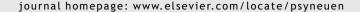


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# Do venepuncture procedures induce cortisol responses? A review, study, and synthesis for stress research



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#### **KEYWORDS**

Cortisol; Stress; Venepuncture; Venipuncture **Summary** Venepuncture procedures are frequently employed to continuously monitor humoral stress markers. As such procedures are conceived as "potent psychological and physiological stressors", there is a need to determine whether venepuncture procedures themselves elicit cortisol responses and if so, how to deal with them appropriately.

In order to assess the rate of cortisol responses to venepuncture, we conducted a literature review, which suggested that venepuncture procedures induce cortisol responses with a probability of approximately 30%. By utilizing Bayesian analysis, this result was integrated with the cortisol data of 18 healthy men who were exposed to a venepuncture procedure twice (time lag: 1 week). The currently observed response rate of 47% differed substantially from the earlier findings, which we attribute to a self-selective sampling of participants. In addition, participants showing a response to the first venepuncture were highly likely to also show a response to the second one. In this regard, we discuss the presumed conditioning of cortisol responses to venepuncture procedures. To prevent the superposition of venepuncture-induced cortisol responses and responses induced by target stressors, we propose a time- and selection-based strategy: cortisol samples taken about 110 min after venepuncture should be virtually adjusted for its superimposing effects. Furthermore, previous experiences of venepuncture were highly predictive for cortisol responsiveness. This association could be utilized in further studies to identify participants who will probably show a cortisol response to venepuncture.

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#### 1. Introduction

To continuously monitor humoral stress markers, venepuncture procedures (or venepuncture for short) are frequently employed in endocrine stress research. Such procedures routinely involve the insertion of indwelling venous or butterfly cannulas into an antecubital vein to maintain access to blood specimens over time (Czarny et al., 1968). Regularly, these specimens are analyzed for a variety of hormones in order to evaluate the association between (changing) hormone concentrations and a target stressor introduced at a specific moment in time. However, venepuncture procedures have also been conceived as "mild pain" (Gunnar et al., 2009, p. 11), "traumatic" (Ginsberg et al., 1988, p. 1257) or "potent psychological and physiological stressors" (Tops et al., 2006, p. 40) and might therefore elicit humoral stress responses themselves. In consequence, stress responses elicited by venepuncture could superimpose the responses elicited by target stressors, and consequently distort research findings (Levine et al., 2007).

To minimize this presumed interference of both kinds of stress responses, the application of the pharmacological five half-lives heuristic seems to be a promising attempt. It states that any (interfering) effect of an administered or secreted substance is virtually excluded after five elimination halflives have elapsed, because at this moment in time 97.5% of its initial amount has already been eliminated by definition (Greenblatt, 1985). Consequently, also stress hormones should remain - after their secretion has been ceased above their steady-state levels for about five half-lives. Regarding two major neuroendocrine stress systems that govern complex stress responses, namely the sympatho-adrenomedullary (SAM) system and the hypothalamus-pituitaryadrenal (HPA) axis, the hormones in guestions are the catecholamines adrenalin and noradrenalin (SAM system) as well as the adrenocorticotrophic hormone (ACTH) and the steroid hormone cortisol (HPA axis; Carrasco and Van de Kar, 2003). In respect to the SAM system, which is reliably activated by venepuncture (Frankenhaeuser et al., 1976; Ward et al., 1983; but see Carruthers et al., 1970), the application of the five half-lives heuristic accumulates to a maximum interval of 15 min (Cohen et al., 1959). Therefore, catecholamine concentrations assessed 15 min after venepuncture are not supposed to be interfered by venepuncture-related catecholamine secretion. On the other hand, the empirical evidence supporting an HPA axis activation in response to venepuncture is inconclusive so far (see below) and even if it was consistent, the application of the five half-lives heuristic can be rarely adopted to control for its confounding effects, as the elimination half-life of cortisol is likely to exceed the half-lives of catecholamines and ACTH by far (Meeran et al., 1993; Trifonova et al., 2013; Veldhuis et al., 1989). Therefore an alternative approach for dealing with venepuncture procedures is needed when the steroid hormone cortisol is primarily utilized to characterize HPA axis activity (Kirschbaum and Hellhammer, 1994).

In order to investigate whether venepuncture procedures elicit cortisol responses and, if so, how to deal with them in endocrine stress research, the present article provides a review of previous findings concerning cortisol responses to venepuncture and their correlation with subjective measures. On the basis of these findings the probability of the

occurrence of a venepuncture-induced cortisol response is estimated. To assess the validity of this estimate, venepuncture-induced cortisol responses of 18 healthy young men were investigated and five common questionnaires were administered to predict their occurrence. Based on that the present study evaluates two possible strategies to deal with this presumed interference of venepunctures: (1) a "time strategy" recurring on the time required until cortisol responses to venepuncture subside, and (2) a "selection strategy" based on a set of exploratory administered questionnaires, which could be utilized to identify the participants being most likely to respond to venepuncture.

## 2. Cortisol responses to venepuncture: a review

Searching for "venepuncture", "venipuncture", "intravenous catheterization" and "cortisol" in PubMed and Psychlnfo data bases by October 2013 revealed N = 129 studies that might have investigated cortisol responses to venepuncture procedures. Out of N = 56 human studies that remained after the rejection of animal studies and double entries (N = 73), only N = 7 studies met the following inclusion criteria (see Table 1; excluded studies are appended in Table A.

- (a) Utilization of a venepuncture procedure to maintain access to blood over time (i.e., biopsies, cystoscopies or sternal punctures are excluded; see Rodriguesz and Terris, 1998; Vanhelleputte et al., 2003).
- (b) Collection of saliva and/or blood samples preceding and/or succeeding the venepuncture.
- (c) Report of a test statistic or a visual comparison of cortisol concentrations that are temporarily related to venepuncture.<sup>1</sup>
- (d) Investigation of a (sub-)sample that consists of full-aged participants without any history of physical or psychiatric disorder (for a review on responses to venepuncture in infancy and adolescence see Gunnar et al., 2009).

Supplementary Table A can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2014.04.012.

Moreover studies examining blood donation were discarded because haemorrhage acts as a hypovolemic stressor, which has been reported to induce cortisol responses in particular if the blood loss exceeds 500 ml (Bellitti et al., 1994; Gann, 1979; Skillman et al., 1967). Proceeding analogously, the references of all studies meeting these criteria were also scanned resulting in a final number of N = 11 studies included in the present review. Data from these studies were independently extracted and cross-validated by two reviewers (LJW and RM).

<sup>&</sup>lt;sup>1</sup> This criterion was established to address the less rigorous methodological standards of the 1970s and 1980s, and to consider that graphics are able to convey more powerful data information than statistical analyses (Everitt, 2009. Without such quantifiable information the intended quantitative integration would not have been feasible.

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