum $H_o$ of 0.32 if the $H_t$ is 0.18 and a minimum $H_o$ of 0.36 if the $H_t$ is 0.21, and a fractional blood volume loss of 0.61–1.12 over the range of $H_o$ (0.25–0.45) and $H_t$ (0.18–0.30). For the

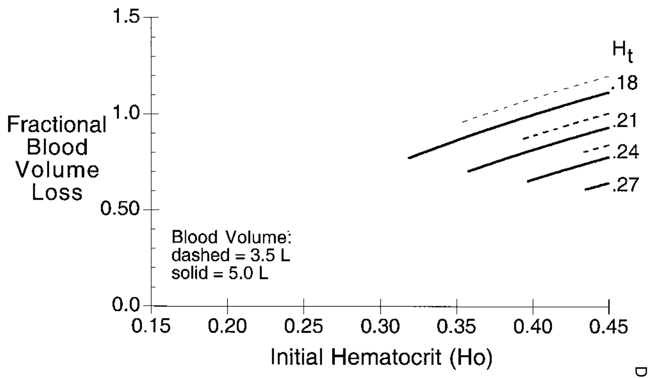

**Fig. 5. Fractional blood volume loss required for acute normovolemic hemodilution to save 180 ml (1.0 unit) erythrocytes for trigger hematocrit, $H_t$, and initial hematocrit, $H_o$, with a blood volume of 5.0 l (solid lines) or 3.5 l (dashed lines), as defined by equation 13. Absence of a plotted curve for a given $H_o$ and $H_t$ indicates that is not possible to save 180 ml erythrocytes for those conditions.**

**Table 1. Minimum Initial Hematocrit ($H_o$) and Fractional Blood Volume Loss ($V_{LOSSmax}/V_{Bld}$) Needed to Save 180 ml Erythrocytes with a Blood Volume of 5,000 ml for a Range of "Trigger" Hematocrits ($H_t$)**

| $H_t$ | Minimum $H_o$ | $V_{LOSSmax}/V_{Bld}$ |
|---|---|---|
| 0.30 | 0.472 | 0.573 |
| 0.27 | 0.435 | 0.610 |
| 0.24 | 0.397 | 0.653 |
| 0.21 | 0.358 | 0.705 |
| 0.18 | 0.319 | 0.772 |

Minimum $H_o$ is the lowest initial hematocrit for which it is possible to "save" 180 ml erythrocytes with the use of acute normovolemic hemodilution when transfusing at the "trigger" hematocrit, $H_t$. $V_{LOSSmax}/V_{Bld}$ is the fractional blood volume that must be lost to achieve "savings" of 180 ml of erythrocytes with the use of acute normovolemic hemodilution at that $H_o$ and $H_t$.

recommended $H_t$ of 0.18 or 0.21, the $V_{Rem}/V_{Bld}$ required to save 1 unit of erythrocytes is 0.77 and 0.71, respectively. If a value of 0.30 is chosen for $H_t$, then $H_o$ must be 0.472 or more with a fractional surgical blood volume loss of 0.573.

With a blood volume of 3.5 l, a minimum $H_o$ of 0.35 or 0.39 is required to save 1 unit erythrocytes if $H_t$ is 0.18 or 0.21, respectively (fig. 5). A fractional blood volume loss of 0.80–1.20 is required over the range of $H_o$ and $H_t$ shown in figure 5 to conserve 1 unit erythrocytes. For the recommended $H_t$ of 0.18 or 0.21, the $V_{Rem}/V_{Bld}$ required to save 1 unit erythrocytes is 0.96 and 0.87, respectively. If a value of 0.30 is chosen for $H_t$, then $H_o$ must be 0.512 or more with a fractional surgical blood volume loss of 0.707.

The calculated $V_{LOSSmax}/V_{Bld}$ required to save 0–180 ml erythrocytes is shown in figure 6 for an $H_o$ of 0.45 with an $H_t$ of 0.18 for blood volumes of 5.0 l (range of $V_{LOSSmax}/V_{Bld}$, 0.92–1.12) and 3. 5 l (range of $V_{LOSSmax}/V_{Bld}$, 0.92–1.20).

