Characterization of a prospective human model for study of the reproductive hormone responses to major illness

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Spratt DI, Kramer RS, Morton JR, Lucas FL, Becker K, Longcope C. Characterization of a prospective human model for study of the reproductive hormone responses to major illness. *Am J Physiol Endocrinol Metab* 295: E63–E69, 2008. First published April 15, 2008; doi:10.1152/ajpendo.00472.2007.—With critical illness, serum testosterone levels fall markedly, whereas estrogen levels rise. Although animal studies suggest adaptive advantages, no prospective model has been available for studies in humans. We hypothesized that coronary artery bypass graft (CABG) surgery would provide such a model by eliciting the same reproductive hormone and other endocrine responses as reported with major nonsurgical illnesses. We further hypothesized that those responses would occur consistently in all CABG patients with predictable time courses, providing reliable windows for prospective studies. In 17 men undergoing CABG, serum levels of reproductive hormones, cortisol, thyroid hormones, and IGF-I were measured before and for up to 5 wk after surgery. Changes in serum levels of reproductive and other hormones were similar to those reported in nonsurgical critically ill patients. Time course for onset, duration, and recovery of reproductive hormone changes were consistent among all patients. A window for studying the testosterone and estrogen responses was established as the first 5 days following CABG. Practical use of this model was demonstrated by evaluating, in another seven men, changes in gonadotroph responsiveness to GnRH following CABG. Finally, to determine whether our findings in CABG could be extended to other surgeries, we demonstrated similar endocrine responses in 12 men following abdominal aortic aneurysm resection. We conclude that patients undergoing CABG surgery provide a useful human model for the prospective evaluation of the reproductive axis responses to acute illness. Other major surgeries are likely to also be suitable for these studies.

critical illness; testosterone; estrogen; cardiac surgery; gonadotropins

THE PHYSIOLOGY OF THE REPRODUCTIVE SYSTEM changes dramatically with the onset of major illness. Serum testosterone and gonadotropin concentrations fall to prepubertal levels (5–7, 36, 40, 44, 45, 48, 55, 60, 61, 64). In contrast, estrogen concentrations rise, often markedly (5, 7, 36, 48). Studies in rodent models suggest that these opposing changes in serum androgen and estrogen levels may be adaptive in critical illness and may decrease morbidity and mortality (2, 11, 14, 15, 19, 20, 30, 35, 37, 38, 62, 65). However, this phenomenon has been difficult to study prospectively in humans. Onset of critical illness is unpredictable, and the time course of recovery is variable.

Many concomitant factors that can independently affect the reproductive axis, such as drugs and alcohol (10, 16, 26, 53, 56, 59), hepatic or renal failure (12, 21, 57), and head trauma (39), are often present. Furthermore, obtaining informed consent can be difficult in critically ill patients.

We hypothesized that coronary artery bypass graft (CABG) surgery would meet the essential criteria for use as a prospective model for study of reproductive hormone responses to acute illness. First, patients should have no evidence of endocrine responses to illness prior to surgery so that they may serve as their own controls. In addition, CABG should elicit the same reproductive hormone responses as nonsurgical illnesses such as burns, sepsis, and myocardial infarction. These responses should be present in most if not all patients and should be consistent from patient to patient with respect to time of onset, duration, and time course of recovery. The sex steroid responses should occur in the milieu of other endocrine responses reported in nonsurgical patients. The responses described in nonsurgical illnesses include hypercortisolism, euthyroid sick syndrome (ESS), and increased serum growth hormone levels with decreased IGF-I levels (43, 58). CABG has been demonstrated in separate studies to produce each of these responses (3, 13, 27, 47, 50). However, the consistency with which they occur following CABG and the timing of their onset, duration, and recovery have not been defined.

To characterize these aspects of the reproductive hormones responses, we studied changes in all four endocrine systems simultaneously in men undergoing CABG who were in good clinical health prior to surgery. In addition, we assessed the reproductive hormone responses in more detail by profiling postoperative changes in sex hormone-binding globulin (SHBG) and determining whether unbound (bioactive) sex steroid levels changed in parallel with total levels. After establishing windows of opportunity for studying endocrine responses following CABG, we demonstrated the practical use of this model by prospectively evaluating pituitary responsiveness to physiological doses of gonadotropin-releasing hormone (GnRH) before and after CABG. Finally, we evaluated postoperative serum concentrations of selected hormones from the reproductive, thyroid, and adrenal axes as well as IGF-I following abdominal aortic anuerysm (AAA) to assess whether our prospective model in CABG may be extended to other surgeries.

