

Recalibration of thinking about adrenocortical function assessment: how the ‘random’ cortisol relates to the short synacthen test results

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Background The short synacthen test (SST) is the most commonly performed investigation to assess adrenal function. Appropriate criteria for when an SST is performed are subject to debate. We investigated how random serum cortisol levels relate to SST response.

Methods We examined random cortisol measurements taken between 04.40–23.55 p.m. results of SST baseline and 30-/60-min cortisol performed over 12 months (225 SSTs) at Salford Royal Hospital. Serum cortisol was measured on the Siemens Centaur Analyser.

A 30–60-min cortisol concentration of ≥ 450 nmol/L defined a pass; 350–449 nmol/L defined borderline.

Results Patients only proceeded to SST if random cortisol was < 400 nmol/L. For those not on corticosteroids for at least 2 weeks, 42/43 (97.7%) cases with random cortisol concentration of ≥ 200 nmol/L had an SST ‘pass’. The relation was less clear with corticosteroid treatment (19/35 cases; 54%).

For those not taking glucocorticoid treatment (including inhaled/topical corticosteroids) in the previous 2 weeks, 91.8% of SSTs were pass/2.7% borderline/5.5% fail. For those on steroids, 51.9% of SSTs were a pass/11.4% were borderline.

In relation to the postsynacthen cortisol pass cut-off of ≥ 450 nmol/L, in 15/207 (7.2%) of cases, the 60-min

cortisol was ≥ 450 nmol/L (adequate adrenocortical function), but 30-min cortisol was below this. In all cases where the 30-min cortisol did indicate a pass (i.e. was ≥ 450 nmol/L) the 60-min cortisol was also ≥ 450 nmol/L.

Conclusion Our findings suggest that if the random cortisol level is ≥ 200 nmol/L, regardless of the time of day and the person was not taking corticosteroid treatment in the previous 2 weeks, SST may not be needed. Our data also suggests that 60-min cortisol retains utility. *Cardiovasc Endocrinol Metab* 10: 137–145 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Primary adrenal insufficiency is caused by the failure of the adrenal glands to produce physiological amounts of cortisol and aldosterone. This can be a consequence of pituitary insufficiency or suppression of endogenous cortisol production as a result of taking exogenous steroids for a prolonged period.

The signs and symptoms associated with adrenal insufficiency, such as chronic exhaustion, fatigue, muscle weakness and weight loss [1], are often nonspecific. Adrenal

insufficiency may cause changes in serum electrolyte levels, particularly low serum sodium and high serum potassium, as well as acute symptoms at times of intercurrent illness. Elevation of blood urea and borderline anemia may also ensue [2].

In order to confirm the diagnosis of adrenal insufficiency, a short synacthen test (SST) is recommended [3], with the insulin tolerance test (ITT) being the gold standard in relation to the assessment of adrenocortical function [2].

The decision about whether to undertake the SST is normally taken by the clinicians looking after the individual, often after consultation with their local clinical laboratory. An SST is generally a hospital day case test, requiring hospital resources in terms of specialist healthcare

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professional oversight (and hence time), often on a day ward, with at least 2 h in hospital for the person undergoing the test.

In the presence of an adequate morning (08:00–09:00 a.m.) serum cortisol (generally accepted as ≥ 400 nmol/L), an SST may not be necessary. Furthermore, a very low basal serum cortisol at any time (< 100 nmol/L), may be assumed to demonstrate cortisol deficiency, thereby often not requiring an SST [4]. Due to variation between assays [5] exact cut-offs may vary.

In this single-center study covering a 12 month period, we undertook to evaluate the relation between random cortisol measurements from samples taken at various times of the day, and the results of the subsequent SST, with a view to understanding how random cortisol levels taken at times throughout the day may relate to the biochemical response to synacthen (pass/borderline/fail) on the STT. Furthermore, in some centers, including our own a 60-min postsynacthen cortisol is measured. Here we looked at whether this has utility in relation to the assessment of adrenocortical function.

This piece of work follows on from the comprehensive evaluation of random cortisol vs. SST assessed adrenocortical function reported by Mackenzie *et al.* [6] in 2019. They found that a morning (8 a.m.–12 p.m.) serum cortisol of < 275 nmol/L identified subnormal-stimulated cortisol with 96.2% sensitivity. For afternoon (12 p.m.–6 p.m.) samples, a cut-off of < 250 nmol/L achieved 96.1% sensitivity for adrenocortical dysfunction.

Our aim was to understand more fully how a random cortisol measurement relates to the SST results in relation to a history of pituitary/nonpituitary disease and recent corticosteroid treatment. Our hypothesis was that many fewer SSTs could be done if we have the right criteria for an SST in place.

