Diagnostic Dosages of Protirelin (TRH) Elevate BP by Noncatecholamine Mechanisms

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• While performing thyroid function tests, we noticed that protirelin (TRH) raised BP, and, therefore, we investigated the effect of diagnostic dosages of protirelin (500 μg) on plasma catecholamine levels and cardiovascular function in eight patients one day before, one day after, and four weeks following heart surgery. Mean arterial pressure (MAP), heart rate (HR), plasma norepinephrine (NE), epinephrine (EPI), dopamine (DA), thyroid hormone (triiodothyronine [T_3], thyroxine), and thyrotropin (TSH) levels were measured before and after the intravenous injection of protirelin. Protirelin increased MAP transiently from 88 ± 2 to 103 ± 3 mm Hg (before surgery), 86 ± 4 to 102 ± 4 mm Hg (one day after surgery), and 86 ± 4 to 104 ± 5 mm Hg (four weeks after surgery). There were no notable changes in HR or plasma NE, EPI, or DA levels. The T_3 and TSH response to protirelin was normal on all three study days. Protirelin raised MAP by an effect on systemic vascular resistance (SVR) rather than an increase in cardiac output. We conclude the following: (1) diagnostic dosages of protirelin transiently elevate MAP and SVR by a noncatecholamine mechanism, (2) clinicians who perform protirelin tests should be aware of protirelin's transient pressor effects.

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Thyrotropin-releasing hormone (TRH) was originally identified as the hypothalamic factor regulating the pituitary gland's secretion of thyrotropin (TSH).[1] The function of TRH was thought to relate solely to thyroid gland homeostasis. Further work, however, demonstrated TRH to be widely distributed throughout the CNS, retina, pancreas, and gastrointestinal tract.[2-7] In addition, its concentration in synaptosomes,[3,8,9] its analeptic (brain-activating) properties,[5,7,10] its effect on the electrical activity of single neurons,[7,11] and its antagonism of opioid effects[4,5,12,13] led to the concept that TRH is a neurotransmitter or modulator of neurotransmission in addition to its neurohumoral actions.

For editorial comment see p 1138.

Endogenous opioid peptides are implicated in the pathogenesis of shock states[13-15] and naloxone hydrochloride, an opioid receptor antagonist, improves cardiovascular function and survival in experimental endotoxin,[16-18] hemorrhagic,[19,20] and spinal[21-23] shock. The therapeutic effects of naloxone appear to be mediated by the autonomic nervous system. In spinal shock, naloxone acts centrally[21,24] on opiate receptors to reverse endorphin effects on parasympathetic outflow. Release of dopamine (DA) also plays a role in the therapeutic effects of naloxone in spinal shock.[22] Like naloxone, protirelin (TRH) antagonizes many opioid effects (except antinociception)[2,4,5,12,13,25] and improves hypotension and survival in experimental endotoxin,[26-28] hemorrhagic,[26,28] and spinal[30] shock. Naloxone and protirelin differ in that protirelin elevates BP in unstressed normotensive individuals and does not act at the opioid receptor.[14] Thus, protirelin is termed a physiologic opiate antagonist. The mechanism of action of protirelin in shock states remains unknown. A great portion of protirelin's beneficial effects undoubtedly relate to its cardiovascular effects. Some[31,32] suggest that the cardiovascular effects of protirelin are catecholamine mediated in that plasma norepinephrine (NE) increases following protirelin administration, while others[7,33,34] think that its effects are independent of adrenergic mechanisms.

Since protirelin or protirelin analogues may have potential therapeutic uses in critically ill patients, we chose to investigate its action before and after surgery in these patients. We specifically were interested in the effect of standard diagnostic dosages (standard dosage of 500 μg used in the evaluation of the hypothalamic-pituitary-thyroid axis) of protirelin on plasma catecholamine levels and cardiovascular function.