For perspective, $V_{LOSSmax}/V_{Bld}$, $V_{Rem}/V_{Bld}$, and $V_{additional}/V_{Bld}$ as a function of $H_o$ for $H_t$ of 0.21 are shown in figure 7, together with the $V_{LOSSmax}/V_{Bld}$ required to save 1 unit erythrocytes with a blood volume of 5.0 l.

The rationale for use of fractional blood loss rather than absolute blood loss to assess the potential usefulness of ANH can be demonstrated by some examples. Table 2 examines three circumstances in each of two patients, both with an initial hematocrit of 0.45, both with a transfusion trigger hematocrit of 0.21, and with blood losses of 4.0, 6.0, and 8.0 l. The hypothetical patients are male: Patient 1 is 60 kg, 157.5 cm in height, with an estimated blood volume of 3.97;[7] l patient 2 is 90 kg, 182.9 cm in height, with an estimated blood volume 5.75 l.[7] The same volume of blood loss represents different fractions of the blood volumes, and thus produces differing results, in these two hypothetical patients. In the larger patient, blood loss of 4.0 l is 0.70 of the blood volume, which is below 0.76 of the blood volume required to cause the hematocrit to reach the transfusion trigger ($V_{Rem}/V_{Bld}$; equation 2 and fig. 1). The final hematocrit would be 0.224; therefore, no strategy or transfusion is required. However, this same volume of blood loss is a greater fraction of the blood volume (1.01) of the smaller patient. This fraction is more than 0.76, indicating that this patient's hematocrit would decrease to a value (0.17) below the transfusion trigger; therefore, a conservation strategy or transfusion would be required. However, the fractional blood loss is less than 1.14, the maximum allowable blood loss if ANH were to be used ($V_{LOSSmax}/V_{Bld}$; equation 8 and fig. 3). Therefore, this degree of blood loss in this patient is within the window of efficacy; use of ANH would obviate the need for transfusion of erythrocytes from a source other than ANH.

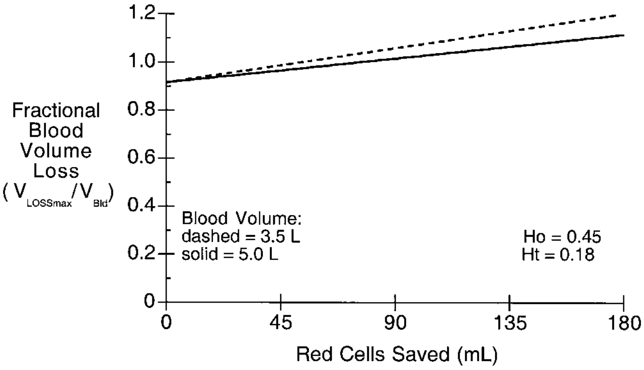

**Fig. 6. Fractional blood volume loss ($V_{LOSSmax}/V_{Bld}$) required for ANH to save 0–180 ml erythrocytes for trigger hematocrit, $H_t$, of 0.18 and initial hematocrit, $H_o$, of 0.45, for blood volumes of 3.5 l (dashed line) and 5.0 l (solid line), as described by equation 13.**

Similarly, ANH has differing efficacy in these two patients when the blood loss is 6.0 l. For the larger patient, ANH would extend allowable blood loss and prevent the need for transfusion of erythrocytes from other sources. In the smaller patient, the fractional blood loss would be more than the maximal savings that can be gained by ANH. Some savings would occur (256 ml erythrocytes), but erythrocytes from a source other than ANH would be required, nevertheless. This also is the case for both patients when the blood loss is 8 l.

However, it should be noted that the volume of erythrocytes saved ($R_{Saved}$) for similar volumes of blood loss does depend on the patient's blood volume (equation 11).

