

## APŽVALGINIS STRAIPSNIS

### New method of tracing blood hemoglobin concentration to hematocrit ratio for monitoring plasma dilution and osmotic origin shifts in blood

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**Key words:** blood, hemoglobin, hematocrit, dilution, osmolality.

**Summary.** Blood hemoglobin concentration and hematocrit are probably the most widely used parameters for outpatient and inpatient examination. In addition to their inherent significance for evaluation of blood viscosity and oxygen carrying capacity, these parameters are traditionally used as tracers of plasma dilution. Blood test derived results are conventionally recorded on multiple pages in patient's medical records making dynamical investigations tedious and time-consuming. In addition, research results describing plasma dilution by means of hemoglobin or hematocrit are presented in a clinically unpractical way.

A new method, referred to as HBS Graphics (patent pending – USA serial # 60/712809) is introduced for the first time in this article. This method of evaluation of dynamical hemoglobin concentration, hematocrit and mean corpuscular hemoglobin concentration value deploys interfering parameter shifts for the evaluation of plasma dilution in relation to osmotic dynamics. The HBS Graphics complements two coordinate systems – hemoglobin concentration and hematocrit – with incorporated mean corpuscular hemoglobin concentration value specific trends referred to as radiating lines. Isosmotic plasma dilution and erythrocyte volume shifts follow radiating lines, while osmotic shifts induce intertrend shifts. This article also reviews other methods of tracing plasma dilution by means of blood hemoglobin concentration and hematocrit dynamics.

#### Introduction

This paper presents HBS Graphics (patent pending – USA serial # 60/712809) – a new graphical method for recording blood hemoglobin concentration (Hb), hematocrit (Hct) and mean corpuscular hemoglobin concentration (MCHC) that also allows evaluating osmotic (Osm) dynamics in plasma. This method applies to both inpatient and outpatient settings, and more specifically to procedures performed in perioperative and intensive care locations. The new method is directly applicable to the care administered by family doctors, anesthesiologists, intensive care doctors, surgeons, and individuals who deliver care under their medical direction or supervision.

Blood hemoglobin concentration and hematocrit values are used to assist in the evaluation of plasma dilution, blood viscosity and oxygen carrying capacity. These values can be obtained through conventional invasive blood tests or new noninvasive techniques like continuous optoacoustic monitoring of hemo-

globin concentration and hematocrit (1). Assuming an easy, fast and cheap availability of Hb and Hct values, these two endogenous tracers are also preferred for the investigation of plasma dilution induced by intravenous infusions. Hemoglobin dilution-time curves are used for the dynamical investigation of blood volume and plasma dilution in human and animal research studies (2). However, such methods have very limited clinical applicability, because they need precise timing and do not provide blood test derived values other than one of the tracers. The lack of a simple, objective, and dynamic method for evaluation of blood test results applicable to both research and clinical practice is an ongoing deficiency. In addition, blood test results are conventionally recorded on multiple pages and stored within a patient's medical records, making the evaluation and dynamical investigation process inefficient.

Osmotic dynamics in plasma, such as monitoring the effects of diuretics and intravenously infused

osmotically active solutions, is important in many clinical settings. However, plasma osmotic state tests are invasive and require blood withdrawal, so frequent blood sampling leads to significant blood loss and increases the overall cost of treatment. A simple and objective method linking osmotic dynamics with plasma dilution tracer's shifts is missing. Therefore, even available values of plasma osmotic dynamics are of negligible value in monitoring infusion therapy.

This new method, HBS Graphics, later referred to as method, is proposed to address these difficulties. Unlike its predecessors, this method for graphical registration and dynamical assessment of interfering Hb, Hct and MCHC values allows the evaluation of osmotic dynamics in plasma without the need for taking additional blood tests. HBS Graphics also provides a new tool that can be used to more effectively register, organize and file blood test results in a patient's medical records.