Methods

All patients attended Salford Royal Foundation Trust (SRFT) for their tests. Data from 225 consecutive SSTs and prior cortisol measurements, including the time of day when the tests were performed, were obtained from the hospital electronic patient record (EPR). This covered a period of 12 months from mid-June 2017 to mid-June 2018. Where there was more than one prior cortisol measurement, the one closest in time to the date of the SST was taken, where a patient had more than one SST following cortisol measurement the one closest in time to the random cortisol was taken, so as not to be including multiple tests on the same individual.

Serum cortisol was measured by immunoassay on the Siemens Centaur XP analyzer (Erlangen, Germany). All samples were processed at the Department of Clinical Biochemistry at SRFT. The analytical range of this assay

is 13.8–2069 nmol/L. Whenever possible, a patient on oral corticosteroids was changed to oral hydrocortisone for 48 h prior to the SST being performed (if they were not already on this) with the omission of hydrocortisone on the evening before and the morning of the test or omission on the morning of the test if on daily prednisolone/dexamethasone. Inhaled/transdermal corticosteroids were not taken/applied until after the STT but were taken/applied on the day before.

Demographic (age and sex) together with clinical data was obtained from the SRFT EPR. All data was fully anonymized prior to analysis by our statisticians (G.Y. and M.M.). History of pituitary pathology was recorded, as was previous pituitary surgery/conservatively managed pituitary condition. History of autoimmune disorders included type 1 diabetes mellitus (T1DM), primary hypothyroidism and connective tissue disorder were also documented. A full list is given in Appendix 1. All steroid use over the 2 weeks previous to the SST was taken into account and included inhaled, nasal and topical steroids.

Women taking the combined oral contraceptive pill (COCP) or estrogen-containing hormone replacement treatment (HRT) were asked to discontinue these medications for 30 days prior to the SST. We analyzed results of SST baseline, 30- and 60-min cortisol performed over the 12-month period (225 SSTs) and related the results to the pre-SST cortisol. For 18/225 patients, the 60-min serum cortisol was not available.

A 30- and/or 60-min cortisol of ≥ 450 nmol/L was taken as indicative of sufficient adrenal reserve (hereafter defined as a ‘pass’). Failure of cortisol to reach 350 nmol/L postsynacthen administration at either 30- or 60-min postsynacthen was taken as a definite adrenal insufficiency (hereafter defined as a ‘fail’). All other results (350–449 nmol/L) were defined as ‘borderline’; potentially requiring further endocrine evaluation. These are departmentally-agreed criteria that take into account the performance of the Siemens cortisol assay and the findings of the United Kingdom National Audit published in 2010 [7].

This project was deemed by Salford Royal NHS Foundation Trust, Research and Innovation Department as a quality improvement (QI) project. No individual patient was contacted in the course of the evaluation, and data was fully anonymized prior to analysis. This project was denoted as a service evaluation exercise.

The data that we have analyzed to write this paper will be available to researchers in an anonymized form on request to the corresponding author.

All analyses were performed using StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Texas, USA: StataCorp LP. The relation between random cortisol and postsynacthen cortisol is illustrated by a scatter

diagram and Pearson (Spearman) correlation coefficient. Comparison of means was done either by the one-way analysis of variance (ANOVA) and *t* test or corresponding nonparametric tests, Kruskal–Wallis or Mann–Whitney *U* test, respectively. Comparison of proportions was by chi-squared test.

Results

Descriptive data

The baseline characteristics by SST result are given in Table 1. Age at the time of the test varied from 16.8 to 100.3 years. The mean age was 52.9 years (SD \pm 17.8 years). A total of 65.8% of individuals tested were women; 81.6% of men and 83.1% of women were under the age of 70 years.

Of the 225 people included, 61/225 (27.1%) had a prior diagnosis of pituitary pathology. A total 51/225 (22.7%) had a history of the autoimmune disorder, including type 1 diabetes mellitus (T1DM), primary hypothyroidism and connective tissue disorder (Appendix 1). A total 79/225 (35.1%) reported steroid treatment in the previous 14 days. 70/79 (88.6%) were taking systemic glucocorticoids (hydrocortisone, prednisolone or dexamethasone) (discontinued as per protocol period to the SST) and 9/79 (11.4%) regular inhaled or nasal corticosteroids.

With regard to the healthcare setting, 54/225 (24.0%) of tests were carried out on inpatients and 171/225 (76.0%) as outpatients. None of the patients were in a critical care setting (high dependency unit or ICU) at the time of the random serum cortisol or SST.