It is also possible to use the equations presented here to determine the relative efficacy of various strategies that may be used in performing ANH. For example, some clinicians perform ANH to a hematocrit greater than the minimal one they will accept during surgery. Performing ANH in a patient with a blood volume of 5 l and an initial

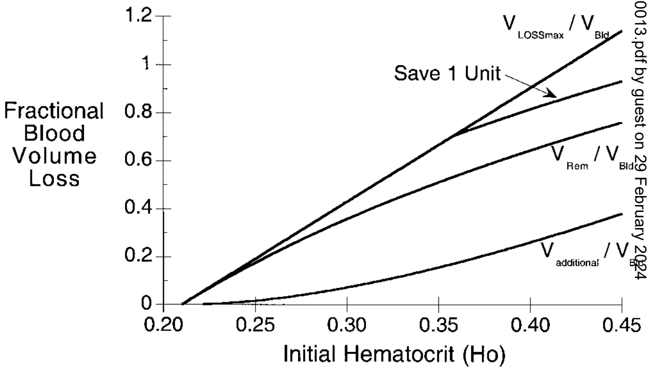

**Fig. 7. Fractional blood volume loss required before any erythrocyte-saving strategy is required ($V_{Rem}/V_{Bld}$), additional fractional blood volume loss permitted by acute normovolemic hemodilution ($V_{additional}/V_{Bld}$), fractional blood volume loss permitted with the use of acute normovolemic hemodilution ($V_{LOSSmax}/V_{Bld}$), and fractional blood volume loss required to save 1 unit erythrocytes ("save 1 unit"), for an $H_t$ of 0.21. All but the latter are independent of blood volume; the fractional blood volume loss indicated as required to save 1 unit erythrocytes is shown for a blood volume of 5.0 l.**

**Table 2. Comparison of Potential Efficacy of ANH in Two Theoretical Patients of Differing Sizes, with Expected Surgical Blood Losses of 4.0, 6.0, and 8.0 l**

| | | | | EBL = 4.0 l | | | EBL = 6.0 l | | | EBL = 8.0 l | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | $V_{Bld}$ (l) | $\frac{V_{Rem}}{V_{Bld}}$ | $\frac{V_{LOSSmax}}{V_{Bld}}$ | $\frac{EBL}{V_{Bld}}$ | Result | $R_{saved}$ (ml) | $\frac{EBL}{V_{Bld}}$ | Result | $R_{saved}$ (ml) | $\frac{EBL}{V_{Bld}}$ | Result | $R_{saved}$ (ml) |
| 1 | 3.97 | 0.762 | 1.14 | 1.01 | $\frac{V_{LOSSmax}}{V_{Bld}} > \frac{EBL}{V_{Bld}} > \frac{V_{Rem}}{V_{Bld}}$ | 203 | 1.15 | $\frac{EBL}{V_{Bld}} > \frac{V_{LOSSmax}}{V_{Bld}}$ | 256 | 2.02 | $\frac{EBL}{V_{Bld}} > \frac{V_{LOSSmax}}{V_{Bld}}$ | 256 |
| 2 | 5.75 | 0.762 | 1.14 | 0.70 | $\frac{V_{Rem}}{V_{Bld}} > \frac{EBL}{V_{Bld}}$ | * | 1.04 | $\frac{V_{LOSSmax}}{V_{Bld}} > \frac{EBL}{V_{Bld}} > \frac{V_{Rem}}{V_{Bld}}$ | 340 | 1.39 | $\frac{EBL}{V_{Bld}} > \frac{V_{LOSSmax}}{V_{Bld}}$ | 460 |

Theoretical patient 1 is male, 60 kg, 157.5 cm tall. Theoretical patient 2 is male, 90 kg, 182.9 cm tall. Blood volume was estimated using the equation from reference 8. For both patients, $H_o = 0.45$ and $H_t = 0.21$. Note that the determinants of the likely utility of acute normovolemic hemodilution (ANH), $V_{Rem}/V_{Bld}$ and $V_{LOSSmax}/V_{Bld}$ are the same for both patients but that the degree of efficacy (erythrocytes saved) is not.

* Use of any conservation strategy, including ANH, or transfusion of erythrocytes would not be necessary (expected blood loss/$V_{Bld}$ is less than $V_{Rem}/V_{Bld}$).

