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Diagnosing adrenal insufficiency in critical illness: time to go back to the start.

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Diagnosing and delineating the thresholds for “adrenal insufficiency” in critical illness is still the subject of many manuscripts, hours of conference time and the subject of “position statements” [1]. This is because the existence of the disorder, how to diagnose it (if it exists) and how to treat it are still controversial. The fundamental problem in moving towards answering these questions is that we still do not have an accurate model for HPA axis function in critical illness. The linked paper by Mongardon and colleagues[2] adds another small piece to the jigsaw, but in the process, it illustrates many of the reasons we still haven’t made forward progress. The rationale for performing the study was after Jung *et al* [3] who showed that patients with septic shock, who did not have enlarged adrenal glands, were at an increased risk of death. The proposed hypothesis being that those with a large inflammatory stimulus should have increased arterial flow to the adrenals and in the context of a fixed venous drainage this would lead to engorgement.

The authors in the linked study in *this* issue of Resuscitation analysed 138 suitable admission CT scans from 775 patients admitted to one intensive care unit (ICU) after out-of-hospital-cardiac arrest (OHCA). Two radiologists calculated adrenal volume and attempts were made to correlate these with available tests of adrenal function and outcomes. The CT scans had a median time from return of spontaneous circulation (ROSC) to scan of 3 hrs (IQR 2.5-4.5). This is very early for development of any adrenal dysfunction and is probably only the very beginning of being able to detect neuro-humoral inflammatory changes after an index event[4,5]. It therefore seems an early point to choose a snapshot view of an inflammatory process. The CT scans in the cited Jung *et al* study[3] were within 48 hrs of admission – but given the insidious onset of sepsis, this is likely to be some time after the onset of the illness and this is probably one reason for the differences seen. This illustrates the first point about

HPA-axis function in critical illness; critical illness is a continuum and the point at which the HPA-axis function is observed is important. The changes that occur on the day of critical illness onset are not the same as those on the fifth day, which again are different from those on the twentieth – yet much of the literature treats critical illness as a single, unchanging entity.

The authors make an attempt to correlate both cortisol and co-syntropin tests (if performed) with adrenal gland volume, although the absolute and relative number of patients in which this was achieved was quite low. The Mongardon study[2] (as do many others) take these tests and use them as a reference for other markers of poor adrenal function (in this case – adrenal volume). The temporal relationship of the tests to the observed adrenal volume is not clear, but more importantly, the place of these two tests to diagnose “adrenal insufficiency” has still not been validated and it is therefore not logical to use them as a comparative reference for inadequate adrenal function. With regard to point plasma cortisol samples, there is substantial evidence that both cortisol and ACTH are pulsatile, with amplitudes of up to 400nmol/L in health[6,7], after major surgery[4] and in chronic[8] and critical illness[9]. The oscillations of cortisol are so large in this context that measuring point cortisol values gives us no indication of what the concentration may be even 30 minutes later[10]. Compounding this is that aggregating these pulsatile profiles leads to smooth lines[4]. Therefore, there is a situation in which the model for the aggregated population bears no resemblance to the individuals within that population – yet in much clinical research and practice, we apply the population model to the individual.

Using a dynamic test such as a co-syntropin stimulation test is unlikely to be useful as well. Persistent negative feedback to the pituitary from circulating high levels of cortisol will reduce

secretion of adreno-cortico-trophic hormone (ACTH) with a consequently negative trophic effect on the adrenals[4,9,11]. This is likely to take at least a few days to develop but *will* eventually reduce the size of the adrenal glands. It also means that using a co-syntropin test to diagnose insufficiency may in fact be treating the disorder it is trying to diagnose. Adrenal sensitivity to ACTH can also change after acute inflammatory insults[4]. It would seem sensible to modify the thresholds of a co-syntropin test in this context – but yet this is not done[1]. Co-syntropin was licenced before the introduction of tight drug regulations and there are no studies informing us as to what plasma levels 250µg of co-syntropin achieve in a normal adult in health[12], let alone critical illness. All of these make it difficult to interpret its result. Additionally, the reduced cortisol metabolism seen in critical illness[13] means that circulating cortisol concentrations are potentially higher than in health regardless of whether they respond to a stimulus or not. The validation of these tests, in the middle of the 20th century, were designed for the outpatient setting and not the critically ill, but yet are still used.

Treating critical illness as one disease process rather than delineating between different underlying causes also leads to confusion within the literature, although not in this case. There is a difference between the point inflammatory insult of cardiac arrest and the ongoing stimulus of sepsis. The disease course and outcomes are sufficiently different[14,15] for the HPA axis response not to be treated as a singular.

A more rational approach to understanding the HPA-axis is required. The persistence in performing clinical studies and therapeutic drug trials without an accurate, longitudinal model of dynamic HPA-axis function in the critically ill will not yield the information we need

to answer our questions, nor provide us with a robust baseline to design diagnostic and therapeutic studies. Carefully observing what happens in these different subsets of patients may be regarded as a retrograde step but is what is needed. In this regard, Mongardon and colleagues' study adds value.

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Conflicts of Interest

None

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Competing interests

None

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