Taking all tests into account, irrespective of medical/drug history, 183/225 (81.3%) of SSTs were defined as a pass, with 12/225 (5.3%) borderline and 30/225 (13.4%) fail.

For those not on glucocorticoid treatment (including inhaled and topical corticosteroids) in the previous 2 weeks, 134/146 were a pass (91.8%), 4/146 were borderline (2.7%) and 8/146 (5.5%) were a fail.

For the 79 patients on glucocorticoid treatment, 41 (51.9%) of SSTs were a pass, 9 (11.4%) were borderline, with 29 (36.7%) a fail. For those with a history of pituitary disease (irrespective of corticosteroid status), 82.0% of SSTs were a pass and 1.6% borderline, with 16.4% fail.

For inpatient tests (54 tests), the pass rate was 77.8% (9.3% were borderline), while that for outpatient tests (171 tests) was 81.3% (3.5% were borderline) ($\chi^2 = 0.32$, $P = 0.571$).

Relation of baseline cortisol to postsynacthen cortisol level

For those not on corticosteroids

We related baseline serum cortisol to 30-min cortisol for those individuals not on corticosteroids and with no known pituitary pathology. For those not on corticosteroids (including inhaled and topical steroids), 42/43 cases with a random cortisol concentration of ≥ 200 nmol/L had

an SST pass (Fig. 1a). The one case where the 30-min postsynacthen cortisol was 334 nmol/L (i.e. not a 'pass') had an adrenal adenoma.

The reason why there are very few random cortisol levels more than 450 nmol/L in Fig. 1a is that our specialist endocrinology service advises that, unless there is clinical suspicion of adrenal insufficiency in cases where the random serum cortisol is 400 nmol/L or more, an SST is not indicated.

The cortisol values for patients not on steroid treatment in the previous 2 weeks, where both 30- and 60-min SST values were available ($n = 140$), are shown in Table 2 for the random cortisol, 30- and 60-min postsynacthen cortisol values. Random cortisol was numerically higher for the 'pass' group than 'fail', but because of low numbers, there was no statistically significant difference.

For those on corticosteroid treatment

The relation was less clear for those on corticosteroid treatment, including inhaled and topical corticosteroids and those on a decreasing oral corticosteroid regime; for cases with random cortisol of ≥ 200 nmol/L, 19/35 passed (Fig. 1b). Thus 54% with random cortisol of ≥ 200 nmol/L passed the test and 46% failed on the basis of the 30-min cortisol.

For those with a history of pituitary disease

For those with a history of pituitary disease, irrespective of prior steroid use, with random cortisol of ≥ 200 nmol/L, 10/16 were a pass (Fig. 1c). For those with a history of pituitary disease with no recent steroid use, both patients passed the SST.

For none of these categories was there a lower limit of random cortisol below which the SST was invariably a 'fail'.

Random cortisol and time of the day

For 'random' serum cortisol measurements taken between 04.40–23.55 h, (Fig. 2), after 1500 h there was a nonstatistically significant trend for the random cortisol levels to be lower, that is, more readings in the higher than the lower range.

Utility of 30- vs. 60-min cortisol

207/225 SSTs had both a 30- and 60-min cortisol. In relation to the postsynacthen cortisol pass cut-off of ≥ 450 nmol/L, in 15/207 (7.2%) cases, the 60-min cortisol was ≥ 450 nmol/L (adequate adrenocortical function), but 30-min cortisol was below this. In all cases where the 30-min cortisol did indicate a pass (142 cases) (i.e. was ≥ 450 nmol/L) the 60-min cortisol was also ≥ 450 nmol/L.

Age/estrogen effect

We also looked at the age of the person at the time of the test (≥ 70 vs. < 70 years) for people not on corticosteroid

Table 1 Baseline characteristics and cortisol results by short synacthen test (SST) result

Age	Pass	Borderline	Fail	Overall
Age (years) mean	54.8	53.2	64.3	52.9
Range	16.8–100.3	30.1–81.1	32.2–78.9	16.8–100.3
SST result				
All cases: <i>n</i> (%)	183 (81.3%)	12 (5.3%)	30 (13.4%)	225 (100%)
No steroids in previous 2 weeks <i>n</i> (%)	134 (91.8%)	4 (2.7%)	8 (5.5%)	146
Steroids taken in previous 2 weeks <i>n</i> (%)	41 (51.9%)	9 (11.4%)	29 (36.7%)	79
Pituitary disease, <i>n</i> (%)	50 (82.0%)	1 (1.6%)	10 (16.4%)	61
Autoimmune disorder	38 (74.5%)	2 (3.9%)	11 (21.6%)	51

Pass: 30-min cortisol 450 nmol/L or more. Borderline: 30-min cortisol 350–449 nmol/L. Fail: 30-min cortisol <350 nmol/L (see appendix for definition of autoimmune disorders).

treatment. There was no decrease in baseline SST cortisol levels in those in the older age category. A total of 12 women patients were on the combined oral contraceptive pill (COCP) ($n = 3$) or hormone replacement treatment (HRT) ($n = 9$). All discontinued the COCP or HRT for 30 days prior to the SST.

