LETTER TO THE EDITOR

Variability of symmetric dimethylarginine in apparently healthy dogs

Dear Editors,

We wish to comment on: Kopke MA, Burchell RK, Ruaux CG, Burton SE, Lopez-Villalobos N, Gal A. Variability of symmetric dimethylarginine in apparently healthy dogs. J Vet Intern Med. 2018;32(2):736-742, and the erratum that was published online on August 22, 2018.

1. Corrected results: The corrected results from table 2 of critical difference (C\text{CD}) for symmetric dimethylarginine (SDMA) as 5.98 μg/dL and for creatinine as 22.8 μmol/L differ greatly from the original results of 1.34 μg/dL and 0.9 μmol/L, respectively. Likewise, the C\text{DO} expressed as a percentage of the mean (C\text{DO} % mean), an unusual way to describe what is routinely known as reference change value (RCV), has been corrected to 47% (from 10.5%) for SDMA and 23.7% (from 0.93%) for creatinine.

These corrections directly challenge the conclusion that no dogs had stable creatinine measurements.

2. We question reporting C\text{CD} as an appropriate measure for an individual patient, when determined from homeostatic set point. In a population study, RCV is more relevant to report as it applies to all individuals. RCV is used in this study to discuss the stability of creatinine measurements.

3. Symmetric dimethylarginine analyzer variation (CV\text{A}) is very high: It is difficult to make conclusions when CV\text{A} > 0.5CV\text{I}. In this case, CV\text{A} = 0.68CV\text{I}; therefore, it is hard to determine how much variation is due to analyzer or within patient variation. With CV\text{A} being so high, it is inappropriate to determine RCV (or C\text{DO}). Running in samples in duplicate is essentially assessing within-day imprecision, and comparing between only 2 samples should be a “best case scenario” in determining imprecision.

Such a high CV\text{A} of 9.5% indicates an issue with the assay or the equipment used.

4. Varying sampling intervals: Different duration sampling intervals can be expected to give different SDs about the mean (and therefore CVs) with the expectation that shorter duration sampling intervals will give lower CVs. Assessing CV from varying sampling intervals does not “average out” CV or determine a CV applicable to all durations tested but rather tends toward the higher CV (typically the longer duration between testing).

It has been demonstrated in human biological variation studies that variation increases with greater duration between sampling1-3 up to a point where further variation in CV\text{I} is not obtained; the sampling interval where no further variation in CV\text{I} is obtained is considered to be the optimal sampling interval for the measurand. More frequent sampling (smaller between-sample intervals) may suffer from autocorrelation and result in lower CV\text{I}.

We can never know what the best sampling frequency will turn out to be without testing with multiple studies, each with different intervals; however, by providing varying intervals within the one study, we don’t know what we are testing. That is why we recommend that initial studies of biologic variation use a standardized interval of 1 week between collections; this should help minimize autocorrelation but still provide a study over a period of time in which the individual’s health and physiologic status are likely to remain stable.

5. Index of individuality: Fraser and Harris4 noted that “Adoption of the reciprocal index ... would have advantages because analytes with a high degree of individuality would have a high index of individuality.” This almost seems to indicate that the adoption of the traditionally used Index of Individuality \[\frac{1}{\sqrt{CV\text{I}^2 + CV\text{A}^2}/CV\text{G}}\] was an historical accident. The veterinary biological variation group, following on from much veterinary biological variation literature from nearly 2012, has recommended the use of the “reciprocal formula” as reflected in the published biological variation study recommendations.5

6. Conclusion: The conclusion that “SDMA is superior to sCR as a biomarker for detecting early kidney dysfunction” is difficult to justify. Lower CV\text{G} (interindividual variability) and RCV (C\text{DO}) as cited reasons do not, in themselves, reduce “the probability that a given SDMA test result would be outside the individual’s homeostatic set point (HSP) for SDMA” because this conclusion does not take into account the reliability of that individual result. The reliability of the result is indicated by the number of measurements required to determine the HSP which is determined to be 4 times as many for SDMA than creatinine. The HSP formula can be expressed differently to determine the “dispersion” around an individual result in that:

\[\text{Dispersion} = Z \times \sqrt{\left(\frac{CV\text{A}^2}{CV\text{G}}\right) + \left(\frac{CV\text{I}^2}{CV\text{G}}\right)^{1/2}}\]
Taking \( Z = 1.96 \) for 95% confidence and assuming a sample not run in replicate (as is typical in practice), then, with the results of this study, dispersion is 16.73% for creatinine and 33.16% for SDMA.

This means a clinical result at the mean found for creatinine of 96.1 \( \mu \text{mol/L} \) is an estimate in the range of 80-112.2 \( \mu \text{mol/L} \), and a clinical result at the mean found for SDMA of 12.7 \( \mu \text{g/dL} \) is an estimate in the range of 8.5-16.9 \( \mu \text{g/dL} \). Therefore, the probability that a given test result would be outside an individual’s HSP (or not) is also highly reliant upon the test’s imprecision.

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[Correction added on 27 December 2018 after first online publication: First author middle initial added; affiliations corrected.]

REFERENCES

1. Rotterdam E, Katan M, Knuiman J. Importance of time interval between repeated measurements of total or high-density lipoprotein cholesterol when estimating an individual's baseline concentrations. Clin Chem. 1987;33:1913-1915.
2. Voortman A, Melse-Boonstra A, Schulz JM, Burema J, Katan MB, Verhoef P. Optimal time interval between repeated blood sampling for measurements of total homocysteine in healthy individuals. Clin Chem. 2001;47:1839-1841.
3. Sölétormos G, Semjonow A, Sibley PE, et al. Biological variation of total prostate-specific antigen: a survey of published estimates and consequences for clinical practice. Clin Chem. 2005;51:1342-1351.
4. Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci. 1989;27:409-437.
5. Freeman KP, Baral RM, Dhand NK, Nielsen SS, Jensen AL. Recommendations for designing and conducting veterinary clinical pathology biologic variation studies. Vet Clin Pathol. 2017;46:211-220.