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METHODS

Patients. The primary study population included 24 men (aged 42–75 yr, mean 59 ± 1.8 SE) electively scheduled for CABG. In the first 17 men, serial serum sampling was undertaken to profile the time course of changes in serum levels of hormones from the reproductive axis and other endocrine systems. In a subsequent group of seven men, changes in gonadotroph responsiveness to GnRH following CABG were evaluated. In addition, 12 men (aged 54–78 yr, mean 67 ± 1.9) undergoing AAA resection were also studied to determine whether endocrine responses observed in CABG also occur in other surgery patients. Inclusion criteria for CABG and AAA patients were *1*) ambulatory prior to surgery with good general health except for coronary artery disease, *2*) aspartate aminotransferase and bilirubin within the normal range and <1.5 mg/dl creatinine, *3*) no history of pituitary, gonadal, thyroid, or adrenal disease, *4*) no current use of drugs known to affect the reproductive, thyroid, or adrenal axes (androgens, glucocorticoids, calcium channel blockers, opioids, clonidine, amiodarone), *5*) no history of alcohol or drug abuse, and *6*) body mass index between 19 and 30 kg/m^2. Additional criteria for CABG patients were *1*) New York Heart Association classification III or less with ejection fraction >40% prior to surgery and *2*) preoperative levels of total testosterone, triiodothyronine (T$_3$), TSH, and morning cortisol (0700-0900) within the normal range. The study was approved by the Maine Medical Center Institutional Review Board. Written, informed consent was obtained from each patient prior to CABG surgery.

All CABG patients received fentanyl and flurane or isoflurane for intraoperative anesthesia with no anesthetic agents administered postoperatively except intravenous morphine. All underwent extracorporeal circulation of blood during surgery. No CABG or AAA patients had intraoperative complications, and all had uneventful recoveries. Dopamine was administered to four of 24 CABG patients within the first 24 h after surgery at doses (<3 ug·kg^{-1}·min^{-1}) lower than previously reported to suppress LH secretion (54). Other than the anesthetic agents and pain medications mentioned above and intraoperative heparin, no patients received drugs known to affect the reproductive, thyroid, or adrenal axes such as glucocorticoids, etomidate, clonidine, calcium channel blockers, amiodarone, or iodine for contrast studies.

Profiling of changes in serum levels of hormones from the reproductive and other endocrine systems. In the first 17 men undergoing CABG, serial serum samples were obtained prior to, during, and after hospitalization for CABG. Thus, patients served as their own controls by being studied in a healthy state before surgery and again during their postoperative illness phase. Table 1 displays the CABG blood-sampling schedule for measuring hormones of the reproductive, thyroid, and adrenal axes and SHBG. Free (unbound) testosterone and estradiol (E$_2$) were measured on samples obtained preoperatively and samples on the 2nd postoperative day in 12 men in whom sufficient

serum was available. All blood samples were centrifuged within 4 h after collection and frozen at $-30°$C until the time of assay.

Prospective evaluation of changes in pituitary gonadotroph responsiveness to GnRH following CABG. After the above studies were completed and the time windows in which responses of the reproductive axis to CABG could be studied were identified, GnRH stimulation was performed before and after CABG in another 7 men. We previously reported that a bolus dose of 150 ng/kg produces LH pulses in both normal and hypogonadotropic men with amplitudes similar to spontaneous LH pulses (42, 46, 52). This physiological dose of GnRH was administered 1–3 days prior to surgery (between 1200 and 1400) with serum levels of LH and FSH measured just prior to dosing and 10, 20, 30, 45, and 60 min after dosing. Four to five days after surgery (when serum levels of gonadotropins and testosterone remained below preoperative values), each patient received the same dose from the same vial of GnRH at the same time of day as preoperatively. No patients received parenteral analgesics within 24 h prior to GnRH testing. Three patients received acetaminophen with codeine for pain. Pre- and postoperative serum pools were constituted from equal aliquots of samples at each time point in each patient. Concentrations of testosterone, prolactin, and cortisol were measured on serum pools.

