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CASE REPORT

The ABC of weaning failure – testosterone

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Abstract

This report presents a case of complicated and consistently failing weaning attempts in a male ICU patient admitted with respiratory failure. A systematic failure-to-wean analysis was performed but offered insufficient help in this case. Endocrinological evaluation showed a lowered total testosterone which was supplemented after other courses of action seemed exhausted. Interestingly, supplementation was followed by a sudden clinical improvement and successful weaning.

Testosterone levels generally decrease as part of extensive hormonal alterations in critical illness and are inferred to contribute to the catabolic state frequently seen in critically ill men. Low testosterone values have been linked with weaning failure and multiple other adverse outcomes, but studies concerning the effects on weaning are few and not comprehensive. More research concerning testosterone replacement in the ICU is warranted, but the surprising effects of supplementation in this case suggest that analysis of testosterone levels and potential supplementation are valuable considerations in weaning failure.

Case

A 63-year-old man was admitted to the ICU with respiratory failure because of severe pulmonary oedema. The patient had been treated for an infected knee prosthesis in a referring hospital, surgical cleansing and prolonged antibiotic treatment had been carried out for a *Staphylococcus aureus* infection. Apart from the knee replacement, the patient's history included a right-sided nephrectomy, diabetes type 2, a gastric bypass and multiple depressions.

On admission to the ICU the patient was intubated and pressure controlled ventilation was started. Antibiotic therapy was commenced because of pulmonary infiltration on the chest X-ray. Acute renal insufficiency combined with hypoalbuminaemia were established as the cause of the pulmonary and peripheral oedema. Nephrotic syndrome was determined by 24-hour urine, and renal biopsy showed a post-infectious glomerulonephritis. Continuous veno-venous haemofiltration (CVVH) was started to treat the oedema and kidney failure.

Course of mechanical ventilation

Under treatment, the patient's condition ameliorated very slowly but surely. On day 14 the patient's condition was deemed well enough to fully stop sedation and one day later the ventilation mode was switched to pressure support. Slowly pressure, PEEP and fiO2 could be reduced. CPAP ventilation was started twice a day on day 19, and a spontaneous breathing trial was performed on day 22. The oxygen saturation dipped below 90% during the trial and mechanical ventilation was restarted. Tracheostomy proved not to be an option because the patient had a short neck. On day 25, with low ventilation values and after a successful spontaneous breathing trial, the patient was extubated. After 24 hours though, the CO_2 in the arterial blood gas accumulated and the patient became drowsy and developed bradycardia, after which he was re-intubated. In the following days the patient auto-extubated three times. Each time the CO_2 values rose within 24 hours, after which non-invasive ventilation (NIV) was tried at first. But, due to hypoventilation with subsequent CO_2 retention and bradycardias, re-intubation became necessary each time. On day 40 the patient was extubated electively and NIV was started adjacently, later followed by intermittent NIV. After five days the CO_2 values rose to 90 mmHg which again necessitated re-intubation.

Failure-to-wean analysis

Because weaning attempts kept failing, a structured approach to weaning failure was carried out after the third extubation, according to the 'ABC of weaning failure' by Heunks and Van der Hoeven.[1]

Airway and lung – pulmonary oedema was the reason for

admission and was treated successfully by extracting fluids using CVVH. Infiltrative abnormalities found on CT-thorax subsided fully under antibiotic therapy, only a *Sphingomonas paucimobilis* was found in bronchial cultures. CT and ventilation conditions showed no sign of obstruction so bronchoscopy was waived.

Brain – the patient had a delirium during his stay, which slowly subsided after treatment with antipsychotics (CAM-ICU negative). Sleeping problems were treated with mirtazapine, melatonin, and benzodiazepines without causing drowsiness during the daytime. A psychiatrist was consulted and found no signs of active depression or other hindering mood disorders, although the patient did come across as rather passive and lethargic.

Cardiac – ECG showed no relevant abnormalities. A transthoracic echocardiogram showed good function of the left ventricle and grade 1 diastolic dysfunction, which would give no cause for weaning failure. Additionally, NT-proBNP was measured before and after extubation but gave no indication of a decrease in cardiac function.