PATIENTS AND METHODS

Eight adult patients (age range, 40 to 68 years) (six men, two women) undergoing coronary artery bypass surgery were prospectively studied one day before, one day after, and four weeks following surgery. Patients were studied in the supine position after an overnight fast (except medications). An intravenous (IV) catheter was placed in a vein in the antecubital fossa allowing for blood collection. Arterial pressure was monitored by sphygmomanometer (one day before and four weeks after surgery) or indwelling arterial catheter (one day after surgery). Heart rate (HR) was determined by continuous ECG monitoring. Mean arterial pressure (MAP) was calculated as diastolic pressure plus one third of the pulse pressure (systolic minus diastolic). Following a 20-minute rest period, MAP and HR were measured, and blood samples for plasma catecholamine (NE, epinephrine [EPI], and DA) and thyroid hormone determinations (triiodothyronine [T_3], thyroxine [T_4], TSH) were drawn. This procedure was repeated at 1, 5, 30, and 60 minutes following the IV injection of a diagnostic dose of synthetic protirelin (Thypinone, 500 μg). In addition, one day after surgery, we measured central venous pressure (CVP), pulmonary capillary wedge pressure, pulmonary artery pressure, and cardiac output (CO) using a thermodilution Swan-Ganz catheter; systemic vascular resistance (SVR, dyne/s/cm^{-5}) was calculated from these measurements as $(MAP - CVP)/CO \times 79.9$. It is routine in our hospital for patients after coronary artery bypass surgery to have Swan-Ganz and radial artery catheters placed during surgery. This study was approved by the Protection of Human Subjects and Clinical Investigation Committees of our institutions.

Blood samples for measurement of plasma catecholamine concentrations were obtained as previously described.[35] Blood specimens were collected in chilled heparinized test tubes that were immediately placed on wet ice, centrifuged at 4 °C within 30 minutes of collection, and the plasma was separated and stored at −70 °C until assayed. Plasma catecholamine levels were measured by a radioenzymatic technique in which a partially purified enzyme, catechol-o-methyltransferase, catalyzes the transfer of a tritiated methyl group from commercially available tritiated *S*-adenosylmethionine to the metahydroxyl group of endogenous NE, EPI, and DA, forming tritiated normetanephrine, tritiated metanephrine, and tritiated 3-methoxytyramine, respectively.[36]

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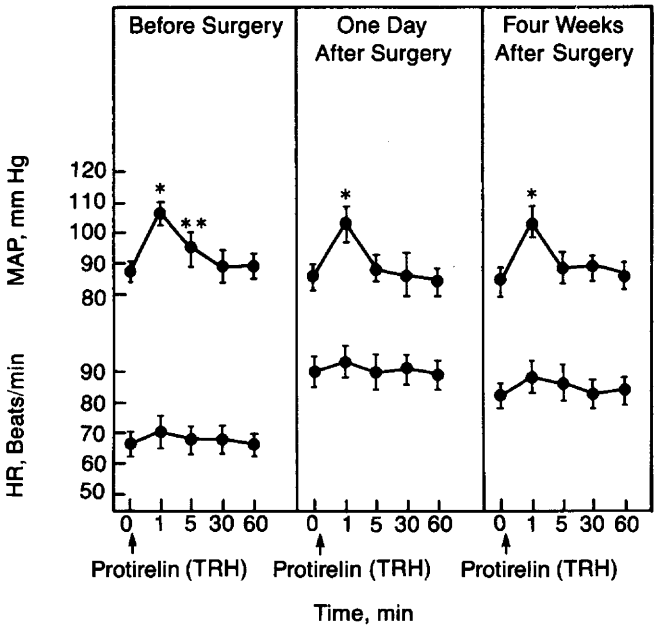

Fig 1.—Mean arterial pressure (MAP) and heart rate (HR) responses to injections of protirelin (TRH) (500 μg) before, one day after, and four weeks after coronary artery surgery. After baseline readings (time 0), protirelin was given intravenously and measurements were made at 1, 5, 30, and 60 minutes. (Asterisk indicates $P<.005$ compared with time 0; double asterisk, $P<.02$ compared with time 0.)

Table 2.—Mean (±SEM) Thyroid Hormone Levels in Study Subjects

Variable	Before Surgery	One Day After Surgery	Four Weeks After Surgery
Serum thyroxine level, μg/dL	7.0±0.8	4.5±0.3*	6.4±0.6
Serum triiodothyronine level, ng/dL	111.8±4.8	51.1±4.1*	112.0±9.0
Serum thyrotropin level, μU/mL	2.1±0.5	1.4±0.1†	2.1±0.3
Serum thyrotropin level 30 minutes after intravenous protirelin, μU/mL	8.4±1.2	7.8±0.9	9.6±1.5

*$P<.005$ compared with preoperative value.
†$P<.05$ compared with preoperative value.