Serum sampling in AAA patients. In the 12 men undergoing AAA, a single serum sample was obtained on the 1st or 2nd postoperative day for measurement of total testosterone, T$_3$, cortisol, and IGF-I.

Assays. Serum levels of LH and FSH were measured with an in-house radioimmunoassay using 2nd IRP (Biodata) as a reference standard, as reported previously (44). Serum levels of testosterone were measured using DPC Coat-a-Count testosterone ^{125}I kit with intra- and interassay coefficients of variation (CVs) of <10% except interassay CVs of 11 and 12% at 76 and 93 ng/dl, respectively, and intra-assay CVs of 18 and 11% at 20 and 76 ng/dl, respectively. T$_3$ was measured using the Ciba-Corning Magic T$_3$ ^{125}I kit with intra- and interassay CVs at $\sim$20, 50, and 80% binding all <10%. Serum levels of thyroxine (T$_4$), cortisol, and SHBG were measured using the following kits: Ciba-Corning Magic T4 ^{125}I, Ciba-Corning Magic Cortisol ^{125}I, and Orion Diagnostica SHBG ^{125}I. Serum IGF-I levels were measured following extraction using a commercial enzyme-linked immunosorbent assay (ELISA; Diagnostics Systems Laboratories, Webster, TX). Intra-assay CVs were 7.1 (26.5 ng/ml), 4.5 (48.4 ng/ml), and 6.5% (169.7 ng/ml). Interassay CVs were 8.8 (42.9 ng/ml), 4.8 (132.6 ng/ml), and 6.4% (379.1 ng/ml). Serum concentrations of androstenedione (A$_4$), estrone (E$_1$), and E$_2$ were determined by radioimmunoassay following extraction with cyclohexane and ethyl acetate and purification over a celite column, as described previously (23, 24). Free testosterone and E$_2$ were assayed and calculated as described previously (9).

Statistics. Serum levels of a given hormone at baseline were compared with subsequent serial values using repeated-measures analysis of variance. Paired hormone values measured at single time points before and after surgery were compared using *t*-tests. Because

Table 1. *Study design for measurement of hormones and SHBG in CABG patients*

| Hormone | Preadmit −D1 | Perioperative | | Postop | | | | | | | | | |
		Preop	Bypass	D1	D2	D3	D4	D5	D6	W2	W4	W5
LH, FSH	X	X	X	X	X	X	X	X	X	X	X	X
Testosterone	X	X	X	X	X	X	X	X	X	X	X	X
E$_1$, E$_2$, A$_4$	X			X		X		X				
IGF-I		X			X							
T$_3$, T$_4$	X	X	X	X	X	X	X	X	X		X	
Cortisol	X	X	X	X	X	X	X	X	X		X	
SHBG	X				X							

SHBG, sex hormone-binding globulin; CABG, coronary artery bypass graft; preop, immediately prior to surgery; postop, postoperative; bypass, 40 min after initiation of extracorporeal bypass circulation; D1–6, 1–6 days after surgery; W2 and W4, 2 and 4 wk after surgery; W5, 4 wk after discharge from the hospital; E$_1$, estrone; E$_2$, estradiol; A$_4$, androstenedione; T$_3$, triiodothyronine; T$_4$, thyroxine.
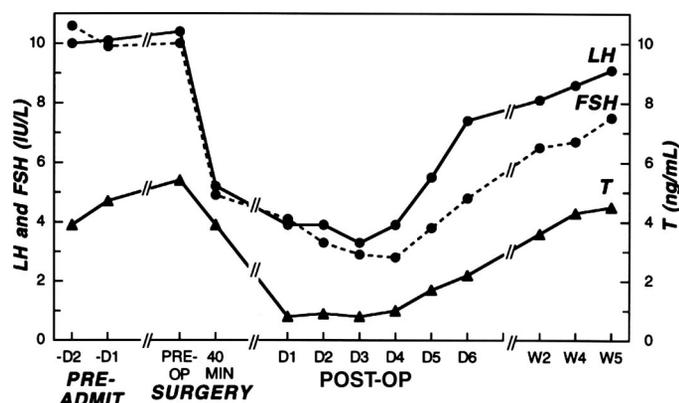
Fig. 1. Mean serum concentrations of LH, FSH, and total testosterone (T) in 17 men measured before, during, and after coronary artery bypass graft (CABG) surgery. Marked, sustained decreases in all 3 hormones were evident postoperatively (see text for significance levels). Preadmit −D2 and −D1, the 2 days just prior to hospitalization; preop, just prior to anesthesia induction; 40 min, 40 min on extracorporeal circulation; D1–6 postop, postoperative *days 1–6*; W2 and W4, 2 and 4 wk, respectively, after surgery; W5, 4 wk after discharge from the hospital.