Discussion

Our findings on the basis of observational data suggest that if the random cortisol level (at any time of the day) is ≥ 200 nmol/L, and the person was not on corticosteroid treatment in the previous 2 weeks, there may be no need to perform an SST unless a specific evaluation is required (this does not apply if the woman is taking the COCP or estrogen-containing HRT at the time of the random cortisol given the potential for cortisol binding globulin and so total serum cortisol to be increased in such circumstances). We accept that this paper reports what should be seen as a ‘quasivaldation’ study. Furthermore, the 60-min cortisol appears to have utility, as it enables some people to avoid further testing.

We are not suggesting here that our findings lead to any change in practice. Rather we aim to contribute to the debate concerning (1) when an SST needs to be arranged and (2) whether the 60-min level offers additional value.

In the large study by Mackenzie *et al.* [6] there was suggested guidance with regard to the interpretation of random cortisol and decisions regarding further testing. In this study, we have added a differentiation on the basis of recent corticosteroid use while also examining the utility of the 60-min SST cortisol in order to rule out a proportion of people as having at least partial adrenal insufficiency.

Our findings suggest that if the random cortisol level is ≥ 200 nmol/L and the person was not on corticosteroid treatment in the previous 2 weeks, there may be no need to perform an SST. This particularly applies if the person was not an inpatient at the time of the random cortisol, and therefore, not unduly physiologically stressed through acute/intercurrent illness. None of the patients were in a critical care setting when the random serum cortisol and SST were carried out. We do not have sufficient numbers of patients with pituitary disease and not taking glucocorticoids to draw any conclusions.

This relation appears to hold irrespective of the time of day when the random sample was taken. The absence of any statistically significant relationship between the time of day of the random cortisol (i.e. cortisol levels on patients tested later in the day were not on the whole lower) and the level of random cortisol may relate to the circumstances of having the blood test for cortisol, in terms of the influence of psychological/physical stress on the level of random cortisol.