EBL = expected blood loss; see text for definitions of other abbreviations.

hematocrit of 0.40 to an hematocrit of 0.30, followed by surgery, with the hematocrit maintained at 0.21, will increase permissible surgical blood loss by 943 ml beyond that which could be lost in the absence of any erythrocyte transfusion strategy and without the need to transfuse erythrocytes. This is a savings of 198 ml erythrocytes, or 1.1 units erythrocytes. Use of the strategy for which the equations and figures were derived (performing ANH to the minimal acceptable hematocrit, the transfusion trigger) would increase permissible surgical blood loss by 1,535 ml, saving 322 ml erythrocytes, or 1.8 units erythrocytes.

### *Assessment of model*

It would seem useful to determine whether data from humans matches the results predicted from the above equations. To enable such an assessment, a substantial amount of information is required for each individual: information to allow estimation of the patients' blood volume (height, weight, gender); information to permit independent assessment of maintenance of isovolemia in each person; determination of hemoglobin concentration or hematocrit at critical times; strictly followed transfusion protocols; and accurate measurement of blood loss. A perusal of the literature indicated that reports of clinically performed hemodilution do not supply data sufficient to allow for adequate evaluation. The only available data sufficient for the purpose are those we obtained in 21 volunteers.[9] Hemoglobin concentration in those volunteers was decreased acutely in several steps to 5 g/dl while isovolemia was preserved by careful maintenance of constant right- and left-heart filling pressures. The data from those volunteers were used to evaluate the applicability of equations 1 and 2, but could not be used to assess erythrocyte savings (equations 3–13). Expected hemoglobin concentrations produced by isovolemic hemodilution were computed from equation 1, using an estimate of each volunteer's blood volume from the equations of Nadler *et al.*[7] Calculated expected hemoglobin concentrations were compared with the measured values by a modification of the technique of Bland and Altman.[10] The measured hemoglobin concentration, rather than the mean of each pair of measured and computed values, was used as the independent variable because the two hemoglobin values are not of equal validity: The measured value was accepted as correct.

During isovolemic hemodilution, 2.7–6.3 l blood was withdrawn from the 21 volunteers. One hundred forty-seven measurements of hemoglobin concentration were available for analysis. The data show a bias for the calculated hemoglobin concentration to slightly exceed the calculated value (fig. 8; $r^2 = 0.087$; $P < 0.001$). At a measured hemoglobin concentration of 10 g/dl, using a linear regression model, the estimate exceeds the true value by 0.2 g/dl; at a measured hemoglobin concentration of 5 g/dl, the difference is 0.4 g/dl.

## Discussion

This analysis has examined the efficacy of acute normovolemic hemodilution as a function of the fraction of

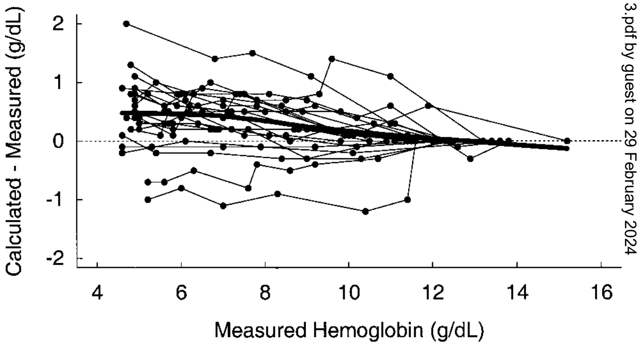

**Fig. 8. Difference between calculated (equation 1) and measured hemoglobin concentrations *versus* measured hemoglobin concentrations in 21 healthy, conscious young adults during hemodilution. Data are from volunteers reported in reference 9. Lines connect data points from each volunteer. The slope of the linear regression equation (not shown) of the data is statistically significantly different from zero ($P < 0.001$), indicating a small bias for the calculated value to exceed the measured value. The heavy line is a "locally smoothed" line produced by S-Plus (MathSoft, Inc., Seattle, Washington).**

