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The arrow of bioimpedance

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The value of bioimpedance in hemodialysis remains under debate. However, when appropriately used, bioimpedance can provide measures of body hydration characterized by a small error, a high sensitivity to changes in water volume, and, above all, a linear relationship over a wide range of volume changes. These features make it very useful to measure body hydration in hemodialysis patients.

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The adjustment and control of fluid balance remain an important problem in renal replacement therapy, and it is usually addressed by the judgment of clinical signs of hydration, which have a close relationship to the cardiovascular system. This implies that these signs also depend on cardiovascular function and control. The measurement of body mass (BM) is of special importance in this question. It is also well accepted that the clinical estimation of body hydration is largely inaccurate.

The problem of identifying optimal body hydration can be approached by posing two questions. First, which measure or which combination of measures will show an optimum at optimal hydration? Before addressing this problem, one has to answer the other question: Which measure is suitable to identify changes in body hydration? In other words — without focusing yet on the exact location of the target — which measure provides an acceptable accuracy in tracing changes in hydration? An answer to the second question is found in the paper by Kräemer *et al.*[1] in this issue.

The inverse problem

The authors addressed the question by analyzing the relationship between measures of hydration (dependent variables on the y axis) and BM (independent variable on the x axis) (Figure 1). The emphasis was on linear models ($y = kx + d$) characterized by the slope k and the intercept d. The quality of such a relationship is usually measured by the standard deviation between measured and estimated dependent variables (σ_y). For diagnostic purposes, however, one has to solve the so-called inverse problem, which in this case means switching the dependent and independent variables and measuring the standard deviation between measured and estimated independent variables (σ_x). In other words, for the identification of target BM, it is important to know the standard deviation in BM expected with a specific measurement of hydration. The standard deviation in x ($\sigma_x = \sigma_y/k$) is obtained by division of the standard deviation in y (σ_y) by the slope k of the linear regression. The relationship shows that σ_x is proportional to σ_y. This appears trivial. But what is often overlooked is the influence of k. Even if σ_y is comparable among measures and/or techniques, only those with a large k will be successful in providing good estimates of x and hence a good estimate of a potential target BM.

Independent variable

Measurement of BM is simple and inexpensive and can be used to assess acute changes in hydration such as those caused by ultrafiltration during hemodialysis. The reliability of BM measurement for assessing anything beyond acute hydration changes, however, must be questioned, and this uncertainty should be considered in an analysis of target BM. The day-to-day variability in BM in healthy subjects is in the range of 0.3%–0.7% and is approximately twice as large as daily water balance variability, estimated at approximately 0.25%–0.5%.[2] From this, one can see that day-to-day BM variability includes a component that is unrelated to hydration. Thus, even with a perfect measure of body hydration, the BM variability caused by food intake and individual bowel habits can be expected to cause an error in BM estimation in the range of ± 0.25%. Over observation periods of several weeks, the difference between any two BM measurements in stable subjects may also exceed 1% because of normal changes in body composition. Therefore, even the best measures of hydration cannot be expected to provide a perfect linear relationship with regard to BM, and an uncertainty of ± 0.5% must be considered as inherent in BM estimations.

Linearity

For acute changes in the individual patient, body hydration and BM are linearly related, and, most importantly, the linearity is maintained over the whole range of possible hydration changes. The linear relationship is not necessarily maintained when sub-compartments such as the extracellular volume (ECV) or the blood volume are examined. Both compartments are of importance in the study by Kräemer *et al.*[1] In general, the linearity between compartment volumes and BM is maintained as long as the partition of fluid between compartments remains unchanged. Changes in fluid volume confined to one compartment represent a particular case of this condition. In hemodialysis it is now accepted that changes in fluid volume occur under isotonic conditions and that they are confined to the ECV.[3] Therefore, it can be assumed that individual changes in ECV and BM are linearly related in hemodialysis even for large changes in hydration (Figure 1a).