Diaphragm and respiratory muscles – a diaphragm ultrasound was performed and showed good movement bilaterally. Neurological examination indicated no sign of neuromuscular disorders and showed reasonable muscle strength overall. The respiratory muscles were trained with inspiratory muscle training and during training the patient had a maximal inspiratory pressure of 62 cmH_2O while intubated (reference 63-year old male: 84-100 cmH_2O).

Endocrine and metabolic – adequate intake was ensured in collaboration with a dietician. Electrolytes were supplemented where necessary and extensive endocrinological diagnostics were performed (*table 1*).

Table 1. Endocrinological evaluation; value (laboratory reference values)

	Value (laboratory reference)
Cortisol	672 nmol/l (100-700)
TSH	6.0 mU/l (0.27-4.20)
fT4	8.9 pmol/l (10-23)
IGF-1	47 µg/l (Z-score -2)
LH	11 U/l (2-9)
FSH	12 U/l (2-12)
Testosterone (total)	0.7 nmol/l (8-25)
Prolactin	569 mU/l (50-400)

Endocrine factors

The 'ABC of weaning failure' mentions low cortisol and fT4 as possible hormonal causes for weaning failure. Cortisol supplementation reduced the duration of weaning in patients with adrenal insufficiency, while the underlying mechanism is unknown.[1] Although there is only anecdotal evidence for T4 supplementation, a markedly low T4 may reduce the respiratory muscle strength and central drive, so supplementation seems reasonable in weaning failure. Cortisol in this patient was normal and fT4 was slightly lowered but in no way atypical for an ICU patient. Thyroid hormone levels in critically ill patients are almost always lowered in light of a non-thyroidal illness syndrome,[2] while generally not impeding the weaning process. No other hormones are mentioned in the ABC of weaning failure as possibly influencing the weaning process.

Coincidentally a markedly lowered testosterone was found; this was noted, but only with thoughts towards supplementation after hospital discharge. Its clinical relevance was deemed low in the present, critical situation. Low IGF-1 values were found, but supplementation was not considered since the most recent research on supplementation is distinctly negative.[1]

On day 49, more or less running short of options and new insights, testosterone supplementation was started with an intramuscular depot (Sustanon 1 ml, 250 mg/ml). Miraculously, one day after supplementation it became possible to successfully reduce ventilation conditions, after five days CPAP ventilation was started and on day 57 the patient was extubated. In contrast to the previous five times, values in the blood gases stayed stable and after good clinical improvement over the following four days, the patient was discharged to the ward in an ambulant state. On the day of the last, and finally successful extubation, testosterone had been supplemented to a value of 18.6 nmol/l. Maximal inspiratory pressure had risen to 94 cmH_2O, well within the normal range for his age.

Discussion

Quite some research has been done about hormonal regulation and dysregulation in ICU patients, with some about testosterone in particular. These studies are not conclusive and most of the studies specifically recommend further investigation regarding the possible effects of testosterone supplementation in ICU patients. To our knowledge such trials have never been performed.

Male hypogonadism in general is associated with significant morbidity, including muscle weakness, decreased muscle mass, cardiomyopathy and osteopenia; healing of wounds or decubiti is also impaired.[3-5]

In critically ill patients specifically, lowered testosterone impairs nitrogen retention[3,6] and therefore may compromise muscle strength and the ability to wean from mechanical ventilation. In combination with protein loss this may lead to depletion of peripheral muscles and the diaphragm after prolonged critical illness, resulting in weakness, difficulty in sustaining spontaneous breathing, inability to cough effectively, and difficulty in participating in physical therapy and training.[7] Furthermore, testosterone deficiency may impede anabolism and growth of new muscle, even with optimal nutritional support.[3]

In our patient all of the impairments mentioned above are likely to have coexisted, if not because of the low testosterone

levels, then because of the prolonged ICU stay and mechanical ventilation. Interestingly, all of the impairments seemed to improve after we started testosterone supplementation, reflected in the maximal inspiratory pressure measurements and in the simple fact that weaning became possible following five failures. The speed at which the clinical parameters and the clinical condition of the patient improved was very surprising though. It also seemed that apart from physical improvement, mental changes such as a marked increase in motivation had a decisive effect on successful weaning. The extremely low testosterone values before supplementation may suggest the patient had a pre-existent deficiency that may potentially have added to the dramatic effect of supplementation. The patient was referred to an endocrinologist for further analysis after hospital discharge.