There are three specific areas within the prior art that can be enhanced by this new method: 1) methods of plasma dilution evaluation by means of blood hemoglobin as tracer; 2) methods of evaluating interfering Hb and Hct values; 3) tracing plasma osmotic state dynamics. For each of these areas, the existing processes that are used, their deficiencies, and the potential solutions and new approaches as proposed by HBS Graphics, are specified.

### **Methods of plasma dilution evaluation by means of blood hemoglobin as tracer**

#### *Dilution tracers*

Currently, numerous exogenous and endogenous plasma dilution tracers have been used for measuring plasma volume in the evaluation of blood dilution. Exogenous tracers (i.e., indocyanine green or ICG) provide very high precision data, but they are not suitable for non-steady-state conditions inherent to most clinical settings. These tracers require an unchanging blood volume for a period of 30–40 minutes in order to conduct an accurate assessment (3). The well-established endogenous tracers of plasma dilution are blood water, plasma albumin, blood hemoglobin, and hematocrit. Albumin, Hb and Hct tests are available in routine laboratories for blood chemistry, whereas blood water testing finds little application.

Despite its questionable precision, Hb dilution is most frequently used to indicate changes in blood volume. Studies performed by C. H. Svensen and R. G. Hahn point to a degree of dilution similar to that indicated by blood water. Currently, hemoglobin concentration is the preferred tracer for plasma diffusion,

presumably because it is nondiffusible (2). Blood hematocrit has found limited applicability in this field due to its susceptibility for osmotic shifts in erythrocyte volume.

### **Methods**

Presently, two major methods use blood hemoglobin for evaluating plasma dilution. Physiologic spaces and their respective changes with intravenous fluid infusion are analyzed either using indicator dilution and mass balance (4, 5) or volume kinetics (3, 6, 7).

#### *Mass balance*

Mass balance is traditionally used to estimate fluid distribution assuming conventional proportions of physiologic fluid spaces and assuming that Hb is uniformly distributed throughout plasma volume (8, 9). According to this approach, retained in circulation fluid is distributed across fluid spaces based on physiologic volumes and the Starling's equilibrium, which governs the distribution of isonatremic, noncolloid fluids between plasma volume and the interstitial fluid volume, the two components of extracellular volume. In mass balance analysis, dilution of Hb can be used to calculate plasma volume expansion (2). The following equation (9) predicts the effect at equilibrium of fluid infusion on plasma volume, and assumes that no fluid is excreted:

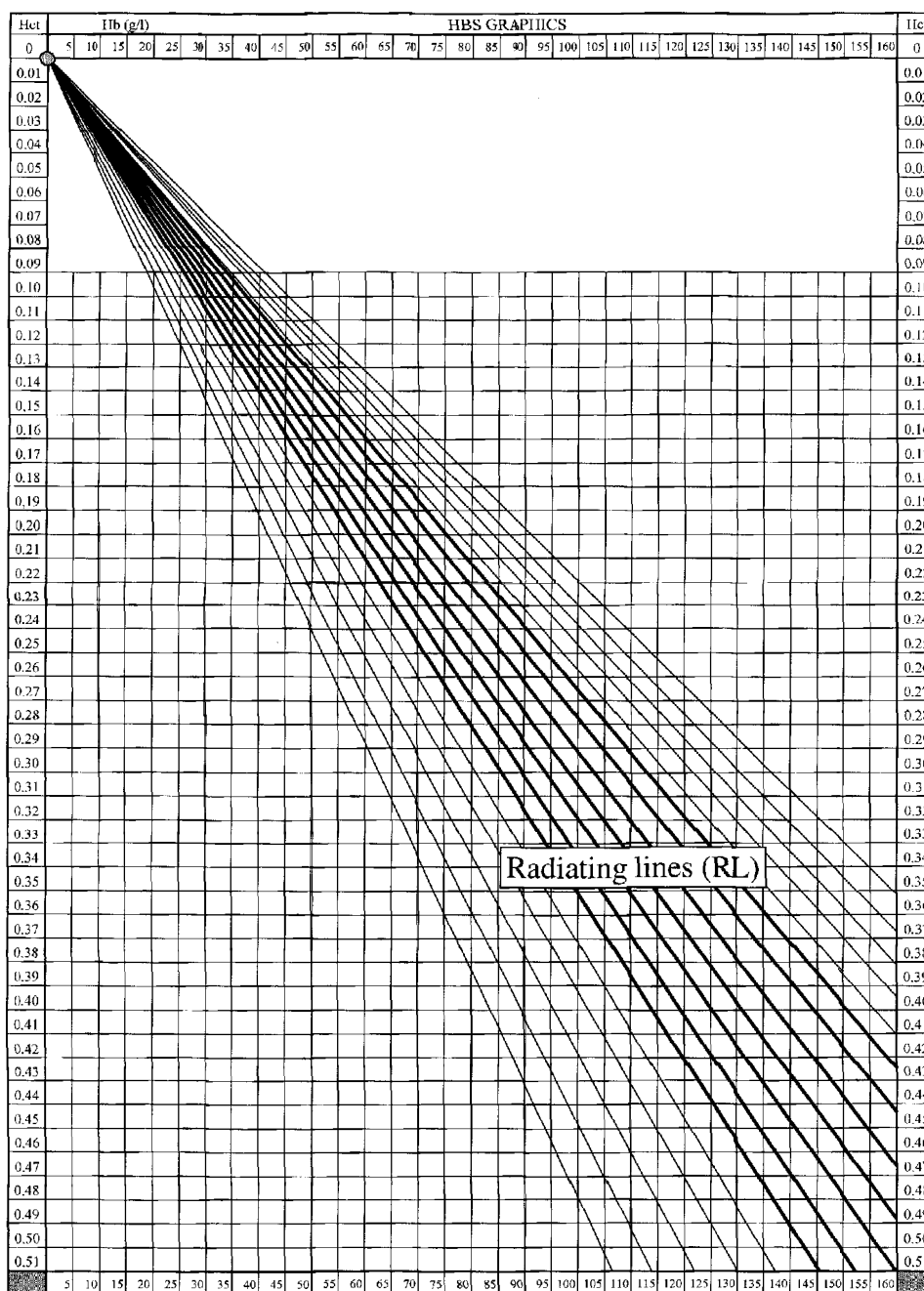
$$PVE=IV\times PV\times V_D^{-1}$$

where: PVE – plasma volume expansion; IV – infused volume; PV – plasma volume;  $V_D$  – distribution volume.

This method does not provide clinically applicable evaluation of plasma dilution, because it assumes a static state. It does not provide clinically practical tools for graphical tracing of Hb, Hct and Osm dynamics either.

#### *Volume kinetic analysis*

Studies focused on the distribution of I.V. fluids during and shortly after their infusion have created the background for volume kinetic models based on well-established pharmacokinetic principles. Volume kinetic analysis and models of volume of fluid spaces (VOFS) were introduced in 1997 by doctor R. G. Hahn and his colleagues (3). Volume kinetics is able to predict the expansion in intravascular volume for a given volume of proper infusion over a set period of time. Volume kinetics is based on serial analysis of tracer dilution. The tracer dilution-time curves obtained by infusions indicate how the plasma expansion of these



**Fig. The graphical form of tracing blood Hb, Hct, MCHC and plasma osmoolality dynamics – HBS Graphics**

Hb – blood hemoglobin concentration; Hct – hematocrit; MCHC – corpuscular hemoglobin concentration.

fluids changes over time, and it appears to be predictable. The dilution-time curves established by monitoring the infusion indicate how the plasma expansion of these fluids changes over time. Hemoglobin dilution-time curves are commonly used by this method for the dynamical investigation of blood volume and plasma dilution in both human and animal studies. However, this method can only be applied through the use of sophisticated software (MatLab Version 3, 4.2 or 5.3 by Math Works Inc., Natick, MA); osmotic

factor-related result corrections require additional blood test-derived data and specific calculations; entering numerous variables into a computer takes time and detracts a physician's attention from the patient. Finally, the derived kinetic modeling results have limited clinical applicability, because they are easily affected by a changing clinical setting. Dynamically changing clinical settings do not follow the standardized dilution-time curves. For example, perioperative bleeding of various intensity and capillary leaks make

preoperative kinetic predictions useless, while offering no method for adjusting related data to the changing clinical conditions. Volume kinetic analysis also does not offer clinically practical tools for graphical tracing of interfering Hb, Hct and Osm dynamics, as dilution-time curves provide data only on the tracer values.