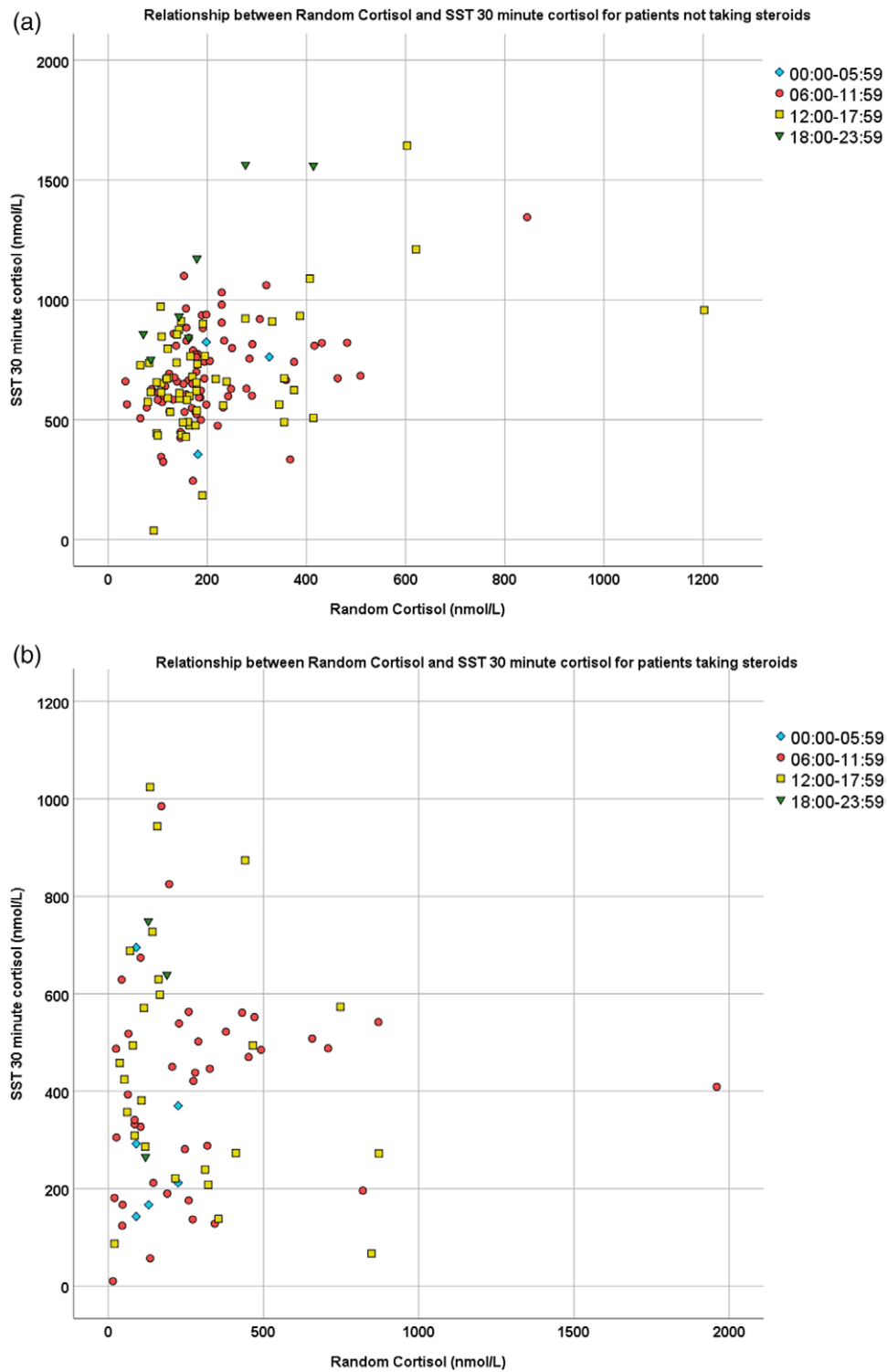
Many individuals on steroid treatment at the time of the test had random cortisol levels of ≥ 200 nmol/L (48.1%) and did not pass the SST. Assay interference by exogenously administered corticosteroids also needs to be taken into account. It is interesting that irrespective of steroid use, 82% of pituitary patients in our series with random cortisol ≥ 200 nmol/L had a pass on the SST. Raising the random cortisol threshold to ≥ 400 nmol/L meant that only one person on steroid treatment with random cortisol in that range failed the SST.

There was no significant difference between the proportion of inpatient (77.8%) vs. outpatient SSTs (81.3%), which were a ‘pass’. However, given that the stress of intercurrent illness can cause cortisol levels to rise, it may be pertinent to limit the utility of the 200 nmol/L cut-point to people not on corticosteroids and to hospital outpatients.

A meta-analysis by Kazlauskaitė *et al.* [5] reported that in the absence of exogenous glucocorticoids, a cut-off threshold for basal morning (0600–1000) cortisol concentrations of 140 nmol/L (5 g/dL) is suggestive of adrenal insufficiency. The diagnosis of adrenal insufficiency was on the basis of an abnormal response to one of the two reference standards for evaluating the integrity of the HPA axis: ITT or overnight metyrapone test. The authors of the meta-analysis relied on individual study investigators to dichotomize the reference test results into adrenal function normal or adrenal insufficiency. The authors also pointed out that the SST lacks sensitivity in the presence of central adrenal insufficiency.

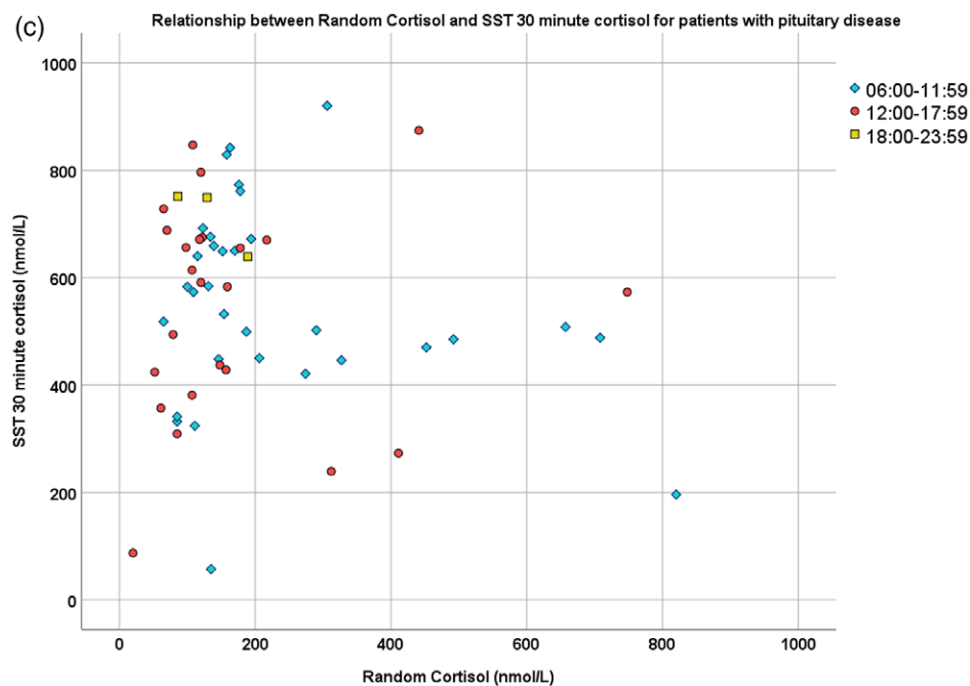
Here, we looked at cortisol levels checked at any time of the day (04.40–23.55) and did not ascertain a lower threshold below which there was adrenocortical insufficiency