Endocrine alterations in the acute phase of critical illness are characterised by low peripheral effector hormone levels, despite an actively secreting pituitary. In prolonged critical illness, however, a reduced pulsatile secretion of anterior pituitary hormones occurs. The adrenal axis with high cortisol levels in the presence of low ACTH levels is a noteworthy exception.[8,9] Beyond the failure of the somatotropic (growth hormone, and insulin-like growth factors (IGF-I and -II)) and thyrotrophic axes (TSH, T3 and T4), hypogonadism has been documented consistently in critical illness,[10-24] and has been inferred to contribute to the catabolic state frequently seen in critically ill men.[12,19,20,24,25] Testosterone levels decrease during the early phase of critical illness. Immediately after the onset of illness or trauma, a primary Leydig cell deficiency, due to a direct effect of cytokines, appears to predominate combined with increased peripheral aromatisation of androgens. In this early phase the secretions of luteinising hormone (LH) and follicle stimulating hormone (FSH) are generally increased to attenuate the decrease in testosterone levels; however, normal or low LH and FSH levels can be observed even though the testosterone level is low. In the chronic phase of critical illness, suppressed LH secretion presumably further reduces serum testosterone concentrations, suggesting a hypothalamic-pituitary dysfunction.[6,14,21] Similar alterations in LH and FSH values are encountered in women.[11,24] Considering our patient was likely to have passed into the chronic phase of his illness at that time, his LH and FSH were found to be relatively high, possibly owing to his extremely low testosterone levels.

Testosterone levels are found to be below normal (defined as a serum total testosterone level <8.7 nmol/l) in a vast majority of critically ill men admitted to the ICU and testosterone levels decline even further in the days following admission. Reported prevalence of low testosterone in ICU patients admitted for septic shock, trauma, cardiac disease, gastrointestinal bleeding, diabetic keto-acidosis, COPD exacerbation, and postoperative patients ranges from 62.5% to 100%.[10-21,23,24] In men admitted specifically with acute respiratory failure and in need of mechanical ventilation for more than 24 hours, testosterone levels were below normal in 93% of the cases with a serum testosterone of 3.8 ± 3 nmol/l (mean ± SD).[26]

Testosterone circulates in peripheral blood in three states: tightly bound to sex hormone binding globulin (SHBG), weakly bound to serum albumin and corticosteroid-binding globulin (CBG), and as free testosterone. Only the free and albumin-bound fractions are metabolically active and therefore bioavailable.[27] Total serum testosterone measurements comprise all three states, thus including both bioavailable and non-bioavailable testosterone.
The levels of SHBG or binding affinity of SHBG for testosterone are not significantly affected by other (non-androgenic) stress steroids, acute-phase proteins, or any nonsteroidal drugs commonly used in critical care.[25,28,29] High-dose steroids can suppress the gonadal axis and influence SHBG binding affinity but our patient was not given steroids. Furthermore the biopotency of gonadotropins is not influenced across the course of acute illness.[25] Neither are testosterone levels affected by use of CVVH.[30] Prolactin levels, which in higher concentrations can suppress the gonadal axis, were slightly elevated in our patient, possibly because of decreased renal excretion due to the kidney failure. The slight elevation in this case is unlikely to have caused significant suppression.

Several studies have observed a correlation between low testosterone levels in ICU patients and disease severity,[10,18,19] severity of septic shock,[12] and worse outcomes, including mortality,[12,14,31] ICU length of stay and duration of hospital stay,[14,26] although other studies found no statistically significant correlations or no correlations whatsoever.[10,17] Interestingly, in one study in mechanically ventilated men admitted for respiratory failure, testosterone levels were inversely related to ICU length of stay and also to the number of ventilation days.[26] Another study found that testosterone depression correlated with the degree of arterial hypoxia in COPD patients with respiratory failure.[32]
The relationship between low serum testosterone and worse outcomes does not necessarily imply that hypogonadism per se could worsen the vital prognosis during hospitalisation. Testosterone may simply behave as a marker of health, as do other biological markers such as albumin, glucose,[33] and triiodothyronine.[34] However, the dramatic improvements in our specific patient after supplementation of testosterone point towards the hypothesis that lowered testosterone in itself is a cause of worse outcomes, which warrants fundamental research on the effects of testosterone supplementation on disease outcome.