### Methods of evaluating interfering Hb and Hct values

Linear graphical trends are well known to reflect Hb to Hct ratio dynamics during isosmotic plasma dilution. Deviations from linear ratio trends are induced by osmotic shifts that cause osmotic erythrocyte volume changes.

Mean corpuscular hemoglobin concentration or MCHC is a mathematically derived value reflecting Hb to Hct ratio (10, 11). It can be described by the following equation:

$$\text{MCHC} = \text{Hb} \times \text{Hct}^{-1}$$

where: MCHC – mean corpuscular hemoglobin concentration in g/l; Hb – blood hemoglobin concentration in g/l; Hct – blood hematocrit in decimal values.

However, Hct is affected by both erythrocyte number and osmotic volume shifts that induce deviations from linear ratio pattern. Meanwhile MCHC is sensible only to the fluctuations of osmotic origin erythrocyte volume in the setting of unchanging erythropoietic brand content. To our best knowledge, the MCHC value specific trends have never been added to the graphical two coordinate Hb to Hct ratio systems, and the ability to evaluate osmotic deviations using these trends has yet to be established. This limits the existing applicability of methods to nonclinical purposes.

Also, to the best of our knowledge, there are no approved graphical methods for the clinical recording and dynamical evaluation of interfering Hb, Hct, and MCHC dynamics in a patient's medical records. Blood test results are conventionally recorded on multiple pages or files, which make evaluation and dynamical investigation tedious and time-consuming.

### Tracing plasma osmotic state dynamics

Red blood cells (RBCs) in the human body are produced by erythropoiesis and released into blood circulation as normal or abnormal forms that are referred to as erythropoietic brands. There is a continuous release of new cells to replace worn-out cells that are withdrawn from circulation. Normally there are negligible differences in brands that are typically released in the body of the same person. However, pathologic states and blood transfusions can change

this status quo. The main characteristics of the erythropoietic brand are mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) content and osmotic fragility or resistance.

Erythrocyte volume acts as a fluid compartment in osmotic plasma fluid shifts. Osmotic erythrocyte volume deviations are proportional to appropriate MCV shifts. Consequently, plasma osmotic deviations can be traced by mean corpuscular volume dynamics, too. Only MCV, and not MCH, is sensitive to osmotic erythrocyte volume shifts. The MCV value is in direct proportion with ratio Hct to erythrocyte count (EC) as can be seen in the following formula:

$$\text{MCV} = 1000 \times \text{Hct} \times \text{EC}^{-1} \quad (2)$$

where: MCV – mean corpuscular volume (fl); Hct – blood hematocrit in decimal value; EC – blood erythrocyte concentration (million cells per  $\mu\text{l}$ ).

The MCH value is in direct proportion with ratio Hb to RBC count (EC) in the following formula:

$$\text{MCH} = \text{Hb} \times \text{EC}^{-1} \quad (3)$$

where: MCH – mean corpuscular hemoglobin content (pg); Hb – blood hemoglobin concentration (g/l); EC – blood erythrocyte count (million cells per  $\mu\text{l}$ ).