These metabolites were separated by thin layer chromatography and quantified by liquid scintillation spectrometry (Packard Tricarb 460C). The resultant measurements are accurate above catecholamine concentrations of 20 pg/mL.

Thyroid hormone levels were measured by radioimmunoassay. Serum ionized calcium levels were measured in three patients following protirelin injection using an ion selective electrode system (Nova 2).

Standard statistical methods were used to calculate means and SEMs. Data were analyzed by two-tailed paired Student's *t* tests.

RESULTS

The MAP increased significantly ($P<.005$) at one minute following protirelin injection (Fig 1), while the HR remained unchanged. Similar protirelin-induced increments in MAP (15 to 17 mm Hg) were seen before and after surgery. These increments in MAP occurred despite β-adrenergic blockade for angina pectoris before surgery (propranolol hydrochloride was being taken by six of the eight patients) and aspirin was used to maintain graft

Table 1.—Medications Taken by Study Patients

Medications	Before Surgery	One Day After Surgery	Four Weeks After Surgery
Propranolol hydrochloride, mg/24 hr	256±27 n=6	0	0
Isosorbide dinitrate, mg/24 hr	130±26 n=3	0	0
Transdermal nitroglycerin	1 every day n=1	0	0
Nifedipine, mg/24 hr	90 n=1	0	0
Digoxin, mg/24 hr	0.25 n=1	0	0
Aspirin, mg/24 hr	0	0	1,200±0 n=6

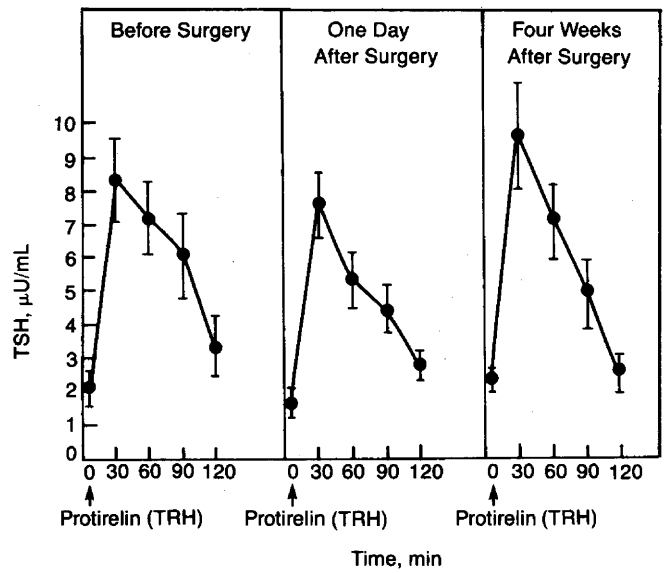

Fig 2.—Thyrotropin (TSH) (μU/mL) response to protirelin (TRH) (500 μg) before, one day after, and four weeks after coronary artery surgery. After baseline readings (time 0), protirelin was given intravenously and measurements were made at 30, 60, 90, and 120 minutes.

patency following surgery (given to six of eight patients) (Table 1). All patients were clinically and chemically euthyroid before surgery (Table 2). One day after surgery, patients fulfilled the criteria for the "sick euthyroid syndrome" (low serum T_3 and T_4 levels, normal or low TSH levels, and normal serum TSH response to protirelin[37,38]) (Table 2, Fig 2). Despite raising MAP, protirelin caused no significant changes in plasma NE, EPI, or DA levels from baseline values (Fig 3). Plasma catecholamine levels were uniformly elevated one day after surgery ($P<.01$) when compared with preoperative levels and returned to normal by four weeks following surgery (Fig 3). Protirelin raised MAP significantly ($P<.005$) by increasing SVR (Table 3). There was no effect of protirelin on serum ionized calcium levels in the three patients in whom this variable was analyzed.