blood volume lost during surgery. Mathematic expressions (rather than computerized iterations), and their graphic display, were developed to permit a theoretical but precise determination of the fractional blood loss that may be incurred without the need for erythrocyte transfusion or conservation strategy, the additional fractional blood volume loss permitted by the use of ANH, and the maximum fractional blood volume loss that may be sustained with the use of ANH. The findings for these values are in agreement with earlier mathematical analyses of ANH.[1,2] However, this analysis was performed in terms of fraction of blood volume lost, rather than absolute volume, to provide equations and figures that are valid for all blood volumes. This analysis permits accurate estimation of the potential efficacy of ANH and enables the evaluation of recommendations that ANH be considered when the expected surgical blood loss exceeds 20% of the blood volume.[4,5] For example, a loss of 20% of blood volume would reduce an initial hematocrit of 0.45 to 0.37, a value not ordinarily requiring transfusion or an erythrocyte-saving strategy. The current analysis indicates that, ordinarily, more than 50% of the blood volume must be lost for ANH to begin to save erythrocytes if the National Institutes of Health consensus conference guideline of transfusion at a hemoglobin concentration of 7 g/dl is followed,[11] and that a greater blood loss is needed if the American Society of Anesthesiologists guideline of a hemoglobin concentration of 6 g/dl is used.[12] Lesser loss requires neither erythrocyte conservation strategy nor transfusion. Greater initial hematocrit and lesser trigger hematocrit increase the fractional blood volume loss required before use of erythrocyte conservation techniques or transfusion is required. Greater $H_o$ and lesser $H_t$ also extend the maximal fractional blood volume loss over which ANH can continue to be efficacious.

However, quantification of the efficacy of ANH cannot be gauged in terms of fractional blood volume loss alone. This is because the quantity of erythrocytes required to replace lost cells at $H_t$ is equal to $H_t$ multiplied by the absolute volume of blood lost, and not a function of volume lost relative to the person's entire blood volume.

In the current analysis, an estimate of efficacy of ANH is also provided. Determination of efficacy of ANH is not straightforward. Efficacy is composed of two separate, but related, issues. An erythrocyte conservation strategy, such as ANH, may be termed efficacious if either of the following two occurs. First, if the fractional blood volume lost during surgery exceeds the minimum, as defined by equation 2, but is less than the maximum, as defined by equation 8 (a "window" of efficacy), then no matter how small the erythrocyte savings, transfusion of erythrocytes would not be required, whereas it should have been had ANH not been used.[1] However, given the ordinarily unpredictability of the exact amount of blood loss during surgical procedures with large volumes of blood loss, it is likely to be difficult, *a priori*, to estimate whether the surgical blood loss would fall within this potential window of efficacy, as shown in figure 4. It should also be noted that intraoperative estimates of blood loss typically are approximately half the true loss.[13] Additionally, a clinician may not transfuse a unit erythrocytes if the final hematocrit or hemoglobin concentration is only very slightly below the selected $H_t$.

A second possible definition of efficacy is more subjective. A definition of efficacy may be that of erythrocyte savings of 180 ml (1 unit) or more. This amount of savings decreases exposure of the recipient to erythrocytes from other sources, either autologous or allogeneic, and thus decreases the risks associated with transfusion of these units of erythrocytes.

The current analysis indicates that for a usual surgical patient without presurgical donation of autologous blood, 0.71–1.20 of her or his blood volume must be lost before ANH can save 180 ml of erythrocytes. When examined from the perspective of fractional blood loss required to initiate erythrocyte savings or produce savings of 1 unit of erythrocytes, this analysis does not support the two published suggestions that ANH be considered if fractional surgical blood volume loss, $V_{Rem}/V_{Bld}$, is expected to be 0.20 or more.[4,5]

The potential efficacy of ANH should be judged against its potential risks, which include those potentially associated with the decrease in oxygen-carrying capacity produced by ANH and those associated with the implementation of the technique. It was not the intent of this analysis to evaluate these risks, which are discussed, in part, elsewhere.[14] It should be noted that healthy, resting humans tolerate hemoglobin concentrations of 5 g/dl (reference 9) and oxygen delivery as low as 7.3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ (reference 15) without evidence of inadequate systemic oxygenation. Furthermore, the equations provided here may be used for any chosen trigger hematocrit.