The situation is different with blood volume. Expansion of the ECV by isotonic fluid accumulation leads to an increase in blood volume for small to moderate levels of volume expansion. Continued volume expansion, however, causes the blood volume to level off, with all further fluid entering the interstitial space.[4] This implies a change in the partition of excess ECV between intra- and extravascular spaces. Therefore, changes in blood volume and changes in BM are not linearly related in

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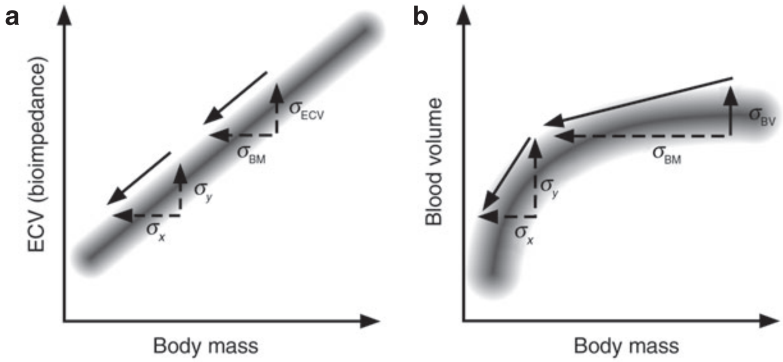

Figure 1 | Linear and non-linear measures of hydration. (**a**) Linear measures. (**b**) Non-linear measures. σ_x, standard deviation of the independent variable; σ_y, standard deviation of the dependent variable; σ_{BM}, standard deviation of estimated body mass; σ_{BV}, standard deviation of measured blood volume; σ_{ECV}, standard deviation of measured extracellular volume.

the individual patient, especially when the whole range of possible hydration changes is examined together (Figure 1b). The cause of this non-linearity can be traced to the non-linearity of vascular compliance — the distension of blood vessels such as the vena cava is limited — and to non-linear aspects of blood volume and blood pressure control that affect the partition of fluid between intra- and extravascular volumes.[4] The inherent non-linearity between changes in blood volume or venous distension and the changes in hydration in the high range of hydration can be expected to increase the standard deviation (σ_y) and to decrease the slope k of the hydration-to-BM relationship, thereby increasing the error (σ_x) in the detection of true changes in BM (Figure 1b).

Dependent variables

In the study by Kräemer *et al.*, hydration was assessed by bioimpedance analysis measuring ECV, vena cava diameter, vena cava collapsibility, and changes in relative blood volume.[1] Bioimpedance provided the best results and was able to detect changes in BM (presumably caused by changes in hydration) with an accuracy of approximately 0.9 kg. Both vena cava diameter and bioimpedance were measured before hemodialysis, so that body fluids could be assumed to be equilibrated. These measurements were also done without interference with the fluid balance and blood pressure control system. In contrast, changes in relative blood volume were measured during hemodialysis, and the equilibrium in fluid balance was intentionally perturbed by an ultrafiltration challenge test. The poor performance of the ultrafiltration challenge test in detecting changes in BM can be understood, as such a perturbation interferes with the blood volume and pressure control systems, which are not linearly related to hydration. Although they are unsuitable for gross fluid adjustment, the real value of relative blood volume measurements may well lie in the fine tuning of fluid balance in everyday treatments when the patient is closer to target hydration.[5,6]

Bioimpedance

Bioimpedance analysis has become popular for the assessment of body water.[7] It has the potential to provide information on so-called extensive variables, such as the volumes of various body water compartments, that are difficult to assess by other techniques. Under the assumption of constant compartment resistivities — which are determined by electrolyte concentrations and temperature — changes in bioimpedance can be used to determine changes in compartment volumes.

Difficulties with bioimpedance analysis are related to body geometry and to inhomogeneities in tissue distribution, especially when measurements are taken from the wrist and the ankle by so-called whole-body bioimpedance analysis. These measurements are susceptible to changes in regional fluid distribution — for example, those caused by changes in body position or by ultrafiltration.[8]

There are, however, important practical issues in favor of bioimpedance. Bioimpedance as analyzed by Kräemer *et al.* provides a volume estimate.[1] This is essential for hemodialysis, because, in the end, the prescription of a target BM calls for a volume to be removed from the overhydrated patient. Therefore, the measurement should also be available before the treatment is started. Of course, this does not prevent serial intradialytic measurements, which may help to better identify the patient's target BM, especially when the patient is close to the target hydration.[9]

Outlook

In conclusion, the arrow of bioimpedance will fly a straight line because, at stable body composition, ECV and BM are linearly related. Moreover, there is little wobbling (small σ_y), and the target is visible from a favorable angle (large k). No matter how far the patient is from the target BM (or clinical dry weight), bioimpedance points in the same direction, independent of the distance between actual and target BM (Figure 1a). The distance to the target, however, relates to locating the exact point of optimal hydration. Bioimpedance can help to answer this question as well, as shown in a previous paper by this group of authors.[10]

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