Fig. 1



Relation between random cortisol and 30-min postsynacthen cortisol for those not on steroid treatment (including inhaled corticosteroids) in the previous 2 weeks (a), for those with a history of steroid use in the previous 2 weeks (b) and for those with a history of the pituitary disease (irrespective of recent steroid use) (c). Data is shown as scatter plots with 6-hourly time bands denoted by different colored points. (a) Patients not on steroids for 2 weeks prior to the SST. One patient with random cortisol 200 nmol/L 'failed' the SST. (b) Patients on steroids in the 2 weeks prior to the SST. (c) Patients with a history of pituitary disease.

Fig. 1



Continued.

Table 2 Cortisol values (nmol/L) for patients not on steroid treatment in the previous 2 weeks ($n = 146$) given as mean (range)

	Pass ($n = 134$)	Borderline ($n = 4$)	Fail ($n = 8$)
Random cortisol	206 (35–1202)	181 (181–181)	173 (92–367)
30-min cortisol*	732 (428–1643)	355 (355–355)	245 (37–345)
60-min cortisol**	845 (506–1889)	364 (364–364)	307 (38–348)

* $P = 0.009$ for pass vs. fail** $P = 0.005$ for pass vs. fail.

on the basis of the SST. Our focus was on those cases that may not require an SST.

In 7.2% of cases, an adequate response was seen at 60 min but not at 30 min. The 60-min cortisol, therefore, retains utility in ruling out adrenocortical insufficiency. Determination of the 60-min cortisol is done in some endocrine centers and was supported by the work of Chitale *et al.* [8]. The authors of that paper stated that individuals passing the SST only at 60 min tend to exhibit a ‘delayed response’ to exogenous adrenocorticotrophic hormone (ACTH) but, in essence, have normally functioning adrenal glands. If their management was to be based solely on the 30-min sample, they would be commenced on unnecessary, long-term steroid replacement therapy.

In order to justify omitting the 60 min sample, the percentage of individuals with a ‘delayed response’ to synacthen would need to be as close to zero as possible. We and Chitale *et al.* [8] found that a significant percentage of subjects in

both centers are at risk of misdiagnosis without the 60 min sample, so providing evidence for its value in improving the accuracy of diagnosis in the SST has been brought to light. We propose that there may be a subgroup of people who have a delayed response to synacthen in whom measurement of the 60-min cortisol is helpful. Indeed, on the basis of our data, it may be advocated that the 60-min value is preferable to the 30-min value. This conclusion was also supported in a recent paper by Butt *et al.* [9], who looked at 849 people undergoing SSTs and reported that 9.5% of patients had a suboptimal response at 30 min, but reached the threshold value at 60 min.

Our aim with this relatively small series is to stimulate debate in terms of (1) when an SST needs to be arranged and (2) whether the 60-min level offers additional value. The SST is an expensive test in terms of hospital staff time – in most countries, the test is performed as a hospital day case – and also entails significant inconvenience for the patient. The undertaking of less SSTs as a whole by application of the 200 nmol/L cut-point for random cortisol might well free up resource for measurement of the 60-min postsynacthen cortisol in terms of staff time. Certainly, a proportion of people passed on the basis of the 60-min cortisol when they would not have passed on the basis of the 30-min cortisol.

With regards to the interpretation of the SST result itself, concurrent factors, such as the taking of the oral contraceptive pill or HRT, may influence the results [10]. Immunoassays

use different detection antibodies that provide results that may demonstrate significant bias between methods. For example, the low reference limit for cortisol 30 min after corticotropin stimulation ranges from 418 to 574 nmol/L (15.2–20.8 g/dL) [11,12]. The actual cut-point used in clinical practice to make the diagnosis should be on the basis of assay-specific normative data. The laboratory providing the result should be able to provide the performance bias of the cortisol method in use. There is the possibility in the future of the application of an adjustment factor between different assays to facilitate national and international comparison as is done for some other analytes.