Table 3. *Testosterone, cortisol, and IGF-I in CABG patients compared with AAA patients*

	Testosterone, ng/ml	T_3, ng/dl	Cortisol, μg/ml	IGF-I, ng/ml
CABG preop	5.1±0.5	134.9±4.1	12.1±1.1	155.6±10.8
CABG postop	1.3±0.2[1]	56.0±4.9[1]	19.7±2.9[3]	99.4±10.1[1]
AAA postop	1.5±0.3[1]	35.5±3.5[1]	19.7±2.2[3]	98.1±13.5

AAA, abdominal aortic aneurysm. [1]$P < 0.0001$, [2]$P < 0.001$, and [3]$P < 0.03$ vs. preop.

the number of patients was not always sufficient to determine whether values were distributed normally, comparisons of paired hormone levels were also made using the Wilcoxon signed-rank test. Because *P* values were similar with both parametric and nonparametric testing, only *P* values from signed-rank tests are listed. All mean values are listed as means ± SE.

RESULTS

Preoperative serum hormone concentrations. Mean serum concentrations of LH, FSH, total testosterone, cortisol, T_4, T_3, and IGF-I were all well within their normal ranges prior to surgery (Figs. 1–4 and Tables 2 and 3). Values of each hormone for individual CABG patients were also within their normal ranges. Normal ranges for reproductive axis hormones were as follows: LH, 4–18 IU/l; FSH, 3–12 IU/l; and testosterone, 2.8–9.0 ng/ml.

Profile of changes in reproductive hormones (n = 17 CABG patients). Gonadotropins but not testosterone decreased profoundly during surgery ($P < 0.0001$; Fig. 1). A marked decrease in serum testosterone concentrations was evident on the first day after surgery ($P < 0.0001$). The low levels of LH persisted throughout hospitalization ($P < 0.001$ for *days 1–4*, $P < 0.01$ for *day 5*, and $P < 0.03$ for *day 6* after surgery vs. baseline). The duration of FSH suppression was longer than LH ($P < 0.001$ for *days 1–6*, $P < 0.005$ for 2 wk, and $P < 0.05$ for 4 wk after surgery). Low-serum testosterone levels also persisted for 2 wk following surgery ($P < 0.001$ for *days 1–6*, $P < 0.005$ for 2 wk, and $P = 0.06$ for 4 wk after surgery). A trend toward increasing serum levels of LH, FSH, and testosterone was evident by the 5th postoperative day (Fig. 1).

Figure 2 demonstrates serum total sex steroid concentrations for the first 5 postoperative days compared with preoperative values. The increases in serum E_1 and the constancy of serum E_2 levels contrast with the marked decrease in serum testosterone. E_2-testosterone ratios were markedly increased ($P < 0.0001$ vs. preoperative for all postoperative time points). Serum A_4 levels did not change significantly. Decreased serum SHBG levels were evident by the 2nd postoperative day (26.7 ± 4.6 nmol/l preop vs. 15.7 ± 3.0 nmol/l postop, $P < 0.01$).

Profile of changes in serum concentrations of free sex steroids (n = 12 CABG patients). Because of the decrease in serum concentrations of SHBG, serum concentrations of free (unbound) testosterone and E_2 were measured in 12 subjects with sufficient sample volumes available preoperatively on the 2nd postoperative day to confirm a decrease in free testosterone and to determine whether an increase in free E_2 was evident. SHBG decreased from 34.4 ± 4.4 before to 22.0 ± 3.0 nmol/l after surgery ($P < 0.0005$). Decreases were observed in both free (0.0923 ± 0.0070 to 0.0304 ± 0.0044 ng/ml, $P < 0.0001$) and total testosterone (4.93 ± 1.0 to 1.22 ± 0.6 ng/ml, $P < 0.0001$). The percent decrease in free testosterone (66.4 ± 4.8%) was less than in total testosterone (75.7 ± 3.5%) ($P < 0.001$). The observed change in free E_2 (0.58 ± 0.04 to 0.83 ± 0.83 pg/ml) was not statistically significant ($P = 0.14$). However, the percent change in free E_2 (55.1 ± 5.8%) was markedly greater than the change in total E_2 (32.3 ± 3.1 to 33.8 ± 4.8 pg/ml or 6.6 ± 16.5%, $P = 0.01$).