COMMENT

Unlike naloxone, protirelin-induced increases in MAP occurred by an increase in SVR rather than an increase in stroke volume.[16,23] In contrast to Tuck et al[31] and Morley et al,[32] we found no significant increases in plasma NE, EPI, or DA concentrations following diagnostic dosages of protirelin. It is unlikely that a BP change of the magnitude seen

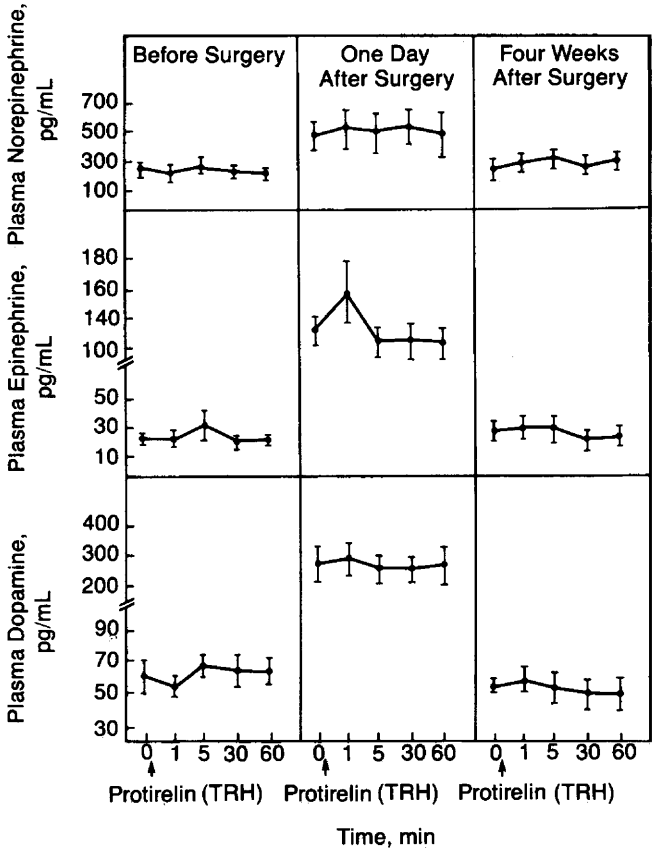

Fig 3.—Plasma norepinephrine, epinephrine, and dopamine concentrations in response to injection of diagnostic dosages of protirelin (TRH) (500 μg) before, one day after, and four weeks after coronary artery surgery. After baseline samples were collected (time 0), protirelin was given intravenously and blood samples were collected at 1, 5, 30, and 60 minutes. Plasma norepinephrine, epinephrine, and dopamine were significantly elevated one day after surgery ($P<.01$) compared with before surgery and returned to baseline by four weeks following surgery.

in this study (15 to 17 mm Hg) would be mediated by a change in catecholamine release without detectable changes in plasma catecholamine levels and strongly suggests (but does not prove) that the hemodynamic effects of protirelin are noncatecholamine mediated. If patients in this study had decreasing baseline catecholamine levels, protirelin may have kept the baseline values constant by causing the release of small amounts of catecholamines (rather than allowing them to decrease). This small change would not explain the raised BP but could explain the difference between our results and those of Tuck et al[31] and Morley et al,[32] who had lower baseline NE concentrations (approximately 160 pg/mL) that increased slightly (200 to 275 pg/mL) following protirelin.

Plasma NE has been used as an index of sympathetic nervous system activity.[39-42] Lack of an increase in plasma NE levels argues against sympathetic mediation of protirelin's pressor effects. Beale et al[33] injected protirelin into the cisterna magna of rabbits and observed increases in BP that were not antagonized by chlorpromazine hydrochloride (a central inhibitor of DA and α-adrenergic receptors). Horita and Carino[34] also demonstrated a pressor response to intraventricular injection of protirelin in rabbits that was not blocked by phenoxybenzamine hydrochloride (α-adrenergic blocker), guanethidine sulfate (catecholamine-depleting agent), reserpine (catecholamine-depleting agent), or atropine sulfate (antimuscarinic agent).[34] We found no effect of propranolol on TRH's pressor response in humans.