A direct relationship of MCHC, MCV and MCH is obvious from the above described formulas and is expressed as follows:

$$\text{MCHC} = (\text{MCH} \times \text{EC}) \times (0.001 \times \text{MCV} \times \text{EC})^{-1} = \frac{1000 \times \text{MCH} \times \text{MCV}^{-1}}{1} \quad [*1]$$

Normal physiologic (isosmotic) or artificial isosmotic plasma dilution fluctuates around ideal baseline without osmotic deviations, which are induced only at advanced hydration or dehydration. Meanwhile pathologic states and osmotically active intravenous solutions may induce osmotic plasma dilution shifts at any point of baseline hydration. The resulting hemoglobin/hematocrit shifts are very similar to the physiologic shift pattern described above. To some extent osmotic fluctuations are present even when using proper infusion regimens of isotonic intravenous solutions such as Ringer's solution (12).

Tracing osmotic shifts in association with plasma dilution can identify dangerous pathologic or artificial states in constellation of medical diagnostic and treatment conditions, and also during all kinds of infusion therapy measures. It is useful for guiding the application of osmotically active infusion solutions, and also may be deployed to trace the efficacy of osmotically active medication such as diuretics.

Verification tests of osmotic state require patient's blood loss and in many cases, especially for critically

injured patients, require a separate blood testing for Hb and Hct. Lowering the overall number of blood sampling in critically ill patients would favor the results of treatment.

As seen from the above formulas, so many interfering parameters are involved in dilution and osmotic shifts. These have been seen as obstacles toward developing a simple and practical system for plasma dilution and osmotic state monitoring. The evaluation of interfering plasma dilution and osmotic dynamics by means of a MCHC parameter in a clinical setting could reduce time and cut costs.

### The HBS Graphics method

The new method, HBS Graphics, offers a simple, objective and accurate method for the graphical registration of interfering Hb, Hct and MCHC values. It deploys horizontal Hb and vertical Hct coordinate axes along with declining MCHC projections referred to as radiating lines (RL). In Fig., the vertical Hc axis provides hematocrit values in decimal SI units; horizontal Hb axis provides hemoglobin concentration values in g/l; radiating MCHC lines are marked by 30 g/l step values in the graphics. The method provides a data registration form for the three blood test derived parameters in one graphical system. It can be used as a tool for manual or PC based recording of blood test results in a patient's medical records or research result interpretation. It can be operated by means of a conventional Microsoft Office Excel program. Inter-MCHC-trend or just intertrend shifts are deployed as markers of osmotic shifts in plasma as it affects mean corpuscular (erythrocyte) volume and hematocrit. The later concept has been derived from the following theoretical background.

As previously outlined under [\*1], this value is calculated as follows:

$$\text{MCHC} = (\text{MCH} \times \text{EC}) \times (0.001 \times \text{MCV} \times \text{EC})^{-1} = \frac{1000 \times \text{MCH} \times \text{MCV}^{-1}}{1000 \times \text{MCH} \times \text{MCV}^{-1}}$$

where: MCHC – mean corpuscular hemoglobin concentration (g/l); MCH – mean corpuscular hemoglobin content (pg); MCV – mean corpuscular volume (fl); EC – blood erythrocyte count (million cells per  $\mu\text{l}$ ).

We assume that the influence of MCH dynamics on osmotic MCHC shifts is negligible; therefore, it can be ignored. This is because normally the MCH value is not changing if RBCs are not transfused and erythropoietic erythrocyte brand content stays the same, which is normally the case. In such a setting, MCHC and MCV ratios are derived from the equation [\*1], as shown in the following formula:

$$\text{MCHC} = 1000 \times \text{MCV}^{-1}$$

Following is an equation of deviation proportions:

$$\text{MCHC}_2 \div \text{MCHC}_1 = \text{MCV}_1 \div \text{MCV}_2$$

or

$$\Delta \text{MCHC} = \text{MCHC} \times (\Delta \text{MCV})^{-1}$$

where: MCHC<sub>1</sub> – preosmotic shift mean corpuscular hemoglobin concentration (g/l); MCHC<sub>2</sub> – postosmotic shift mean corpuscular hemoglobin concentration (g/l); MCV<sub>1</sub> – preosmotic shift mean corpuscular volume (fl); MCV<sub>2</sub> – postosmotic shift mean corpuscular volume (fl).