Profile of changes in cortisol and thyroid hormones (n = 17 CABG patients). Morning cortisol levels in the initial 17 men increased following surgery ($P = 0.05$ for *day 1* and $P < 0.03$ for *days 2* and *3* after surgery) and were not significantly different from preoperative levels by the 4th postoperative day (Fig. 3). Marked decreases in serum total T_3 and T_4 occurred with surgery ($P < 0.0001$ vs. baseline; Fig. 4). Serum T_3 levels remained significantly below baseline for the 6 days in the hospital ($P < 0.0001$) through 4 wk after discharge ($P < 0.005$). A trend toward recovery was evident by the 2nd postoperative day (Fig. 4). Recovery of serum T_4 levels occurred more rapidly ($P < 0.0001$ for *days 1–3*, $P < 0.005$ for *day 4*, $P < 0.02$ for *day 5*, and $P = 0.3$ for *day 6* after surgery vs. baseline).

Table 2. *Serum hormone levels at the time of GnRH testing*

	Basal LH, IU/l	Basal FSH, IU/l	ΔLH	ΔFSH	Testosterone, ng/dl	Prolactin, ng/ml	Cortisol, μg/dl*
Preop	5.6±2.0	7.8±3.4	16.6±3.6	3.7±1.1	3.4±0.3	7.8±1.2	6.9±1.2
Postop	2.1±0.8[1]	2.6±1.0[1]	24.3±5.4[2]	3.9±1.3	0.8±0.1[3]	12.8±2.2[1]	18.2±3.0[2]

Values are means ± SE. GnRH, gonadotropin-releasing hormone; ΔLH and ΔFSH, difference between basal and peak (following GnRH stimulation) serum concentrations. *Measured in the early afternoon both preop and postop. [1]$P < 0.05$, [2]$P < 0.03$, and [3]$P < 0.0001$.
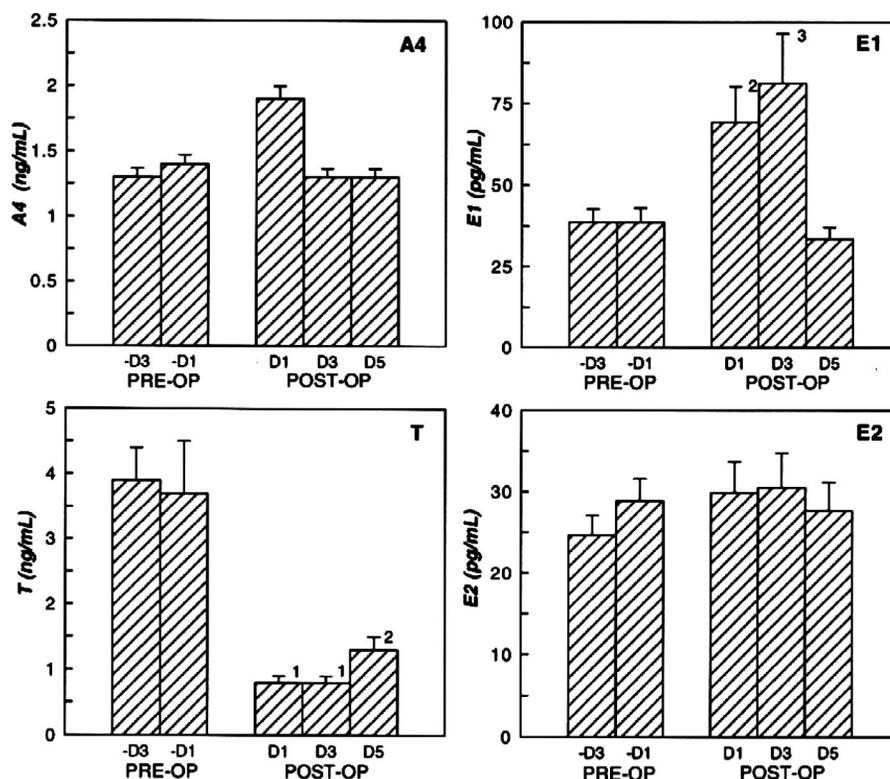
Fig. 2. Mean ($\pm$SE) serum concentrations of androstenedione (A_4), T, estrone (E_1), and estradiol (E_2) in 17 men measured before and after surgery. $-D3$ and $-D1$, 1 and 3 days prior to hospitalization; D1, D3, and D5, postoperative *days 1, 2,* and *3,* respectively. Serum levels of T decreased markedly, whereas serum E_1 levels rose and E_2 levels remained constant. Serum A_4 levels remained constant. [1]$P < 0.005$, [2]$P < 0.01$, and [3]$P < 0.02$ vs. baseline.

