Editorial

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Blood sampling for metanephrines: to stick or stick and wait?

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The Endocrine Society guidelines recommend measurements of plasma-free or urinary-fractionated metanephrines for diagnosis of pheochromocytoma and paraganglioma [1]. For the former test, those guidelines and subsequent studies have highlighted the importance of sampling blood in the supine position [1–3]. However, there has been no recommendation about whether sampling should be by venipuncture or via an intravenous cannula with sampling carried out after recovery of the needle stick at the end of the supine rest period. At our center, we use a butterfly and luer lock needle set to allow for recovery from any acute stress of the needle stick. Whether this recovery period is truly necessary is unclear.

Some have suggested little or no need for preanalytical precautions at blood sampling for measurements of plasma-free metanephrines, this based on a common misconception that the metabolites have a long circulatory half-life [4]. Plasma-free metanephrines, however, are cleared from the circulation nearly as rapidly as their catecholamine precursors and show reasonably rapid increases and decreases with stimuli that influence sympathoadrenal activity [5]. For plasma catecholamines, it is known that the stress of a needle stick does result in elevated plasma concentrations [6], though available evidence has indicated little if any effect on the O-methylated catecholamine metabolites [7].

The article by Eijkelenkamp and colleagues provides useful information to settle the aforementioned issues by showing that sampling blood during direct venipuncture does increase plasma-free metanephrines compared to sampling by way of an indwelling cannula inserted 30 min before sampling [8]. The effect was relatively small, but with a modeled drop in specificity from 94.9% to 92.3%, sampling at the time of venipuncture rather than after recovery can be expected to result in a 50% increase in false-positives.

The authors suggest that to counter the expected increase in false-positives, reference intervals should be established according to sampling conditions. It is, however, disputable or at least a matter of differing

opinion whether under all circumstances reference intervals should be established under the same sampling conditions used in patients. For example, dietary influences can substantially increase plasma methoxytyramine into the pathological range [2, 9]. For this reason, blood sampling for measurements that include this metabolite should always be carried out after an overnight fast. Even if patients are routinely sampled without fasting, it would be inappropriate to establish reference intervals under non-fasting conditions as this would lead to false-negatives in some patients with purely dopamine-producing tumors.

The same has already been established with the use of inappropriately high upper cut-offs of reference intervals for plasma metanephrines, where this leads to missed diagnoses in patients with pheochromocytoma or paraganglioma [2, 10]. Thus, as outlined in the Endocrine Society guidelines [1], reference intervals for plasma-free metanephrines should be established for supine sampling conditions. The reason for this recommendation reflects recognition that in patients with pheochromocytomas or paragangliomas, secretion of catecholamines and production of downstream metabolites occur independently of normal homeostatic regulatory mechanisms; thus, such patients do not show increases in plasma-free metanephrines from supine to seated sampling [11], whereas patients without the tumors show rapid increases associated with sympathetic nervous system activation [2, 12].

In essence, any preanalytical influence that reduces the difference in results of a diagnostic test between patients with and without disease will negatively impact the diagnostic performance of that test. While use of higher upper cut-offs established in populations with sampling in seated or non-fasting conditions – or as now outlined with venipuncture instead of an indwelling intravenous line – may certainly improve specificity and minimize numbers of false-positive results, the invariable result is also reduced diagnostic sensitivity and increased potential for missed diagnoses [2, 10].

Presumably, there is considerable inter-individual variability in responses of catecholamines and their O-methylated metabolites to needle stick. Thus, as

pointed out by the authors, the findings of the study are likely most relevant in children and patients with needle phobia. The findings are also important for ruling out false-positive results in patients with previous borderline positive results. For such follow-up, all attempts should be made to minimize sympathoadrenal activation or any other influences that can lead to non-tumor-associated elevations of plasma metanephrines. A prolonged period of supine rest under stress-free conditions is useful in such cases. Warm rather than cold ambient temperature at the time of blood sampling is also associated with lowered plasma concentrations of normetanephrine [13]; this is also useful to consider. Now, as shown by Eijkelenkamp et al. [8], sampling with an indwelling intravenous line can be similarly expected to minimize the likelihood of false-positives.

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