Traditionally, a peak cortisol concentration after acute stimulation with corticotropin exceeding 500 nmol/L (18 g/dL) is accepted as evidence for sufficient adrenocortical responsiveness [12–16], but studies advocating this level generally do not allude to the between assay differences. Importantly Erturk *et al.* [17] asserted some time ago that the baseline morning serum cortisol concentration has limited predictive power in differentiating between normal and impaired HPA function and that insulin-induced hypoglycemia is still the best indicator of the integrity of the response of the HPA axis to stress. Insulin-induced hypoglycemia is no longer practical in most hospital investigation units.

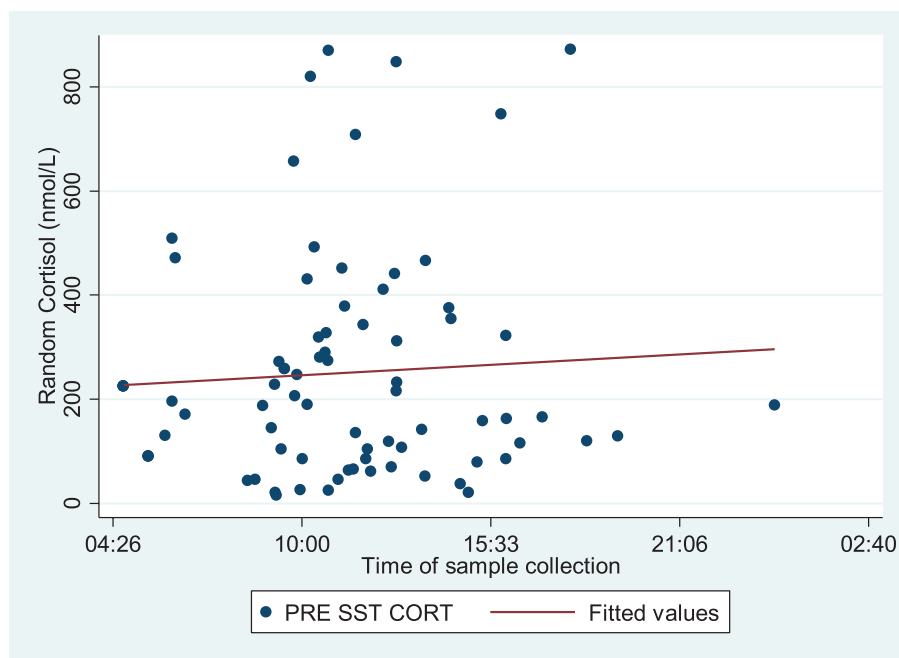
In a separate paper, Struja *et al.* [18] showed that basal cortisol levels ≤ 100 and ≥ 450 nmol/L, respectively, ruled

in adrenocortical insufficiency and ruled out adrenocortical insufficiency, abolishing the need for formal ACTH testing in such circumstances. Furthermore, Gasco *et al.* [19] reported that the cut-off of morning serum cortisol concentration that best predicted a deficient response to ITT was ≤ 126.4 nmol/L, while the cut-off of morning serum cortisol concentration that best predicted a normal response to ITT was >444.7 nmol/L [19].

In our study, there was a slight difference in the number of people deemed as a pass on the SST if baseline cortisol was 200 nmol/L or more between a 30-min cortisol cut-off of 450 nmol/L (4/81 did not pass) vs. a 30-min serum cortisol cut-off of 500 nmol/L (6/81 did not pass).

In relation to strengths and weaknesses, we were able to access the clinical details on all the people undergoing an SST at our hospital over a 12-month period. All cortisol measurements were performed on the same assay platform, and all the outpatient evaluations were carried out on our day ward. Our findings may have more weight for random cortisol measurements taken after 1500 h in view of the diurnal variation in serum cortisol levels. The purpose of our paper is to assert (with evidence) that for any assay, there is a cut-point lower than 400 nmol/L for random cortisol vs. likely adrenocortical insufficiency rather than precisely defining that cut-point. We recognize that there are differences between assay platforms and within assay platforms. For example, the Siemens Advia Centaur

Fig. 2



Relation between random cortisol levels (nmol/L) and time of sample collection.

platform as used here has a positive bias vs. mass spectrometry of 11–14%, whereas the Abbott Architect has a negative bias vs. mass spectrometry of –5.0 to –6.5%.