Prospective evaluation of changes in pituitary gonadotroph responsiveness to GnRH following CABG (n = 7 CABG patients). Figure 5 illustrates LH and FSH responses to a physiological dose of GnRH. Although basal levels of gonadotropins were lower after surgery than before surgery ($P <$ 0.05; Table 3), the LH (but not FSH) response was enhanced. The absolute increase in LH after surgery (24.3 ± 5.4 IU/l) was greater than before surgery (16.6 ± 3.6 IU/l) ($P < 0.03$). Serum prolactin and afternoon cortisol levels were mildly elevated at the time of postoperative GnRH testing compared with preoperative values (Table 2).

Comparison of serum hormone concentrations in AAA and CABG patients. Serum hormones levels in patients following AAA surgery are provided in Table 3. Values are compared with pre- and postoperative results of all 24 CABG patients. Similar very low values of testosterone are evident in both

populations following surgery. Postoperative values for nonreproductive hormones (T_3, cortisol, and IGF-I) are also similar.

DISCUSSION

Our data demonstrate that patients undergoing CABG meet essential criteria for a valid prospective model in which to study the reproductive hormone responses to acute illness. First, patients who are reasonably healthy and demonstrate no endocrine responses to illness prior to surgery can be selected. Thus, patients can serve as their own controls, thereby reducing variables between control and study measurements and decreasing the number of subjects required for studies. Four previous studies have used CABG patients as their own controls to study reproductive responses but have not confirmed
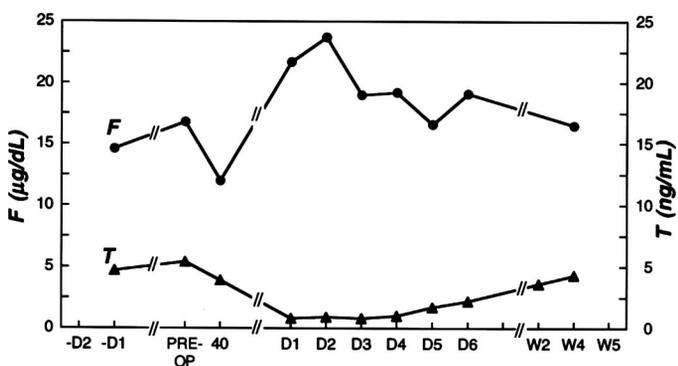

Fig. 3. Mean serum levels of total cortisol (F) and T before, during, and after CABG (see Fig. 1 for captions). Note that the return of serum levels of F toward baseline begins earlier than serum T levels.