In studies of community-based hypogonadal men, testosterone replacement has been shown to have many beneficial effects, including nitrogen retention,[35] positive protein balance, increased muscle mass,[36] and decreased adipose tissue.[5]

Testosterone replacement also enhances memory retention and improves mood, energy level, and sense of well-being.[4,37] Although no such research exists in critically ill patients, this line of evidence argues for the administration of anabolic steroids to critically ill patients to improve their catabolic state. Another line of evidence in animal models, however, suggests that testosterone may suppress the immune system and myocardial function in critical illness.[6,38] While similar models also demonstrate beneficial effects of oestrogens on these systems, thus speculating that oestrogen, and not testosterone therapy, may prove to be a valuable intervention during the catabolic phases of acute and chronic critical illness.[6,39] Another clinical study makes a case for stimulating the pituitary gland with pulsatile GnRH administration, instead of directly supplying effector hormones, as this would reduce side effects.[21,40,41]

This case report aims to bring to the attention of clinicians the surprising effects of testosterone supplementation in this particular case. We do not propose testosterone supplementation or testing for low testosterone in all male ICU patients because, as illustrated, there is simply too little evidence to support this. However, considering the knowledge of this exceptional case together with the evidence that does exist, we think analysis of testosterone levels and potential supplementation would be a very useful consideration when weaning fails, and thus would be a valuable addition to the 'ABC of weaning failure' as used in clinical practice.