The predicted results described in this report depend on the validity of the mathematical model and the degree to which clinical experience approximates the assumptions and the derived equations. Available data sufficient to test the equations exist only for isovolemic dilution and not for savings of erythrocytes. During isovolemic hemodilution, the calculated hemoglobin concentrations exceeded the measured values by a small amount. There are several possible reasons for this small discrepancy. First, intravascular mixing might not have been sufficiently complete to allow for the measured hemoglobin to reflect accurately the dilution. This appears unlikely because measurements were made 10–15 min after simultaneous blood withdrawal and fluid replacement. Second, it is possible that isovolemia was not maintained in the volunteers. Excessive replacement of withdrawn blood would have produced excessive dilution and lower measured hemoglobin concentrations. However, right- and left-heart filling pressures were care-

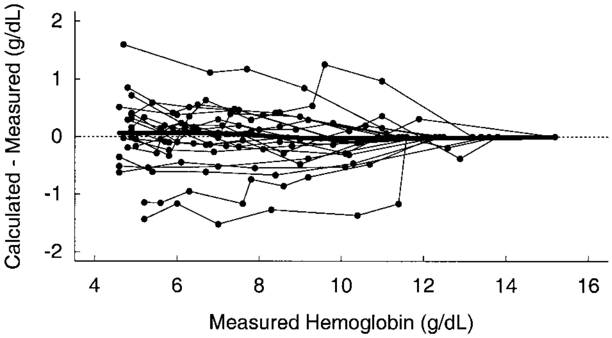

**Fig. 9. Difference between calculated (equation 1) and measured hemoglobin concentrations *versus* measured hemoglobin concentrations in 21 healthy, conscious young adults during hemodilution, after a reduction of 8% of the calculated blood volume. The hemoglobin data are from volunteers reported in reference 9. Lines connect data points from each volunteer. The slope of the linear regression equation (not shown) of the data is not different from zero ($P = 0.2$). The heavy line is a "data-smoothed" line produced by S-Plus (MathSoft, Inc., Seattle, Washington).**

fully maintained unchanged, which should have preserved isovolemia. Thus, the last possibility is the most likely: that the equations used to estimate blood volume are slightly in error. Nadler *et al.*[7] injected $I^{131}$-labeled albumin intravenously in subjects to estimate blood volume. It should be noted that the data used to develop their equations for estimation of blood volume have a variance that is greater than the difference between the estimated and calculated hemoglobin concentrations reported here. In addition, there is an inherent error in the technique of ±5% related to $I^{131}$-labeled albumin injection and measurement errors.[7] Last, their calculations assumed that the intravenously administered albumin was distributed solely in the intravascular space. More recent data, however, indicate that only 90–95% of intravenously administered albumin remains in the intravascular space.[16,17] Therefore, the equations of Nadler *et al.*[7] likely overestimated blood volume, which would have resulted in an erroneously large calculated hemoglobin concentration in this report. Recalculating estimated blood volume to give the least error when comparing measured with calculated hemoglobin concentrations yields a blood volume 92% of that estimated from the equations of Nadler *et al.*[7] Recalculating the expected hemoglobin using blood volumes that are 8% less than those predicted by the accepted equations results in no statistical difference between measured and calculated hemoglobin concentrations (fig. 9). This is the approximate blood volume that would be expected if the equations of Nadler *et al.*[7] were developed based on the current understanding of albumin kinetics. The fitted regression equation of the modified data gives a maximal difference between the calculated and measured hemoglobin concentrations of 0.04 g/dl at measured hemoglobin concentrations between 5 g/dl and 16 g/dl. Nevertheless, the analysis presented here cannot distinguish between errors in the equations for estimating blood volume or our having not maintained isovolemia in the volunteers during hemodilution.

In summary, the efficacy of ANH has been described mathematically in terms of the fraction of surgical blood loss/blood volume. This form of analysis permits accurate estimation of the potential efficacy of the technique. The range of efficacy for ANH may be described by this fraction, but the quantification of efficacy cannot. These calculations do not support the recent recommendations that ANH be considered when the expected blood loss is 0.2 or more blood volumes but rather suggest that expected surgical blood loss should be 0.71–1.20 or more of the patient's blood volume for ANH to be efficacious.

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