Fig. 4. Mean serum levels of total triiodothyronine (T_3), thyroxine (T_4), and T before, during, and after CABG (see Fig. 1 for captions). Note that the return of serum levels of T_4 toward baseline begins earlier than serum T levels, whereas the course of recovery of T_3 levels is similar to that of T.
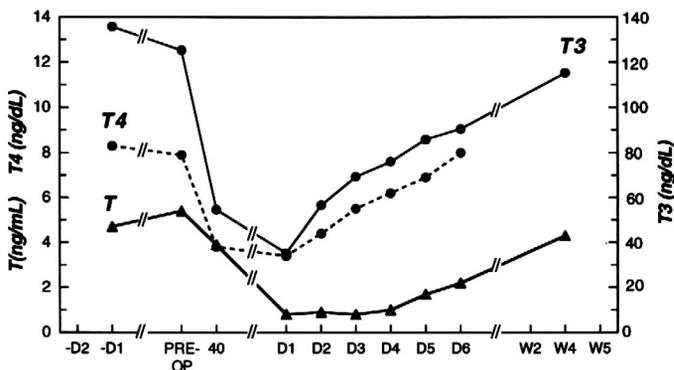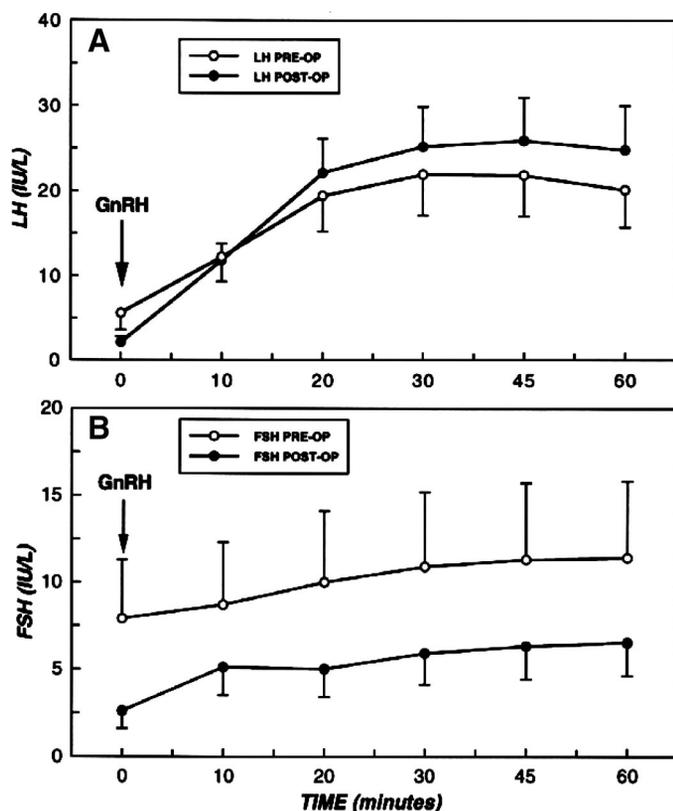
Fig. 5. Mean (±SE) serum levels of LH and FSH following gonadotropin-releasing hormone (GnRH) injection in 7 men before and after CABG. Baseline levels of both LH and FSH were lower following CABG than before ($P < 0.05$). However, the LH (but not FSH) response to GnRH was increased ($P < 0.03$).

the absence of endocrine responses to illness prior to surgery (3, 27, 47, 50).

Next, we confirmed that CABG patients mount the same set of endocrine responses as reported in nonsurgical patients with critical illness: decreased serum testosterone and IGF-I concentrations, increased serum estrogen and cortisol concentrations, and ESS (43, 58). We also demonstrated that changes in serum-free or unbound serum sex steroid concentrations parallel those of total hormone concentrations. Each of these responses to CABG has previously been reported separately in different studies (3, 13, 27, 47, 50) but not simultaneously in the same set of patients and with sufficient longitudinal data to track duration of the responses and time course of recovery. These longitudinal data allowed us to determine whether the reproductive hormone responses can be anticipated to occur in all CABG patients and with a predictable time course of onset, duration, and recovery. In addition, simultaneous tracking of these responses allowed us for the first time to compare timing of onset, duration, and time course of recovery of responses by different endocrine systems to acute illness.

With respect to reproductive hormones, the responses were consistent between patients allowing us to establish the first 5 postoperative days as the optimum time interval for studies of the testosterone response and the first 3 days as the optimum window for studies of the estrogen response. We determined that recovery of the reproductive axis was prolonged, requiring at least 4 wk after surgery. Recovery of FSH values was more prolonged than LH and testosterone values, suggesting that FSH secretion is more susceptible to suppression by illness than LH. The estrogen response appeared to resolve much more quickly with estrone values returning to baseline levels by the 5th postoperative day. This divergence of the time courses of hypogonadotropic hypogonadism and elevated estrogen suggests that the two responses are distinct, with different factors regulating them.

With respect to changes in the cortisol and thyroid axes, both were demonstrated to persist through the time windows identified for study of reproductive endocrine responses. Thus, in CABG patients, the testosterone and estrogen responses can be appropriately studied in the milieu of other responses. Furthermore, this model could be employed to prospectively evaluate other hormonal responses such as ESS. With our longitudinal data we were able to determine that the time course of ESS is similar to the recovery of the testosterone response, suggesting the potential of shared mechanisms. The time courses of the cortisol and estrogen responses were also similar.