Disclosures

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References

1. Heunks LM, van der Hoeven JG. Clinical review: the ABC of weaning failure--a structured approach. Cri Care. 2010;14:245.
2. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3:816-25.
3. Bagatell CJ, Bremner WJ. Androgens in men--uses and abuses. New Engl J Med. 1996;334:707-14.
4. Tenover JL. Testosterone and the aging male. J Androl. 1997;18:103-6.
5. Villareal DT, Morley JE. Trophic factors in aging. Should older people receive hormonal replacement therapy? Drugs Aging. 1994;4:492-509.
6. Spratt DI. Altered gonadal steroidogenesis in critical illness: is treatment with anabolic steroids indicated? Best Pract Res Clin Endocrinol Metab. 2001;15:479-94.
7. Lewis MI, Belman MJ. Nutrition and the respiratory muscles. Clin Chest Med. 1988;9:337-48.
8. Langouche L, Van den Berghe G. Hypothalamic-pituitary hormones during critical illness: a dynamic neuroendocrine response. Handbook Clin Neurol. 2014;124:115-26.
9. Van den Berghe G. Endocrine evaluation of patients with critical illness. Endocrinol Metab Clin North Am. 2003;32:385-410.
10. Akbas T, Deyneli O, Sonmez FT, Akalin S. The pituitary-gonadal-thyroid and lactotroph axes in critically ill patients. Endokrynologia Polska. 2016;67:305-12.
11. Akbas T, Karakurt S, Unluguzel G, Celikel T, Akalin S. The endocrinologic changes in critically ill chronic obstructive pulmonary disease patients. COPD. 2010;7:240-7.
12. Christeff N, Benassayag C, Carli-Vielle C, Carli A, Nunez EA. Elevated oestrogen and reduced testosterone levels in the serum of male septic shock patients. J Steroid Biochem. 1988;29:435-40.
13. Dimopoulou I, Kouyialis AT, Orfanos S, et al. Endocrine alterations in critically ill patients with stroke during the early recovery period. Neurocrit Care. 2005;3:224-9.
14. Dong Q, Hawker F, McWilliam D, Bangah M, Burger H, Handelsman DJ. Circulating immunoreactive inhibin and testosterone levels in men with critical illness. Clin Endocrinol. 1992;36:399-404.
15. Fourrier F, Jallot A, Leclerc L, et al. Sex steroid hormones in circulatory shock, sepsis syndrome, and septic shock. Circ Shock. 1994;43:171-8.
16. Luppa P, Munker R, Nagel D, Weber M, Engelhardt D. Serum androgens in intensive-care patients: correlations with clinical findings. Clin Endocrinol.. 1991;34:305-10.
17. Nierman DM, Mechanick JI. Hypotestosteronemia in chronically critically ill men. Crit Care Med. 1999;27:2418-21.
18. Sahana PK, Ghosh A, Mukhopadhyay P, Pandit K, Chowdhury BR, Chowdhury S. A study on endocrine changes in patients in intensive care unit. J Indian Med Assoc. 2008;106:362-4.
19. Spratt DI, Cox P, Orav J, Moloney J, Bigos T. Reproductive axis suppression in acute illness is related to disease severity. J Clin Endocrinol Metab. 1993;76:1548-54.
20. Van den Berghe G, de Zegher F, Lauwers P, Veldhuis JD. Luteinizing hormone secretion and hypoandrogenaemia in critically ill men: effect of dopamine. Clin Endocrinol. 1994;41:563-9.
21. van den Berghe G, Weekers F, Baxter RC, et al. Five-day pulsatile gonadotropin-releasing hormone administration unveils combined hypothalamic-pituitary-gonadal defects underlying profound hypoandrogenism in men with prolonged critical illness. J Clin Endocrinol Metab. 2001;86:3217-26.
22. Vogel AV, Peake GT, Rada RT. Pituitary-testicular axis dysfunction in burned men. J Clin Endocrinol Metab. 1985;60:658-65.
23. Wang C, Chan V, Yeung RT. Effect of surgical stress on pituitary-testicular function. Clin Endocrinol. 1978;9:255-66.
24. Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M. Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab. 1985;60:444-50.
25. Spratt DI, Bigos ST, Beitins I, Cox P, Longcope C, Orav J. Both hyper- and hypogonadotropic hypogonadism occur transiently in acute illness: bio- and immunoactive gonadotropins. J Clin Endocrinol Metab. 1992;75:1562-70.
26. Almoosa KF, Gupta A, Pedroza C, Watts NB. Low Testosterone Levels are Frequent in Patients with Acute Respiratory Failure and are Associated with Poor Outcomes. Endocr Pract 2014;20:1057-63.
27. Winters SJ. Endocrine evaluation of testicular function. Endocrinol Metab Clin North Am. 1994;23:709-23.
28. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab. 1981;53:58-68.
29. Pugeat MM, Dunn JF, Nisula BC. Transport of steroid hormones: interaction of 70 drugs with testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab. 1981;53:69-75.
30. Bellomo R, McGrath B, Boyce N. Effect of continuous venovenous hemofiltration with dialysis on hormone and catecholamine clearance in critically ill patients with acute renal failure. Crit Care Med. 1994;22:833-7.
31. Iglesias P, Prado F, Ridruejo E, et al. Hypogonadism and Mortality in Aged Hospitalized Male Patients: A 5-Year Prospective Observational Study. Experimental Clin Endocrinol Diabetes. 2015;123:589-93.
32. Semple PD, Beastall GH, Watson WS, Hume R. Serum testosterone depression associated with hypoxia in respiratory failure. Clin Sci. 1980;58:105-6.
33. Iglesias P, Polini A, Munoz A, D et al. Fasting hyperglycaemia and in-hospital mortality in elderly population. Int J Clin Pract. 2011;65:308-13.
34. Iglesias P, Munoz A, Prado F, et al. Alterations in thyroid function tests in aged hospitalized patients: prevalence, aetiology and clinical outcome. Clin Endocrinol. 2009;70:961-7.
35. Wilson JD, Griffin JE. The use and misuse of androgens. Metab Clin Exp. 1980;29:1278-95.
36. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men--a clinical research center study. J Clin Endocrinol Metab. 1996;81:3469-75.
37. Wang C, Alexander G, Berman N, et al. Testosterone replacement therapy improves mood in hypogonadal men--a clinical research center study. J Clin Endocrinol Metab. 1996;81:3578-83.
38. Elsherbiny A, Tricomi M, Bhatt D, Dandapantula HK. State-of-the-Art: a Review of Cardiovascular Effects of Testosterone Replacement Therapy in Adult Males. Curr Cardiol Rep. 2017;19:35.
39. Mechanick JI, Nierman DM. Gonadal steroids in critical illness. Crit Care Clin. 2006;22:87-103, vii.
40. Van den Berghe G. Endocrinology in intensive care medicine: new insights and therapeutic consequences. Verhandelingen - Koninklijke Academie voor Geneeskunde van Belgie. 2002;64:167-87; discussion 87-8.
41. Van den Berghe G, Baxter RC, et al. The combined administration of GH-releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. Clin Endocrinol. 2002;56:655-69.