This MCHC and MCV relationship during osmotic shifts is deployed by the new method for tracing osmotic plasma shifts. Osmotic shifts induce intertrend shifts as movement across radiating lines within HBS Graphics. In the setting of unchanging MCH value, shift towards increasing MCHC-trend values reflects an increase in plasma osmolality as it results in erythrocyte shrinking; MCV and Hct values decrease in consequent blood tests and consequently decrease in circulating erythrocyte volume. Similarly, shift towards decreasing MCHC-trend values reflects an decrease in plasma osmolality as it results in erythrocyte swelling; MCV and Hct values increase in consequent blood tests and increase in circulating erythrocyte volume.

### Conclusions

The new method provides a graphical system, HBS Graphics, and a simple algorithm for tracing the interfering dynamics of three major blood test parameters in relation to osmotic state of plasma. Interfering blood hemoglobin concentration and hematocrit shifts along the graphical mean corpuscular hemoglobin concentration value specific trends reflect both plasma dilution and osmotic dynamics. Osmotic dynamics in plasma is reflected by intertrend shifts, so it allows interpretation without knowing the osmotic values from separate blood tests. By means of this new method, tracing the osmotic state in plasma may become continuous and noninvasive if combined with hemoglobin and hematocrit value dynamics obtained by apparatus for noninvasive, real-time, accurate, continuous monitoring of hemoglobin and hematocrit.

In addition to its applicability to monitoring of plasma dilution and osmotic dynamics in plasma, the HBS Graphics method is applicable for dynamical blood test-derived hemoglobin, hematocrit and mean corpuscular hemoglobin concentration value registration and easy interpretation in patient's medical re-

cords and research. It will be less time-consuming, and much easier and objective than the existing art, which involves listing and analyzing numerous blood test file pages.

Life threatening conditions can be detected much easier and faster when tracing the blood tests dynamics on one page of HBS Graphics as compared to a number of test file pages, as it is currently done.

## Naujas kraujo hemoglobino koncentracijos ir hematokrito santykio stebėjimo metodas kraujo plazmos atskiedimui ir kraujo osmosiniams poslinkiams nustatyti

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**Raktažodžiai:** kraujas, hemoglobinas, hematokritas, praskiedimas, osmoliališkumas.

**Santrauka.** Kraujo hemoglobino koncentracija ir hematokritas yra bene dažniausiai naudojami parametrai stacionare ir ambulatoriškai tiriant pacientus. Be šiems parametrams būdingos reikšmės, vertinant kraujo krešumą ir deguonies pernašos gebą, įprastai jie naudojami plazmos atskiedimui nustatyti. Kaip įprasta, kraujo tyrimų rodmenys registruojami atskiruose paciento medicininės dokumentacijos lapuose, dėl to jų būklės dinamikos įvertinimas yra gana sudėtingas ir ilgai trunka.

Šiame straipsnyje pirmą kartą aptariamas naujas metodas, pavadintas „HBS Graphics“ (JAV patento Nr. 60/712809). Šis dinaminio hemoglobino koncentracijos, hematokrito ir vidutinės korpuskulinės hemoglobino koncentracijos eritrocite vertinimo metodas jungia tarpusavyje susijusius šių parametru poslinkius plazmos atskiedimui ir osmosinei dinamikai vertinti. Metodą sudaro dvi koordinačių sistemos: hemoglobino koncentracijos ir hematokrito ir į jas įeina vidutinę korpuskulinę hemoglobino koncentracijos vertę atitinkančios projekcijos, pavadintos iradijuojančiomis linijomis. Izoosmosinis plazmos atskiedimas rodo kraujo parametru projekcinio taško judėjimą viena iradijuojančia linija, o osmosinius poslinkius rodo taško judėjimas grafine projekcija, kertančia gretimas iradijuojančias linijas. Šioje literatūros apžvalgoje trumpai aprašomi ir kiti plazmos atskiedimo vertinimo metodai.

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