Potential confounding factors were minimal in our patients. None had evidence of hepatic or renal dysfunction. Our patient population was reasonably drug free during the windows identified for study. During the study, no patients received glucocorticoids, a drug that possibly increases aromatase expression (17, 25). By *days 3* and *4* after surgery, patients were not receiving drugs such as potent opioid analgesics that could suppress gonadotropins or testosterone secretion. Furthermore, several factors indicate that the anesthetic agents administered during CABG do not appreciably affect endocrine measurements performed the day after surgery. Volatile anesthetic agents, particularly halothane, have been reported to decrease hepatic blood flow and hepatic clearance rates. However, the inhaled agents in our patients, flurane and isoflurane, are short acting and have a negligible effect on hepatic blood flow and clearance following surgery (8, 18, 31). Also, clearance rates of sex steroids are actually increased rather than decreased after CABG (51).

We demonstrated use of this model to prospectively evaluate changes in pituitary gonadotroph responsiveness during acute illness. Using a physiological dose of GnRH (42, 46, 52), neither the LH nor the FSH response was blunted postoperatively. In fact, the LH response was slightly greater after surgery than before. This increase in the LH but not FSH response again suggests that FSH secretion is more sensitive to suppression by illness than LH secretion. Our observations suggest that the pituitary as well as the hypothalamus may be affected by acute illness. The lack of an increase in the FSH response and the minimal increase in LH response despite very low circulating levels of testosterone suggest that the pituitary response to GnRH may be blunted. These results parallel those from a study administering low-dose pulsatile GnRH to men with nonsurgical illness that suggested mixed effects at both the hypothalamic and pituitary levels (55), further supporting CABG as a representative model of major illness.

The use of CABG as a prospective model of illness has previously been reported in five studies of endocrine responses (3, 13, 27, 47, 50). We have employed the CABG model to identify mechanisms of decreased testosterone and increased estrogen levels during illness (50) and to study the physiological and clinical effects of euthyroid syndrome (47). Use of the CABG model in those studies was based on preliminary

information that we reported in an abstract (49). The current study provides much more thorough characterization of CABG as a representative model of major illness providing new information regarding time courses of the reproductive hormone responses and their relationship to other endocrine responses and confirming appropriate windows for study of the responses. Thus, this study provides a solid foundation to validate data in previous studies and to provide CABG as a useful tool for future human studies. Our results also indicate that the characterization of CABG as a prospective research model may be extended to other forms of major surgery, such as AAA.

Additional studies are of interest because reports in animal models suggest that the hypogonadotropic hypogonadism and accompanying increased estrogen production may be adaptive (2, 11, 14, 15, 19, 20, 30, 35, 37, 38, 62, 65). Using rodent models of acute illness, these studies have reported improved cardiovascular, hepatic, renal, pulmonary, and immune function as well as decreased mortality in situations where more circulating estrogen is present (11, 14, 15, 19, 20, 30, 65). These improvements in organ functions and in mortality were also observed when testosterone effect was reduced by either orchiectomy or flutamide, a potent androgen blocker (2, 30, 35, 37, 38, 62, 65). Further translational studies blending animal and human models are of interest to explore the clinical significance of these findings. Studies indicate that men are more susceptible than women to sepsis, and its complications suggest that the milieu of sex steroids in critically ill patients may be clinically relevant (1, 63).

Finally, data gathered regarding the testosterone and estrogen responses to acute illness may be relevant in other situations of physical or mental stress. Testosterone levels decrease in male medical and ob/gyn residents during on-call rotations (4, 41). Estrogen levels were not evaluated in those studies. Testosterone levels also decrease during intensive military training and decrease further with greater sleep deprivation (22, 28, 29, 32–34). Estradiol levels were measured in two of those studies involving 5 days of intensive war training. In the first study, estradiol levels did not change during the initial 48 h and then decreased (34). In the subsequent study, two sessions of training were evaluated (32). In the first, estradiol increased during the initial 48 h and then decreased. In the second session, the only differences were worse weather and a smaller number of subjects. Estradiol levels remained stable throughout all 5 days. These results indicate that both the testosterone and estrogen responses are present in other forms of physical or mental stress beyond major illness but that increases in estrogen secretion appear more prominent in settings of severe illness. The clinical relevance in these other forms of stress also has not yet been studied.

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