Table 3.—Changes in Hemodynamic Variables After Protirelin Injection

Variable*	Time After Injection, min 0	1	5	30
MAP, mm Hg	86±4	103±4†	89±5	87±6
CVP, mm Hg	9.3±1.1	10.3±1.2	10.0±1.3	9.4±1.1
PCWP, mm Hg	12.4±0.6	13.0±0.9	12.5±1.0	11.6±1.1
CO, mm Hg	5.0±0.3	4.8±0.3	4.9±0.3	4.8±0.3
SVR, dyne/s/cm^{-5}	1276±108	1579±88†	1301±105	1300±138

*MAP indicates mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; and SVR, systemic vascular resistance.
†$P<.005$.

In the study of Horita and Carino,[34] the TRH pressor response remained intact in animals with spinal transections below T1 but transections in the cervical cord region abolished the response. MK-771, a protirelin analogue, raises BP in anesthetized cats[7] by an effect that is not antagonized by mecamylamine hydrochloride, a ganglionic blocking agent. These data taken together suggest that the pressor response to protirelin is centrally mediated but not expressed through classic autonomic pathways. The pressor response to intraventricular protirelin in endotoxic rats is abolished by adrenal demedullation.[43] However, IV protirelin still produces a pressor response in these animals. Therefore, protirelin appears to increase cardiovascular values via the adrenal medullary system as well as some other effector system.

The pressor response to protirelin was unaffected by the use of aspirin (600 mg orally twice a day in six of eight patients). Since aspirin acetylates and deactivates the cyclo-oxygenase pathway involved in prostaglandin production,[44,45] these data argue against prostaglandin mediation of the TRH pressor response.

Hypercalcemia may raise BP[46,47] and thus we investigated the effect of protirelin on ionized calcium levels in three patients. No effect was found.

Protirelin causes release of a variety of hormones including TSH, prolactin, follicle-stimulating hormone, growth hormone (in acromegaly), and glucagon.[4,5] Release of these hormones occurs too slowly to explain the pressor effect of protirelin. Goldstein and Pavel[48] demonstrated release of vasotocin following intracarotid injection of protirelin in cats. Although they do not report hemodynamic variables, CSF vasotocin activity greatly increased within five minutes of protirelin injection. The role of vasotocin in the TRH pressor response is unknown.

Evidence favors a beneficial effect of naloxone hydrochloride[16-23] and protirelin[26-30] in pharmacologic doses (2 mg/kg/hr) in shock states and suggests that these opioid antagonists favorably increase blood flow to vital organs and improve survival from experimental shock. Naloxone (in pharmacologic dosages) acts at cardiovascular sites within the CNS and/or at peripheral sites to improve myocardial contractility in experimental shock,[13,14,21,22,24] is associated with DA release,[22] and its action depends on adrenal medullary integrity.[44] Protirelin (a physiologic opiate antagonist)[13,14] elevates BP in both normotensive and hypotensive individuals. As shown by our data, diagnostic dosages of protirelin increase BP without increasing plasma catecholamine levels or CO. Preliminary evidence[49] suggests that protirelin and naloxone have additive effects

when used together in the treatment of experimental shock. Although naloxone reverses shock resulting from a variety of causes, it may also potentiate pain processes by blocking opiate receptors. The potential advantage of protirelin over naloxone is that it does not act at opiate receptors and, hence, it does not antagonize antinociception.[14]

Protirelin may work via opioid antagonism, release of an unknown humoral substance, or antagonism of some hypotensive factor. Protirelin is effective when given orally at 20 to 30 times the IV dose[5] and may have potential use in treating shock in field situations. It is not affected by adrenergic or cholinergic blockade[33,34] and may be useful in the hypotensive patient taking propranolol. Future work into the mechanisms by which protirelin and naloxone work in shock may provide us with both new insights into the pathophysiology of these disease states as well as new therapeutic tools. These agents are not approved for human use in shock; use should be restricted to controlled trials.

We have demonstrated a similar (15– to 20–mm Hg) pressor response in patients with essential hypertension. Clinicians who perform protirelin tests should become aware of the pressor effect described in this report and BP should be measured before and after protirelin injection, especially in patients with hypertension or cardiac disease.

Evaluation of thyroid function in patients undergoing cardiac surgery is the subject of a future report. However, preliminary evidence suggests that TSH and the TSH response to protirelin (Fig 2) remain intact following cardiac surgery and may be of value in ruling out hypothyroidism in these patients.

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