This study represents an evaluation in a real-world setting. Hence, we did not have sufficient individuals with a measurement of ACTH to include this in our analysis, the decision as to whether to proceed to an SST was made by the clinician on the basis of laboratory recommendation. While caution is always the main consideration in terms of not missing adrenocortical insufficiency, in this retrospective analysis, we had no influence on which individuals proceeded to an SST following the cortisol check. This paper must be seen as a ‘quasivaldation’ study. Nevertheless, our findings may help to guide clinician decision-making.

It should also be pointed out that the reason why there are very few random cortisol levels more than 450 nmol/L in Fig. 1 is that our endocrinology service advises that, unless there is clinical suspicion of adrenal insufficiency in cases where the random serum cortisol is 400 nmol/L or more, an SST is not indicated. Furthermore, the random serum cortisol cut-off of 200 nmol/L or more is on the basis of the Siemens assay platform.

Conclusion

In conclusion, our findings suggest that if the random cortisol level is ≥ 200 nmol/L and the person was not on corticosteroid treatment in the previous 2 weeks, there may be no need to perform an SST. Exclusions include women on the COCP or on estrogen-containing HRT. In 7.2% of cases, an adequate response was seen at 60 min but not at 30 min. The 60-min cortisol, therefore, retains utility as a tool to assess adrenal insufficiency. Performing fewer ‘unnecessary’ SSTs would potentially free up resource on day units for the 60-min test.

Any reduction in the number of ‘unnecessary’ SSTs will reduce hospital investigation costs and result in less inconvenience for patients. Clearly, a larger study is required before any definitive conclusions can be drawn. Finally, standardization of assays in terms of the cortisol reference range for the SST must be a priority for laboratories.

A single measurement of serum cortisol carries the potential significantly to reduce the need for dynamic testing in the investigation of adrenal insufficiency

What is known about this subject

- The short synacthen test (SST) is the most commonly performed investigation to assess suspected adrenocortical insufficiency. The criteria for when an SST should be performed is subject to debate.
- In the presence of adequate random serum cortisol, an SST may not be necessary.

What this paper adds

- We related random serum cortisol measurements taken between 04.40–23.55 h to the results of 225 consecutive SST baseline and 30-/60-min cortisol performed over 12 months (225 SSTs) at a single center. We also looked at the value of measuring 60-min as well as 30-min postsynacthen cortisol.
- Our findings suggest that if the random serum cortisol level (at any time of the day) is ≥ 200 nmol/L, in individuals not on exogenous glucocorticoid therapy, and not taking any estrogen therapy at the time of the random cortisol check, there may be no need to perform an SST.
- The 60-min cortisol retains utility as part of the SST as it enables some people to avoid further testing who otherwise would have to undergo this.

Summary

- A single measurement of serum cortisol with careful interpretation carries the potential significantly to reduce the need for dynamic testing in the investigation of adrenal insufficiency.

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A.H.H. and A.R. conceived the study. M.M. and L.M. collected the data. M.M., A.A.F. and G.Y. conducted the data analysis. C.J.D., M.L. and A.A.F. provided perspective from THE laboratory. A.N. assisted with the literature review. M.M., L.M., G.Y., M.L., S.D., A.R., A.N., A.A.F., C.J.D., P.T. and A.H.H. all contributed to the writing of the article. A.A.F. and P.T. provided an overview of the article.

Dr. Heald as the corresponding author affirms that this is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have

been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

As this project was deemed by our local Research and Development Committee as a quality improvement (QI) project, no individual patient was contacted in the course of the evaluation, and data was fully anonymized prior to analysis, it was not felt that formal ethics permission was required.

Dissemination to interested patient groups both locally and nationally will be done once the analysis has been finalized.

Patient consent was not deemed necessary as no individual patient was contacted or asked to do anything beyond their usual clinical care.

We used patient-level data which was fully anonymized prior to analysis. Any requests for access to this data should be made to the corresponding author, Dr Adrian Heald.

Conflicts of interest

There are no conflicts of interest.

Appendix 1: Autoimmune diseases

Arthropathies (rheumatoid arthritis, inflammatory arthropathy, ankylosing spondylitis) $N = 12$

Inflammatory bowel disease (Crohn's ulcerative colitis) $N = 10$

Autoimmune thyroid disease $N = 9$

Type 1 diabetes $N = 6$

Adrenal insufficiency $N = 3$

Systemic lupus $N = 2$

Celiac disease $N = 2$

Sjogren's $\times 1$

Pancreatitis $\times 1$

Eczema $N = 1$

ANCA vasculitis $N = 1$

Primary biliary cirrhosis $N = 1$

$N = 4$ patients had more than one autoimmune diagnosis

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